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# First Genome Wide Association Study of Latent Autoimmune Diabetes in Adults Reveals Novel Insights Linking Immune and Metabolic Diabetes

Short title: LADA GWAS links immune and metabolic diabetes

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[9]Division of Molecular & Clinical Medicine, Medical Research Institute, University of Dundee, Dundee, UK; [10]Odense University Hospital, Odense, Denmark; [11]Department of Endocrinology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; [12]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway; [13]Vaasa Health Care Center and Department of Primary Health Care, Vaasa Central Hospital, Vaasa, Finland; [14]Department of Public Health, Aarhus University, Aarhus, Denmark; [15]Weill Cornell Medical College, NY, USA; [16] Florida Hospital Translational Research Institute for Metabolism and Diabetes, Orlando FL;[17]Institute for Diabetes, Obesity and Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [18]Mayo Clinic, Rochester Minnesota; [19]University of Alabama, Birmingham AL; [20]Geisinger Health System, Danville PA; [21]Health Diagnostic Lab Inc., Richmond, VA; [22]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [23]Centre National de la Recherche Scientifique (CNRS) 8199, Université Lille Nord de France, Pasteur Institute, Lille, France; [24]Department of Genomics of Common Disease, Imperial College London, London, UK; [25]National Disease Research Interchange, Philadelphia, PA 19103; [26]Hospital Universitari Germans Trias i Pujol, Spain; [27]German Diabetes Center, Düsseldorf, German; [28]Diabetes Research Centre, University of Leicester, Leicester, UK; [29]Main Line Health System, Wynnewood, PA, USA; [30]Department of Systems, Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [31]Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [32] Helsinki University Hospital, Department of Endocrinology, Helsinki, Finland; [33]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore and Imperial College, London, UK [34]Department of Internal Medicine I, Ulm University Medical Centre, Ulm, Germany; [35]HUNT Research Center, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Levanger, Norway; [36]Clinical and Molecular Medicine, Norwegian University of Science and Technology, Norway;[37]Folkhälsan Research Centre; Research Programs Unit, Diabetes and Obesity; University of Helsinki; Helsinki, Finland; [38]Finnish Institute for Molecular Medicine, Helsinki, Finland.

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**Figures: 1**

**ABSTRACT**

**Objective:** Latent autoimmune diabetes in adults (LADA) shares clinical features with both type 1 and type 2 diabetes; however there is ongoing debate regarding the precise definition of LADA. Understanding its genetic basis is one potential strategy to gain insight in to appropriate classification of this diabetes subtype.

**Research Design and Methods:** We performed the first genome-wide association study of LADA in cases of European ancestry versus population controls (n = 2,634 vs. 5,947), cases with type 1 diabetes (n = 2,454 vs. 968) and type 2 diabetes (n = 2,779 vs. 10, 396).

**Results:** The leading genetic signals were principally shared with type 1 diabetes, although we observed positive genetic correlations genome-wide with both type 1 and type 2 diabetes. Additionally, we observed a novel independent signal at the known type 1 diabetes locus harboring *PFKFB3*, encoding a regulator of glycolysis and insulin signaling in type 2 diabetes and inflammation and autophagy in autoimmune disease, as well as an attenuation of key type 1-associated HLA haplotype frequencies in LADA, suggesting that these are factors that distinguish childhood-onset type 1 diabetes from adult autoimmune diabetes.

**Conclusion:** Our results support the need for further investigations of the genetic factors that distinguish forms of autoimmune diabetes, as well as more precise classification strategies.

**MAIN TEXT**

The relationship between LADA and both type 1 diabetes and type 2 diabetes is not fully elucidated and not appropriately encapsulated in the term ‘type 1.5 diabetes’**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"wRENPitc","properties":{"formattedCitation":"(1\\uc0\\u8211{}3)","plainCitation":"(1–3)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Ew0MDqii","uris":["http://zotero.org/users/local/99dTDuE7/items/V98Z5MPW"],"uri":["http://zotero.org/users/local/99dTDuE7/items/V98Z5MPW"],"itemData":{"id":"6oFxHo8j/nG5HU9Ss","type":"article-journal","title":"The many faces of diabetes: a disease with increasing heterogeneity","container-title":"The Lancet","page":"1084-1094","volume":"383","issue":"9922","source":"CrossRef","DOI":"10.1016/S0140-6736(13)62219-9","ISSN":"01406736","shortTitle":"The many faces of diabetes","language":"en","author":[{"family":"Tuomi","given":"Tiinamaija"},{"family":"Santoro","given":"Nicola"},{"family":"Caprio","given":"Sonia"},{"family":"Cai","given":"Mengyin"},{"family":"Weng","given":"Jianping"},{"family":"Groop","given":"Leif"}],"issued":{"date-parts":[["2014",3]]}}},{"id":4,"uris":["http://zotero.org/users/4642149/items/RH35ILFJ"],"uri":["http://zotero.org/users/4642149/items/RH35ILFJ"],"itemData":{"id":4,"type":"article-journal","title":"Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank","container-title":"The Lancet Diabetes & Endocrinology","page":"122-129","volume":"6","issue":"2","source":"CrossRef","DOI":"10.1016/S2213-8587(17)30362-5","ISSN":"22138587","shortTitle":"Frequency and phenotype of type 1 diabetes in the first six

decades of life","language":"en","author":[{"family":"Thomas","given":"Nicholas J"},{"family":"Jones","given":"Samuel E"},{"family":"Weedon","given":"Michael N"},{"family":"Shields","given":"Beverley M"},{"family":"Oram","given":"Richard A"},{"family":"Hattersley","given":"Andrew T"}],"issued":{"date-parts":[["2018",2]]}}},{"id":2,"uris":["http://zotero.org/users/4642149/items/MU34D7XU"],"uri":["http://zotero.org/users/4642149/items/MU34D7XU"],"itemData":{"id":2,"type":"article-journal","title":"Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables","container-title":"The Lancet Diabetes & Endocrinology","URL":"https://www.sciencedirect.com/science/article/pii/S2213858718300512","DOI":"10.1016/S2213-8587(18)30051-2","ISSN":"2213-8587","journalAbbreviation":"The Lancet Diabetes & Endocrinology","author":[{"family":"Ahlqvist","given":"Emma"},{"family":"Storm","given":"Petter"},{"family":"Käräjämäki","given":"Annemari"},{"family":"Martinell","given":"Mats"},{"family":"Dorkhan","given":"Mozhgan"},{"family":"Carlsson","given":"Annelie"},{"family":"Vikman","given":"Petter"},{"family":"Prasad","given":"Rashmi B"},{"family":"Aly","given":"Dina Mansour"},{"family":"Almgren","given":"Peter"},{"family":"Wessman","given":"Ylva"},{"family":"Shaat","given":"Nael"},{"family":"Spégel","given":"Peter"},{"family":"Mulder","given":"Hindrik"},{"family":"Lindholm","given":"Eero"},{"family":"Melander","given":"Olle"},{"family":"Hansson","given":"Ola"},{"family":"Malmqvist","given":"Ulf"},{"family":"Lernmark","given":"Åke"},{"family":"Lahti","given":"Kaj"},{"family":"Forsén","given":"Tom"},{"family":"Tuomi","given":"Tiinamaija"},{"family":"Rosengren","given":"Anders H"},{"family":"Groop","given":"Leif"}]}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} **}**. In many populations, LADA is at least as prevalent as childhood-onset type 1 diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"j8rSsXaW","properties":{"formattedCitation":"(4)","plainCitation":"(4)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/KP64jtvW","uris":["http://zotero.org/users/local/nQ7dt7bm/items/BAUSUI23"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/BAUSUI23"],"itemData":{"id":144,"type":"article-journal","title":"Adult-Onset Autoimmune Diabetes in Europe Is Prevalent With a Broad Clinical Phenotype","container-title":"Diabetes Care","page":"908-913","volume":"36","issue":"4","source":"proxy.library.upenn.edu:2372","abstract":"OBJECTIVE Specific autoantibodies characterize type 1 diabetes in childhood but are also found in adult-onset diabetes, even when initially non–insulin requiring, e.g., with latent autoimmune diabetes (LADA). We aimed to characterize adult-onset autoimmune diabetes.\nRESEARCH DESIGN AND METHODS We consecutively studied 6,156 European diabetic patients attending clinics within 5 years of diagnosis (age range, 30–70 years) examined cross-sectionally clinically and for GAD antibodies (GADA) and antibodies to insulinoma-associated antigen-2 (IA-2A) and zinc-transporter 8 (ZnT8A).\nRESULTS Of 6,156 patients, 541 (8.8%) had GADA and only 57 (0.9%) IA-2A or ZnT8A alone. More autoantibody-positive than autoantibody-negative patients were younger, leaner, on insulin (49.5 vs. 13.2%), and female ($P < 0.0001$ for each), though LADA patients (9.7% of total) did not show categorically distinct clinical features from autoantibody-negative type 2 diabetes. Similarly, more GADA patients with high (>200 World Health Organization IU) (n = 403) compared with low (n = 138) titer were female, lean, and insulin treated (54.6 vs. 39.7%) ($P < 0.02$ for each). Autoantibody-positive patients usually had GADA (541 of 598; 90.5%) and had LADA more often than type 1 autoimmune diabetes (odds ratio 3.3).\nCONCLUSIONS Adult-onset autoimmune diabetes emerges as a prevalent form of

autoimmune diabetes. Our results indicate that adult-onset autoimmune diabetes in Europe encompasses type 1 diabetes and LADA in the same broad clinical and autoantibody-positive spectrum. At diagnosis, patients with adult-onset autoimmune diabetes are usually non–insulin requiring and clinically indistinguishable from patients with type 2 diabetes, though they tend to be younger and leaner. Only with screening for autoantibodies, especially GADA, can they be identified with certainty.","DOI":"10.2337/dc12-0931","ISSN":"0149-5992, 1935-5548","note":"PMID: 23248199","language":"en","author":[{"family":"Hawa","given":"Mohammed I."},{"family":"Kolb","given":"Hubert"},{"family":"Schloot","given":"Nanette"},{"family":"Beyan","given":"Huriya"},{"family":"Paschou","given":"Stavroula A."},{"family":"Buzzetti","given":"Raffaella"},{"family":"Mauricio","given":"Didac"},{"family":"Leiva","given":"Alberto De"},{"family":"Yderstraede","given":"Knud"},{"family":"Beck-Neilsen","given":"Henning"},{"family":"Tuomilehto","given":"Jaakko"},{"family":"Sarti","given":"Cinzia"},{"family":"Thivolet","given":"Charles"},{"family":"Hadden","given":"David"},{"family":"Hunter","given":"Steven"},{"family":"Schernthaner","given":"Guntram"},{"family":"Scherbaum","given":"Werner A."},{"family":"Williams","given":"Rhys"},{"family":"Brophy","given":"Sinead"},{"family":"Pozzilli","given":"Paolo"},{"family":"Leslie","given":"Richard David"},{"family":"Consortium","given":"on behalf of the Action LADA"}],"issued":{"date-parts":[["2013",4,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, but is frequently misdiagnosed as type 2 diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"epWHPPoL","properties":{"formattedCitation":"(5,6)","plainCitation":"(5,6)","no

teIndex":0},"citationItems":[{"id":"GKyl1X7D/NNpkAnc3","uris":["http://zotero.org/users/local/nQ7dt7bm/items/23HAUJUK"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/23HAUJUK"],"itemData":{"id":186,"type":"article-journal","title":"Latent autoimmune diabetes of the adult: current knowledge and uncertainty","container-title":"Diabetic Medicine","page":"843-852","volume":"32","issue":"7","source":"PubMed Central","abstract":"Patients with adult-onset autoimmune diabetes have less Human Leucocyte Antigen (HLA)-associated genetic risk and fewer diabetes-associated autoantibodies compared with patients with childhood-onset Type 1 diabetes. Metabolic changes at diagnosis reflect a broad clinical phenotype ranging from diabetic ketoacidosis to mild non-insulin-requiring diabetes, also known as latent autoimmune diabetes of the adult (LADA). This latter phenotype is the most prevalent form of adult-onset autoimmune diabetes and probably the most prevalent form of autoimmune diabetes in general. Although LADA is associated with the same genetic and immunological features as childhood-onset Type 1 diabetes, it also shares some genetic features with Type 2 diabetes, which raises the question of genetic heterogeneity predisposing to this form of the disease. The potential value of screening patients with adult-onset diabetes for diabetes-associated autoantibodies to identify those with LADA is emphasized by their lack of clinically distinct features, their different natural history compared with Type 2 diabetes and their potential need for a dedicated management strategy. The fact that, in some studies, patients with LADA show worse glucose control than patients with Type 2 diabetes, highlights the need for further therapeutic studies. Challenges regarding classification, epidemiology, genetics, metabolism, immunology, clinical presentation and treatment of LADA were discussed at a 2014 workshop arranged by the Danish Diabetes Academy. The presentations and discussions are summarized in this review, which sets out the current ideas and controversies surrounding this form of

diabetes.","DOI":"10.1111/dme.12700","ISSN":"0742-3071","note":"PMID: 25601320\nPMCID: PMC4676295","shortTitle":"Latent autoimmune diabetes of the adult","journalAbbreviation":"Diabet Med","author":[{"family":"Laugesen","given":"E"},{"family":"Østergaard","given":"J A"},{"family":"Leslie","given":"R D G"}],"issued":{"date-parts":[["2015",7]]}},{"id":"GKyl1X7D/y37eAGoG","uris":["http://zotero.org/users/local/nQ7dt7bm/items/3WZF42UV"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/3WZF42UV"],"itemData":{"id":191,"type":"article-journal","title":"Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies.","container-title":"Diabetes","page":"150-157","volume":"48","issue":"1","source":"proxy.library.upenn.edu:3348","abstract":"The aim of the study was 1) to establish the prevalence of GAD antibodies (GADab) in a population-based study of type 2 diabetes in western Finland, 2) to genetically and phenotypically characterize this subgroup, and 3) to provide a definition for latent autoimmune diabetes in adults (LADA). The prevalence of GADab was 9.3% among 1,122 type 2 diabetic patients, 3.6% among 558 impaired glucose tolerance (IGT) subjects, and 4.4% among 383 nondiabetic control subjects. Islet antigen 2 antibodies (IA2ab) or islet cell antibodies were detected in only 0.5% of the GADab- patients. The GADab+ patients had lower fasting C-peptide concentrations (median [interquartile range]: 0.46 [0.45] vs. 0.62 [0.44] nmol/l, P = 0.0002) and lower insulin response to oral glucose compared with GADab- patients. With respect to features of the metabolic syndrome, the GADab+ patients had lower systolic (140 [29.1] vs. 148 [26.0] mmHg, P = 0.009) and diastolic (79.2 [17.6] vs. 81.0 [13.1] mmHg, P = 0.030) blood pressure values, as well as lower triglyceride concentrations (1.40 [1.18] vs. 1.75 [1.25] mmol/l, P = 0.003). GADab+ men had a lower waist-to-hip ratio compared with GADab- patients. Compared with GADab- patients and

control subjects, the GADab+ patients had an increased frequency HLA-DQB1*0201/0302 (13 vs. 4%; P = 0.002) and other genotypes containing the *0302 allele (22 vs. 12%; P = 0.010). However, the frequency of these high-risk genotypes was significantly lower in GADab+ type 2 patients than in type 1 diabetes of young or adult onset (0201/0302 or 0302/X: 36 vs. 66 vs. 64%, P < 0.001). The GADab+ type 2 group did not differ from control subjects with respect to genotypes containing the protective DQB1-alleles *0602 or *0603, nor with respect to the type 1 high-risk genotype in the IDDM1 (Hph1 +/+). We conclude that GADab+ patients differ from both GADab- type 2 diabetic patients and type 1 diabetic patients with respect to beta-cell function, features of the metabolic syndrome, and type 1 diabetes susceptibility genes. Further, we propose that LADA be defined as GADab positivity (>5 relative units) in patients older than 35 years at onset of type 2 diabetes.","DOI":"10.2337/diabetes.48.1.150","ISSN":"0012-1797, 1939-327X","note":"PMID: 9892237","language":"en","author":[{"family":"Tuomi","given":"T."},{"family":"Carlsson","given":"A."},{"family":"Li","given":"H."},{"family":"Isomaa","given":"B."},{"family":"Miettinen","given":"A."},{"family":"Nilsson","given":"A."},{"family":"Nissén","given":"M."},{"family":"Ehrnström","given":"B. O."},{"family":"Forsén","given":"B."},{"family":"Snickars","given":"B."},{"family":"Lahti","given":"K."},{"family":"Forsblom","given":"C."},{"family":"Saloranta","given":"C."},{"family":"Taskinen","given":"M. R."},{"family":"Groop","given":"L. C."}],"issued":{"date-parts":[["1999",1,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** given its presentation in adults without need for insulin. As such, subjects with LADA could be present in cohort studies for type 2 diabetes that do not screen out autoantibody-positive cases, potentially resulting in the identification of

genetic associations for type 2 diabetes that are etiologically related to autoimmunity. Furthermore, LADA has a natural history distinct from that of type 2 diabetes and is likely mismanaged as a result.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ao64c5e7j4","properties":{"formattedCitation":"(5)","plainCitation":"(5)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/NNpkAnc3","uris":["http://zotero.org/users/local/nQ7dt7bm/items/23HAUJUK"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/23HAUJUK"],"itemData":{"id":186,"type":"article-journal","title":"Latent autoimmune diabetes of the adult: current knowledge and uncertainty","container-title":"Diabetic Medicine","page":"843-852","volume":"32","issue":"7","source":"PubMed Central","abstract":"Patients with adult-onset autoimmune diabetes have less Human Leucocyte Antigen (HLA)-associated genetic risk and fewer diabetes-associated autoantibodies compared with patients with childhood-onset Type 1 diabetes. Metabolic changes at diagnosis reflect a broad clinical phenotype ranging from diabetic ketoacidosis to mild non-insulin-requiring diabetes, also known as latent autoimmune diabetes of the adult (LADA). This latter phenotype is the most prevalent form of adult-onset autoimmune diabetes and probably the most prevalent form of autoimmune diabetes in general. Although LADA is associated with the same genetic and immunological features as childhood-onset Type 1 diabetes, it also shares some genetic features with Type 2 diabetes, which raises the question of genetic heterogeneity predisposing to this form of the disease. The potential value of screening patients with adult-onset diabetes for diabetes-associated autoantibodies to identify those with LADA is emphasized by their lack of clinically distinct features, their different natural history compared with Type 2 diabetes and their potential need for a dedicated management strategy. The fact that, in some studies, patients with LADA show worse glucose control than patients with Type 2 diabetes, highlights the need for further therapeutic studies.

Challenges regarding classification, epidemiology, genetics, metabolism, immunology, clinical presentation and treatment of LADA were discussed at a 2014 workshop arranged by the Danish Diabetes Academy. The presentations and discussions are summarized in this review, which sets out the current ideas and controversies surrounding this form of diabetes.","DOI":"10.1111/dme.12700","ISSN":"0742-3071","note":"PMID: 25601320\nPMCID: PMC4676295","shortTitle":"Latent autoimmune diabetes of the adult","journalAbbreviation":"Diabet Med","author":[{"family":"Laugesen","given":"E"},{"family":"Østergaard","given":"J A"},{"family":"Leslie","given":"R D G"}],"issued":{"date-parts":[["2015",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** The challenge to define adult autoimmune diabetes, including LADA, as distinct from the generality of type 2 diabetes is acute given the increasingly larger datasets assembled to identify additional, common genetic risk factors of increasingly smaller effect sizes. Indeed, reflecting this concern, recent genome-wide association study (GWAS) analyses of type 2 diabetes have reported associations at type 1 diabetes-associated regions such as *HLA-DQA1* in European ancestry populations**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a5skc3g6b2","properties":{"formattedCitation":"(7)","plainCitation":"(7)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Ja9kyCwG","uris":["http://zotero.org/users/local/nQ7dt7bm/items/UT9C82V3"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/UT9C82V3"],"itemData":{"id":182,"type":"article-journal","title":"An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans","container-title":"Diabetes","page":"db161253","source":"proxy.library.upenn.edu:3348","abstract":"To

characterise type 2 diabetes (T2D) associated variation across the allele frequency spectrum, we conducted a meta-analysis of genome-wide association data from 26,676 T2D cases and 132,532 controls of European ancestry after imputation using the 1000 Genomes multi-ethnic reference panel. Promising association signals were followed-up in additional data sets (of 14,545 or 7,397 T2D cases and 38,994 or 71,604 controls). We identified 13 novel T2D-associated loci ($p<5\times10^{-8}$), including variants near the GLP2R, GIP, and HLA-DQA1 genes. Our analysis brought the total number of independent T2D associations to 128 distinct signals at 113 loci. Despite substantially increased sample size and more complete coverage of low-frequency variation, all novel associations were driven by common SNVs. Credible sets of potentially causal variants were generally larger than those based on imputation with earlier reference panels, consistent with resolution of causal signals to common risk haplotypes. Stratification of T2D-associated loci based on T2D-related quantitative trait associations revealed tissue-specific enrichment of regulatory annotations in pancreatic islet enhancers for loci influencing insulin secretion, and in adipocytes, monocytes and hepatocytes for insulin action-associated loci. These findings highlight the predominant role played by common variants of modest effect and the diversity of biological mechanisms influencing T2D pathophysiology.","DOI":"10.2337/db16-1253","ISSN":"0012-1797, 1939-327X","note":"PMID: 28566273","language":"en","author":[{"family":"Scott","given":"Robert A."},{"family":"Scott","given":"Laura J."},{"family":"Mägi","given":"Reedik"},{"family":"Marullo","given":"Letizia"},{"family":"Gaulton","given":"Kyle J."},{"family":"Kaakinen","given":"Marika"},{"family":"Pervjakova","given":"Natalia"},{"family":"Pers","given":"Tune H."},{"family":"Johnson","given":"Andrew

D."},{"family":"Eicher","given":"John D."},{"family":"Jackson","given":"Anne U."},{"family":"Ferreira","given":"Teresa"},{"family":"Lee","given":"Yeji"},{"family":"Ma","given":"Clement"},{"family":"Steinthorsdottir","given":"Valgerdur"},{"family":"Thorleifsson","given":"Gudmar"},{"family":"Qi","given":"Lu"},{"family":"Zuydam","given":"Natalie R. Van"},{"family":"Mahajan","given":"Anubha"},{"family":"Chen","given":"Han"},{"family":"Almgren","given":"Peter"},{"family":"Voight","given":"Ben F."},{"family":"Grallert","given":"Harald"},{"family":"Müller-Nurasyid","given":"Martina"},{"family":"Ried","given":"Janina S."},{"family":"Rayner","given":"William N."},{"family":"Robertson","given":"Neil"},{"family":"Karssen","given":"Lennart C."},{"family":"Leeuwen","given":"Elisabeth M.","dropping-particle":"van"},{"family":"Willems","given":"Sara M."},{"family":"Fuchsberger","given":"Christian"},{"family":"Kwan","given":"Phoenix"},{"family":"Teslovich","given":"Tanya M."},{"family":"Chanda","given":"Pritam"},{"family":"Li","given":"Man"},{"family":"Lu","given":"Yingchang"},{"family":"Dina","given":"Christian"},{"family":"Thuillier","given":"Dorothee"},{"family":"Yengo","given":"Loic"},{"family":"Jiang","given":"Longda"},{"family":"Sparso","given":"Thomas"},{"family":"Kestler","given":"Hans A."},{"family":"Chheda","given":"Himanshu"},{"family":"Eisele","given":"Lewin"},{"family":"Gustafsson","given":"Stefan"},{"family":"Frånberg","given":"Mattias"},{"family":"Strawbridge","given":"Rona J."},{"family":"Benediktsson","given":"Rafn"},{"family":"Hreidarsson","given":"Astradur B."},{"family":"Kong","given":"Augustine"},{"family":"Sigurðsson","given":"Gunnar"},{"fami

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y":"Pedersen","given":"Oluf"},{"family":"Barroso","given":"Inês"},{"family":"Lannfelt","given":"Lars"},{"family":"Ingelsson","given":"Erik"},{"family":"Lind","given":"Lars"},{"family":"Lindgren","given":"Cecilia M."},{"family":"Cauchi","given":"Stephane"},{"family":"Froguel","given":"Philippe"},{"family":"Loos","given":"Ruth JF"},{"family":"Balkau","given":"Beverley"},{"family":"Boeing","given":"Heiner"},{"family":"Franks","given":"Paul W."},{"family":"Gurrea","given":"Aurelio Barricarte"},{"family":"Palli","given":"Domenico"},{"family":"Schouw","given":"Yvonne T.","dropping-particle":"van der"},{"family":"Altshuler","given":"David"},{"family":"Groop","given":"Leif C."},{"family":"Langenberg","given":"Claudia"},{"family":"Wareham","given":"Nicholas J."},{"family":"Sijbrands","given":"Eric"},{"family":"Duijn","given":"Cornelia M.","dropping-particle":"van"},{"family":"Florez","given":"Jose C."},{"family":"Meigs","given":"James B."},{"family":"Boerwinkle","given":"Eric"},{"family":"Gieger","given":"Christian"},{"family":"Strauch","given":"Konstantin"},{"family":"Metspalu","given":"Andres"},{"family":"Morris","given":"Andrew D."},{"family":"Palmer","given":"Colin NA"},{"family":"Hu","given":"Frank B."},{"family":"Thorsteinsdottir","given":"Unnur"},{"family":"Stefansson","given":"Kari"},{"family":"Dupuis","given":"Josée"},{"family":"Morris","given":"Andrew P."},{"family":"Boehnke","given":"Michael"},{"family":"McCarthy","given":"Mark I."},{"family":"Prokopenko","given":"Inga"},{"family":"Consortium","given":"for the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM)"}],"issued":{"date-parts":[["2017",5,25]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** and *HLA-B* and *INS-IGF2* in African ancestry

populations.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xfecyRwK","properties":{"formattedCitation":"(8)","plainCitation":"(8)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Ifi8Mwsm","uris":["http://zotero.org/users/local/nQ7dt7bm/items/JI6RJXTX"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/JI6RJXTX"],"itemData":{"id":198,"type":"article-journal","title":"Meta-Analysis of Genome-Wide Association Studies in African Americans Provides Insights into the Genetic Architecture of Type 2 Diabetes","container-title":"PLOS Genetics","page":"e1004517","volume":"10","issue":"8","source":"PLoS Journals","abstract":"Author Summary Despite the higher prevalence of type 2 diabetes (T2D) in African Americans than in Europeans, recent genome-wide association studies (GWAS) were examined primarily in individuals of European ancestry. In this study, we performed meta-analysis of 17 GWAS in 8,284 cases and 15,543 controls to explore the genetic architecture of T2D in African Americans. Following replication in additional 6,061 cases and 5,483 controls in African Americans, and 8,130 cases and 38,987 controls of European ancestry, we identified two novel and three previous reported T2D loci reaching genome-wide significance. We also examined 158 loci previously reported to be associated with T2D or regulating glucose homeostasis. While 56% of these loci were shared between African Americans and the other populations, the strongest associations in African Americans are often found in nearby single nucleotide polymorphisms (SNPs) instead of the original SNPs reported in other populations due to differential genetic architecture across populations. Our results highlight the importance of performing genetic studies in non-European populations to fine map the causal genetic variants.","DOI":"10.1371/journal.pgen.1004517","ISSN":"1553-7404","journalAbbreviation":"PLOS Genetics","author":[{"family":"Ng","given":"Maggie C.

Y."},{"family":"Shriner","given":"Daniel"},{"family":"Chen","given":"Brian H."},{"family":"Li","given":"Jiang"},{"family":"Chen","given":"Wei-Min"},{"family":"Guo","given":"Xiuqing"},{"family":"Liu","given":"Jiankang"},{"family":"Bielinski","given":"Suzette J."},{"family":"Yanek","given":"Lisa R."},{"family":"Nalls","given":"Michael A."},{"family":"Comeau","given":"Mary E."},{"family":"Rasmussen-Torvik","given":"Laura J."},{"family":"Jensen","given":"Richard A."},{"family":"Evans","given":"Daniel S."},{"family":"Sun","given":"Yan V."},{"family":"An","given":"Ping"},{"family":"Patel","given":"Sanjay R."},{"family":"Lu","given":"Yingchang"},{"family":"Long","given":"Jirong"},{"family":"Armstrong","given":"Loren L."},{"family":"Wagenknecht","given":"Lynne"},{"family":"Yang","given":"Lingyao"},{"family":"Snively","given":"Beverly M."},{"family":"Palmer","given":"Nicholette D."},{"family":"Mudgal","given":"Poorva"},{"family":"Langefeld","given":"Carl D."},{"family":"Keene","given":"Keith L."},{"family":"Freedman","given":"Barry I."},{"family":"Mychaleckyj","given":"Josyf C."},{"family":"Nayak","given":"Uma"},{"family":"Raffel","given":"Leslie J."},{"family":"Goodarzi","given":"Mark O."},{"family":"Chen","given":"Y.-D. Ida"},{"family":"Jr","given":"Herman A. Taylor"},{"family":"Correa","given":"Adolfo"},{"family":"Sims","given":"Mario"},{"family":"Couper","given":"David"},{"family":"Pankow","given":"James S."},{"family":"Boerwinkle","given":"Eric"},{"family":"Adeyemo","given":"Adebowale"},{"family":"Doumatey","given":"Ayo"},{"family":"Chen","given":"Guanjie"},{"family":"Mathias","given":"Rasika

A."},{"family":"Vaidya","given":"Dhananjay"},{"family":"Singleton","given":"Andrew B."},{"family":"Zonderman","given":"Alan B."},{"family":"Jr","given":"Robert P. Igo"},{"family":"Sedor","given":"John R."},{"family":"Consortium","given":"the FIND"},{"family":"Kabagambe","given":"Edmond K."},{"family":"Siscovick","given":"David S."},{"family":"McKnight","given":"Barbara"},{"family":"Rice","given":"Kenneth"},{"family":"Liu","given":"Yongmei"},{"family":"Hsueh","given":"Wen-Chi"},{"family":"Zhao","given":"Wei"},{"family":"Bielak","given":"Lawrence F."},{"family":"Kraja","given":"Aldi"},{"family":"Province","given":"Michael A."},{"family":"Bottinger","given":"Erwin P."},{"family":"Gottesman","given":"Omri"},{"family":"Cai","given":"Qiuyin"},{"family":"Zheng","given":"Wei"},{"family":"Blot","given":"William J."},{"family":"Lowe","given":"William L."},{"family":"Pacheco","given":"Jennifer A."},{"family":"Crawford","given":"Dana C."},{"family":"Consortium","given":"the","dropping-particle":"eMERGE"},{"family":"Consortium","given":"the DIAGRAM"},{"family":"Grundberg","given":"Elin"},{"family":"Consortium","given":"the MuTHER"},{"family":"Rich","given":"Stephen S."},{"family":"Hayes","given":"M. Geoffrey"},{"family":"Shu","given":"Xiao-Ou"},{"family":"Loos","given":"Ruth J. F."},{"family":"Borecki","given":"Ingrid B."},{"family":"Peyser","given":"Patricia A."},{"family":"Cummings","given":"Steven R."},{"family":"Psaty","given":"Bruce M."},{"family":"Fornage","given":"Myriam"},{"family":"Iyengar","given":"Sudha K."},{"family":"Evans","given":"Michele K."},{"family":"Becker","given":"Diane M."},{"family":"Kao","given":"W. H. Linda"},{"family":"Wilson","given":"James G."},{"family":"Rotter","given":"Jerome I."},{"family":"Sale","given":"Michèle

M."},{"family":"Liu","given":"Simin"},{"family":"Rotimi","given":"Charles N."},{"family":"Bowden","given":"Donald W."},{"family":"Consortium","given":"for the MEta-analysis of type 2 DIabetes in African Americans (MEDIA)"}],"issued":{"date-parts":[["2014",8,7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** As such, understanding the genetic etiology of adult autoimmune diabetes will not only aid the characterization of this relatively common form of diabetes, but will also facilitate our understanding of both type 1 diabetes and type 2 diabetes.

To date, the relatively limited candidate gene studies carried out for LADA have supported a role for both type 1 and type 2 diabetes risk loci.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mgHjjH3H","properties":{"formattedCitation":"(1,9\\uc0\\u8211{}15)","plainCitation":"(1,9–15)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/evVjBlsv","uris":["http://zotero.org/users/local/99dTDuE7/items/GKDRERFU"],"uri":["http://zotero.org/users/local/99dTDuE7/items/GKDRERFU"],"itemData":{"id":190,"type":"article-journal","title":"An association analysis of the HLA gene region in latent autoimmune diabetes in adults","container-title":"Diabetologia","page":"68","volume":"50","issue":"1","source":"proxy.library.upenn.edu:2063","abstract":"Pathophysiological similarities between latent autoimmune diabetes in adults (LADA) and type 1 diabetes indicate an overlap in genetic susceptibility. HLA-DRB1 and HLA-DQB1 are major susceptibility genes for type 1 diabetes but studies of these genes ...","DOI":"10.1007/s00125-006-0513-z","note":"PMID: 17143607","author":[{"family":"Desai","given":"M."},{"family":"Zeggini","given":"E."},{"family":"Horton","given":"V. A."},{"family":"Owen","given":"K. R."},{"family":"Hattersley","given":"A. T."},{"family":"Levy","given":"J.

C."},{"family":"Walker","given":"M."},{"family":"Gillespie","given":"K. M."},{"family":"Bingley","given":"P. J."},{"family":"Hitman","given":"G. A."},{"family":"Holman","given":"R. R."},{"family":"McCarthy","given":"M. I."},{"family":"Clark","given":"A."}],"issued":{"date-parts":[["2007",1]]}}},{"id":"GKyl1X7D/i2uGAYF2","uris":["http://zotero.org/users/local/99dTDuE7/items/QIQ53UZM"],"uri":["http://zotero.org/users/local/99dTDuE7/items/QIQ53UZM"],"itemData":{"id":201,"type":"article-journal","title":"Similar Genetic Features and Different Islet Cell Autoantibody Pattern of Latent Autoimmune Diabetes in Adults (LADA) Compared With Adult-Onset Type 1 Diabetes With Rapid Progression","container-title":"Diabetes Care","page":"452-457","volume":"26","issue":"2","source":"proxy.library.upenn.edu:3384","abstract":"OBJECTIVE—To compare the clinical parameters, C-peptide levels, pattern of islet cell-specific autoantibodies, and prevalence of predisposing genotypes in subjects with latent autoimmune diabetes in adults (LADA) and those with adult-onset type 1 diabetes with rapid progression.\nRESEARCH DESIGN AND METHODS—We evaluated the clinical parameters, C-peptide levels, and islet cell-specific autoantibodies in 54 LADA, 57 adult-onset type 1 diabetic, and 190 type 2 diabetic patients. Islet cell autoantibodies were also compared between subgroups of newly diagnosed patients with LADA and those with newly diagnosed adult-onset and childhood-onset type 1 diabetes. The genetic study was performed in subjects with LADA and those with adult-onset type 1 diabetes in comparison with a control population.\nRESULTS—There were no differences in the clinical parameters between LADA and adult-onset type 1 diabetes. Patients with LADA had lower BMI (P < 0.0001), waist-to-hip ratio (0.0029), total cholesterol (P = 0.001), and triglycerides (P = 0.001); higher HDL

cholesterol levels (P < 0.0001); and lower prevalence of hypertension (P = 0.0028) compared with patients with type 2 diabetes. C-peptide levels were similar at onset (P = 0.403) but decreased less rapidly in LADA than in adult-onset type 1 diabetes (P = 0.0253). Single-autoantibody positivity was more often seen in LADA than in type 1 diabetes (P = 0.0001). The prevalence of predisposing HLA-DQB1*0302, -DR4, -DR3, and -DR3/DR4 genotypes and the DR4-DQB1*0302 haplotype were increased in both LADA and adult-onset type 1 diabetic subjects compared with the control population. There were no differences in the frequencies of these risk alleles and haplotypes between the two patient groups.\nCONCLUSIONS—Subjects with LADA had clinical characteristics similar to those with adult-onset type 1 diabetes with rapid progression. C-peptide levels did not differ at onset but decreased less rapidly in LADA. Patients with LADA rather had single islet cell-specific autoantibody positivity. The prevalence of HLA-DQB1*0302, -DR4, -DR3, and -DR3/DR4 risk alleles and the DR4-DQB1*0302 high-risk haplotype did not differ in the two forms of autoimmune diabetes.","DOI":"10.2337/diacare.26.2.452","ISSN":"0149-5992, 1935-5548","note":"PMID: 12547879","language":"en","author":[{"family":"Hosszúfalusi","given":"Nóra"},{"family":"Vatay","given":"Ágnes"},{"family":"Rajczy","given":"Katalin"},{"family":"Prohászka","given":"Zoltán"},{"family":"Pozsonyi","given":"Éva"},{"family":"Horváth","given":"Laura"},{"family":"Grosz","given":"Andrea"},{"family":"Gerõ","given":"László"},{"family":"Madácsy","given":"László"},{"family":"Romics","given":"László"},{"family":"Karádi","given":"István"},{"family":"Füst","given":"George"},{"family":"Pánczél","given":"Pál"}],"issued":{"date-parts":[["2003",2,1]]}}},{"id":"GKyl1X7D/dJGU3dfq","uris":["http://zotero.org/users/local/99dTDuE7/items/JH5ASEQ5"],"uri":["http://zotero.org/users/local/99dTDuE7/items/JH5ASEQ5"],"itemData":{"id":84,"type":"article-journal","title":"Type 2 diabetes susceptibility gene variants

predispose to adult-onset autoimmune diabetes","container-title":"Diabetologia","page":"1859-1868","volume":"57","issue":"9","source":"proxy.library.upenn.edu:2071","abstract":"Latent autoimmune diabetes in adults (LADA) is phenotypically a hybrid of type 1 and type 2 diabetes. Genetically LADA is poorly characterised but does share genetic predisposition with type 1 diabete","DOI":"10.1007/s00125-014-3287-8","ISSN":"0012-186X, 1432-0428","journalAbbreviation":"Diabetologia","language":"en","author":[{"family":"Andersen","given":"Mette K."},{"family":"Sterner","given":"Maria"},{"family":"Forsén","given":"Tom"},{"family":"Kärä jämäki","given":"Annemari"},{"family":"Rolandsson","given":"Olov"},{"family":"Forsblom","given":"Carol"},{"family":"Groop","given":"Per-Henrik"},{"family":"Lahti","given":"Kaj"},{"family":"Nilsson","given":"Peter M."},{"family":"Groop","given":"Leif"},{"family":"Tuomi","given":"Tiinamaija"}],"issued":{"date-parts":[["2014",9,1]]}}},{"id":"GKyl1X7D/sPC6qY0b","uris":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"itemData":{"id":111,"type":"article-journal","title":"Relative contribution of type 1 and type 2 diabetes loci to the genetic etiology of adult-onset, non-insulin-requiring autoimmune diabetes","container-title":"BMC Medicine","page":"88","volume":"15","issue":"1","source":"proxy.library.upenn.edu:2931","abstract":"In adulthood, autoimmune diabetes can present as non-insulin-requiring diabetes, termed as ‘latent autoimmune diabetes in adults’ (LADA). In this study, we investigated established type 1 diabetes (T1D) and type 2 diabetes (T2D) genetic loci in a large cohort of LADA cases to assess where LADA is situated relative to these two well-characterized, classic forms of

diabetes. We tested the association of T1D and T2D GWAS-implicated loci in 978 LADA cases and 1057 non-diabetic controls of European ancestry using a linear mixed model. We then compared the associations of T1D and T2D loci between LADA and T1D and T2D cases, respectively. We quantified the difference in genetic risk between each given disease at each locus, and also calculated genetic risk scores to quantify how genetic liability to T1D and T2D distinguished LADA cases from controls. Overall, our results showed that LADA is genetically more similar to T1D, with the exception of an association at the T2D HNF1A locus. Several T1D loci were associated with LADA, including the major histocompatibility complex region, as well as at PTPN22, SH2B3, and INS. Contrary to previous studies, the key T2D risk allele at TCF7L2 (rs7903146-T) had a significantly lower frequency in LADA cases, suggesting that this locus does not play a role in LADA etiology. When constrained on antibody status, the similarity between LADA and T1D became more apparent; however, the HNF1A and TCF7L2 observations persisted. LADA is genetically closer to T1D than T2D, although the genetic load of T1D risk alleles is less than childhood-onset T1D, particularly at the major histocompatibility complex region, potentially accounting for the later disease onset. Our results show that the genetic spectrum of T1D extends into adult-onset diabetes, where it can clinically masquerade as T2D. Furthermore, T2D genetic risk plays a small role in LADA, with a degree of evidence for the HNF1A locus, highlighting the potential for genetic risk scores to contribute towards defining diabetes subtypes.","DOI":"10.1186/s12916-017-0846-0","ISSN":"1741-7015","language":"En","author":[{"family":"Mishra","given":"Rajashree"},{"family":"Chesi","given":"Alessandra"},{"family":"Cousminer","given":"Diana L."},{"family":"Hawa","given":"Mohammad I."},{"family":"Bradfield","given":"Jonathan P."},{"family":"Hodge","given":"Kenyaita M."},{"family":"Guy","given":"Vanessa

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A."}],"issued":{"date-
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to differentiate autoimmune from non-autoimmune diabetes in young (15–34 years) but not in
middle-aged (40–59 years) diabetic patients","container-title":"Diabetologia","page":"2224-
2232","volume":"51","issue":"12","source":"proxy.library.upenn.edu:2320","abstract":"Type 1
diabetes in children is characterised by autoimmune destruction of pancreatic beta cells and the
presence of certain risk genotypes. In adults the same situation is often referred to as
latent","DOI":"10.1007/s00125-008-1161-2","ISSN":"0012-186X, 1432-
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C."}],"issued":{"date-

parts":[["2008",12,1]]}}},{"id":"GKyl1X7D/sVyEDlM9","uris":["http://zotero.org/users/local/nQ7dt7bm/items/364WTIXJ"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/364WTIXJ"],"itemData":{"id":263,"type":"article-journal","title":"Latent Autoimmune Diabetes in Adults Differs Genetically From Classical Type 1 Diabetes Diagnosed After the Age of 35 Years","container-title":"Diabetes Care","page":"2062-2064","volume":"33","issue":"9","source":"proxy.library.upenn.edu:2372","abstract":"OBJECTIVE We studied differences between patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes, and classical type 1 diabetes diagnosed after age 35 years.\nRESEARCH DESIGN AND METHODS Polymorphisms in HLA-DQB1, INS, PTPN22, and CTLA4 were genotyped in patients with LADA (n = 213), type 1 diabetes diagnosed at >35 years of age (T1D>35y; n = 257) or <20 years of age (T1D<20y; n = 158), and type 2 diabetes.\nRESULTS Although patients with LADA had an increased frequency of HLA-DQB1 and PTPN22 risk genotypes and alleles compared with type 2 diabetic subjects, the frequency was significantly lower compared with T1D>35y patients. Genotype frequencies, measures of insulin secretion, and metabolic traits within LADA differed according to GAD antibody (GADA) quartiles, but even the highest quartile differed from type 1 diabetes. Having two or more risk genotypes was associated with lower C-peptide concentrations in LADA.\nCONCLUSIONS LADA patients differed genetically and phenotypically from both T1D>35y and type 2 diabetic patients in a manner dependent on GADA levels.","DOI":"10.2337/dc09-2188","ISSN":"0149-5992, 1935-5548","note":"PMID: 20805278","language":"en","author":[{"family":"Andersen","given":"Mette K."},{"family":"Lundgren","given":"Virve"},{"family":"Turunen","given":"Joni A."},{"family":"Forsblom","given":"Carol"},{"family":"Isomaa","given":"Bo"},{"family":"Gro

op","given":"Per-Henrik"},{"family":"Groop","given":"Leif"},{"family":"Tuomi","given":"Tiinamaija"}],"issued":{"date-parts":[["2010",9,1]]}}},{"id":"GKyl1X7D/Ew0MDqii","uris":["http://zotero.org/users/local/99dTDuE7/items/V98Z5MPW"],"uri":["http://zotero.org/users/local/99dTDuE7/items/V98Z5MPW"],"itemData":{"id":"LjfjbenP/um3EQQG4","type":"article-journal","title":"The many faces of diabetes: a disease with increasing heterogeneity","container-title":"The Lancet","page":"1084-1094","volume":"383","issue":"9922","source":"CrossRef","DOI":"10.1016/S0140-6736(13)62219-9","ISSN":"01406736","shortTitle":"The many faces of diabetes","language":"en","author":[{"family":"Tuomi","given":"Tiinamaija"},{"family":"Santoro","given":"Nicola"},{"family":"Caprio","given":"Sonia"},{"family":"Cai","given":"Mengyin"},{"family":"Weng","given":"Jianping"},{"family":"Groop","given":"Leif"}],"issued":{"date-parts":[["2014",3]]}}},{"id":"GKyl1X7D/OrqXFUQE","uris":["http://zotero.org/users/local/nQ7dt7bm/items/3SRX2K5E"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/3SRX2K5E"],"itemData":{"id":284,"type":"article-journal","title":"Genetic Analysis of Adult-Onset Autoimmune Diabetes","container-title":"Diabetes","page":"2645-2653","volume":"60","issue":"10","source":"proxy.library.upenn.edu:3348","abstract":"OBJECTIVE In contrast with childhood-onset type 1 diabetes, the genetics of autoimmune diabetes in adults are not well understood. We have therefore investigated the genetics of diabetes diagnosed in adults positive for autoantibodies.\nRESEARCH DESIGN AND METHODS GAD autoantibodies (GADAs), insulinoma-associated antigen-2 antibodies (IA-2As), and islet cell autoantibodies were measured at time of diagnosis. Autoantibody-positive diabetic subjects (n = 1,384) and population-based control subjects (n = 2,235) were genotyped at 20 childhood-onset

type 1 diabetes loci and FCRL3, GAD2, TCF7L2, and FTO.\nRESULTS PTPN22 (1p13.2), STAT4 (2q32.2), CTLA4 (2q33.2), HLA (6p21), IL2RA (10p15.1), INS (11p15.5), ERBB3 (12q13.2), SH2B3 (12q24.12), and CLEC16A (16p13.13) were convincingly associated with autoimmune diabetes in adults ($P \leq 0.002$), with consistent directions of effect as reported for pediatric type 1 diabetes. No evidence of an HLA-DRB1*03/HLA-DRB1*04 (DR3/4) genotype effect was obtained ($P = 0.55$), but it remained highly predisposing (odds ratio 26.22). DR3/4 was associated with a lower age at diagnosis of disease, as was DR4 ($P = 4.67 \times 10{-}6$) but not DR3. DR3 was associated with GADA positivity ($P = 6.03 \times 10{-}6$) but absence of IA-2A ($P = 3.22 \times 10{-}7$). DR4 was associated with IA-2A positivity ($P = 5.45 \times 10{-}6$).\nCONCLUSIONS Our results are consistent with the hypothesis that the genetics of autoimmune diabetes in adults and children are differentiated by only relatively few age-dependent genetic effects. The slower progression toward autoimmune insulin deficiency in adults is probably due to a lower genetic load overall combined with subtle variation in the HLA class II gene associations and autoreactivity.","DOI":"10.2337/db11-0364","ISSN":"0012-1797, 1939-327X","note":"PMID: 21873553","language":"en","author":[{"family":"Howson","given":"Joanna M. M."},{"family":"Rosinger","given":"Silke"},{"family":"Smyth","given":"Deborah J."},{"family":"Boehm","given":"Bernhard O."},{"family":"Group","given":"the ADBW-END Study"},{"family":"Todd","given":"John A."}],"issued":{"date-parts":[["2011",10,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** Most notable from these previous studies is the implicated role of the key type 2-associated *TCF7L2* locus in the pathogenesis of LADA.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a8jrd2t8lt","properties":{"formattedCitation":"(11,13,16)","plainCitation":"(11,13

,16)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/pNHpGhaD","uris":["http://zotero.org/users/local/nQ7dt7bm/items/BN2TJ67U"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/BN2TJ67U"],"itemData":{"id":119,"type":"article-journal","title":"Common variants in the TCF7L2 gene help to differentiate autoimmune from non-autoimmune diabetes in young (15–34 years) but not in middle-aged (40–59 years) diabetic patients","container-title":"Diabetologia","page":"2224-2232","volume":"51","issue":"12","source":"proxy.library.upenn.edu:2320","abstract":"Type 1 diabetes in children is characterised by autoimmune destruction of pancreatic beta cells and the presence of certain risk genotypes. In adults the same situation is often referred to as latent","DOI":"10.1007/s00125-008-1161-2","ISSN":"0012-186X, 1432-0428","journalAbbreviation":"Diabetologia","language":"en","author":[{"family":"Bakhtadze","given":"E."},{"family":"Cervin","given":"C."},{"family":"Lindholm","given":"E."},{"family":"Borg","given":"H."},{"family":"Nilsson","given":"P."},{"family":"Arnqvist","given":"H. J."},{"family":"Bolinder","given":"J."},{"family":"Eriksson","given":"J. W."},{"family":"Gudbjörnsdottir","given":"S."},{"family":"Nyström","given":"L."},{"family":"Agardh","given":"C.-D."},{"family":"Landin-Olsson","given":"M."},{"family":"Sundkvist","given":"G."},{"family":"Groop","given":"L. C."}],"issued":{"date-parts":[["2008",12,1]]}}},{"id":"GKyl1X7D/dJGU3dfq","uris":["http://zotero.org/users/local/99dTDuE7/items/JH5ASEQ5"],"uri":["http://zotero.org/users/local/99dTDuE7/items/JH5ASEQ5"],"itemData":{"id":"IzLNWkNn/aY0Gbi7b","type":"article-journal","title":"Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes","container-title":"Diabetologia","page":"1859-

1868","volume":"57","issue":"9","source":"proxy.library.upenn.edu:2071","abstract":"Latent autoimmune diabetes in adults (LADA) is phenotypically a hybrid of type 1 and type 2 diabetes. Genetically LADA is poorly characterised but does share genetic predisposition with type 1 diabete","DOI":"10.1007/s00125-014-3287-8","ISSN":"0012-186X, 1432-0428","journalAbbreviation":"Diabetologia","language":"en","author":[{"family":"Andersen","given":"Mette K."},{"family":"Sterner","given":"Maria"},{"family":"Forsén","given":"Tom"},{"family":"Kärä jämäki","given":"Annemari"},{"family":"Rolandsson","given":"Olov"},{"family":"Forsblom","given":"Carol"},{"family":"Groop","given":"Per-Henrik"},{"family":"Lahti","given":"Kaj"},{"family":"Nilsson","given":"Peter M."},{"family":"Groop","given":"Leif"},{"family":"Tuomi","given":"Tiinamaija"}],"issued":{"date-parts":[["2014",9,1]]}}},{"id":50,"uris":["http://zotero.org/users/4642149/items/65NED6J3"],"uri":["http://zotero.org/users/4642149/items/65NED6J3"],"itemData":{"id":50,"type":"article-journal","title":"Genetic Similarities Between Latent Autoimmune Diabetes in Adults, Type 1 Diabetes, and Type 2 Diabetes","container-title":"Diabetes","page":"1433-1437","volume":"57","issue":"5","source":"Crossref","DOI":"10.2337/db07-0299","ISSN":"0012-1797, 1939-327X","language":"en","author":[{"family":"Cervin","given":"C."},{"family":"Lyssenko","given":"V."},{"family":"Bakhtadze","given":"E."},{"family":"Lindholm","given":"E."},{"family":"Nilsson","given":"P."},{"family":"Tuomi","given":"T."},{"family":"Cilio","given":"C. M."},{"family":"Groop","given":"L."}],"issued":{"date-parts":[["2008",5,1]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} **}** More recently, we constructed genetic risk scores combining known type 1 and type 2 diabetes loci and assessed their impact in LADA, and our results implicated a role for both sets of loci.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1mbqr6posf","properties":{"formattedCitation":"(12)","plainCitation":"(12)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/sPC6qY0b","uris":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"itemData":{"id":111,"type":"article-journal","title":"Relative contribution of type 1 and type 2 diabetes loci to the genetic etiology of adult-onset, non-insulin-requiring autoimmune diabetes","container-title":"BMC Medicine","page":"88","volume":"15","issue":"1","source":"proxy.library.upenn.edu:2931","abstract":"In adulthood, autoimmune diabetes can present as non-insulin-requiring diabetes, termed as ‘latent autoimmune diabetes in adults’ (LADA). In this study, we investigated established type 1 diabetes (T1D) and type 2 diabetes (T2D) genetic loci in a large cohort of LADA cases to assess where LADA is situated relative to these two well-characterized, classic forms of diabetes. We tested the association of T1D and T2D GWAS-implicated loci in 978 LADA cases and 1057 non-diabetic controls of European ancestry using a linear mixed model. We then compared the associations of T1D and T2D loci between LADA and T1D and T2D cases, respectively. We quantified the difference in genetic risk between each given disease at each locus, and also calculated genetic risk scores to quantify how genetic liability to T1D and T2D distinguished LADA cases from controls. Overall, our results showed that LADA is genetically more similar to T1D, with the exception of an association at the T2D HNF1A locus. Several T1D loci were associated with LADA, including the major histocompatibility complex region, as well as at PTPN22, SH2B3, and INS. Contrary to previous studies, the key T2D risk allele at TCF7L2

(rs7903146-T) had a significantly lower frequency in LADA cases, suggesting that this locus does not play a role in LADA etiology. When constrained on antibody status, the similarity between LADA and T1D became more apparent; however, the HNF1A and TCF7L2 observations persisted. LADA is genetically closer to T1D than T2D, although the genetic load of T1D risk alleles is less than childhood-onset T1D, particularly at the major histocompatibility complex region, potentially accounting for the later disease onset. Our results show that the genetic spectrum of T1D extends into adult-onset diabetes, where it can clinically masquerade as T2D. Furthermore, T2D genetic risk plays a small role in LADA, with a degree of evidence for the HNF1A locus, highlighting the potential for genetic risk scores to contribute towards defining diabetes subtypes.","DOI":"10.1186/s12916-017-0846-0","ISSN":"1741-7015","language":"En","author":[{"family":"Mishra","given":"Rajashree"},{"family":"Chesi","given":"Alessandra"},{"family":"Cousminer","given":"Diana L."},{"family":"Hawa","given":"Mohammad I."},{"family":"Bradfield","given":"Jonathan P."},{"family":"Hodge","given":"Kenyaita M."},{"family":"Guy","given":"Vanessa C."},{"family":"Hakonarson","given":"Hakon"},{"family":"Mauricio","given":"Didac"},{"family":"Schloot","given":"Nanette C."},{"family":"Yderstræde","given":"Knud B."},{"family":"Voight","given":"Benjamin F."},{"family":"Schwartz","given":"Stanley"},{"family":"Boehm","given":"Bernhard O."},{"family":"Leslie","given":"Richard David"},{"family":"Grant","given":"Struan F. A."}],"issued":{"date-parts":[["2017",4,25]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** However, no systematic genome-wide appraisal of adult autoimmune diabetes has been performed. Therefore, in this study, we performed the first GWAS of LADA against population controls and further contrasted LADA

against type 1 diabetes and type 2 diabetes to better understand its genomic signature in comparison to these two better characterized forms of diabetes.

## METHODS

*Study subjects*

Cases diagnosed with LADA were included from cohorts of European ancestry (**Supplementary Table 1**), including 'ActionLada-Plus,' All New Diabetics In Scania (ANDIS), the Botnia Study, Copenhagen LADA (including samples from Danish Centre for strategic Research in Type 2 Diabetes (DD2), Vejle Biobank, Odense University Hospital (OUH), Copenhagen Insulin and Metformin Therapy trial (CIMT), Inter99, and Steno Diabetes Center (SDC)), the Diabetes Registry Vasa (DIREVA), GoDARTS, Nord-Trøndelag Health Study (HUNT), and Scania Diabetes Registry (SDR). Controls were population-based (including samples from the Bone Mineral Density in Childhood Study (BMDCS), Copenhagen controls (with samples from the 1936 Birth Cohort and ADDITION-PRO), GoDARTS, HUNT, and the Malmö Diet and Cancer study, DIREVA, and SDR).

Inclusion and exclusion criteria for LADA, type 1 diabetes, type 2 diabetes, and population controls varied by cohort (see **Supplementary Table 1 and Supplementary Note** for details). In general, LADA was defined by an age at diagnosis older than 20, 30 or 35 years, with some cohorts restricting the upper age limit to 70 years; the presence of diabetes-associated autoimmune autoantibodies, in particular GADA-positivity; and the lack of insulin requirement for 6 months or 1 year after diagnosis. In some cases, C-peptide level was also used as a filter.

*Genotyping and imputation*

Each respective cohort performed genome-wide genotyping on the Illumina CoreExome chip, the Illumina OmniExpressExome BeadChip, or the Affymetrix 6 array. Cases and controls from each study center were matched on the same genotyping chip to reduce batch effects.

Standard post-genotyping quality control was performed, including sample exclusions for ambiguous gender, call rate < 95%, and any duplicate or related individuals (pi_hat ≥ 0.2), and SNP exclusions for monomorphic SNPs, SNPs with MAF < 0.05, and SNPs with missingness rate > 0.05. The Haplotype Reference Consortium (HRC) imputation service (Michigan imputation server, https://imputationserver.sph.umich.edu/index.html) was utilized to perform imputation for autosomal SNPs.

*Genome-wide association and meta-analysis: LADA vs. controls, LADA vs. type 1 diabetes, and LADA vs. type 2 diabetes*

SNPTEST**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"237b7kr5vj","properties":{"formattedCitation":"(17)","plainCitation":"(17)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/o3kUOR29","uris":["http://zotero.org/users/local/0MQVkqmF/items/6D9KAWMU"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/6D9KAWMU"],"itemData":{"id":244,"type":"article-journal","title":"A new multipoint method for genome-wide association studies by imputation of genotypes","container-title":"Nature Genetics","page":"906-913","volume":"39","issue":"7","source":"www.nature.com","abstract":"Genome-wide association studies are set to become the method of choice for uncovering the genetic basis of human diseases. A central challenge in this area is the development of powerful multipoint methods that can detect causal variants that have not been directly genotyped. We propose a coherent analysis framework that treats the problem as one involving missing or uncertain genotypes. Central to our approach is a model-based imputation method for inferring genotypes at observed or unobserved SNPs, leading to improved power over existing methods for

multipoint association mapping. Using real genome-wide association study data, we show that our approach (i) is accurate and well calibrated, (ii) provides detailed views of associated regions that facilitate follow-up studies and (iii) can be used to validate and correct data at genotyped markers. A notable future use of our method will be to boost power by combining data from genome-wide scans that use different SNP sets.","DOI":"10.1038/ng2088","ISSN":"1061-4036","journalAbbreviation":"Nat Genet","language":"en","author":[{"family":"Marchini","given":"Jonathan"},{"family":"Howie","given":"Bryan"},{"family":"Myers","given":"Simon"},{"family":"McVean","given":"Gil"},{"family":"Donnelly","given":"Peter"}],"issued":{"date-parts":[["2007",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** or EPACTS (**{** HYPERLINK "http://genome.sph.umich.edu/wiki/EPACTS" \t "pmc_ext" **}**) was used by each respective cohort to perform case-control GWAS of LADA (n = 2,634) vs. population controls (n = 5,947), LADA (n = 2,454) vs. cases with type 1 diabetes (n = 968), and LADA (n = 2,779) vs. cases with type 2 diabetes (n = 10, 396), including sex and principal components as covariates (see **Supplementary Table 1** for cohort-specific covariates).

After GWAS, filtering was performed centrally to include only SNPs with a MAF > 0.05, INFO quality score > 0.4, and a Hardy-Weinberg equilibrium $P > 1x10^{-7}$. Meta-analysis was then performed for LADA vs. population controls, LADA vs. type 1 diabetes, and LADA vs. type 2 diabetes with GWAMA**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"222nkpiihd","properties":{"formattedCitation":"(18)","plainCitation":"(18)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/PVgfDNOl","uris":["http://zotero.org/users/local/0MQVkqmF/items/EUT54858"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/EUT5485

8"],"itemData":{"id":513,"type":"article-journal","title":"GWAMA: software for genome-wide association meta-analysis","container-title":"BMC Bioinformatics","page":"288","volume":"11","source":"BioMed Central","abstract":"Despite the recent success of genome-wide association studies in identifying novel loci contributing effects to complex human traits, such as type 2 diabetes and obesity, much of the genetic component of variation in these phenotypes remains unexplained. One way to improving power to detect further novel loci is through meta-analysis of studies from the same population, increasing the sample size over any individual study. Although statistical software analysis packages incorporate routines for meta-analysis, they are ill equipped to meet the challenges of the scale and complexity of data generated in genome-wide association studies.","DOI":"10.1186/1471-2105-11-288","ISSN":"1471-2105","shortTitle":"GWAMA","journalAbbreviation":"BMC Bioinformatics","author":[{"family":"Mägi","given":"Reedik"},{"family":"Morris","given":"Andrew P."}],"issued":{"date-parts":[["2010"]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** with two rounds of genomic control (**Supplementary Table 2; Supplementary Fig. 1-2**).

Signals in the secondary tier ($P$ = 1 x $10^{-6}$ – 5 x $10^{-8}$) for the LADA vs. population controls analysis were followed up in the GODARTS and HUNT cohorts (LADA, n = 345; controls, n = 1,664) and meta-analyzed with the discovery set (total LADA, n = 2,979; controls, n = 7,611) to assess whether any novel signals would reach genome-wide significance.

*Enrichment of directional consistency among T1D/T2D loci in LADA*

To estimate whether the concordance in direction of effects for T1D and T2D loci in LADA is significantly different from chance, a binomial test was used assuming a null hypothesis of 50% agreement.

*Conditional analysis*

Approximate conditional analysis for known type 1 diabetes-associated loci was carried out for the LADA vs controls summary statistics results for the 10p15.1 locus using Genome-wide Complex Trait Analysis (GCTA).**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"BHKcUnxU","properties":{"formattedCitation":"(19)","plainCitation":"(19)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/iaO9hlnG","uris":["http://zotero.org/users/local/nQ7dt7bm/items/2KJPRIQD"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/2KJPRIQD"],"itemData":{"id":93,"type":"article-journal","title":"GCTA: A Tool for Genome-wide Complex Trait Analysis","container-title":"The American Journal of Human Genetics","page":"76-82","volume":"88","issue":"1","source":"CrossRef","DOI":"10.1016/j.ajhg.2010.11.011","ISSN":"00029297","shortTitle":"GCTA","language":"en","author":[{"family":"Yang","given":"Jian"},{"family":"Lee","given":"S. Hong"},{"family":"Goddard","given":"Michael E."},{"family":"Visscher","given":"Peter M."}],"issued":{"date-parts":[["2011",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** For this locus, LADA vs controls + HUNT summary statistics were conditioned on the following type 1 diabetes-associated SNPs: rs61839660,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2ee3afvrmc","properties":{"formattedCitation":"(20)","plainCitation":"(20)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/dFnEByem","uris":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"itemData":{"id":225,"type":"article-journal","title":"Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene

enhancers","container-title":"Nature Genetics","page":"381-386","volume":"47","issue":"4","source":"www.nature.com","abstract":"Genetic studies of type 1 diabetes (T1D) have identified 50 susceptibility regions, finding major pathways contributing to risk, with some loci shared across immune disorders. To make genetic comparisons across autoimmune disorders as informative as possible, a dense genotyping array, the Immunochip, was developed, from which we identified four new T1D-associated regions (P < 5 × 10−8). A comparative analysis with 15 immune diseases showed that T1D is more similar genetically to other autoantibody-positive diseases, significantly most similar to juvenile idiopathic arthritis and significantly least similar to ulcerative colitis, and provided support for three additional new T1D risk loci. Using a Bayesian approach, we defined credible sets for the T1D-associated SNPs. The associated SNPs localized to enhancer sequences active in thymus, T and B cells, and CD34+ stem cells. Enhancer-promoter interactions can now be analyzed in these cell types to identify which particular genes and regulatory sequences are causal.","DOI":"10.1038/ng.3245","ISSN":"1061-4036","journalAbbreviation":"Nat Genet","language":"en","author":[{"family":"Onengut-Gumuscu","given":"Suna"},{"family":"Chen","given":"Wei-Min"},{"family":"Burren","given":"Oliver"},{"family":"Cooper","given":"Nick J."},{"family":"Quinlan","given":"Aaron R."},{"family":"Mychaleckyj","given":"Josyf C."},{"family":"Farber","given":"Emily"},{"family":"Bonnie","given":"Jessica K."},{"family":"Szpak","given":"Michal"},{"family":"Schofield","given":"Ellen"},{"family":"Achuthan","given":"Premanand"},{"family":"Guo","given":"Hui"},{"family":"Fortune","given":"Mary D."},{"family":"Stevens","given":"Helen"},{"family":"Walker","given":"Neil M."},{"family":"Ward","given":"Lucas

D."},{"family":"Kundaje","given":"Anshul"},{"family":"Kellis","given":"Manolis"},{"family":"Daly","given":"Mark J."},{"family":"Barrett","given":"Jeffrey C."},{"family":"Cooper","given":"Jason D."},{"family":"Deloukas","given":"Panos"},{"literal":"Type 1 Diabetes Genetics Consortium"},{"family":"Todd","given":"John A."},{"family":"Wallace","given":"Chris"},{"family":"Concannon","given":"Patrick"},{"family":"Rich","given":"Stephen S."}],"issued":{"date-parts":[["2015",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** rs10795791,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2fsrdnb8c","properties":{"formattedCitation":"(20)","plainCitation":"(20)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/dFnEByem","uris":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"itemData":{"id":225,"type":"article-journal","title":"Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers","container-title":"Nature Genetics","page":"381-386","volume":"47","issue":"4","source":"www.nature.com","abstract":"Genetic studies of type 1 diabetes (T1D) have identified 50 susceptibility regions, finding major pathways contributing to risk, with some loci shared across immune disorders. To make genetic comparisons across autoimmune disorders as informative as possible, a dense genotyping array, the Immunochip, was developed, from which we identified four new T1D-associated regions ($P < 5 \times 10^{-8}$). A comparative analysis with 15 immune diseases showed that T1D is more similar genetically to other autoantibody-positive diseases, significantly most similar to juvenile idiopathic arthritis

and significantly least similar to ulcerative colitis, and provided support for three additional new T1D risk loci. Using a Bayesian approach, we defined credible sets for the T1D-associated SNPs. The associated SNPs localized to enhancer sequences active in thymus, T and B cells, and CD34+ stem cells. Enhancer-promoter interactions can now be analyzed in these cell types to identify which particular genes and regulatory sequences are causal.","DOI":"10.1038/ng.3245","ISSN":"1061-4036","journalAbbreviation":"Nat Genet","language":"en","author":[{"family":"Onengut-Gumuscu","given":"Suna"},{"family":"Chen","given":"Wei-Min"},{"family":"Burren","given":"Oliver"},{"family":"Cooper","given":"Nick J."},{"family":"Quinlan","given":"Aaron R."},{"family":"Mychaleckyj","given":"Josyf C."},{"family":"Farber","given":"Emily"},{"family":"Bonnie","given":"Jessica K."},{"family":"Szpak","given":"Michal"},{"family":"Schofield","given":"Ellen"},{"family":"Achuthan","given":"Premanand"},{"family":"Guo","given":"Hui"},{"family":"Fortune","given":"Mary D."},{"family":"Stevens","given":"Helen"},{"family":"Walker","given":"Neil M."},{"family":"Ward","given":"Lucas D."},{"family":"Kundaje","given":"Anshul"},{"family":"Kellis","given":"Manolis"},{"family":"Daly","given":"Mark J."},{"family":"Barrett","given":"Jeffrey C."},{"family":"Cooper","given":"Jason D."},{"family":"Deloukas","given":"Panos"},{"literal":"Type 1 Diabetes Genetics Consortium"},{"family":"Todd","given":"John A."},{"family":"Wallace","given":"Chris"},{"family":"Concannon","given":"Patrick"},{"family":"Rich","given":"Stephen S."}],"issued":{"date-parts":[["2015",4]]}}},"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} **}** rs7090530,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2d0gbu14fe","properties":{"formattedCitation":"(21)","plainCitation":"(21)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/ToiCvNRA","uris":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"itemData":{"id":"sZuy1wbs/IMkHKPl0","type":"article-journal","title":"A Genome-Wide Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci","container-title":"PLOS Genetics","page":"e1002293","volume":"7","issue":"9","source":"PLoS Journals","abstract":"Author Summary Despite the fact that there is clearly a large genetic component to type 1 diabetes (T1D), uncovering the genes contributing to this disease has proven challenging. However, in the past three years there has been relatively major progress in this regard, with advances in genetic screening technologies allowing investigators to scan the genome for variants conferring risk for disease without prior hypotheses. Such genome-wide association studies have revealed multiple regions of the genome to be robustly and consistently associated with T1D. More recent findings have been a consequence of combining of multiple datasets from independent investigators in meta-analyses, which have more power to pick up additional variants contributing to the trait. In the current study, we describe the largest meta-analysis of T1D genome-wide genotyped datasets to date, which combines six large studies. As a consequence, we have uncovered three new signals residing at the chromosomal locations 13q22, 2p23, and 6q27, which went on to be replicated in independent sample sets. These latest associated regions add to the growing repertoire of gene networks predisposing to T1D.","DOI":"10.1371/journal.pgen.1002293","ISSN":"1553-

7404","journalAbbreviation":"PLOS Genetics","author":[{"family":"Bradfield","given":"Jonathan P."},{"family":"Qu","given":"Hui-Qi"},{"family":"Wang","given":"Kai"},{"family":"Zhang","given":"Haitao"},{"family":"Sleiman","given":"Patrick M."},{"family":"Kim","given":"Cecilia E."},{"family":"Mentch","given":"Frank D."},{"family":"Qiu","given":"Haijun"},{"family":"Glessner","given":"Joseph T."},{"family":"Thomas","given":"Kelly A."},{"family":"Frackelton","given":"Edward C."},{"family":"Chiavacci","given":"Rosetta M."},{"family":"Imielinski","given":"Marcin"},{"family":"Monos","given":"Dimitri S."},{"family":"Pandey","given":"Rahul"},{"family":"Bakay","given":"Marina"},{"family":"Grant","given":"Struan F. A."},{"family":"Polychronakos","given":"Constantin"},{"family":"Hakonarson","given":"Hakon"}],"issued":{"date-parts":[["2011",9,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** rs12251307,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"as7f6rl5lm","properties":{"formattedCitation":"(22)","plainCitation":"(22)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Yzw3CSkA","uris":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"itemData":{"id":214,"type":"article-journal","title":"Genome-wide association study and meta-analysis finds over 40 loci affect risk of type 1 diabetes","container-title":"Nature genetics","page":"703-707","volume":"41","issue":"6","source":"PubMed Central","abstract":"Type 1 diabetes (T1D) is a common autoimmune disorder that arises from the action of multiple genetic and environmental risk factors. We report the findings of a new

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{"citationID":"a2iv1i0qph8","properties":{"formattedCitation":"(22)","plainCitation":"(22)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Yzw3CSkA","uris":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"itemData":{"id":214,"type":"article-journal","title":"Genome-wide association study and meta-analysis finds over 40 loci affect risk of type 1 diabetes","container-title":"Nature genetics","page":"703-707","volume":"41","issue":"6","source":"PubMed Central","abstract":"Type 1 diabetes (T1D) is a common autoimmune disorder that arises from the action of multiple genetic and environmental risk factors. We report the findings of a new genome-wide association study of T1D, combined in a meta-analysis with two previously published studies. The total sample set included 7,514 cases and 9,045 reference samples. Forty-one distinct genomic locations provided evidence for association to T1D in the meta-analysis (P < 10-6). After excluding previously reported associations, 27 regions were further tested in an independent set of 4,267 cases, 4,463 controls and 2,319 affected sib-pair (ASP) families. Of these, 18 regions were replicated (P < 0.01; overall P < 5 × 10-8) and four additional regions provided nominal evidence of replication (P < 0.05). The many new candidate genes suggested by these results include IL10, IL19, IL20, GLIS3, CD69 and IL27.","DOI":"10.1038/ng.381","ISSN":"1061-4036","note":"PMID: 19430480\nPMCID: PMC2889014","journalAbbreviation":"Nat Genet","author":[{"family":"Barrett","given":"Jeffrey C."},{"family":"Clayton","given":"David"},{"family":"Concannon","given":"Patrick"},{"family":"Akolkar","given":"Beena"},{"family":"Cooper","given":"Jason D."},{"family":"Erlich","given":"Henry A."},{"family":"Julier","given":"Cécile"},{"family":"Morahan","given":"Grant"},{"family":"Ne

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and the MHC, *PTPN22*, and *INS* loci were not conditioned as the top signals were identified as type 1 diabetes-associated SNPs.

*Stratification analysis by GAD autoantibody titer*

Cases with LADA are heterogeneous in terms of GAD autoantibody titer **{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"w9SjKVl4","properties":{"formattedCitation":"(23)","plainCitation":"(23)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Ei2Vvt1f","uris":["http://zotero.org/users/local/qKD4zhlo/items/LVN98V5T"],"uri":["http://zotero.org/users/local/qKD4zhlo/items/LVN98V5T"],"itemData":{"id":139,"type":"article-journal","title":"High Titer of Autoantibodies to GAD Identifies a Specific Phenotype of Adult-Onset Autoimmune Diabetes","container-title":"Diabetes Care","page":"932-938","volume":"30","issue":"4","source":"CrossRef","DOI":"10.2337/dc06-1696","ISSN":"0149-5992, 1935-5548","language":"en","author":[{"family":"Buzzetti","given":"R."},{"family":"Di Pietro","given":"S."},{"family":"Giaccari","given":"A."},{"family":"Petrone","given":"A."},{"family":"Locatelli","given":"M."},{"family":"Suraci","given":"C."},{"family":"Capizzi","given":"M."},{"family":"Arpi","given":"M. L."},{"family":"Bazzigaluppi","given":"E."},{"family":"Dotta","given":"F."},{"family":"Bosi","given":"E."},{"literal":"for the Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study Group"}],"issued":{"date-parts":[["2007",4,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. Therefore, to further understand the genetic landscape of LADA in the context of different GAD levels, we stratified cases into tertiles in

ActionLADA and ANDIS, DIREVA, and SDR. We performed three GWAS, on (1) the top tertile with the highest GAD titers (n = 627) vs. population controls (n = 4314); (2) the top two tertiles with the highest GAD titers (n = 1012) vs. population controls (n = 4314); and (3) the bottom tertile with the lowest GAD titers (n = 562) vs. population controls (n = 4314).

*LD Score Regression*

To test for genetic correlations genome-wide between LADA, type 1 diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ZEDSaMfO","properties":{"formattedCitation":"(21)","plainCitation":"(21)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/ToiCvNRA","uris":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"itemData":{"id":"AjlMWpFa/KzdbL5XB","type":"article-journal","title":"A Genome-Wide Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci","container-title":"PLOS Genetics","page":"e1002293","volume":"7","issue":"9","source":"PLoS Journals","abstract":"Author Summary Despite the fact that there is clearly a large genetic component to type 1 diabetes (T1D), uncovering the genes contributing to this disease has proven challenging. However, in the past three years there has been relatively major progress in this regard, with advances in genetic screening technologies allowing investigators to scan the genome for variants conferring risk for disease without prior hypotheses. Such genome-wide association studies have revealed multiple regions of the genome to be robustly and consistently associated with T1D. More recent findings have been a consequence of combining of multiple datasets from independent investigators in meta-analyses, which have more power to pick up

additional variants contributing to the trait. In the current study, we describe the largest meta-analysis of T1D genome-wide genotyped datasets to date, which combines six large studies. As a consequence, we have uncovered three new signals residing at the chromosomal locations 13q22, 2p23, and 6q27, which went on to be replicated in independent sample sets. These latest associated regions add to the growing repertoire of gene networks predisposing to T1D.","DOI":"10.1371/journal.pgen.1002293","ISSN":"1553-7404","journalAbbreviation":"PLOS Genetics","author":[{"family":"Bradfield","given":"Jonathan P."},{"family":"Qu","given":"Hui-Qi"},{"family":"Wang","given":"Kai"},{"family":"Zhang","given":"Haitao"},{"family":"Sleiman","given":"Patrick M."},{"family":"Kim","given":"Cecilia E."},{"family":"Mentch","given":"Frank D."},{"family":"Qiu","given":"Haijun"},{"family":"Glessner","given":"Joseph T."},{"family":"Thomas","given":"Kelly A."},{"family":"Frackelton","given":"Edward C."},{"family":"Chiavacci","given":"Rosetta M."},{"family":"Imielinski","given":"Marcin"},{"family":"Monos","given":"Dimitri S."},{"family":"Pandey","given":"Rahul"},{"family":"Bakay","given":"Marina"},{"family":"Grant","given":"Struan F. A."},{"family":"Polychronakos","given":"Constantin"},{"family":"Hakonarson","given":"Hakon"}],"issued":{"date-parts":[["2011",9,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, and type 2 diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"AKn9BuP2","properties":{"formattedCitation":"(24)","plainCitation":"(24)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/MWVFcTPn","uris":["http://zotero.org/users/loca

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ndex":0},"citationItems":[{"id":"GKyl1X7D/LQhHsFdl","uris":["http://zotero.org/users/local/0MQVkqmF/items/PBS4FI9Q"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/PBS4FI9Q"],"itemData":{"id":507,"type":"article-journal","title":"LD Score regression distinguishes confounding from polygenicity in genome-wide association studies","container-title":"Nature Genetics","page":"291-295","volume":"47","issue":"3","source":"www.nature.com","abstract":"Both polygenicity (many small genetic effects) and confounding biases, such as cryptic relatedness and population stratification, can yield an inflated distribution of test statistics in genome-wide association studies (GWAS). However, current methods cannot distinguish between inflation from a true polygenic signal and bias. We have developed an approach, LD Score regression, that quantifies the contribution of each by examining the relationship between test statistics and linkage disequilibrium (LD). The LD Score regression intercept can be used to estimate a more powerful and accurate correction factor than genomic control. We find strong evidence that polygenicity accounts for the majority of the inflation in test statistics in many GWAS of large sample size.","DOI":"10.1038/ng.3211","ISSN":"1061-4036","journalAbbreviation":"Nat Genet","language":"en","author":[{"family":"Bulik-Sullivan","given":"Brendan K."},{"family":"Loh","given":"Po-Ru"},{"family":"Finucane","given":"Hilary K."},{"family":"Ripke","given":"Stephan"},{"family":"Yang","given":"Jian"},{"literal":"Schizophrenia Working Group of the Psychiatric Genomics Consortium"},{"family":"Patterson","given":"Nick"},{"family":"Daly","given":"Mark J."},{"family":"Price","given":"Alkes L."},{"family":"Neale","given":"Benjamin M."}],"issued":{"date-parts":[["2015",3]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**.

*Pathway analysis*

DEPICT pathway analysis{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"168jsencde","properties":{"formattedCitation":"(26)","plainCitation":"(26)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/fdztKTIy","uris":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"itemData":{"id":536,"type":"article-journal","title":"Biological interpretation of genome-wide association studies using predicted gene functions","container-title":"Nature Communications","page":"5890","volume":"6","source":"www.nature.com","abstract":"Identifying which genes and pathways explain genetic associations is challenging. Here, the authors present DEPICT, a tool for gene prioritization, pathway analysis and tissue/cell-type enrichment analysis that can be used to generate testable hypotheses from genetic association studies.","DOI":"10.1038/ncomms6890","ISSN":"2041-1723","language":"en","author":[{"family":"Pers","given":"Tune H."},{"family":"Karjalainen","given":"Juha M."},{"family":"Chan","given":"Yingleong"},{"family":"Westra","given":"Harm-Jan"},{"family":"Wood","given":"Andrew R."},{"family":"Yang","given":"Jian"},{"family":"Lui","given":"Julian C."},{"family":"Vedantam","given":"Sailaja"},{"family":"Gustafsson","given":"Stefan"},{"family":"Esko","given":"Tonu"},{"family":"Frayling","given":"Tim"},{"family":"Speliotes","given":"Elizabeth K."},{"family":"Boehnke","given":"Michael"},{"family":"Raychaudhuri","given":"Soumya"},{"family":"Fehrmann","given":"Rudolf S. N."},{"family":"Hirschhorn","given":"Joel

N."},{"family":"Franke","given":"Lude"}],"issued":{"date-parts":[["2015",1,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** was used to perform gene set enrichment, tissue enrichment, and gene prioritization analyses.

*HLA imputation/analysis*

The HLA imputation software SNP2HLA**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"ao0ahp6hk5","properties":{"formattedCitation":"(27)","plainCitation":"(27)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/tvwVAORq","uris":["http://zotero.org/users/local/99dTDuE7/items/ZP8C6RDE"],"uri":["http://zotero.org/users/local/99dTDuE7/items/ZP8C6RDE"],"itemData":{"id":243,"type":"article-journal","title":"Imputing Amino Acid Polymorphisms in Human Leukocyte Antigens","container-title":"PLoS ONE","volume":"8","issue":"6","source":"proxy.library.upenn.edu:2063","abstract":"DNA sequence variation within human leukocyte antigen (HLA) genes mediate susceptibility to a wide range of human diseases. The complex genetic structure of the major histocompatibility complex (MHC) makes it difficult, however, to collect genotyping ...","URL":"https://proxy.library.upenn.edu:2063/pmc/articles/PMC3675122/","DOI":"10.1371/journal.pone.0064683","note":"PMID: 23762245","author":[{"family":"Jia","given":"Xiaoming"},{"family":"Han","given":"Buhm"},{"family":"Onengut-Gumuscu","given":"Suna"},{"family":"Chen","given":"Wei-Min"},{"family":"Concannon","given":"Patrick J."},{"family":"Rich","given":"Stephen S."},{"family":"Raychaudhuri","given":"Soumya"},{"family":"Bakker","given":"Paul I. W.","dropping-particle":"de"}],"issued":{"date-parts":[["2013"]]},"accessed":{"date-

parts":[["2017",2,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** was used to impute chromosome 6 in ActionLADA-Plus (n = 1,365), Swedish cases with LADA (n = 794), BMDCS (n = 1,056) and type 1 diabetes cases from the WTCCC (n = 1,990). HLA alleles with 4-digit resolution were imputed. The R package 'BIGDAWG' (https://cran.r-project.org/web/packages/BIGDAWG)**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a5vm5dvr6j","properties":{"formattedCitation":"(28)","plainCitation":"(28)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/s90bKbPO","uris":["http://zotero.org/users/local/nQ7dt7bm/items/ZD322G7C"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/ZD322G7C"],"itemData":{"id":289,"type":"article-journal","title":"Bridging Immunogenomic Data Analysis Workflow Gaps (bigdawg): An Integrated Case-Control Analysis Pipeline","container-title":"Human immunology","page":"283","volume":"77","issue":"3","source":"proxy.library.upenn.edu:2065","abstract":"Bridging ImmunoGenomic Data-Analysis Workflow Gaps (BIGDAWG) is an integrated data-analysis pipeline designed for the standardized analysis of highly-polymorphic genetic data, specifically for the HLA and KIR genetic systems. Most modern genetic analysis ...","DOI":"10.1016/j.humimm.2015.12.006","note":"PMID: 26708359","shortTitle":"Bridging Immunogenomic Data Analysis Workflow Gaps (bigdawg)","author":[{"family":"Pappas","given":"Derek J."},{"family":"Marin","given":"Wesley"},{"family":"Hollenbach","given":"Jill A."},{"family":"Mack","given":"Steven J."}],"issued":{"date-parts":[["2016",3]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** was used to test for allele frequency

differences for established type 1 diabetes-associated HLA haplotypes between LADA versus type 1 diabetes, as well as LADA versus BMDCS. Haplotypes with frequencies less than 1% across LADA, type 1 diabetes, and BMDCS were removed from the analysis given that rare haplotypes can result in unstable variance estimates and unreliable test statistics.

**RESULTS**

*Genome-wide association of LADA versus population controls*

We first conducted GWAS in patients with LADA (n = 2,634) versus population-based controls (n = 5,947) of European ancestry in a discovery meta-analysis setting (**Supplementary Table 1;** power calculations can be found in **Supplementary Table 3**). Four signals achieved genome-wide significance ($P < 5x10^{-8}$), all at established type 1 diabetes risk loci (*HLA*, *PTPN22*, *INS*, and *SH2B3*; **Table 1, Supplementary Figures 1 and 2**). Pathway analysis with DEPICT**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a23egcq3esl","properties":{"formattedCitation":"(26)","plainCitation":"(26)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/fdztKTIy","uris":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"itemData":{"id":"sfQESt5R/ZHunBnGI","type":"article-journal","title":"Biological interpretation of genome-wide association studies using predicted gene functions","container-title":"Nature Communications","page":"5890","volume":"6","source":"www.nature.com","abstract":"Identifying which genes and pathways explain genetic associations is challenging. Here, the authors present DEPICT, a tool for gene prioritization, pathway analysis and tissue/cell-type enrichment analysis that can be used to generate testable hypotheses from genetic association studies.","DOI":"10.1038/ncomms6890","ISSN":"2041-1723","language":"en","author":[{"family":"Pers","given":"Tune H."},{"family":"Karjalainen","given":"Juha M."},{"family":"Chan","given":"Yingleong"},{"family":"Westra","given":"Harm-Jan"},{"family":"Wood","given":"Andrew R."},{"family":"Yang","given":"Jian"},{"family":"Lui","given":"Julian

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N."},{"family":"Franke","given":"Lude"}],"issued":{"date-parts":[["2015",1,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** for signals at $P < 10^{-5}$ supported a strong immune role in the pathogenesis of LADA (**Supplementary Tables 4-5**), with gene set enrichment analysis implicating 'abnormal cytotoxic T cell physiology' (nominal $P = 6.39 \times 10^{-7}$) as well as the 'mTOR subnetwork' ($P = 6.03 \times 10^{-5}$) and 'cell cycle' ($P = 1.67 \times 10^{-5}$) as also seen in a previous epigenome-wide association study of type 1 diabetes,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a16uneb3ob2","properties":{"formattedCitation":"(7)","plainCitation":"(7)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Ja9kyCwG","uris":["http://zotero.org/users/local/nQ7dt7bm/items/UT9C82V3"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/UT9C82V3"],"itemData":{"id":182,"type":"article-journal","title":"An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans","container-title":"Diabetes","page":"db161253","source":"proxy.library.upenn.edu:3348","abstract":"To characterise type 2 diabetes (T2D) associated variation across the allele frequency spectrum, we conducted a meta-analysis of genome-wide association data from 26,676 T2D cases and 132,532 controls of European ancestry after imputation using the 1000 Genomes multi-ethnic reference panel. Promising association signals were followed-up in additional data sets (of 14,545 or 7,397

T2D cases and 38,994 or 71,604 controls). We identified 13 novel T2D-associated loci ($p<5\times10^{-8}$), including variants near the GLP2R, GIP, and HLA-DQA1 genes. Our analysis brought the total number of independent T2D associations to 128 distinct signals at 113 loci. Despite substantially increased sample size and more complete coverage of low-frequency variation, all novel associations were driven by common SNVs. Credible sets of potentially causal variants were generally larger than those based on imputation with earlier reference panels, consistent with resolution of causal signals to common risk haplotypes. Stratification of T2D-associated loci based on T2D-related quantitative trait associations revealed tissue-specific enrichment of regulatory annotations in pancreatic islet enhancers for loci influencing insulin secretion, and in adipocytes, monocytes and hepatocytes for insulin action-associated loci. These findings highlight the predominant role played by common variants of modest effect and the diversity of biological mechanisms influencing T2D pathophysiology.","DOI":"10.2337/db16-1253","ISSN":"0012-1797, 1939-327X","note":"PMID: 28566273","language":"en","author":[{"family":"Scott","given":"Robert A."},{"family":"Scott","given":"Laura J."},{"family":"Mägi","given":"Reedik"},{"family":"Marullo","given":"Letizia"},{"family":"Gaulton","given":"Kyle J."},{"family":"Kaakinen","given":"Marika"},{"family":"Pervjakova","given":"Natalia"},{"family":"Pers","given":"Tune H."},{"family":"Johnson","given":"Andrew D."},{"family":"Eicher","given":"John D."},{"family":"Jackson","given":"Anne U."},{"family":"Ferreira","given":"Teresa"},{"family":"Lee","given":"Yeji"},{"family":"Ma","given":"Clement"},{"family":"Steinthorsdottir","given":"Valgerdur"},{"family":"Thorleifsson","given":"Gudmar"},{"family":"Qi","given":"Lu"},{"family":"Zuydam","given":"Natalie R.

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concentrations of serum autoantibodies against GAD65 were measured by direct radioligand assay. The potential association of the frequency of NK cells with clinical measures was analyzed. In comparison with that in the HC, significantly higher frequency of peripheral blood NK and NKp46+ NK cells, but lower frequency of KIR3DL1+ NK cells were detected in patients with newly diagnosed LADA ($p < 0.0001$, $p < 0.0001$, $p = 0.0039$, respectively). The percentages of inducible IFN-γ+ NK cells were significantly higher in the LADA patients than that in the HC ($p < 0.0001$). Moreover, the percentages of NKp46+ NK cells were negatively correlated with the levels of fasting plasma C-peptide in patients ($R = -0.4877$, $p = 0.0099$). There was no significant difference in the frequency of spontaneous and inducible CD107a+ between patients and controls. Our data indicate a higher frequency of activated NKp46+ NK cells may be associated with the development of LADA in humans.","DOI":"10.3109/08916934.2014.990629","ISSN":"0891-6934","journalAbbreviation":"Autoimmunity","author":[{"family":"Wang","given":"Ye"},{"family":"Yuan","given":"Weijun"},{"family":"Guo","given":"Hui"},{"family":"Jiang","given":"Yanfang"}],"issued":{"date-parts":[["2015",5,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**

*Replication supports a novel locus at PFKFB3*

Using cases with LADA and population samples from an additional two study centers, we attempted validation of 13 signals with suggestive association ($P < 5x10^{-5}$) (**Supplementary Table 6**). We observed a novel signal at 10p15.1 between the two established type 1 diabetes loci at *IL2RA* and *PRKCQ*, which achieved genome-wide significance (rs1983890-C, OR (95% CI) = 1.16 (1.14-1.32), $P = 3.02 \times 10^{-8}$) (**Fig. 1A-B**). Given that the LADA signal is situated in

close proximity to known type 1 diabetes risk loci and was in moderate to low LD with established type 1 diabetes-associated alleles (**Supplementary Table 7**), we conditioned on the type 1 diabetes SNPs and observed that rs1983890 remained strongly associated with LADA (OR (95% CI) = 1.15 (1.13-1.19), $P = 4.35 \times 10^{-8}$) (**Fig. 1C**). This signal reached suggestive association in a study of type 1 diabetes ($P = 1.3 \times 10^{-7}$) **{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"6eDT0u0b","properties":{"formattedCitation":"(31)","plainCitation":"(31)","noteIndex":0},"citationItems":[{"id":95,"uris":["http://zotero.org/users/4642149/items/MT9QQCMD"],"uri":["http://zotero.org/users/4642149/items/MT9QQCMD"],"itemData":{"id":95,"type":"article-journal","title":"A Genome-Wide Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci","container-title":"PLOS Genetics","page":"e1002293","volume":"7","issue":"9","source":"PLoS Journals","abstract":"Diabetes impacts approximately 200 million people worldwide, of whom approximately 10% are affected by type 1 diabetes (T1D). The application of genome-wide association studies (GWAS) has robustly revealed dozens of genetic contributors to the pathogenesis of T1D, with the most recent meta-analysis identifying in excess of 40 loci. To identify additional genetic loci for T1D susceptibility, we examined associations in the largest meta-analysis to date between the disease and ~2.54 million SNPs in a combined cohort of 9,934 cases and 16,956 controls. Targeted follow-up of 53 SNPs in 1,120 affected trios uncovered three new loci associated with T1D that reached genome-wide significance. The most significantly associated SNP (rs539514, P = 5.66×10−11) resides in an intronic region of the LMO7 (LIM domain only 7) gene on 13q22. The second most significantly associated SNP (rs478222, P = 3.50×10−9) resides in an intronic region of the EFR3B (protein EFR3 homolog

B) gene on 2p23; however, the region of linkage disequilibrium is approximately 800 kb and harbors additional multiple genes, including NCOA1, C2orf79, CENPO, ADCY3, DNAJC27, POMC, and DNMT3A. The third most significantly associated SNP (rs924043, P = 8.06×10−9) lies in an intergenic region on 6q27, where the region of association is approximately 900 kb and harbors multiple genes including WDR27, C6orf120, PHF10, TCTE3, C6orf208, LOC154449, DLL1, FAM120B, PSMB1, TBP, and PCD2. These latest associated regions add to the growing repertoire of gene networks predisposing to

T1D.","DOI":"10.1371/journal.pgen.1002293","ISSN":"1553-

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Genetics","language":"en","author":[{"family":"Bradfield","given":"Jonathan

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"}],"issued":{"date-parts":[["2011",9,29]]}}}],"schema":"https://github.com/citation-style-

language/schema/raw/master/csl-citation.json"} **}**, and as such may not represent a unique LADA

association. DEPICT gene prioritization analysis{ ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1r0vlt8bih","properties":{"formattedCitation":"(26)","plainCitation":"(26)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/fdztKTIy","uris":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/NM8EWSXD"],"itemData":{"id":"sfQESt5R/ZHunBnGI","type":"article-journal","title":"Biological interpretation of genome-wide association studies using predicted gene functions","container-title":"Nature Communications","page":"5890","volume":"6","source":"www.nature.com","abstract":"Identifying which genes and pathways explain genetic associations is challenging. Here, the authors present DEPICT, a tool for gene prioritization, pathway analysis and tissue/cell-type enrichment analysis that can be used to generate testable hypotheses from genetic association studies.","DOI":"10.1038/ncomms6890","ISSN":"2041-1723","language":"en","author":[{"family":"Pers","given":"Tune H."},{"family":"Karjalainen","given":"Juha M."},{"family":"Chan","given":"Yingleong"},{"family":"Westra","given":"Harm-Jan"},{"family":"Wood","given":"Andrew R."},{"family":"Yang","given":"Jian"},{"family":"Lui","given":"Julian C."},{"family":"Vedantam","given":"Sailaja"},{"family":"Gustafsson","given":"Stefan"},{"family":"Esko","given":"Tonu"},{"family":"Frayling","given":"Tim"},{"family":"Speliotes","given":"Elizabeth K."},{"family":"Boehnke","given":"Michael"},{"family":"Raychaudhuri","given":"Soumya"},{"family":"Fehrmann","given":"Rudolf S. N."},{"family":"Hirschhorn","given":"Joel N."},{"family":"Franke","given":"Lude"}],"issued":{"date-

parts":[["2015",1,19]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** identified the gene encoding '6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3' (*PFKFB3*), the nearest gene to the LADA signal, as the most likely functional candidate (**Supplementary Table 8**).

*Candidate loci for type 1 diabetes and type 2 diabetes*

Some of the loci that were suggestively associated with LADA in this study overlap previously documented type 1 diabetes associations, including rs11755527 (*BACH2*) and rs941576 (*DLK1*),**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a26b9s0m4kf","properties":{"formattedCitation":"(20\\uc0\\u8211{}22)","plainCitation":"(20–22)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/ToiCvNRA","uris":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"itemData":{"id":"Jn9ZhVVO/U6DmnaI1","type":"article-journal","title":"A Genome-Wide Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci","container-title":"PLOS Genetics","page":"e1002293","volume":"7","issue":"9","source":"PLoS Journals","abstract":"Author Summary Despite the fact that there is clearly a large genetic component to type 1 diabetes (T1D), uncovering the genes contributing to this disease has proven challenging. However, in the past three years there has been relatively major progress in this regard, with advances in genetic screening technologies allowing investigators to scan the genome for variants conferring risk for disease without prior hypotheses. Such genome-wide association studies have revealed multiple regions of the genome to be robustly and consistently

associated with T1D. More recent findings have been a consequence of combining of multiple datasets from independent investigators in meta-analyses, which have more power to pick up additional variants contributing to the trait. In the current study, we describe the largest meta-analysis of T1D genome-wide genotyped datasets to date, which combines six large studies. As a consequence, we have uncovered three new signals residing at the chromosomal locations 13q22, 2p23, and 6q27, which went on to be replicated in independent sample sets. These latest associated regions add to the growing repertoire of gene networks predisposing to T1D.","DOI":"10.1371/journal.pgen.1002293","ISSN":"1553-7404","journalAbbreviation":"PLOS Genetics","author":[{"family":"Bradfield","given":"Jonathan P."},{"family":"Qu","given":"Hui-Qi"},{"family":"Wang","given":"Kai"},{"family":"Zhang","given":"Haitao"},{"family":"Sleiman","given":"Patrick M."},{"family":"Kim","given":"Cecilia E."},{"family":"Mentch","given":"Frank D."},{"family":"Qiu","given":"Haijun"},{"family":"Glessner","given":"Joseph T."},{"family":"Thomas","given":"Kelly A."},{"family":"Frackelton","given":"Edward C."},{"family":"Chiavacci","given":"Rosetta M."},{"family":"Imielinski","given":"Marcin"},{"family":"Monos","given":"Dimitri S."},{"family":"Pandey","given":"Rahul"},{"family":"Bakay","given":"Marina"},{"family":"Grant","given":"Struan F. A."},{"family":"Polychronakos","given":"Constantin"},{"family":"Hakonarson","given":"Hakon"}],"issued":{"date-parts":[["2011",9,29]]}}},{"id":"GKyl1X7D/Yzw3CSkA","uris":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCU

JE"],"itemData":{"id":214,"type":"article-journal","title":"Genome-wide association study and meta-analysis finds over 40 loci affect risk of type 1 diabetes","container-title":"Nature genetics","page":"703-707","volume":"41","issue":"6","source":"PubMed Central","abstract":"Type 1 diabetes (T1D) is a common autoimmune disorder that arises from the action of multiple genetic and environmental risk factors. We report the findings of a new genome-wide association study of T1D, combined in a meta-analysis with two previously published studies. The total sample set included 7,514 cases and 9,045 reference samples. Forty-one distinct genomic locations provided evidence for association to T1D in the meta-analysis (P < 10-6). After excluding previously reported associations, 27 regions were further tested in an independent set of 4,267 cases, 4,463 controls and 2,319 affected sib-pair (ASP) families. Of these, 18 regions were replicated (P < 0.01; overall P < 5 × 10-8) and four additional regions provided nominal evidence of replication (P < 0.05). The many new candidate genes suggested by these results include IL10, IL19, IL20, GLIS3, CD69 and IL27.","DOI":"10.1038/ng.381","ISSN":"1061-4036","note":"PMID: 19430480\nPMCID: PMC2889014","journalAbbreviation":"Nat Genet","author":[{"family":"Barrett","given":"Jeffrey C."},{"family":"Clayton","given":"David"},{"family":"Concannon","given":"Patrick"},{"family":"Akolkar","given":"Beena"},{"family":"Cooper","given":"Jason D."},{"family":"Erlich","given":"Henry A."},{"family":"Julier","given":"Cécile"},{"family":"Morahan","given":"Grant"},{"family":"Nerup","given":"Jørn"},{"family":"Nierras","given":"Concepcion"},{"family":"Plagnol","given":"Vincent"},{"family":"Pociot","given":"Flemming"},{"family":"Schuilenburg","given":"Helen"},{"family":"Smyth","given":"Deborah

J."},{"family":"Stevens","given":"Helen"},{"family":"Todd","given":"John A."},{"family":"Walker","given":"Neil M."},{"family":"Rich","given":"Stephen S."}],"issued":{"date-parts":[["2009",6]]}}},{"id":"GKyl1X7D/dFnEByem","uris":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/SBGZ8WHG"],"itemData":{"id":225,"type":"article-journal","title":"Fine mapping of type 1 diabetes susceptibility loci and evidence for colocalization of causal variants with lymphoid gene enhancers","container-title":"Nature Genetics","page":"381-386","volume":"47","issue":"4","source":"www.nature.com","abstract":"Genetic studies of type 1 diabetes (T1D) have identified 50 susceptibility regions, finding major pathways contributing to risk, with some loci shared across immune disorders. To make genetic comparisons across autoimmune disorders as informative as possible, a dense genotyping array, the Immunochip, was developed, from which we identified four new T1D-associated regions ($P < 5 \times 10^{-8}$). A comparative analysis with 15 immune diseases showed that T1D is more similar genetically to other autoantibody-positive diseases, significantly most similar to juvenile idiopathic arthritis and significantly least similar to ulcerative colitis, and provided support for three additional new T1D risk loci. Using a Bayesian approach, we defined credible sets for the T1D-associated SNPs. The associated SNPs localized to enhancer sequences active in thymus, T and B cells, and CD34+ stem cells. Enhancer-promoter interactions can now be analyzed in these cell types to identify which particular genes and regulatory sequences are causal.","DOI":"10.1038/ng.3245","ISSN":"1061-4036","journalAbbreviation":"Nat Genet","language":"en","author":[{"family":"Onengut-Gumuscu","given":"Suna"},{"family":"Chen","given":"Wei-

Min"},{"family":"Burren","given":"Oliver"},{"family":"Cooper","given":"Nick J."},{"family":"Quinlan","given":"Aaron R."},{"family":"Mychaleckyj","given":"Josyf C."},{"family":"Farber","given":"Emily"},{"family":"Bonnie","given":"Jessica K."},{"family":"Szpak","given":"Michal"},{"family":"Schofield","given":"Ellen"},{"family":"Achuthan","given":"Premanand"},{"family":"Guo","given":"Hui"},{"family":"Fortune","given":"Mary D."},{"family":"Stevens","given":"Helen"},{"family":"Walker","given":"Neil M."},{"family":"Ward","given":"Lucas D."},{"family":"Kundaje","given":"Anshul"},{"family":"Kellis","given":"Manolis"},{"family":"Daly","given":"Mark J."},{"family":"Barrett","given":"Jeffrey C."},{"family":"Cooper","given":"Jason D."},{"family":"Deloukas","given":"Panos"},{"literal":"Type 1 Diabetes Genetics Consortium"},{"family":"Todd","given":"John A."},{"family":"Wallace","given":"Chris"},{"family":"Concannon","given":"Patrick"},{"family":"Rich","given":"Stephen S."}],"issued":{"date-parts":[["2015",4]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** and the type 2 diabetes association at rs11888640 (*THADA*). Taking a candidate gene approach, we extracted 66 established type 1 diabetes-associated loci from the LADA vs. population controls meta-analysis and found that 17 of these yielded association with LADA after multiple-test correction ($P < 7.6 \times 10^{-4}$, **Supplementary Table 9**). Taking a similar approach with 65 established type 2 diabetes loci, none surpassed the significance threshold; however, at the nominal significance level ($P < 0.05$), eleven type 1 diabetes and eleven type 2 diabetes variants were associated with LADA, all having the same direction of effect as seen for type 1 diabetes and type 2 diabetes, respectively,

except for the type 2 diabetes locus *CILP2* (rs10401969-T, OR = 0.820 (0.726-0.927), *P* = 0.0016; **Supplementary Table 10**). On the whole, both type 1 diabetes and type 2 diabetes loci had lower *P*-values in LADA than expected by chance (**Supplementary Figure 3**). Approximately 90.6% of T1D loci **(Supplementary Table 9)** had directional consistency in LADA **(*P*-value = 4.51 x $10^{-12}$)** and 72.3% of T2D loci **(Supplementary Table 10)** had directional consistency in LADA (*P*-value = 2.10 x $10^{-4}$). Combining T1D and T2D loci, 81.4% had directional consistency in LADA (*P*-value = 1.40 x $10^{-13}$). Therefore, we observed a significant enrichment of established T1D and T2D loci having the same directional effect in LADA.

*GWAS of LADA versus type 2 diabetes and type 1 diabetes*

Next, we compared LADA with type 2 diabetes at the genome-wide level. Similar to the results of LADA vs. population controls, LADA (n = 2,454) vs. type 2 diabetes (n = 10,396) yielded genome-wide significance for the same four type 1 diabetes risk loci (**Table 1**). We then performed a GWAS of LADA (n = 2,454) vs. type 1 diabetes (n = 968) to assess whether any differences could be detected. Only the HLA region was significantly different between type 1 diabetes and LADA, representing a relative depletion of the lead signal in LADA when compared to type 1 diabetes (rs9273368-A, OR (95% CI) = 0.335 (0.256-0.385), *P* = 8.46 x $10^{-40}$; **Table 1**). Leveraging the entire genome-wide summary statistics, genetic correlation analyses showed that LADA was positively correlated with both type 1 diabetes (with the inclusion of the HLA; $r_g$ (SE) = 0.385 (0.136), *P* = 0.0047) and type 2 diabetes (without the HLA; $r_g$ (SE) = 0.281 (0.106), *P* = 0.008).

*Stratified GWAS of LADA by GAD autoantibody tertile*

Stratifying LADA cases into tertiles resulted in the detection of the same four loci, although the magnitude of the associations differed between the top tertile vs. population controls, the top 2 tertiles vs. population controls, and the bottom tertile vs. population controls (**Supplementary Table 11**). As expected, the ORs for the leading loci were strongest in the LADA cases with the highest GAD autoantibody titers. For example, rs9273368 (*HLA-DQB1*) showed the strongest association with LADA in the analysis including the top tertile of GAD autoantibody titer (OR (95% CI) = 3.30 (2.81-3.88), $P = 1.89 \times 10^{-47}$) and the lowest association in the bottom GAD autoantibody tertile (OR (95% CI) = 2.42 (2.06-2.85), $P = 2.13 \times 10^{-26}$). Furthermore, only the *HLA-DQB1* locus was significantly associated in the LADA cases with the lowest GAD titers, while the *PTPN22*, *INS*, and *SH2B3* loci were only evident among cases with higher GAD titers. Furthermore, rs7903146 at *TCF7L2* had a slightly higher OR in the group with the lowest GAD titer than that with the lowest GAD titer (1.09 vs. 1.05, respectively).

*HLA haplotype analysis*

To further investigate differences in the HLA region between LADA and type 1 diabetes, we imputed this region using SNP2HLA**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2vevbmg79","properties":{"formattedCitation":"(27)","plainCitation":"(27)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/tvwVAORq","uris":["http://zotero.org/users/local/99dTDuE7/items/ZP8C6RDE"],"uri":["http://zotero.org/users/local/99dTDuE7/items/ZP8C6RDE"],"itemData":{"id":243,"type":"article-journal","title":"Imputing Amino Acid Polymorphisms in Human Leukocyte Antigens","container-title":"PLoS

ONE","volume":"8","issue":"6","source":"proxy.library.upenn.edu:2063","abstract":"DNA sequence variation within human leukocyte antigen (HLA) genes mediate susceptibility to a wide range of human diseases. The complex genetic structure of the major histocompatibility complex (MHC) makes it difficult, however, to collect genotyping ...","URL":"https://proxy.library.upenn.edu:2063/pmc/articles/PMC3675122/","DOI":"10.1371/journal.pone.0064683","note":"PMID: 23762245","author":[{"family":"Jia","given":"Xiaoming"},{"family":"Han","given":"Buhm"},{"family":"Onengut-Gumuscu","given":"Suna"},{"family":"Chen","given":"Wei-Min"},{"family":"Concannon","given":"Patrick J."},{"family":"Rich","given":"Stephen S."},{"family":"Raychaudhuri","given":"Soumya"},{"family":"Bakker","given":"Paul I. W.","dropping-particle":"de"}],"issued":{"date-parts":[["2013"]]},"accessed":{"date-parts":[["2017",2,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** in 2,159 LADA cases from the ActionLADA + CHOP + Swedish cohorts and 1,990 patients with type 1 diabetes (WTCCC**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a998s58cqr","properties":{"formattedCitation":"(32)","plainCitation":"(32)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/prvak5yW","uris":["http://zotero.org/users/local/99dTDuE7/items/7MPGEX5I"],"uri":["http://zotero.org/users/local/99dTDuE7/items/7MPGEX5I"],"itemData":{"id":246,"type":"article-journal","title":"Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls","container-title":"Nature","page":"661","volume":"447","issue":"7145","source":"proxy.library.upenn.edu:2063","abstract":"There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human

diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) ...","DOI":"10.1038/nature05911","note":"PMID: 17554300","author":[{"family":"Consortium","given":"The Wellcome Trust Case Control"}],"issued":{"date-parts":[["2007",6,7]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**) and compared the frequencies of the leading type 1 diabetes-associated HLA haplotypes (**Supplementary Table 12**). After removing haplotypes with less than 1% frequency, fifteen known type 1 diabetes-associated HLA haplotypes were tested for association in LADA compared to type 1 diabetes. Eleven type 1 diabetes haplotypes were significantly different in frequency between LADA and type 1 diabetes cases after correction for multiple testing ($P < 0.003$), with all but four being protective against type 1 diabetes.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1o44kjhe2d","properties":{"formattedCitation":"(33)","plainCitation":"(33)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/pbo89MDT","uris":["http://zotero.org/users/local/99dTDuE7/items/ZGJDRTHI"],"uri":["http://zotero.org/users/local/99dTDuE7/items/ZGJDRTHI"],"itemData":{"id":249,"type":"article-journal","title":"Genetics of Type 1 Diabetes","container-title":"Cold Spring Harbor Perspectives in Medicine","volume":"2","issue":"1","source":"proxy.library.upenn.edu:2063","abstract":"Genetic susceptibility to type 1 diabetes (T1D) has been a subject of intensive study for nearly four decades. This article will present the history of these studies, beginning with observations of the Human Leukocyte Antigen (HLA) association in the ...","URL":"https://proxy.library.upenn.edu:2063/pmc/articles/PMC3253030/","DOI":"10.1101/cshperspect.a007732","note":"PMID: 22315720","author":[{"family":"Noble","given":"Janelle A."},{"family":"Erlich","given":"Henry A."}],"issued":{"date-

parts":[["2012",1]]},"accessed":{"date-parts":[["2017",2,21]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** The four type 1 diabetes susceptibility haplotypes, HLA-DRB1*0301-DQA1*0501-DQB1*0201, HLA-DRB1*0401-DQA1*0301-DQB1*0302, HLA-DRB1*0404-DQA1*0301-DQB1*0302, and HLA-DRB1*0405-DQA1*0301-DQB1*0302**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"amk762ljj9","properties":{"formattedCitation":"(33)","plainCitation":"(33)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/pbo89MDT","uris":["http://zotero.org/users/local/99dTDuE7/items/ZGJDRTHI"],"uri":["http://zotero.org/users/local/99dTDuE7/items/ZGJDRTHI"],"itemData":{"id":249,"type":"article-journal","title":"Genetics of Type 1 Diabetes","container-title":"Cold Spring Harbor Perspectives in Medicine","volume":"2","issue":"1","source":"proxy.library.upenn.edu:2063","abstract":"Genetic susceptibility to type 1 diabetes (T1D) has been a subject of intensive study for nearly four decades. This article will present the history of these studies, beginning with observations of the Human Leukocyte Antigen (HLA) association in the ...","URL":"https://proxy.library.upenn.edu:2063/pmc/articles/PMC3253030/","DOI":"10.1101/cshperspect.a007732","note":"PMID: 22315720","author":[{"family":"Noble","given":"Janelle A."},{"family":"Erlich","given":"Henry A."}],"issued":{"date-parts":[["2012",1]]},"accessed":{"date-parts":[["2017",2,21]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, had significantly lower frequencies in LADA than in type 1 diabetes.

## DISCUSSION

Taken collectively, GWAS and HLA haplotype analyses based on established associations, along with gene set enrichment analyses, support the hypothesis that the strongest genetic risk loci for LADA are shared with type 1 diabetes, but that established type 2 diabetes alleles also play a weaker role, as evidenced by the enrichment of established type 2 diabetes loci in LADA and the positive genetic correlation between LADA and type 2 diabetes. The strong type 1 diabetes-like signature seen here in adult autoimmune diabetes could be explained by the differing genetic architectures between the two main types of diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"3oEa01Pc","properties":{"formattedCitation":"(34)","plainCitation":"(34)","noteIndex":0},"citationItems":[{"id":37,"uris":["http://zotero.org/users/4642149/items/S57IWTAK"],"uri":["http://zotero.org/users/4642149/items/S57IWTAK"],"itemData":{"id":37,"type":"article-journal","title":"Genetic architecture: the shape of the genetic contribution to human traits and disease","container-title":"Nature Reviews Genetics","page":"110-124","volume":"19","issue":"2","source":"Crossref","DOI":"10.1038/nrg.2017.101","ISSN":"1471-0056, 1471-0064","shortTitle":"Genetic architecture","author":[{"family":"Timpson","given":"Nicholas J."},{"family":"Greenwood","given":"Celia M. T."},{"family":"Soranzo","given":"Nicole"},{"family":"Lawson","given":"Daniel J."},{"family":"Richards","given":"J. Brent"}],"issued":{"date-parts":[["2017",12,11]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, with type 1 diabetes having multiple low-frequency risk variants with high odds ratios while type 2 diabetes has many common risk

variants with smaller effect sizes. Given these architectural differences, any trait with a type 1 diabetes-like genetic component will detect type 1 signals first, and would only subsequently detect the type 2 signals with increased statistical power (**Supplementary Table 3**).

Furthermore, this has important implications for genetic studies of type 2 diabetes, in which misdiagnosed autoimmune diabetes cases are not routinely screened out. With increasing sample sizes and the ability to detect additional loci, type 2 diabetes GWAS that are 'contaminated' with adult autoimmune cases will inevitably begin to detect type 1 diabetes-associated genetic loci, potentially mis-assigning these loci to type 2 diabetes etiology.

In comparing LADA to the general population, we identified a novel independent genome-wide significant signal at the *PFKFB3* locus that persisted after conditioning on the two nearby type 1 diabetes-associated signals on chromosome 10p15. Cumulative evidence for the 10p15 locus suggests it is a complex region associated with autoimmune diabetes, given that it already harbors two established risk alleles for type 1 diabetes**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"aq703idb8t","properties":{"formattedCitation":"(21,22)","plainCitation":"(21,22)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/Yzw3CSkA","uris":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/WPWXCUJE"],"itemData":{"id":214,"type":"article-journal","title":"Genome-wide association study and meta-analysis finds over 40 loci affect risk of type 1 diabetes","container-title":"Nature genetics","page":"703-707","volume":"41","issue":"6","source":"PubMed Central","abstract":"Type 1 diabetes (T1D) is a common autoimmune disorder that arises from the action of multiple genetic and environmental risk factors. We report the findings of a new genome-wide association study of T1D, combined in a meta-analysis with two previously

published studies. The total sample set included 7,514 cases and 9,045 reference samples. Forty-one distinct genomic locations provided evidence for association to T1D in the meta-analysis (P < 10-6). After excluding previously reported associations, 27 regions were further tested in an independent set of 4,267 cases, 4,463 controls and 2,319 affected sib-pair (ASP) families. Of these, 18 regions were replicated (P < 0.01; overall P < 5 × 10-8) and four additional regions provided nominal evidence of replication (P < 0.05). The many new candidate genes suggested by these results include IL10, IL19, IL20, GLIS3, CD69 and IL27.","DOI":"10.1038/ng.381","ISSN":"1061-4036","note":"PMID: 19430480\nPMCID: PMC2889014","journalAbbreviation":"Nat Genet","author":[{"family":"Barrett","given":"Jeffrey C."},{"family":"Clayton","given":"David"},{"family":"Concannon","given":"Patrick"},{"family":"Akolkar","given":"Beena"},{"family":"Cooper","given":"Jason D."},{"family":"Erlich","given":"Henry A."},{"family":"Julier","given":"Cécile"},{"family":"Morahan","given":"Grant"},{"family":"Nerup","given":"Jørn"},{"family":"Nierras","given":"Concepcion"},{"family":"Plagnol","given":"Vincent"},{"family":"Pociot","given":"Flemming"},{"family":"Schuilenburg","given":"Helen"},{"family":"Smyth","given":"Deborah J."},{"family":"Stevens","given":"Helen"},{"family":"Todd","given":"John A."},{"family":"Walker","given":"Neil M."},{"family":"Rich","given":"Stephen S."}],"issued":{"date-parts":[["2009",6]]}},{"id":"GKyl1X7D/ToiCvNRA","uris":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"uri":["http://zotero.org/users/local/0MQVkqmF/items/B8WC57K3"],"itemData":{"id":"IzLNWkNn/PD5k3TM8","type":"article-journal","title":"A Genome-Wide

Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci","container-title":"PLOS Genetics","page":"e1002293","volume":"7","issue":"9","source":"PLoS Journals","abstract":"Author Summary Despite the fact that there is clearly a large genetic component to type 1 diabetes (T1D), uncovering the genes contributing to this disease has proven challenging. However, in the past three years there has been relatively major progress in this regard, with advances in genetic screening technologies allowing investigators to scan the genome for variants conferring risk for disease without prior hypotheses. Such genome-wide association studies have revealed multiple regions of the genome to be robustly and consistently associated with T1D. More recent findings have been a consequence of combining of multiple datasets from independent investigators in meta-analyses, which have more power to pick up additional variants contributing to the trait. In the current study, we describe the largest meta-analysis of T1D genome-wide genotyped datasets to date, which combines six large studies. As a consequence, we have uncovered three new signals residing at the chromosomal locations 13q22, 2p23, and 6q27, which went on to be replicated in independent sample sets. These latest associated regions add to the growing repertoire of gene networks predisposing to T1D.","DOI":"10.1371/journal.pgen.1002293","ISSN":"1553-7404","journalAbbreviation":"PLOS Genetics","author":[{"family":"Bradfield","given":"Jonathan P."},{"family":"Qu","given":"Hui-Qi"},{"family":"Wang","given":"Kai"},{"family":"Zhang","given":"Haitao"},{"family":"Sleiman","given":"Patrick M."},{"family":"Kim","given":"Cecilia E."},{"family":"Mentch","given":"Frank D."},{"family":"Qiu","given":"Haijun"},{"family":"Glessner","given":"Joseph T."},{"family":"Thomas","given":"Kelly A."},{"family":"Frackelton","given":"Edward

C."},{"family":"Chiavacci","given":"Rosetta M."},{"family":"Imielinski","given":"Marcin"},{"family":"Monos","given":"Dimitri S."},{"family":"Pandey","given":"Rahul"},{"family":"Bakay","given":"Marina"},{"family":"Grant","given":"Struan F. A."},{"family":"Polychronakos","given":"Constantin"},{"family":"Hakonarson","given":"Hakon"}],"issued":{"date-parts":[["2011",9,29]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** as well as our signal for LADA. Previous studies strongly support *PFKFB3* as a plausible biological candidate in diabetes, given its gene product's role as a regulator of glycolysis and insulin signaling**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"qLO3XyDs","properties":{"formattedCitation":"(35)","plainCitation":"(35)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/hzEC999x","uris":["http://zotero.org/users/local/nQ7dt7bm/items/7NMCFUZR"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/7NMCFUZR"],"itemData":{"id":303,"type":"article-journal","title":"Pfkfb3 is transcriptionally upregulated in diabetic mouse liver through proliferative signals","container-title":"The FEBS Journal","page":"4555-4568","volume":"276","issue":"16","source":"proxy.library.upenn.edu:2278","abstract":"The ubiquitous isoform of 6- phosphofructo- 2- kinase/fructose- 2,6- bisphosphatase (uPFK- 2), a product of the Pfkfb3 gene, plays a crucial role in the control of glycolytic flux. In this study, we demonstrate...","DOI":"10.1111/j.1742-4658.2009.07161.x","ISSN":"1742-4658","language":"en","author":[{"family":"Duran","given":"Joan"},{"family":"Obach","given":"Mercè"},{"family":"Navarro- Sabate","given":"Aurea"},{"family":"Manzano","given":"Anna"},{"family":"Gómez","given":"Marta"},{"family":"Rosa","given":"Jose

L."},{"family":"Ventura","given":"Francesc"},{"family":"Perales","given":"Jose C."},{"family":"Bartrons","given":"Ramon"}],"issued":{"date-parts":[["2009",8,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**. In mice, a pair of complementary studies showed that disrupted *PFKFB3* in adipose tissue exacerbated insulin resistance and adipose tissue inflammation,**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2jf3senhn1","properties":{"formattedCitation":"(36)","plainCitation":"(36)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/j6AmemmK","uris":["http://zotero.org/users/local/nQ7dt7bm/items/GREW7BDK"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/GREW7BDK"],"itemData":{"id":306,"type":"article-journal","title":"Disruption of Inducible 6-Phosphofructo-2-kinase Ameliorates Diet-induced Adiposity but Exacerbates Systemic Insulin Resistance and Adipose Tissue Inflammatory Response","container-title":"Journal of Biological Chemistry","page":"3713-3721","volume":"285","issue":"6","source":"proxy.library.upenn.edu:2285","abstract":"Adiposity is commonly associated with adipose tissue dysfunction and many overnutrition-related metabolic diseases including type 2 diabetes. Much attention has been paid to reducing adiposity as a way to improve adipose tissue function and systemic insulin sensitivity. PFKFB3/iPFK2 is a master regulator of adipocyte nutrient metabolism. Using PFKFB3+/− mice, the present study investigated the role of PFKFB3/iPFK2 in regulating diet-induced adiposity and systemic insulin resistance. On a high-fat diet (HFD), PFKFB3+/− mice gained much less body weight than did wild-type littermates. This was attributed to a smaller increase in adiposity in PFKFB3+/− mice than in wild-type controls. However, HFD-induced systemic insulin resistance was more severe in PFKFB3+/− mice than in wild-type littermates. Compared with wild-type littermates,

PFKFB3+/− mice exhibited increased severity of HFD-induced adipose tissue dysfunction, as evidenced by increased adipose tissue lipolysis, inappropriate adipokine expression, and decreased insulin signaling, as well as increased levels of proinflammatory cytokines in both isolated adipose tissue macrophages and adipocytes. In an in vitro system, knockdown of PFKFB3/iPFK2 in 3T3-L1 adipocytes caused a decrease in the rate of glucose incorporation into lipid but an increase in the production of reactive oxygen species. Furthermore, knockdown of PFKFB3/iPFK2 in 3T3-L1 adipocytes inappropriately altered the expression of adipokines, decreased insulin signaling, increased the phosphorylation states of JNK and NFκB p65, and enhanced the production of proinflammatory cytokines. Together, these data suggest that PFKFB3/iPFK2, although contributing to adiposity, protects against diet-induced insulin resistance and adipose tissue inflammatory response.","DOI":"10.1074/jbc.M109.058446","ISSN":"0021-9258, 1083-351X","note":"PMID: 19948719","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Huo","given":"Yuqing"},{"family":"Guo","given":"Xin"},{"family":"Li","given":"Honggui"},{"family":"Wang","given":"Huan"},{"family":"Zhang","given":"Weiyu"},{"family":"Wang","given":"Ying"},{"family":"Zhou","given":"Huaijun"},{"family":"Gao","given":"Zhanguo"},{"family":"Telang","given":"Sucheta"},{"family":"Chesney","given":"Jason"},{"family":"Chen","given":"Y. Eugene"},{"family":"Ye","given":"Jianping"},{"family":"Chapkin","given":"Robert S."},{"family":"Wu","given":"Chaodong"}],"issued":{"date-parts":[["2010",2,5]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}**, while overexpression of the gene was protective.**{** ADDIN ZOTERO_ITEM CSL_CITATION

{"citationID":"a1upf0magh2","properties":{"formattedCitation":"(37)","plainCitation":"(37)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/4HKaLaWM","uris":["http://zotero.org/users/local/nQ7dt7bm/items/PAQI73DF"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/PAQI73DF"],"itemData":{"id":309,"type":"article-journal","title":"Targeted Overexpression of Inducible 6-Phosphofructo-2-kinase in Adipose Tissue Increases Fat Deposition but Protects against Diet-induced Insulin Resistance and Inflammatory Responses","container-title":"Journal of Biological Chemistry","page":"21492-21500","volume":"287","issue":"25","source":"proxy.library.upenn.edu:2285","abstract":"Increasing evidence demonstrates the dissociation of fat deposition, the inflammatory response, and insulin resistance in the development of obesity-related metabolic diseases. As a regulatory enzyme of glycolysis, inducible 6-phosphofructo-2-kinase (iPFK2, encoded by PFKFB3) protects against diet-induced adipose tissue inflammatory response and systemic insulin resistance independently of adiposity. Using aP2-PFKFB3 transgenic (Tg) mice, we explored the ability of targeted adipocyte PFKFB3/iPFK2 overexpression to modulate diet-induced inflammatory responses and insulin resistance arising from fat deposition in both adipose and liver tissues. Compared with wild-type littermates (controls) on a high fat diet (HFD), Tg mice exhibited increased adiposity, decreased adipose inflammatory response, and improved insulin sensitivity. In a parallel pattern, HFD-fed Tg mice showed increased hepatic steatosis, decreased liver inflammatory response, and improved liver insulin sensitivity compared with controls. In both adipose and liver tissues, increased fat deposition was associated with lipid profile alterations characterized by an increase in palmitoleate. Additionally, plasma lipid profiles also displayed an increase in palmitoleate in HFD-Tg mice compared with controls. In cultured 3T3-L1 adipocytes, overexpression of PFKFB3/iPFK2 recapitulated metabolic and inflammatory

changes observed in adipose tissue of Tg mice. Upon treatment with conditioned medium from iPFK2-overexpressing adipocytes, mouse primary hepatocytes displayed metabolic and inflammatory responses that were similar to those observed in livers of Tg mice. Together, these data demonstrate a unique role for PFKFB3/iPFK2 in adipocytes with regard to diet-induced inflammatory responses in both adipose and liver tissues.","DOI":"10.1074/jbc.M112.370379","ISSN":"0021-9258, 1083-351X","note":"PMID: 22556414","journalAbbreviation":"J. Biol. Chem.","language":"en","author":[{"family":"Huo","given":"Yuqing"},{"family":"Guo","given":"Xin"},{"family":"Li","given":"Honggui"},{"family":"Xu","given":"Hang"},{"family":"Halim","given":"Vera"},{"family":"Zhang","given":"Weiyu"},{"family":"Wang","given":"Huan"},{"family":"Fan","given":"Yang-Yi"},{"family":"Ong","given":"Kuok Teong"},{"family":"Woo","given":"Shih-Lung"},{"family":"Chapkin","given":"Robert S."},{"family":"Mashek","given":"Douglas G."},{"family":"Chen","given":"Yanming"},{"family":"Dong","given":"Hui"},{"family":"Lu","given":"Fuer"},{"family":"Wei","given":"Lai"},{"family":"Wu","given":"Chaodong"}],"issued":{"date-parts":[["2012",6,15]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** Furthermore, PFKFB3 plays a role in autoimmune diseases; in T cells from rheumatoid arthritis patients, PFKFB3 is lost leading to decreased T cell glucose consumption and impaired autophagy, which in turn lead to an inability to mount a normal immune response and an increase in T cell apoptosis.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Uaozt5Fy","properties":{"formattedCitation":"(38)","plainCitation":"(38)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/9YHRxmaq","uris":["http://zotero.org/users/local/n

Q7dt7bm/items/EFUUVV77"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/EFUUVV77
"],"itemData":{"id":314,"type":"article-journal","title":"Phosphofructokinase deficiency impairs
ATP generation, autophagy, and redox balance in rheumatoid arthritis T cells","container-
title":"The Journal of Experimental Medicine","page":"2119-
2134","volume":"210","issue":"10","source":"PubMed Central","abstract":"T cells from RA
patients are hypoglycolytic due to insufficient induction of the glycolytic activator PFKFB3,
resulting in impaired autophagy and reduced ROS production., In the HLA class II–associated
autoimmune syndrome rheumatoid arthritis (RA), CD4 T cells are critical drivers of pathogenic
immunity. We have explored the metabolic activity of RA T cells and its impact on cellular
function and fate. Naive CD4 T cells from RA patients failed to metabolize equal amounts of
glucose as age-matched control cells, generated less intracellular ATP, and were apoptosis-
susceptible. The defect was attributed to insufficient induction of 6-phosphofructo-2-
kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), a regulatory and rate-limiting glycolytic
enzyme known to cause the Warburg effect. Forced overexpression of PFKFB3 in RA T cells
restored glycolytic flux and protected cells from excessive apoptosis. Hypoglycolytic RA T cells
diverted glucose toward the pentose phosphate pathway, generated more NADPH, and consumed
intracellular reactive oxygen species (ROS). PFKFB3 deficiency also constrained the ability of
RA T cells to resort to autophagy as an alternative means to provide energy and biosynthetic
precursor molecules. PFKFB3 silencing and overexpression identified a novel extraglycolytic
role of the enzyme in autophagy regulation. In essence, T cells in RA patients, even those in a
naive state, are metabolically reprogrammed with insufficient up-regulation of the glycolytic
activator PFKFB3, rendering them energy-deprived, ROS- and autophagy-deficient, apoptosis-
sensitive, and prone to undergo senescence.","DOI":"10.1084/jem.20130252","ISSN":"0022-

1007","note":"PMID: 24043759\nPMCID: PMC3782046","journalAbbreviation":"J Exp Med","author":[{"family":"Yang","given":"Zhen"},{"family":"Fujii","given":"Hiroshi"},{"family":"Mohan","given":"Shalini V."},{"family":"Goronzy","given":"Jorg J."},{"family":"Weyand","given":"Cornelia M."}],"issued":{"date-parts":[["2013",9,23]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** Further studies are thus warranted to investigate the role of PFKFB3 in LADA, and to determine whether this signal is truly a distinguishing feature between adult and childhood-onset autoimmune diabetes.

Although the lead genome-wide significant loci are shared with those for type 1 diabetes risk, they clearly have a diminished impact in LADA. To further investigate the differences between LADA and type 1 diabetes at the HLA region, we performed a comparative haplotype analysis that showed a decreased frequency of type 1 diabetes-associated risk haplotypes in LADA. This could be partly explained by the established age gradient in HLA frequencies seen in type 1 diabetes patients;**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"akik6dnc0v","properties":{"formattedCitation":"(39)","plainCitation":"(39)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/DpAlbGn0","uris":["http://zotero.org/users/local/nQ7dt7bm/items/VM36GGED"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/VM36GGED"],"itemData":{"id":141,"type":"article-journal","title":"Negative association between type 1 diabetes and HLA DQB1*0602- DQA1*0102 is attenuated with age at onset","container-title":"International Journal of Immunogenetics","page":"117-127","volume":"26","issue":"2- 3","source":"proxy.library.upenn.edu:2278","abstract":"HLA- associated relative risks of type 1 (insulin- dependent) diabetes mellitus were analysed in population- based Swedish patients and controls aged 0–34 years. The age dependence of

HLA- associated relative...","DOI":"10.1111/j.1600-0609.2006.00789.x-i1","ISSN":"1365-2370","language":"en","author":[{"family":"Graham","given":"Jinko"},{"family":"Kockum","given":"Ingrid"},{"family":"Sanjeevi","given":"Carani B."},{"family":"Landin- Olsson","given":"Mona"},{"family":"Nyström","given":"Lennarth"},{"family":"Sundkvist","given":"Göran"},{"family":"Arnqvist","given":"Hans"},{"family":"Blohmé","given":"Göran"},{"family":"Lithner","given":"Folke"},{"family":"Littorin","given":"Bengt"},{"family":"Scherstén","given":"Bengt"},{"family":"Wibell","given":"Lars"},{"family":"Östman","given":"Jan"},{"family":"Lernmark","given":"Åke"},{"family":"Breslow","given":"Norman"}],"issued":{"date-parts":[["1999",4,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** however, HLA risk genotype frequencies have also been shown to differ between LADA patients and type 1 diabetes patients with age at onset >35 yrs.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"63MAcI97","properties":{"formattedCitation":"(14,40)","plainCitation":"(14,40)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/sVyEDlM9","uris":["http://zotero.org/users/local/nQ7dt7bm/items/364WTIXJ"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/364WTIXJ"],"itemData":{"id":263,"type":"article-journal","title":"Latent Autoimmune Diabetes in Adults Differs Genetically From Classical Type 1 Diabetes Diagnosed After the Age of 35 Years","container-title":"Diabetes Care","page":"2062-2064","volume":"33","issue":"9","source":"proxy.library.upenn.edu:2372","abstract":"OBJECTIVE We studied differences between patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes, and classical type 1 diabetes diagnosed after age 35 years.\nRESEARCH DESIGN AND METHODS Polymorphisms in HLA-DQB1, INS, PTPN22, and CTLA4 were genotyped in patients with LADA (n = 213), type 1 diabetes diagnosed at >35 years of age

(T1D>35y; n = 257) or <20 years of age (T1D<20y; n = 158), and type 2 diabetes.\nRESULTS Although patients with LADA had an increased frequency of HLA-DQB1 and PTPN22 risk genotypes and alleles compared with type 2 diabetic subjects, the frequency was significantly lower compared with T1D>35y patients. Genotype frequencies, measures of insulin secretion, and metabolic traits within LADA differed according to GAD antibody (GADA) quartiles, but even the highest quartile differed from type 1 diabetes. Having two or more risk genotypes was associated with lower C-peptide concentrations in LADA.\nCONCLUSIONS LADA patients differed genetically and phenotypically from both T1D>35y and type 2 diabetic patients in a manner dependent on GADA levels.","DOI":"10.2337/dc09-2188","ISSN":"0149-5992, 1935-5548","note":"PMID: 20805278","language":"en","author":[{"family":"Andersen","given":"Mette K."},{"family":"Lundgren","given":"Virve"},{"family":"Turunen","given":"Joni A."},{"family":"Forsblom","given":"Carol"},{"family":"Isomaa","given":"Bo"},{"family":"Groop","given":"Per-Henrik"},{"family":"Groop","given":"Leif"},{"family":"Tuomi","given":"Tiinamaija"}],"issued":{"date-parts":[["2010",9,1]]}}},{"id":"GKyl1X7D/0DdssWT8","uris":["http://zotero.org/users/local/nQ7dt7bm/items/GHZWRAZA"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/GHZWRAZA"],"itemData":{"id":270,"type":"article-journal","title":"HLA Genetic Discrepancy Between Latent Autoimmune Diabetes in Adults and Type 1 Diabetes: LADA China Study No. 6","container-title":"The Journal of Clinical Endocrinology & Metabolism","page":"1693-1700","volume":"101","issue":"4","source":"proxy.library.upenn.edu:2325","abstract":"Context: The discrepancies in terms of human leukocyte antigen (HLA)-DRB1-DQA1-DQB1 conferred

risks between latent autoimmune diabetes in adults (LADA) and type 1 diabetes (T1D) patients remained almost completely unknown. The goal of the current study is to determine and compare HLA-conferred risks between LADA and T1D.Design:A case-control study was conducted in a representative Chinese data set containing 520 T1D patients, 562 LADA patients, and 1065 controls. The frequencies and odds ratios for HLA susceptible haplotypes and genotypes and for arginine at residue 52 in the DQ-α chain or aspartic acid at residue 57 in the DQ-β chain were analyzed.Results:DRB1*0405-DQA1*03-DQB1*0401 and DRB1*0901-DQA1*03-DQB1*0303 are the major LADA susceptible haplotypes, which also confer comparable risks for T1D (odds ratio 2.02 vs 2.20 and 1.61 vs 2.30, respectively). The strongly associated T1D haplotype DRB1*0301-DQA1*05-DQB1*0201 is also associated with LADA but confers only half of the T1D risk (odds ratio 2.65 vs 4.84). Interestingly, the most susceptible T1D haplotypes, DRB1*0901-DQA1*05-DQB1*0201, DRB1*0301-DQA1*03-DQB1*0201, and DRB1*0301-DQA1*03-DQB1*0303, are not associated with LADA. Genotypes for DR3/DR3, DR3/DR9, and DR9/DR9 are highly associated with T1D susceptibility, whereas only DR9/DR9 confers risk for LADA. DR3/DR3 is the high-risk genotype in Chinese T1D patients, which manifests similar risk as the DR3/DR4 genotype in Caucasians but with a lower frequency. DR9/DR9 is the high risk LADA genotype in Chinese. Alleles with DQ-α arginine at residue 52-positive, DQ-β aspartic acid at residue 57-negative, and their combination formed in cis or trans confer susceptibility to T1D but not to LADA.Conclusion:Our results suggest that LADA risk conferred by HLA-DRB1-DQA1-DQB1 loci in Chinese differs significantly from that of T1D risk. This information would be useful for classifying Asian LADA patients, which should provides novel insight into the understanding of its pathoetiology as well.","DOI":"10.1210/jc.2015-3771","ISSN":"0021-972X","shortTitle":"HLA Genetic Discrepancy Between Latent

Autoimmune Diabetes in Adults and Type 1 Diabetes","journalAbbreviation":"J Clin Endocrinol Metab","author":[{"family":"Luo","given":"Shuoming"},{"family":"Lin","given":"Jian"},{"family":"Xie","given":"Zhiguo"},{"family":"Xiang","given":"Yufei"},{"family":"Zheng","given":"Peilin"},{"family":"Huang","given":"Gan"},{"family":"Li","given":"Xia"},{"family":"Liao","given":"Yu"},{"family":"Hagopian","given":"William A."},{"family":"Wang","given":"Cong-Yi"},{"family":"Zhou","given":"Zhiguang"}],"issued":{"date-parts":[["2016",4,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** Future in-depth studies of the differences in HLA risk haplotypes between type 1 diabetes and LADA taking age and ethnicity into account are therefore also warranted.

In terms of type 2 diabetes-associated loci, our results differ from previous candidate studies. For instance, our previously reported *HNF1A***{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"alenjofbes","properties":{"formattedCitation":"(12)","plainCitation":"(12)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/sPC6qY0b","uris":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/KR4Z2HP2"],"itemData":{"id":111,"type":"article-journal","title":"Relative contribution of type 1 and type 2 diabetes loci to the genetic etiology of adult-onset, non-insulin-requiring autoimmune diabetes","container-title":"BMC Medicine","page":"88","volume":"15","issue":"1","source":"proxy.library.upenn.edu:2931","abstract":"In adulthood, autoimmune diabetes can present as non-insulin-requiring diabetes, termed as ‘latent autoimmune diabetes in adults’ (LADA). In this study, we investigated established type 1 diabetes (T1D) and type 2 diabetes (T2D) genetic loci in a large cohort of LADA cases to assess where LADA is situated relative to these two well-characterized, classic forms of

diabetes. We tested the association of T1D and T2D GWAS-implicated loci in 978 LADA cases and 1057 non-diabetic controls of European ancestry using a linear mixed model. We then compared the associations of T1D and T2D loci between LADA and T1D and T2D cases, respectively. We quantified the difference in genetic risk between each given disease at each locus, and also calculated genetic risk scores to quantify how genetic liability to T1D and T2D distinguished LADA cases from controls. Overall, our results showed that LADA is genetically more similar to T1D, with the exception of an association at the T2D HNF1A locus. Several T1D loci were associated with LADA, including the major histocompatibility complex region, as well as at PTPN22, SH2B3, and INS. Contrary to previous studies, the key T2D risk allele at TCF7L2 (rs7903146-T) had a significantly lower frequency in LADA cases, suggesting that this locus does not play a role in LADA etiology. When constrained on antibody status, the similarity between LADA and T1D became more apparent; however, the HNF1A and TCF7L2 observations persisted. LADA is genetically closer to T1D than T2D, although the genetic load of T1D risk alleles is less than childhood-onset T1D, particularly at the major histocompatibility complex region, potentially accounting for the later disease onset. Our results show that the genetic spectrum of T1D extends into adult-onset diabetes, where it can clinically masquerade as T2D. Furthermore, T2D genetic risk plays a small role in LADA, with a degree of evidence for the HNF1A locus, highlighting the potential for genetic risk scores to contribute towards defining diabetes subtypes.","DOI":"10.1186/s12916-017-0846-0","ISSN":"1741-7015","language":"En","author":[{"family":"Mishra","given":"Rajashree"},{"family":"Chesi","given":"Alessandra"},{"family":"Cousminer","given":"Diana L."},{"family":"Hawa","given":"Mohammad I."},{"family":"Bradfield","given":"Jonathan P."},{"family":"Hodge","given":"Kenyaita M."},{"family":"Guy","given":"Vanessa

C."},{"family":"Hakonarson","given":"Hakon"},{"family":"Mauricio","given":"Didac"},{"famil
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O."},{"family":"Leslie","given":"Richard David"},{"family":"Grant","given":"Struan F.
A."}],"issued":{"date-parts":[["2017",4,25]]}}}],"schema":"https://github.com/citation-style-
language/schema/raw/master/csl-citation.json"} **}** locus was not observed in this setting.
Furthermore, while previous studies showed an association for the leading type 2 diabetes risk
locus at *TCF7L2* with LADA,**{** ADDIN ZOTERO_ITEM CSL_CITATION
{"citationID":"D1cjbA37","properties":{"formattedCitation":"(11,16)","plainCitation":"(11,16)",
"noteIndex":0},"citationItems":[{"id":"GKyl1X7D/dJGU3dfq","uris":["http://zotero.org/users/lo
cal/99dTDuE7/items/JH5ASEQ5"],"uri":["http://zotero.org/users/local/99dTDuE7/items/JH5AS
EQ5"],"itemData":{"id":84,"type":"article-journal","title":"Type 2 diabetes susceptibility gene
variants predispose to adult-onset autoimmune diabetes","container-
title":"Diabetologia","page":"1859-
1868","volume":"57","issue":"9","source":"proxy.library.upenn.edu:2071","abstract":"Latent
autoimmune diabetes in adults (LADA) is phenotypically a hybrid of type 1 and type 2 diabetes.
Genetically LADA is poorly characterised but does share genetic predisposition with type 1
diabete","DOI":"10.1007/s00125-014-3287-8","ISSN":"0012-186X, 1432-
0428","journalAbbreviation":"Diabetologia","language":"en","author":[{"family":"Andersen","g
iven":"Mette
K."},{"family":"Sterner","given":"Maria"},{"family":"Forsén","given":"Tom"},{"family":"Kärä
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given":"Carol"},{"family":"Groop","given":"Per-Henrik"},{"family":"Lahti","given":"Kaj"},{"family":"Nilsson","given":"Peter M."},{"family":"Groop","given":"Leif"},{"family":"Tuomi","given":"Tiinamaija"}],"issued":{"date-parts":[["2014",9,1]]}},{"id":50,"uris":["http://zotero.org/users/4642149/items/65NED6J3"],"uri":["http://zotero.org/users/4642149/items/65NED6J3"],"itemData":{"id":50,"type":"article-journal","title":"Genetic Similarities Between Latent Autoimmune Diabetes in Adults, Type 1 Diabetes, and Type 2 Diabetes","container-title":"Diabetes","page":"1433-1437","volume":"57","issue":"5","source":"Crossref","DOI":"10.2337/db07-0299","ISSN":"0012-1797, 1939-327X","language":"en","author":[{"family":"Cervin","given":"C."},{"family":"Lyssenko","given":"V."},{"family":"Bakhtadze","given":"E."},{"family":"Lindholm","given":"E."},{"family":"Nilsson","given":"P."},{"family":"Tuomi","given":"T."},{"family":"Cilio","given":"C. M."},{"family":"Groop","given":"L."}],"issued":{"date-parts":[["2008",5,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** our data shows relatively limited support of this finding (**Supplementary Table 10**) (LADA vs. population controls, rs7903146-T: OR (95% CI) = 1.107 (1.024-1.20), *P* = 0.011), which may be due to the limited power of our study to detect type 2 diabetes signals (**Supplementary Table 2**). To understand the evidence supporting the previous association, we examined the allele frequencies of the lead variant in each contributing cohort. This revealed that the difference in risk allele frequency between cases and controls was cohort-specific, with only one case-control set (ActionLADA cases vs BMDCS controls) not supporting this association, principally due to the higher frequency of the risk allele

in the control set (**Supplementary Table 13**). One possibility is that inclusion or exclusion of type 2 diabetes patients from control cohorts would affect the frequency of the risk allele; however, sensitivity analysis with control sets that either excluded or included diabetic patients in Swedish and Danish samples showed the persistence of an association (**Supplementary Table 13**), although not at the genome-wide significance level. Interestingly, a recent study found that the type 2 diabetes risk allele at the key *TCF7L2* locus was associated with type 1 diabetes cases who were older than 12 years at onset and were positive for only a single autoimmune antibody.**{** ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a1sbqjvgido","properties":{"formattedCitation":"(41)","plainCitation":"(41)","noteIndex":0},"citationItems":[{"id":"GKyl1X7D/cpZKSWRq","uris":["http://zotero.org/users/local/nQ7dt7bm/items/N3V6BRK4"],"uri":["http://zotero.org/users/local/nQ7dt7bm/items/N3V6BRK4"],"itemData":{"id":334,"type":"article-journal","title":"TCF7L2 Genetic Variants Contribute to Phenotypic Heterogeneity of Type 1 Diabetes","container-title":"Diabetes Care","page":"dc170961","source":"care.diabetesjournals.org","abstract":"OBJECTIVE The phenotypic diversity of type 1 diabetes suggests heterogeneous etiopathogenesis. We investigated the relationship of type 2 diabetes–associated transcription factor 7 like 2 (TCF7L2) single nucleotide polymorphisms (SNP) with immunologic and metabolic characteristics at type 1 diabetes diagnosis.\nRESEARCH DESIGN AND METHODS We studied TrialNet participants with newly diagnosed autoimmune type 1 diabetes with available TCF7L2 rs4506565 and rs7901695 SNP data (n = 810; median age 13.6 years; range 3.3–58.6). We modeled the influence of carrying a TCF7L2 variant (i.e., having 1 or 2 minor alleles) on the number of islet autoantibodies and oral glucose tolerance test (OGTT)–stimulated C-peptide and glucose measures at diabetes diagnosis. All analyses were adjusted for known

confounders.\nRESULTS The rs4506565 variant was a significant independent factor of expressing a single autoantibody, instead of multiple autoantibodies, at diagnosis (odds ratio [OR] 1.66 [95% CI 1.07, 2.57], P = 0.024). Interaction analysis demonstrated that this association was only significant in participants ≥12 years old (n = 504; OR 2.12 [1.29, 3.47], P = 0.003) but not younger ones (n = 306, P = 0.73). The rs4506565 variant was independently associated with higher C-peptide area under the curve (AUC) (P = 0.008) and lower mean glucose AUC (P = 0.0127). The results were similar for the rs7901695 SNP.\nCONCLUSIONS In this cohort of individuals with new-onset type 1 diabetes, type 2 diabetes–linked TCF7L2 variants were associated with single autoantibody (among those ≥12 years old), higher C-peptide AUC, and lower glucose AUC levels during an OGTT. Thus, carriers of the TCF7L2 variant had a milder immunological and metabolic phenotype at type 1 diabetes diagnosis, which could be partly driven by type 2 diabetes–like pathogenic mechanisms.","DOI":"10.2337/dc17-0961","ISSN":"0149-5992, 1935-5548","note":"PMID: 29025879","language":"en","author":[{"family":"Redondo","given":"Maria J."},{"family":"Geyer","given":"Susan"},{"family":"Steck","given":"Andrea K."},{"family":"Sosenko","given":"Jay"},{"family":"Anderson","given":"Mark"},{"family":"Antinozzi","given":"Peter"},{"family":"Michels","given":"Aaron"},{"family":"Wentworth","given":"John"},{"family":"Xu","given":"Ping"},{"family":"Pugliese","given":"Alberto"}],"issued":{"date-parts":[["2017",9,12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} **}** That study provides further evidence for a role for type 2 diabetes genetic risk in later-onset autoimmune diabetes and resonates with the genome-wide observations we report here in adults.

The precise diagnostic criteria used to distinguish LADA from adult-onset type 1 and type 2 diabetes remain under debate. These differences in opinion have hindered the collection of well-phenotyped, clearly defined LADA cohorts for genetic studies, and are reflected in the cohorts we included in this study, e.g. in terms of heterogeneous age inclusion thresholds and differences in autoantibody testing. In this study, we strove to be inclusive to maximize our sample size and statistical power, but we acknowledge that stringent, deeply phenotyped cohorts are needed to truly address where adult autoimmune diabetes is placed on the diabetes spectrum. Another debate surrounds the idea that LADA cohorts may simply be collections of poorly phenotyped cases with adult-onset type 1 and type 2 diabetes, and refute the idea that LADA is a unique disease entity. However, GAD assays have a specificity of 95–98%, so by implication, some cases with type 2 diabetes with low-level GAD can be incorrectly classified as LADA cases; these would, however, represent only a very small fraction of cases since the predictive specificity of GAD would have been increased by our cohort enrichment as with any biomarker assay. Conversely, the small percentage of cases with LADA who do not have GAD positivity but have other islet autoantibodies and are misclassified as having type 2 diabetes, could affect the estimate of genetic correlation between LADA and type 2 diabetes to a small degree. Future studies should focus on defining the heterogeneity and misdiagnosis rates among patients with LADA.

Despite these limitations, using the definition of LADA presented here, we identified factors which potentially distinguish this form of adult autoimmune diabetes from childhood-onset type 1 diabetes as well as type 2 diabetes: (1) a novel signal at the *PFKFB3* locus, and (2) attenuation of type 1-associated HLA risk haplotypes. Overall, we find the presence of both a type 1 diabetes-like autoimmune genetic component and a type 2 diabetes-like

metabolic/anthropometric genetic component consistent with the phenotypic features of both main diabetes types, suggesting that LADA as defined here is a hybrid of these two major diseases. Our findings promote the hypothesis that the polygenic component that contributes susceptibility to type 2 diabetes can act as a modifier to type 1 diabetes risk, possibly as a 'second hit' in individuals who have moderate underlying autoimmune susceptibility that is insufficient to trigger childhood type 1 diabetes but greater than that of the general population and sufficient to lead to clinical diabetes in adulthood. Taken together, future studies should examine the role of body mass index, which is lower in type 1 diabetes and higher among patients with type 2 diabetes, in adult autoimmune diabetes, as well as further defining the role of factors that potentially distinguish adult autoimmune diabetes from type 1 and type 2 diabetes.

## CONCLUSION

In this first GWAS of LADA, we show that the leading genome-wide significant signals point towards LADA as being a late-onset form of type 1 diabetes, albeit with a genetically attenuated potency of key type 1 diabetes-associated HLA haplotypes, but also with a type 2 diabetes-like genetic component. Further in-depth studies are necessary to address how LADA and insulin dependence develops and to study the impact of heterogeneity among cases with LADA, as well as a need for functional studies to investigate how the glycolytic regulator PFKFB3 is situated at the intersection of autoimmune and metabolic diabetes. Furthermore, our LADA dataset should act as a resource to help mitigate the unaccounted presence of autoimmune diabetes in patients masquerading as type 2 diabetes, with implications both for GWAS studies and for clinical management.

**ACKNOWLEDGEMENTS** (general)

For cohort-specific acknowledgements, please see the Supplementary Note. D.L.C. and S.F.A.G are the guarantors of this word and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest.

**ETHICAL APPROVAL**

This study was approved by local institutional ethical review boards.

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## AUTHOR CONTRIBUTIONS

Study concept and design: D.L.C., E.A., R.M., M.K.A., A.C., S.S., T.H., T.T., B.O.B., L.G., R.D.L., S.F.A.G.; Analysis and interpretation of data: D.L.C., E.A., R.M., M.K.A., A.C., J.P.B., K.Z., B.F.V., T.H., T.T., B.O.B., L.G., R.D.L., S.F.A.G.; Resources: M.I.H., A.D., K.M.H., V.C.G., M.A., M.W., L.F., H.V., J.S., K.H., A.L., A.K., I.B., C.E.K., D.W., E.P.S., D.J.B., O.P., H.B.-N., N.G., R.E.P., M.R.P., A.V., F.O., R.L.H., S.V., V.E.R.G., BMDCS, H.H., P.F., J.T.L., D.M., N.C.S., K.K., C.J.G., B.O.A., K.B.Y., E.R.P., T.H., T.T., B.O.B., L.G., R.D.L., S.F.A.G.; Drafting and critical revision of the manuscript: D.L.C., E.A., R.M., M.K.A., A.C., J.P.B., V.E.R.G., N.C.S., B.O.A., B.F.V., T.H., T.T., B.O.B., L.G., R.D.L., S.F.A.G.; Obtained funding: S.S., T.H., B.O.B., R.D.L., S.F.A.G. All authors contributed to the final version of the manuscript. D.L.C., E.A., R.M., M.K.A., B.O.B., L.G., R.D.L., S.F.A.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**REFERENCES**

**{** ADDIN ZOTERO_BIBL {"uncited":[],"omitted":[],"custom":[]} CSL_BIBLIOGRAPHY **}**

**TABLES**

| SNP | Chr | Position (b37) | Ref/other allele | Effect allele freq (cases/ctrls) | OR | 95% CI | *P* | Gene |
|---|---|---|---|---|---|---|---|---|
| LADA (n =2,634 ) vs. population controls (n = 5,947) | | | | | | | | |
| rs9273368 | 6 | 32626475 | A/G | 0.50/0.28 | 3.115 | 2.855-3.398 | 7.87x10-143 | *HLA-DQB1* |
| rs2476601 | 1 | 114377568 | A/G | 0.159/0.102 | 1.717 | 1.539-1.915 | 7.21x10-22 | *PTPN22* |
| rs689 | 11 | 2182224 | T/A | 0.802/0.726 | 1.483 | 1.363-1.613 | 1.07x10-19 | *INS* |
| rs7310615 | 12 | 111865049 | C/G | 0.553/0.492 | 1.284 | 1.193-1.383 | 4.92x10-11 | *SH2B3* |
| LADA (n = 2,779) vs. type 2 diabetes cases (n = 10,396) | | | | | | | | |
| rs9273368 | 6 | 32626475 | A/G | 0.43/0.301 | 2.439 | 2.222-2.676 | 3.17x10-78 | *HLA-DQB1* |
| rs689 | 11 | 2182224 | T/A | 0.783/0.715 | 1.473 | 1.352-1.605 | 9.86x10-19 | *INS* |
| rs2476601 | 1 | 114377568 | A/G | 0.173/0.140 | 1.529 | 1.38-1.693 | 4.52x10-16 | *PTPN22* |
| rs3184504 | 12 | 111884608 | C/T | 0.544/0.52 | 1.24 | 1.151-1.336 | 1.77x10-08 | *SH2B3* |
| LADA (n = 2,454) vs. type 1 diabetes cases (n = 968) | | | | | | | | |
| rs9273368 | 6 | 32626475 | A/G | 0.415/0.65 | 0.335 | 0.256-0.385 | 8.46x10-40 | *HLA-DQB1* |

**Table 1. Genome-wide significant signals associated with LADA.** We performed three genome-wide association approaches, first for LADA versus population controls (top panel), then for LADA versus type 1 diabetes (type 1 diabetes, middle panel) and LADA versus type 2 diabetes (type 2 diabetes, lower panel). Odds ratios (ORs) are given for the LADA risk allele except for rs92773368 in LADA vs. type 1 diabetes, to illustrate that the type 1 diabetes risk allele was depleted in LADA.

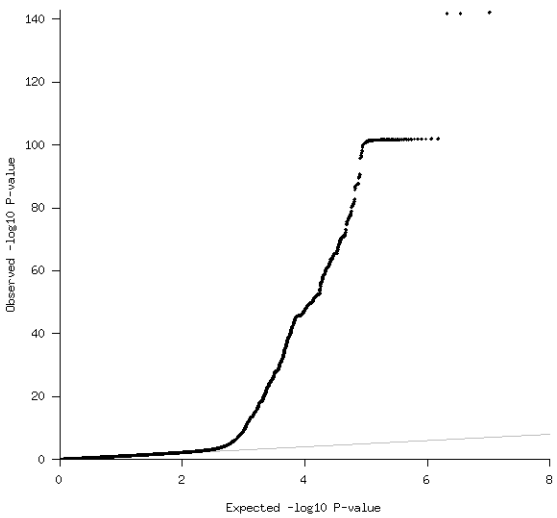
## FIGURE LEGENDS

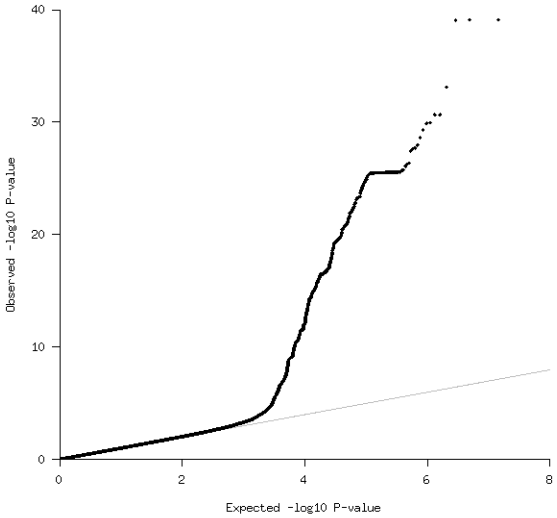
Figure 1. LocusZoom plots for the PFKFB3 locus. (A) In LADA vs. population controls with the addition of replication samples, rs1983890 reached borderline genome-wide significance. (B) This signal lies in between two type 1 diabetes-associated loci at 10p15.1(21). (C) When we conditioned on the two known type 1 diabetes loci, the signal in LADA remained. LocusZoom plots were constructed to show the association data of SNPs 400kb upstream and downstream of the lead LADA-associated signal at rs1983890.

# LADA GWAS Supplementary Material

## Supplementary Figures

**Figure 1.** QQ plots for (A) LADA vs. population controls, (B) LADA vs. T1D, and (C) LADA vs. T2D



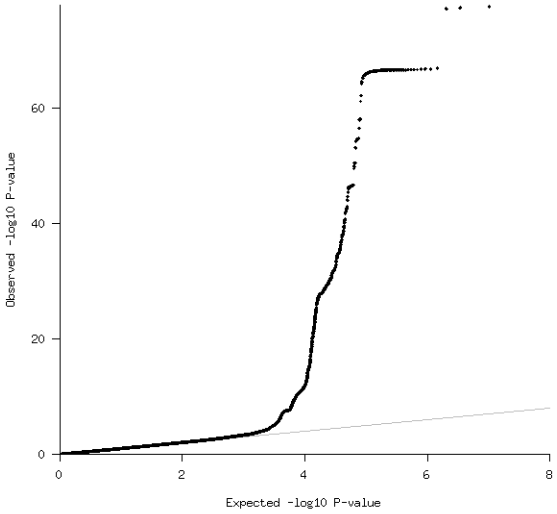
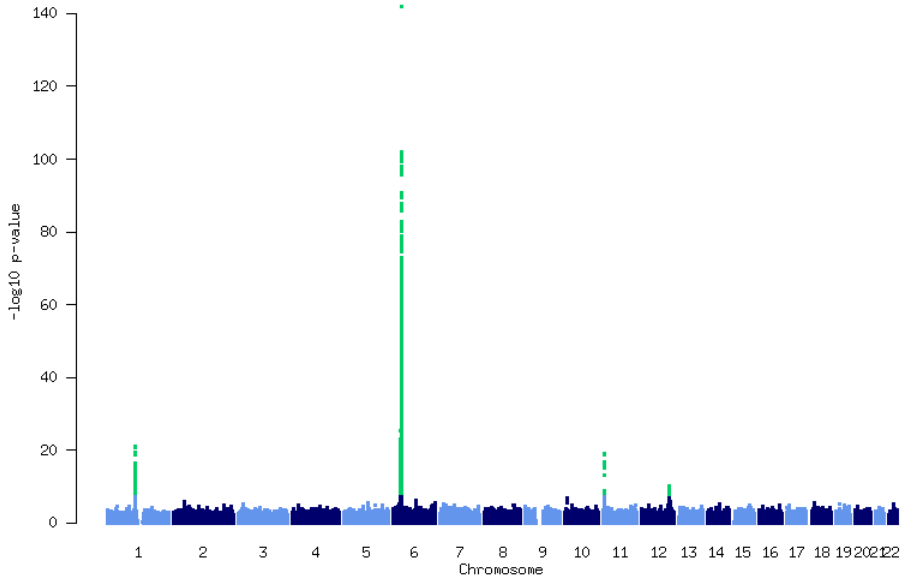
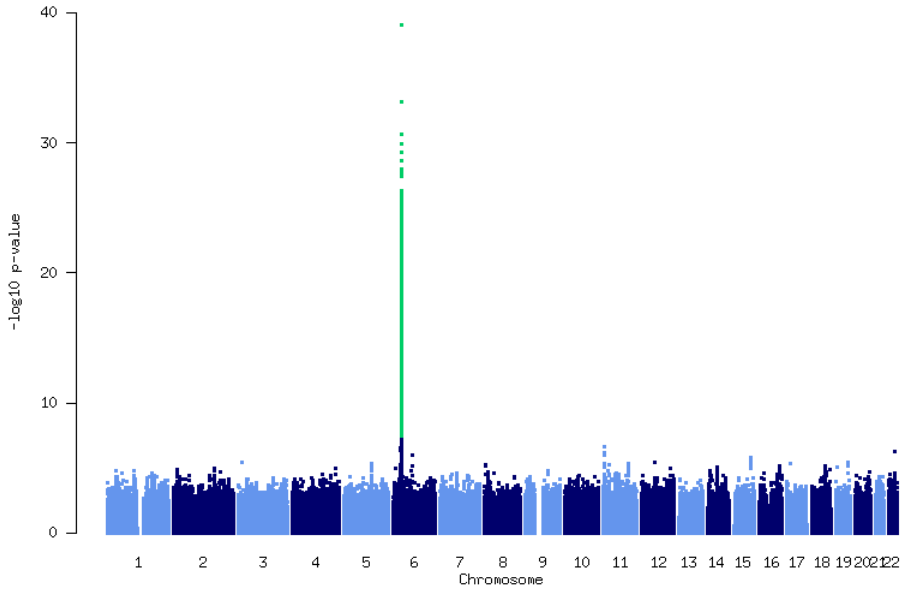
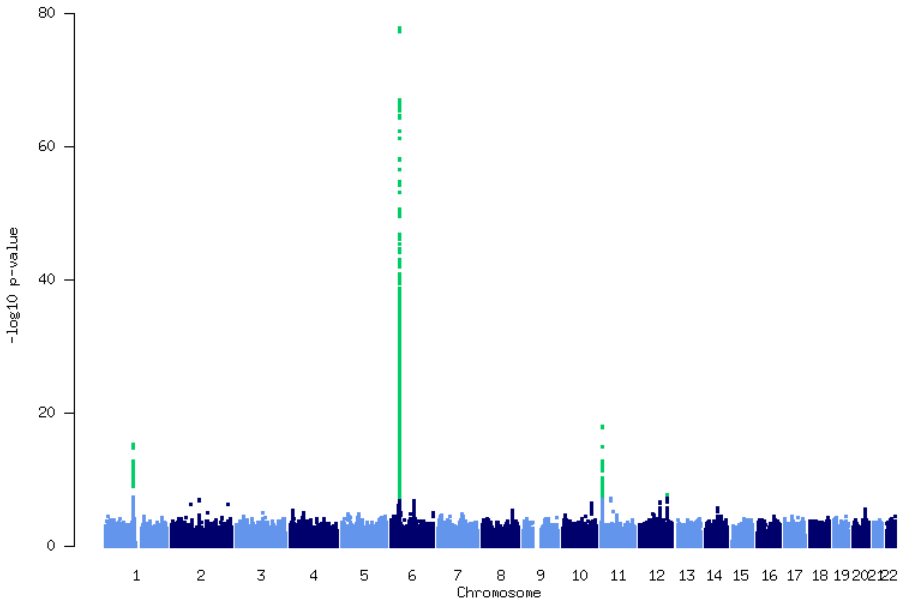



**Figure 2.** Manhattan plots for (A) LADA vs. population controls, (B) LADA vs. T1D, and (C) LADA vs. T2D




80
60
40
20
0
-log10 p-value
1
2
3
4
5
6
7
8
9
10
11
12
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14
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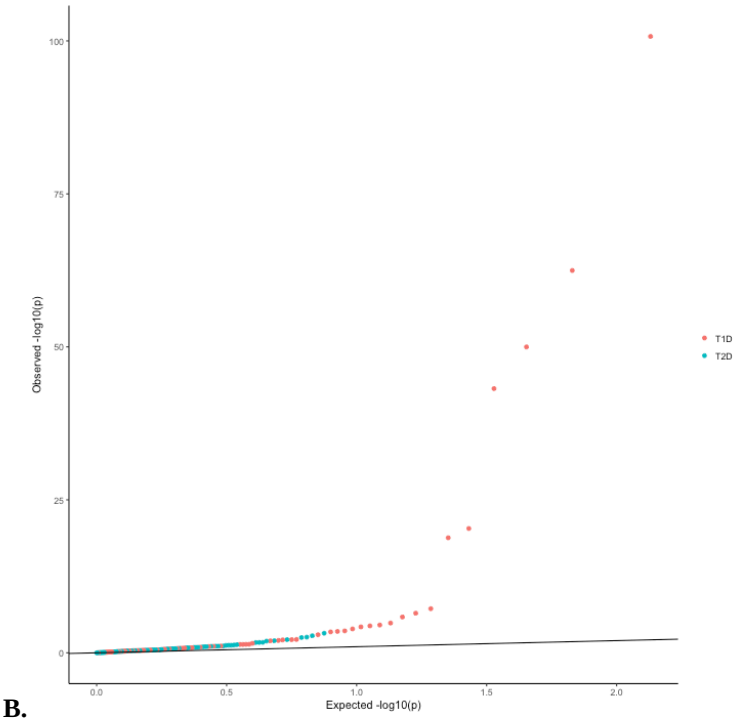
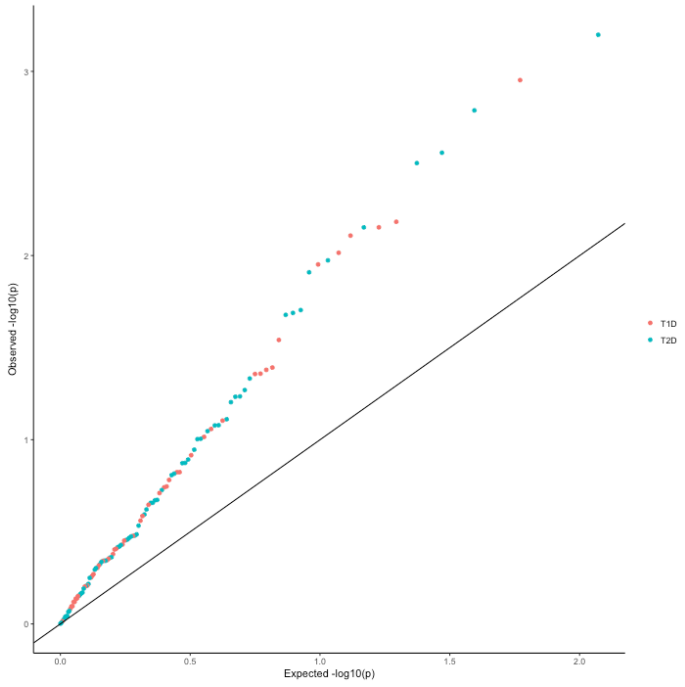
19
20
21
22
Chromosome

**Figure 3.** QQ plots showing established T1D (red) and T2D (blue) loci in LADA vs. population controls. A) All loci; B) zoomed in at 1 > P > ~~<~~ $10^{-4}$ (excluding top T1D signals).~~-~~

**A.**




**B.**



**Supplementary Note: Cohort Information**

**Cohort name:** Action Lada

**Cohort type**: LADA cases

**Inclusion/exclusion criteria:** Patients were designated with diabetes according to standard criteria, and LADA was defined as follows: patients 1) aged 30–70 years, 2) with diabetes associated autoantibodies, and 3) who did not require insulin treatment for at least 6 months post diagnosis. Type 1 autoimmune diabetic patients were defined as case subjects with diabetes and with diabetes-associated autoantibodies where insulin was started at diagnosis or within 1 month of diagnosis. Inclusion criteria for all patients were that patients have diabetes (with at least two recorded fasting blood glucose measurements >7 mmol/L), that time from diagnosis was 5 years for all patients, and that patients were aged 30–70 years at the time of recruitment. Exclusion criteria were insufficient dataset, current pregnancy, renal disease with raised creatinine or proteinuria, or acute illness at the time of testing.

**Number of study subjects:** 1098

**Acknowledgements:** We would like to acknowledge the Action Lada consortium.

**Funding:** This study was partially funded by the 5th Framework Programme of the European Union.

**Cohort reference:** REC Reference P/02/240

**Conflicts of interest:** No potential conflicts of interest relevant to this work.

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**Cohort name:** Action Lada 'Plus'

**Cohort type**: LADA cases

**Inclusion/exclusion criteria:** Patients were designated with diabetes according to standard criteria, and LADA was defined as follows: patients 1) aged 30–70 years, 2) with diabetes associated autoantibodies, and 3) who did not require insulin treatment for at least 6 months post diagnosis. Type 1 autoimmune diabetic patients were defined as case subjects with diabetes and with diabetes-associated autoantibodies where insulin was started at diagnosis or within 1 month of diagnosis. Inclusion criteria for all patients were that patients have diabetes (with at least two recorded fasting blood glucose measurements >7 mmol/L), that time from diagnosis was 5 years for all patients, and that patients were aged 30–70 years at the time of recruitment. Exclusion criteria were insufficient dataset, current pregnancy, renal disease with raised creatinine or proteinuria, or acute illness at the time of testing.

**Number of study subjects:** 441

**Acknowledgements:**

**Funding:**

**Cohort reference:**

**Conflicts of interest:**

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**Cohort name:** All New Diabetics In Scania (ANDIS)

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Inclusion/exclusion criteria:**

GAD

ELISA: Negative:< 5 kE/L, Positive:=> 10 kE/L

RIA: Negative:0-34 U/ml, Positive:> 50 U/ml

LADA

Age at onset ≥ 35 years

GAD (ELISA) > 10 kE/L

GAD (RIA) >50 U/ml

Non-Scandinavian individuals excluded

**Number of study subjects:** 440

**Acknowledgements:** We thank all the patients and the health care providers across Scania and Ostrobothnia for their support and their willingness to participate. We would also like to thank Johan Hultman, Jasmina Kravic, Maria Fälemark, Christina Rosborn, Gabriella Gremsperger, Maria Sterner, Malin Neptin, Lisa Sundman, Paula Kokko, and Ulrika Blom-Nilsson for excellent technical and administrative support. Finally we would like to thank Rita Jedlert and Region Skåne (Scania County) as well as the ANDIS steering committee for their support.

**Funding:** Supported by grants from the Swedish Research Council (including project grants Dnr.521-2010-3490 and infrastructure grants Dnr. 2010-5983 and Dnr 2012-5538 to LG), Linnéus grant 349-2006-237, a strategic research grant (Exodiab Dnr 2009-1039), an ERC Advanced Research grant (GA 269045) and Academy of Finland (grants no. 263401 and 267882) to LG.

**Cohort reference:** http://andis.ludc.med.lu.se/

**Conflicts of interest:** None

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**Cohort name:** Bone Mineral Density in Childhood Study (BMDCS)

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** population controls

**Cohort description:** The Bone Mineral Density in Childhood Study is a multicenter, longitudinal study of bone accrual in healthy children.
**Inclusion/exclusion criteria:** Only individuals of European ancestry were included.

**Number of study subjects:** 1056

**Acknowledgements:** We appreciate the dedication of the study participants and their families, and the support of Dr. Karen Winer, Scientific Director of the Bone Mineral Density in Childhood Study.

**Funding:** The BMDCS was funded by the National Institutes of Health [grant number R01 HD58886 to B.Z. and S.G.]; the Eunice Kennedy Shriver National Institute of Child Health and Human Development [grant numbers N01-HD-1-3228, -3329, -3330, -3331, -3332, -3333]; the Clinical and Translational Science Awards Program [grant number 8 UL1 TR000077]; American Diabetes Association Grant 1-17-PDF-077 [to D.C.]; and the Institute for Translational Medicine and Theraputics (ITMAT) Transdisciplinary Program in Translational Medicine and Therapeutics (to D.C., B.V., and S.G.). The project described was supported by the National Center for Research Resources [grant number UL1RR024134], and is now at the National Center for Advancing Translational Sciences [grant number UL1TR000003]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Conflicts of interest:** None

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**Study cohort: Copenhagen Controls**

The Copenhagen Control sample is collected from two cohorts (The 1936 birth cohort and ADDITION-PRO), and comprises 1974 non-diabetic adults. The control subjects had a mean age of 64.42 (range, 34.44), and 49.9% were male.

**Cohort name:** The 1936 birth cohort

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** Population controls

**Cohort description/inclusion/exclusion criteria:** The cohort consists of all subjects born in 1936, who, on 2 April 1976, were resident in one of four municipalities nearby Glostrup Hospital, Denmark (n=695). The cohort was collected to assess the age-specific prevalence of diabetes mellitus and impaired glucose tolerance in 60-year-old individuals in 1996/97.

**Number of study subjects:** 624 non-diabetic individuals (502 NGTs, 122 IFG/IGTs)

**Acknowledgements:** The authors are grateful to the staff at the Centre of Preventive Medicine, and to MD, general practitioner, Professor Hanne Hollnagel Dr Med. Sci., who initiated the study of the 1936 cohort.

**Funding:** The collection of the cohort was financially supported by The Danish Heart Foundation and The Danish Medical Research Council.

**Cohort reference:** Drivsholm T. Increasing prevalence of diabetes mellitus and impaired glucose tolerance among 60-year-old Danes. *Diabet Med* 2001.

**Conflicts of interest:** NA

**Cohort name:** ADDITION-PRO

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** Controls

**Cohort description/inclusion/exclusion criteria:** ADDITION-PRO is a longitudinal cohort study of 2082 adults (>45 years) collected to have IGT, IFG, or NGT either with high or low risk of developing type 2 diabetes (based on information about age, sex, gestational diabetes, family history of diabetes, hypertension, BMI, and level of physical activity).

The samples were collected in 2009–2011from four Danish research centres (Steno Diabetes Center, Aarhus University Hospital, Holstebro Hospital, and Hospital of South West Jutland, Esbjerg).

**Number of study subjects:** 1350 non-diabetic individuals (812 NGTs, 538 IFG/IGTs)

**Acknowledgements:** The ADDITION-PRO study is managed by the ADDITION-DK steering committee (Torsten Lauritzen, Knut Borch-Johnsen, Annelli Sandbæk, Marit E. Jørgensen, and Daniel Witte).

**Funding:** The ADDITION-PRO study was funded by an unrestricted grant from the European Foundation for the Study of Diabetes/Pfizer for Research into Cardiovascular Disease Risk Reduction in Patients with Diabetes (74550801), the Danish Council for Strategic Research, internal research and equipment funds from Steno Diabetes Center and supported by research grants from the Novo Nordisk Foundation.

**Cohort reference:** Johansen et al. Protocol for ADDITION-PRO: a longitudinal cohort study of the cardiovascular experience of individuals at high risk for diabetes recruited from Danish primary care. *BMC Public Health* 2012.

**Conflicts of interest:** NA

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**Study cohort: Copenhagen LADA**

The Copenhagen LADA sample (n=539) is collected from six cohorts (DD2, Vejle Biobank, OUH, CIMT, Inter99, and SDC). The LADA patients had a mean age of 58.32 (range, 67.31), and 56.2% were male.

The following inclusion criteria for LADA have been applied in all sub-cohorts: GADA positive, ≥20 years at the time of diagnosis, and treated without insulin for the first year after diagnosis or having fasting serum C-peptide ≥300 pmol/L at the time of investigation.

**Cohort name:** Danish Centre for strategic Research in Type 2 Diabetes (DD2)

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** DD2 is nationwide cohort, enrolling patients with newly diagnosed type 2 diabetes from general practitioners and hospital specialist outpatient clinics since 2010. GADA was measured in 5966 patients, with an AESKULISA assay.

**Number of study subjects:** 158 LADA cases

**Acknowledgements:** The DD2-project partners are listed on the website ww.DD2.nu.

**Funding:** The DD2 study is supported by the Danish Agency for Science (grant no. 09-067009 and 09-075724), the Danish Health and Medicines Authority, the Danish Diabetes Association, and an unrestricted donation from Novo Nordisk A/S.

**Cohort reference:** Thomsen et al. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2): Organization of diabetes care in Denmark and supplementary data sources for data collection among DD2 study participants. *Clin Epidemiol* 2012.

**Conflicts of interest:** NA

**Cohort name:** Vejle Biobank

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** The Vejle Diabetes Biobank was established as a regional Bio bank and comprises individuals with diabetes and a gender- and age-matched control population. All participants were aged between 25 and 75 years (both ages included) and residing in the former County of Vejle area on December 31, 2006. Altogether, 3320 patients with type 2 diabetes or type 1 diabetes were recruited from the central database at Vejle Hospital Laboratory Center. GADA were measured in all 3320 patients, with an AESKULISA assay.

**Number of study subjects:** 124 LADA cases

**Acknowledgements:** The laboratory technologists Britta Kristensen, Lene Juul Hansen, Annette Kaaris, Jan Johannsen, Merete Willumsen, Birgitte Henriksen, Camilla Davidsen, and Sara Egsgaard are acknowledged for their continued engagement and dedicated work.

**Funding:** The Vejle Biobank project was funded by the Danish Council for Independent Research/Medical Sciences, the Research Council of Vejle Hospital, the Department of Internal Medicine, Vejle Hospital, Vejle County, the Danish Research Fund, the Lions Club International Denmark, and anonymous donations.

**Cohort reference:** Petersen et al. Vejle Diabetes Biobank – a resource for studies of the etiologies of diabetes and its comorbidities. *Clin Epidemiol*. 2016.

**Conflicts of interest:** NA

**Cohort name:** OUH

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** The OUH LADA cohort is collected from a database of patients with diabetes newly referred to Odense University Hospital (OUH), Denmark, between 1997 and 2011. GAD autoantibodies were measured in 5,671 patients with diabetes, applying an RSR RIA assay, 279 were GADA positive, above 30 years of age, and had fasting C-peptide above 300 pmol/l. Of these DNA was available for 66.

**Number of study subjects:** 66 LADA cases

**Acknowledgements:** Department of Endocrinology, Odense University Hospital, Denmark, is acknowledged for their collection of the OUH cohort.

**Funding:** NA

**Cohort reference:** NA

**Conflicts of interest:** NA

**Cohort name:** CIMT

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** The CIMT trial is a multicenter randomized placebo controlled superiority trail conducted from 2008 to 2012 at eight hospitals in the capital region of Denmark. Inclusion criteria included diagnosis of type 2 diabetes, >30 years at diagnosis, BMI >25 kg/$m^2$, $HbA_{1c}$>7.5%, treatment with oral anti-diabetic drugs for ≥1 year, and/or insulin treatment for ≥3 months. Exclusion criteria included: major cardiovascular disease within the past 3 months, carotid artery stenosis >70%, heart failure, recent cancer, renal or liver disease, alcohol or drug abuse, unstable retinopathy, pregnancy, breastfeeding, fertile women not using anticonception, or allergy towards trial medication. Altogether, 412 type 2 diabetes patients were included in the trial and were screened for the presence of GADA with an RSR ELISA kit.

**Number of study subjects:** 31 LADA cases

**Acknowledgements:** The CIMT trial group is acknowledged for their effort in collecting and characterizing the cohort.

**Funding:** The CIMT study was funded by an unrestricted grant from Novo Nordisk A/S.

**Cohort reference:** Lundby et al. Study rationale and design of the CIMT trial: the Copenhagen Insulin and Metformin Therapy trial. *Diabetes Obes Metab* 2009.

**Conflicts of interest:** NA

**Cohort name:** Inter99

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** Inter99 is a population based intervention cohort, comprising individuals from the Copenhagen area. Altogether 6784 individuals participated in the baseline examination. GADA were measured in 2531 individuals, with an RSR ELISA kit.

**Number of study subjects:** 19 LADA cases

**Acknowledgements:** The staff from Research Centre for Prevention and Health, The capital region, Glostrup, Denmark is acknowledged their effort in making the Inter99 study possible.

**Funding:** The Inter99 study is funded by The Danish Medical Research Council, The Danish Centre for Evaluation and Health Technology Assessment, Novo Nordisk, Copenhagen County, The Danish Heart Foundation, The Danish Pharmaceutical Association, Augustinus foundation, Ib Henriksen foundation and Becket foundation.

**Cohort reference:** Jørgensen et al. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil*. 2003.

**Conflicts of interest:** NA

**Cohort name:** SDC

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases

**Cohort description/inclusion/exclusion criteria:** The SDC cohort comprises patients >18 years with type 2 diabetes (n=1676) recruited from the outpatient clinic at Steno Diabetes Center, Gentofte, Denmark. Individuals in pregnancy, having another cause of diabetes or being of another ethnicity than Danish were excluded. GADA were measured in 1595 individuals. Of the 141 LADA patients, GADA were measured with RSR ELISA in 52 patients, and with AESKULISA in 89 patients.

**Number of study subjects:** 141 LADA cases

**Acknowledgements:** NA

**Funding:** NA

**Cohort reference:** NA

**Conflicts of interest:** NA

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**Copenhagen general acknowledgements**: Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research center at the University of Copenhagen and is partly funded by an unrestricted donation from the Novo Nordisk Foundation. This work was supported by a research grant from the Danish Diabetes Academy supported by the Novo Nordisk Foundation, and grants from The Danish Council for Independent Research - Medical Sciences.

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**Cohort name:** Diabetes Registry Vasa (DIREVA)

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases/ T1D cases/ T2D cases

**Inclusion/exclusion criteria:** LADA

Age at onset ≥ 35 years
C-peptide (KLU) > 0.2 nmol/L
GAD65a (EIA) ≥ 10 U/ml

T1D
Age at onset < 35 years
C-peptide (KLU) < 0.2 nmol/L

T2D
Age at onset ≥ 35 years
C-peptide (KLU) ≥ 0.2 nmol/L
GAD65a (EIA) <10 U/ml

**Number of study subjects:** 3290

**Acknowledgements:** Same as for ANDIS

**Funding:** DIREVA was supported by the Vasa Hospital district.

+funding overlapping with ANDIS

**Cohort reference:** NA

**Conflicts of interest:** None

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**Cohort name**: GoDARTS

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):**

- population controls (replication study only) 969
- LADA cases 206
- T2D cases 4413

**Inclusion/exclusion criteria:**

- Age diagnosis <35
- No insulin within 1 year diagnosis
- GADA positive

**Number of study subjects: (see above)**

**Acknowledgements:** The Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection (GoDARTS) cohort collection was funded by The Wellcome Trust and informatics support is provided by the Chief Scientist Office, Scotland. E.R.P. holds a Wellcome Trust New Investigator Award (102820/Z/13/Z).

**Funding:** NA

**Cohort reference:** Diabetes Care. 2014;37(3):718-24. (PMID: 24186880)

**Conflicts of interest**: NA

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**Cohort name**: HUNT

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA and T2D cases and non-diabetic population controls

**Inclusion/exclusion criteria:** LADA: Self-reported yes to having diabetes, positive for GAD antibodies, initial age at diagnosis >30 years old and no insulin treatment within one year of diagnosis.

T2D: Self-reported yes to having diabetes, GAD antibodies negative, initial age at diagnosis >30 years old and no insulin treatment within one year of diagnosis. Age and gender matched to the LADA cases.

Non-diabetic controls: Self-reported no to ever having diabetes and had non-fasting serum glucose <7.0 mmol/l. Age and gender matched to the LADA cases.

**Number of study subjects:** 139 LADA, 695 T2D and 695 non-diabetic controls

**Acknowledgements**: The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

**Funding:** The K.G. Jebsen Center for Genetic Epidemiology is financed by Stiftelsen Kristian Gerhard Jebsen; Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology; the Liaison Committee between the Central Norway Regional Health Authority and NTNU; and the Liaison Committee between St. Olavs Hospital and the Faculty of Medicine and Health Sciences at NTNU.

The genotyping was financed by the National Institute of Health (NIH), University of Michigan, The Norwegian Research Council, the Liaison Committee between the Central Norway Regional Health Authority and NTNU, and the Liaison Committee between St. Olavs Hospital and the Faculty of Medicine and Health Sciences at NTNU.

**Cohort references:**

Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten L, Lund-Larsen PG. *The Nord-Trøndelag Health Study 1995–97 (HUNT2): objectives. contents. methods and participation.* Norsk Epidemiologi 2003. **13**(1): p. 19-32.

Krokstad S, et al. *Cohort Profile: the HUNT Study. Norway.* Int J Epidemiol. 2013. **42**(4): p. 968-77.

Nielsen JB et al (2018) Genome-wide Study of Atrial Fibrillation Identifies Seven Risk Loci and Highlights Biological Pathways and Regulatory Elements Involved in Cardiac Development. Am J Hum Genet. 102(1):103-115 [29290336].

**Conflicts of interest**: There are no disclosures to report.

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**Cohort name:** Malmö Diet and Cancer study

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** Non-diabetic controls

**Inclusion/exclusion criteria:**

Diabetes

**Number of study subjects:** 3126

**Acknowledgements:** NA

**Funding:** NA

**Cohort reference:** Berglund G, Nilsson P, Eriksson KF, Nilsson JA, Hedblad B, Kristenson H, et al. Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. J Intern Med. 2000;247(1):19-29. Epub 2000/02/15.

**Conflicts of interest:** None

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**Cohort name:** Scania Diabetes Registry (SDR)

**Cohort type (population controls/ LADA cases/ T1D cases/ T2D cases):** LADA cases/ T1D cases/ T2D cases

**Inclusion/exclusion criteria:**

SDR
GAD (Wallenberg lab (AU ref < 5.0)
GAD (Wallenberg lab (IU/ml ref <32)
C-peptide (Klin kem (RIA) ref 0.25-0.75)
C-peptide (Klin kem ref 0.3-1.3)
C-peptide (Lund (ref 0.25-0.75)

LADA
Age at onset ≥ 35
GAD ≥ 10 AU
GAD ≥ 50 IU/ml

T1D
Age at onset < 35
GAD ≥ 20 AU
GAD ≥ 100 IU/ml
C-peptide ≥ 0.25 (Klin kem (RIA))
C-peptide ≥ 0.3 (Klin kem)
C-peptide ≥ 0.25 (Lund)

T2D
BMI > 25
GAD < 5 AU
GAD ≤ 34 IU/ml
C-peptide (Klin kem (RIA)) ≥ 0.75
C-peptide (Klin kem) ≥ 1.3
C-peptide (Lund) ≥ 0.75
For patients that did not fulfill the criteria for any of the above, the diagnosis given by their physician was used

Non-Scandinavian individuals excluded

**Number of study subjects:** 3567

**Acknowledgements:** NA

**Funding:** NA

**Cohort reference:** Lindholm E, Agardh E, Tuomi T, Groop L, Agardh CD. Classifying diabetes according to the new WHO clinical stages. Eur J Epidemiol. 2001;17(11):983-9. Epub 2002/10/17.

**Conflicts of interest:** None

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