Painful punctate palmoplantar keratoderma due to heterozygous mutations in AAGAB

Zamiri, M.; Wilson, N. J.; Mackenzie, A.; Sobey, G.; Leitch, C.; Smith, F. J. D.

Published in:
British Journal of Dermatology

DOI:
10.1111/bjd.17442

Publication date:
2019

Document Version
Peer reviewed version

DR MOZHEH ZAMIRI (Orcid ID : 0000-0001-5152-0792)

Article type : Research Letter

Painful punctate palmoplantar keratoderma due to heterozygous mutations in AAGAB

M. Zamiri[1], N.J. Wilson[2], A. Mackenzie[3], G. Sobey[4], C. Leitch[5], F.J.D. Smith[2,6]

[1]Alan Lyell Centre for Dermatology, Queen Elizabeth University Hospital, Glasgow, UK

[2]Dermatology and Genetic Medicine, Division of Biological Chemistry and Drug Discovery, School of Life Sciences, University of Dundee, Dundee, UK

[3]Department of Dermatology, Borders General Hospital, Melrose, UK

[4]Department of Clinical Genetics, Sheffield Children's Hospital, Sheffield, UK

[5]Department of Dermatology, Lauriston Building, Edinburgh, UK

[6]Pachyonycha Congenita Project, Holladay, Utah, USA

Corresponding author: Dr Mozheh Zamiri

Email: mozheh.zamiri@glasgow.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.17442

Running Title: Mutations in AAGAB causing punctate keratoderma and plantar pain

Conflict of interest: None

Key words: punctate palmoplantar keratoderma, *AAGAB*, autosomal dominant

Funding: FJDS, NJW and MZ were supported by The Centre for Dermatology and Genetic Medicine at the University of Dundee, which is funded by a Wellcome Trust Strategic Award (098439/Z/12/Z), and FJDS and NJW were supported by grants from the Pachyonychia Congenita Project (to F.J.D.S, www.pachyonychia.org)

Dear Editor,

Punctate palmoplantar keratoderma (PPPK) is a rare, autosomal dominant disorder of keratinization with three main variants. PPPK type 1 (MIM 148600), also known as Buschke-Fischer-Brauer disease, is characterized by the progressive development of multiple small hyperkeratotic papules with central indentations that are irregularly distributed on the palms and soles, often deteriorating to more extensive diffuse hyperkeratosis on the weight-bearing areas of plantar skin.[1] The PPPK1 gene was recently identified as the α and γ-adaptin binding protein p34 gene *AAGAB*,[2-4] and in a single case, the *COL14A1* gene.[5]

We report the clinical and genetic features of a series of 16 unrelated pedigrees with autosomal dominant PPPK due to heterozygous mutations, 5 novel (7 families) and 4 recurrent (9 families), in the *AAGAB* gene.

Fourteen families presented to their local dermatology services with a history of PPPK developing in adulthood, with age of onset ranging from 19-55 years. Two families were identified through the International Pachyonychia Congenita Research Registry (Table 1). All pedigrees, except two (families 5 & 9) had a family history of keratoderma where the proband was the only known affected case; the 16 probands were investigated in this study. Plantar pain was reported by twelve of sixteen of the presenting cases, with variable levels of pain when weight-bearing (self-reported as mild/moderate/severe) particularly in association with times of increased hyperkeratosis and partially relieved by physical paring. Simple analgesia had been used intermittently by all twelve patients, including regular paracetamol and non-steroidal anti-inflammatory drugs.

Genetic testing was performed with informed consent and ethical approval by a Western Institutional Review Board that complies with principles of the Helsinki Accord. Genomic DNA extracted from peripheral blood leukocytes or saliva (DNA Genotek, Ontario, Canada) underwent PCR and Sanger sequencing to screen the coding regions and exon/intron boundaries of *AAGAB*.[3] Variants were confirmed as pathogenic by reference to the *in silico* prediction tool, Mutation Taster and by sequencing other family members when available.

Novel mutations were identified in 7 families (Table 1); frameshift mutations c.83delG; p.Gly28Glufs*9 and c.614delC; p.Pro205Glnfs*38, nonsense mutations c.159C>A; p.Tyr53* and c.550_551insAAT; p.Phe184*. None of these variants were present on the database of Single Nucleotide Polymorphisms (dbSNP), 1000 Genome Project, NHLBI Exome Variant Server, Exome Aggregation Consortium (ExAC) or the Genome Aggregation Database (gnomAD). A novel splice site mutation at exon 4 – intron 4 boundary, c.451+3delAAGT, was identified in 3 families. This variant is present on ExAC database but at an extremely low level, (minor allele frequency of 0.000016). To determine the consequence of this variant, cDNA derived from mRNA from a skin biopsy of an affected individual (family 10) was PCR amplified. A shorter PCR product was identified which when sequenced showed mutation c.451+3delAAGT results in skipping of exon 4 due to deletion of 90 bp

resulting in an in-frame deletion with loss of 30 amino acids. Interestingly, another mutation at this splice site, c.451+1G>A, has been reported twice[6,7] which also results in skipping of exon 4.[6]

Nine families had previously reported mutations. Frameshift mutation c.344delA; p.Asp115Valfs*8[3] was identified in three families, frameshift mutation c.473delG; p.Gly158Glufs*2[3] in two families, nonsense mutation c.370C>T; p.Arg124*[2] in 3 families and one family had a previously reported mutation affecting the translation initiation site, c.1A>G[7] (Table 1).

Consistent with previous reports, the most common type of mutations correlating with PPPK were loss of function mutations due to nonsense or frameshift mutations resulting in haploinsufficiency of p34. In addition, one recurrent mutation found (c.1A>G) affects the start codon and it is predicted a start codon downstream of the mutated initiation codon is used.[7] The novel splice site mutation (c.451+3delAAGT) results in an in-frame deletion and skipping of exon 4 as determined from RNA. A different mutation at this splice site, previously reported twice, has been shown to lead to skipping of exon 4[6,7] and predicted loss of part of the p34Rab-like GTPase domain that may be involved in vesicle trafficking.[6] No obvious phenotype-genotype correlations were observed in these 16 pedigrees. However, when possible to assess within pedigrees, intrafamilial variability existed regarding severity of hyperkeratosis, often more severe with increasing age and where occupations involved increased friction at palmoplantar surfaces. This series highlights the problem of plantar pain that is often associated with this form of keratoderma. Plantar pain has been considered the main symptom and a hallmark feature of the inherited keratoderma, pachyonychia congenital,[8] its presence often guiding physicians towards genetic screening for a presumed diagnosis of PC.[6] However, PPPK typically does not present until adolescent or adulthood whereas in PC onset is generally from birth to early childhood and additional features including nail dystrophy, oral leukokeratosis and cysts are normally present.

Plantar pain may be under reported in PPPK but can benefit from manual paring of hyperkeratosis and simple analgesia. *AAGAB* gene screening should be considered in the context of punctate keratoderma and plantar pain.

Acknowledgements

We would like to thank the patients and their family members for their cooperation in this study. This work was supported by the Centre for Dermatology and Genetic Medicine (DGEM), the Dystrophic Epidermolysis Bullosa Research Association and the Pachyonychia Congenita Project.

References

1. Kimyai-Asadi A, Kotcher LB, Jih MH. The molecular basis of hereditary palmoplantar keratodermas. *J Am Acad Dermatol* 2002; **47**: 327-43.
2. Giehl KA, Eckstein GN, Pasternack SM *et al*. Nonsense mutations in AAGAB cause punctate palmoplantar keratoderma type Buschke-Fischer-Brauer. *Am J Hum Genet* 2012; **91**: 754-9.
3. Pohler E, Mamai O, Hirst J *et al*. Haploinsufficiency for AAGAB causes clinically heterogeneous forms of punctate palmoplantar keratoderma. *Nat Genet* 2012; **44**: 1272-6.
4. Pohler E, Zamiri M, Harkins CP *et al*. Heterozygous mutations in AAGAB cause type 1 punctate palmoplantar keratoderma with evidence for increased growth factor signaling. *J Invest Dermatol* 2013; **133**: 2805-8.
5. Guo BR, Zhang X, Chen G *et al*. Exome sequencing identifies a COL14A1 mutation in a large Chinese pedigree with punctate palmoplantar keratoderma. *J Med Genet* 2012; **49**: 563-8.
6. Eytan O, Sarig O, Israeli S *et al*. A novel splice-site mutation in the AAGAB gene segregates with hereditary punctate palmoplantar keratoderma and congenital dysplasia of the hip in a large family. *Clin Exp Dermatol* 2014; **39**: 182-6.

7. Giehl KA, Herzinger T, Wolff H *et al*. Eight novel mutations confirm the role of AAGAB in punctate palmoplantar keratoderma type 1 (Buschke-Fischer-Brauer) and show broad phenotypic variability. *Acta Derm Venereol* 2016; **96**: 468-72.

8. Leachman S, Kaspar RL, Fleckman P *et al*. Clinical and pathological features of pachyonychia congenita. *J Invest Dermatol Symp Proc* 2005; **10**: 3-17.

Table 1. Mutations and clinical details in new cases of punctate palmoplantar keratoderma (PPPK).

		Table 1. Mutations and clinical details in new cases of punctate palmoplantar keratoderma (PPPK)					
Family	**DNA change**	**Protein change**	**Exon**	**Unreported or known mutation**	**Familial or spontaneous**	**Age of onset of PPK**	**Plantar pain (Reported Severity: Mild/Moderate/Severe)**
1	c.1A>G	?	1	Known	Familial	15-16 yrs	Yes - mild
2	c.83delG	p.Gly28Glufs*9	2	Unreported	Familial	15-19 yrs	Yes - painful to walk, moderate - severe
3	c.159C>A	p.Tyr53*	2	Unreported	Familial	Mid 20s	No
4	c.344delA	p.Asp115Valfs*8	3	Known	Familial	Late 30s	Yes - mild
5	c.344delA	p.Asp115Valfs*8	3	Known	Spontaneous	Late 30s	Yes - mild
6	c.344delA	p.Asp115Valfs*8	3	Known	Familial	Late 30s	Yes - discomfort when walking, mild
7	c.370C>T	p.Arg124*	4	Known	Familial	19 years	Yes - primarily when weight bearing, moderate - severe
8	c.370C>T	p.Arg124*	4	Known	Familial	About age 8 & slowly progressed over next 20 yrs	Yes - when standing or walking, moderate - severe
9	c.370C>T	p.Arg124*	4	Known	Spontaneous	21 years	No
10	c.451+3delAAGT	exon 4 skipped	4	Unreported	Familial	23 years	Yes - discomfort when walking, mild - moderate
11	c.451+3delAAGT	exon 4 skipped	4	Unreported	Familial	32 years	Yes, mild - moderate
12	c.451+3delAAGT	exon 4 skipped	4	Unreported	Famiial	Early 20s	Yes, mild - moderate
13	c.473delG	p.Gly158Glufs*2	5	Known	Familial	54 years	Yes, mild - moderate
14	c.473delG	p.Gly158Glufs*2	5	Known	Familial	55 years	No
15	c.550_551insAAT	p.Phe184*	6	Unreported	Familial	Early 20s	Yes, Finds feet uncomfortable - mild
16	c.614delC	p.Pro205Glnfs*38	6	Unreported	Familial	29 years	Yes - if not pared regularly, moderate
	No affected individuals had any history of skin fragility, blistering, hair or cardiac abnormalities.						
	There was no association with malignancy or diabetes mellitus in affected members of any of the families.						
	A more detailed table is available from the corresponding author on request.						