DOCTOR OF PHILOSOPHY

Skin barrier dysfunction in common genetic disorders

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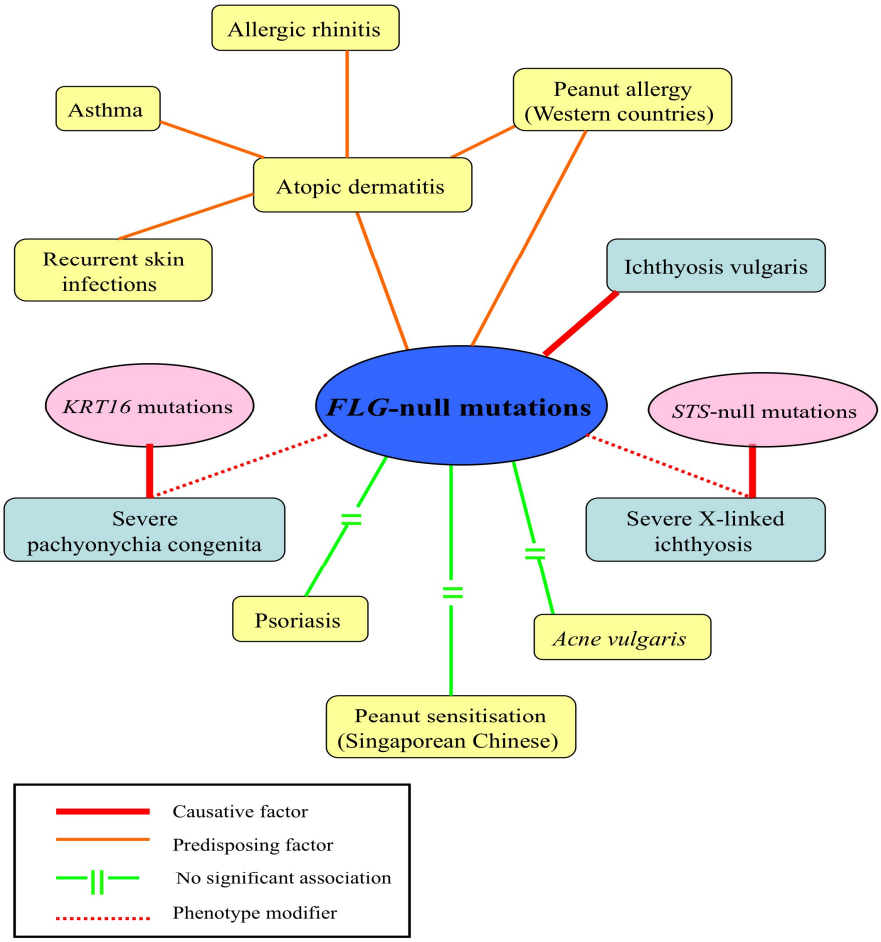
CHAPTER 6

OVERALL CONCLUSIONS AND DISCUSSION

In this thesis, the role of *FLG*-null mutations in various genodermatoses has been examined (**Figure 6.1**). In concurrence with the widely replicated studies in Europe, **Chapter 2** confirmed that loss-of-function mutations in the filaggrin gene cause ichthyosis vulgaris (IV) and are major predisposing factors for atopic dermatitis (AD) in the Singaporean Chinese population. It is a well known clinical observation that AD is associated with the onset of other atopic conditions, such as asthma, allergic rhinitis and food allergies (Marenholz *et al.*, 2006; Smith *et al.*, 2006; Brown *et al.*, 2011), leading to the rapid follow-up association studies in family-based and large case-cohorts, which showed *FLG*-null mutations to be significant players that increase the susceptibility for these atopic diseases as well (van den Oord and Sheikh, 2009). As the expression of filaggrin protein does not extend to the human bronchial mucosa, it has been postulated that *FLG*-null mutations act as risk factors because the initial breach in the skin barrier due to filaggrin haploinsufficiency could increase the cutaneous entry of allergens; this might result in early priming of the immune systems towards these allergens and subsequent cascading into chronic atopic diseases. Interestingly, the examination of Singaporean Chinese patients with *FLG*-involved AD and non-*FLG*-involved AD also showed an increased risk of current skin infections in patients who carried *FLG*-null mutations. This hints at the possibility that filaggrin possesses additional roles in skin homeostasis other than its structural role in forming the stratum corneum and retaining moisture in the skin – natural moisturising factor (NMF) derived from filaggrin degradation include *trans*-urocanic and pyrrolidone

Figure 6.1 Overview of *FLG* mutations in disease associations



This figure summarises the main findings of this thesis and the current knowledge of *FLG*-null mutations' involvment in different genodermatoses. Oval shapes indicate genes; blue rectangles indicate mendelian gene disorders and yellow rectangles indicate complex gene disorders. *FLG*-null mutations were shown to be the underlying genetic basis for ichthyosis vulgaris (IV); they also interact with *STS* and *KRT16* to exacerbate the clinical phenotypes of X-linked ichthyosis (XLI) and pachyonychia congenita (PC) respectively. *FLG* mutations were also proven to be extremely strong predisposing factors for the atopic dermatitis (AD) in widely replicated international studies. In the presence of AD, patients with *FLG* mutations also have increased susceptibility to asthma, rhinitis, peanut allergy and recurrent skin infections. However, *FLG* in not known to play a significant role in psoriasis; it is also not associated with acne vulgaris and peanut sensitisation in the Singaporean Chinese population.

acids, which might also contribute significantly to the maintenance of optimal acidity in human skin to curb unwanted bacterial colonisation (**Chapter 3**).

Following earlier reports of *FLG* interactions with other genes to present an altered clinical phenotype (Liao *et al.*, 2007; Gruber *et al.*, 2009), an Indian female patient with unusually severe XLI was also examined for *FLG* variants – this led to confirmation that her severe phenotype was due to the inheritance of a *FLG*-null mutation from her mother in addition to *STS* deletion on both X-chromosomes. Besides its interaction with other discrete pathways, which are important to maintain the integrity of the skin barrier, it is also highly likely that *FLG* interacts with other components within the profilaggrin biochemical processing pathway to increase disease severity. *KLK7* codes for a serine protease involved in desquamation and possibly cleavage of profilaggin, while *SPINK5* codes for LEKTI, a serine protease inhibitor – these are likely candidate genes that could interact with *FLG*. Several research groups have shown data on the association of polymorphisms in *SPINK5* (p.E420K variant) and *KLK7* (AACC insertion in the 3' UTR) with AD (Walley *et al.*, 2001; Kato *et al.*, 2003) but this association could not be replicated in the large European study described in **Chapter 4** of this thesis. In addition, *KLK7* polymorphism showed no gene-gene interaction with *FLG* and the maternally derived *SPINK5* variant displayed a weak interaction effect with *FLG* to increase susceptibility towards AD. As AD is a multifactorial condition caused by the complex interplay of environmental

influences with a plethora of immune system and skin barrier genes, the emergence of more contributing genes would be expected in due time.

To investigate the role *FLG*-null mutations in other complex disorders, a large cohort of acne vulgaris patients and a small pilot study of peanut-sensitised children in Singapore were also examined for *FLG* mutations. There was no associative effect with acne vulgaris or peanut sensitisation, which indicated that the pathogeneses of these conditions do not involve *FLG* (**Chapter 3**). In view of the recent report of *FLG* mutations as a significant predisposing factor for peanut allergy (Brown *et al.*, 2011), it is possible that the failure of association with *FLG* within the peanut sensitisation pilot study group was attributed to small study number or a more varied spectrum of phenotype. In addition, discrete genetic differences in the European and Asian skin biology could also explain this observation (Muizzuddin *et al.*, 2010).

The difference in genetics between distinct ethnic groups is exemplified in the observation of a widely diverse spectrum of *FLG*-null mutations found in Europe and Asia (**Chapter 2**). Moreover, a smaller proportion of AD patients in Singapore carried *FLG*-null mutations compared to the Irish population, which hints at the possibility that more unknown genes may play a more significant role in the aetiology of AD in Asia. Although the effect of environmental influences such as humidity and temperature is difficult to measure, its interaction with genotype to influence disease phenotype must not be overlooked. For example,

Singapore is a very humid and warm tropical country; frequent sweating in patients with *STS* gene mutations might improve the clinical presentation of XLI and lead to misdiagnosis as IV. Furthermore, the warm weather promotes the thriving of bacteria and could possibly result in relapsing skin infection and ultimately lead to an increase in AD severity. Doctors should take these factors into consideration during clinical diagnosis.

In view of overlapping phenotypes in distinct genodermatoses, several clinical markers associated with specific gene defects would prove to be important tools to aid in diagnostic accuracy. In this thesis (**Chapter 3**) and earlier studies, palmar hyperlinearity and keratosis pilaris have been shown to be high positive predictors of *FLG*-null mutations (Brown *et al.*, 2008). This is especially useful for the diagnosis of *FLG*-involved AD for early treatment because sequencing of the large, repetitive *FLG* gene for mutations remains technically demanding. Recently, the advent of Raman spectroscopy and tape stripping to measure NMF levels in the skin of AD patients have shown favourable progress towards the non-invasive detection methodology for *FLG*-null mutations (Kezic *et al.*, 2010; O'Regan *et al.*, 2010).

In the concluding paragraph of this thesis, the future of *FLG* gene therapy and expected advances in the field of genodermatoses will be briefly discussed. In patients carrying one *FLG*-null mutation, filaggrin haploinsufficiency can be compensated for by increasing the activity of the *FLG* promoter thus leading to

the up-regulation of the other functional copy of *FLG*; whereas for patients carrying *FLG*-null mutations in both alleles, a drug that can read-through premature stop codons (PTCs) will be the most likely way to replenish absent filaggrin. In the McLean laboratory, work has started on the screening of small molecule drug libraries for molecules that have the above qualities in addition to low toxicity, in hope of finding a cure for *FLG*-null mutations as well as other diseases caused by PTCs. To find effective cures for genetic disorders, the fundamental genetic defect must be understood. It is believed that new and rapid sequencing techniques developed within the next few years will bring forth tremendous increases in our understanding of genodermatoses. Currently, next generation sequencing (NGS) is already being applied to skin diseases. This new technology was recently used to identify a gene for cutis laxa because it allows rapid sequencing of more than 80 genes simultaneously (Reversade et al., 2009). By sequencing whole exomes, this technology has the potential to revolutionise genetic testing and cut labour-hours, which is especially important for orphan genetic disorders. Furthermore, it might soon be possible to sequence the entire genome in one run for a very low cost, using so-called future generation sequencing (FGS) that is also in development. Knowing the sequence of whole genomes provides the added advantage of identifying causative variants directly without the need for haplotype linkage analysis using high density SNPs. This will definitely be the way forward to identify definitive susceptibility variants in highly complex gene disorders such as psoriasis in future.

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