Role of Allergic Sensitization, Filaggrin Variants, and DNA Methylation on the Risk of Allergic Disorders

by

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Abstract

**Background:** Allergic disorders, including eczema, asthma, and rhinitis, have emerged as a global public health concern due to their elevated prevalence and the associated clinical morbidity. Environmental, immunologic, and genetic factors have been implicated in the pathogenesis of allergic disorders. Allergic sensitization (representing deviated immune responses) and filaggrin gene (*FLG*) variants (leading to dysfunctional epidermal barrier) have shown to be common predisposing factors in the development of allergic disorders. However, there is a lack of knowledge on their joint effects on the development of single and multiple (coexistence) allergic disorders. More recently, epigenetic mechanisms, such as DNA methylation, have emerged as potentially important factors in the development of such complex diseases; however, the extent to which DNA methylation associates with allergic disorders is unclear.

**Objectives:** This dissertation sought to (i) determine whether eczema and/or allergic sensitization is an effect modifier of the association between ‘*FLG* variants and asthma’ and ‘*FLG* variants and rhinitis’, (ii) test whether *FLG* variants and allergic sensitization jointly predispose to the comorbidity of eczema, asthma and rhinitis, and (iii) examine associations between DNA methylation across the epidermal differentiation complex (EDC) genomic region with eczema status.

**Methods:** The Isle of Wight (IOW) birth cohort, a population-based sample of 1,456 infants born between January 1989 and February 1990, was prospectively assessed at
ages 1, 2, 4, 10, and 18 years. Repeated measurements of eczema, asthma, rhinitis, and allergic sensitization (documented by skin prick tests) were available for all follow-ups. *FLG* variants R501X, 2282del4, and S3247X were genotyped in 1,150 participants. Log-binomial regression models were applied to test for associations and statistical interactions on multiplicative scale. On the other hand, DNA methylation was measured in a subsample (n = 367) of the IOW participants at age 18 years (*discovery cohort*) and in two semi-independent samples (*replication cohorts I and II*). Associations between eczema status and DNA methylation were assessed using linear regression.

**Results:** *FLG* variants were associated with increased risk of asthma and rhinitis. Both eczema status (*RR* interaction = 1.96, *P* interaction = 0.006) and allergic sensitization (*RR* interaction = 1.58, *P* interaction = 0.013) modified the association between *FLG* variants and asthma, but not the association with rhinitis. The combined effect of both risk factors increased the risk of coexisting “eczema and asthma” (*RR* = 13.67, 95% CI: 7.35 – 25.42), “asthma and rhinitis” (*RR* = 7.46, 95% CI: 5.07 – 10.98), and “eczema, asthma, and rhinitis” (*RR* = 23.44, 95% CI: 12.27 – 44.78). On the other hand, Differential DNA methylation of CpG site cg12048339 (located within promoter of *S100A6* gene) was associated with eczema specifically among female participants of all study cohorts; whereas, aberrant DNA methylation of CpG site cg10959711 (located within promoter of *S100A11* gene) associated with eczema among male participants in all study samples.

**Conclusions:** Allergic sensitization and eczema modulated the association between *FLG* variants and asthma, but not rhinitis; implying that the mechanisms and pathways through which *FLG* variants predispose to increased risk of asthma and rhinitis may be different. Moreover, the coexistence of allergic disorders is frequent and allergic sensitization and
FLG variants jointly increased risk of allergic comorbidities, which may represent more severe and complex clinical phenotypes. Results of an exploratory investigation demonstrated that DNA methylation of the EDC locus could be an important factor in the development of eczema in a sex-specific manner. Future studies corroborating our findings are needed.