

First results of the GENEVA study: Research on the genetics of food allergy in children

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Food allergy is a potentially lethal disease and its prevalence is increasing in the Western world¹. Furthermore, food allergy reduces quality of life in patients to a greater extent than diabetes² and is strongly heritable³. One study reported a 5-fold increase for the risk of peanut allergy for a child with a peanut allergic sibling or parents⁴. Remarkably, only 1 in 2 children suspected to be food allergic and sensitised to food has a positive outcome of a double blind placebo-controlled food challenge (DBPCFC) and is thereby diagnosed as clinically reactive⁵.

We hypothesize that the genetic makeup of a child influences the difference between sensitisation with and without clinical reactivity to food. Specifically, we hypothesize that genes that contribute to skin epithelial integrity are associated with clinical food allergy.

To study this hypothesis we use the database of the Food Challenge Unit of the Beatrix Children's Hospital of the UMCG which contains phenotypic information on food allergy as well as other atopic morbidities on over one thousand children who have been diagnosed by the gold standard test, the Double-Blind Placebo Controlled Food Challenge. This will be coupled to a DNA collection which will be expanded to include samples from 800 children and their parents. This will be achieved by collecting DNA from blood- and saliva samples. We will focus on candidate genes involved in epithelial integrity, and are aiming to perform a genome-wide association study in the future.

The first results of the GENEVA study examined the association between food allergy and the filaggrin gene (*FLG*). The *FLG* gene is located on chromosome 1q21 and is part of the epidermal differentiation complex. These genes play an important role in skin barrier function since the filaggrin protein helps aggregate the epidermal cytoskeleton to form a protein-lipid barrier⁶. An impaired barrier function may permit intact proteins to pass the barrier and to elicit an immune response. Loss of function (LOF) variants of the *FLG* gene result in a defective form of the filaggrin protein and have a prevalence of about 10% in Western populations⁷. *FLG* LOF variants are associated with ichthyosis vulgaris, characterized by palmar hyperlinearity, keratosis pilaris and a fine white scale on the extremities. Ichthyosis vulgaris is strongly associated with atopy⁸. Furthermore, the *FLG* LOF variants are strong risk factors for atopic dermatitis⁹ and are associated with allergic rhinitis and sensitization¹⁰. In children with atopic dermatitis, these variants are also associated with asthma¹¹. Other studies suggest a role of *FLG* in sensitization to foods and clinical food allergy¹².

We showed that in high risk children suspected of being food allergic, those carrying one or more loss of function variants of the *FLG* gene are 1.5 times more likely to be clinically allergic as diagnosed by the DBPCFC than children carrying wild type alleles. This strong association is replicated using a family based design, confirming the robustness of this observation¹³. We furthermore showed that genetic markers may be useful as an addition to clinical assessment in the diagnosis of food allergy¹³.

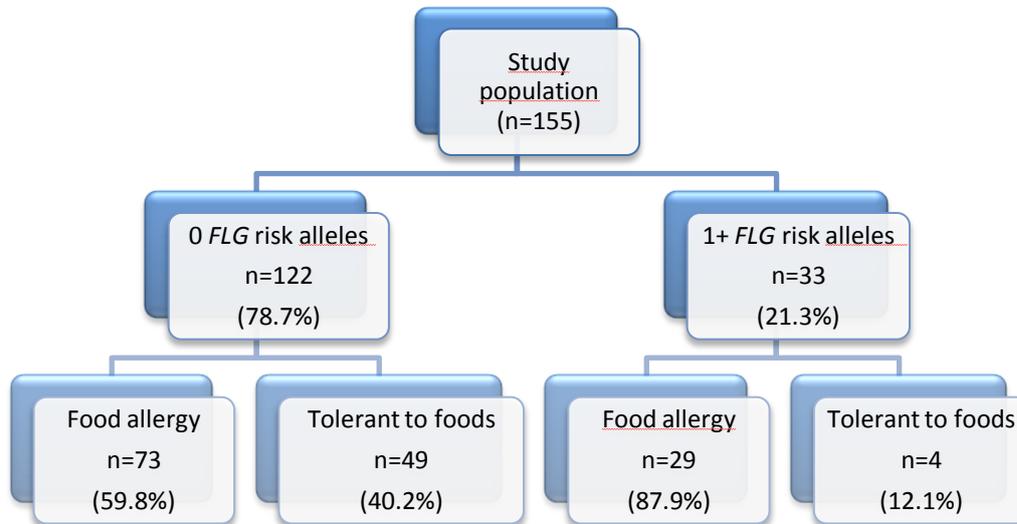


Figure 1. Prevalence of food allergy in subjects with and without *FLG* risk alleles.

The genetic findings of *FLG* being an important gene for food allergy have led to the dual-allergen exposure hypothesis for the pathogenesis of food allergy. This proposes that low-dose cutaneous exposure to food allergens triggers Th2 responses and IgE production by B cells while early oral exposure induces tolerance by stimulating regulatory T cells and Th1 cells¹⁴. This hypothesis is supported by a study showing that epicutaneous exposure to peanut protein causes Th2-type immunity with high levels of peanut specific IgE and prevents the development of oral tolerance to peanut¹⁵. A recent study showed that early life environmental exposure to peanuts, as measured by peanut in household dust, is indeed associated with peanut sensitization and allergy as confirmed by open food challenges, but only in children carrying *FLG* mutations¹⁶. This percutaneous priming is also proposed for the role of *FLG* in asthma and rhinitis¹⁰.

In conclusion, we recently showed that in high risk children, loss of function variants of the filaggrin gene are associated with clinical food allergy, as diagnosed by the double blind placebo-controlled food challenges. The *FLG* gene is therefore likely to be important in the mechanism driving the difference between asymptomatic sensitisation and food allergy, most likely through an impaired skin barrier. Since children carrying one or more loss of function variants of the *FLG* gene are 1.5 times more likely to be food allergic, such genetic markers may be useful as an addition to clinical assessment in the diagnosis of food allergy.

After completing the DNA collection, we hope to replicate the results of the filaggrin gene in a larger study population and study the effect and diagnostic role of the other candidate genes. Furthermore we will use the genome wide data of the LifeLines cohort in the search for new genetic variants associated with food allergy.

The GENEVA study is supported by grants of the Nutricia Research Foundation and the JK de Cock stichting.

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