# Association of STAT6 Gene Variants with Food Allergy

Thesis

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*of M. Sc Degree in* ***Pediatrics***

By

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# List of Abbreviations

| Abb. | Full term |
|---|---|
| *ABC* | *Activated-B-cell* |
| *AD* | *Atopic dermatitis* |
| *AF* | *Artificially fed* |
| *APT* | *Atopy patch testing* |
| *AR* | *Allergic rhinitis* |
| *BA* | *Bronchial asthma* |
| *BAT* | *Basophil activation testing* |
| *BF* | *Breastfed* |
| *CMA* | *Cow's milk allergy* |
| *CMF* | *Cow-milk formula* |
| *CRD* | *Component-resolved diagnostics* |
| *DBPCFC* | *Double-blind placebo-controlled food challenge* |
| *DLBCLs* | *Diffuse large B-cell lymphomas* |
| *EEACI* | *European Academy of Allergy and Clinical Immunology* |
| *EGAC* | *Egyptian Accreditation Council* |
| *EoE* | *Eosinophilic esophagitis* |
| *EPIT* | *Epicutaneous immunotherapy* |
| *FA* | *Food allergy* |
| *FAM* | *Fluorescein amidites* |
| *FCER1A* | *Fc Fragment Of IgE Receptor Ia* |
| *FDA* | *US food and drug administration* |
| *FH* | *Family history* |
| *FLG-LOF* | *Fillagrin loss of function* |
| *GCB* | *Germinal center B-cell* |
| *GIT* | *Gastrointestinal* |
| *GWA* | *Genome wide association* |
| *HLA* | *Human leukocyte antigen* |
| *Ig* | *Immunoglobulin* |
| *IgE* | *Immunoglobulin E* |
| *IL* | *Interleukin* |
| *IQR* | *Interquartile range* |

# List of Abbreviations cont...

| Abb. | Full term |
|---|---|
| *IT* | *Immunotherapy* |
| *JAKs* | *Janus kinases* |
| *LEAP* | *Learning Early About Peanut Allergy* |
| *MGB* | *Minor groove binder* |
| *NS* | *Nonsignificant* |
| *OFC* | *Oral food challenge* |
| *OIT* | *Oral immunotherapy* |
| *ORMDL3* | *Orosomucoid-like 3* |
| *PA* | *Peanut allergy* |
| *PAI* | *Pediatric Allergy and Immunology Unit* |
| *PCR* | *Polymerase chain reaction* |
| *pSTAT6* | *Phospho-STAT6* |
| *S* | *Significant* |
| *SD* | *Standard deviation* |
| *serpin* | *Serine protease inhibitor* |
| *SERPINB* | *Serine protease inhibitors B* |
| *SNP* | *Single nucleotide polymorphism* |
| *SPSS* | *Statistical package for Social Science* |
| *SPT* | *Skin prick test* |
| *TAMRA* | *Tetramethyl-6-Carboxyrhodamine* |
| *TH2* | *Type-2 T helper cells* |
| *UCFA* | *Utrecht Center for Food Allergy* |
| *UK* | *United Kingdom* |
| *VIC* | *Victoria* |

# INTRODUCTION

Food allergy (FA) is a global health concern as it affects as many as 10% of children and has significant effects on family economics and health-related quality of life. It causes anaphylaxis which carries the risk of death. Several factors play important roles as risk factors for FA including genetics, host's intestinal flora, the timing, dosage, and frequency of exposure to various dietary allergens, as well as the allergenicity of various food proteins ***(Ferreira et al., 2007).*** A family history of atopy, especially of FA, is used to identify individuals at risk of FA ***(Hossny et al., 2011).***

Genetic predispositions may result in dysregulation of the immune system and lead to FA when exposed to environmental factors ***(Lack, 2008).*** Reproducible associations with FA were found for a limited number of genes such as Fillagrin loss of function (FLG-LOF) mutations ***(Venkataraman et al., 2014),*** variants of HLA genes ***(Hong et al., 2015),*** FCER1A, STAT6, IL13 genes ***(Suaini et al., 2019)*** and the SERPINB gene cluster on chromosome 18 ***(Max Delbrück Center for Molecular Medicine in the Helmholtz Association, 2017).***

The transcription factor STAT6 plays a role in activating cytokine signaling both in the immune cells and in target tissue cells including airway epithelium, keratinocytes and esophageal epithelial cells. STAT6 is activated by the cytokines IL-4 and IL-13 to mediate the pathogenesis of allergic disorders such as

asthma, atopic dermatitis, food allergy and eosinophilic esophagitis (EoE) ***(Krishnamurthy et al., 2016).*** Single nucleotide polymorphisms (SNPs) in the genes encoding IL-4, IL-13 and STAT6 are linked to FA and asthma ***(Tamura et al., 2003).***

Two SNPs in STAT6 gene were previously described to be associated with food allergy; rs324015 and rs1059513. As regards r324015, it was found to be associated with nut and cow's milk allergy ***(Amoli et al., 2002; van Ginkel et al., 2018),*** mild atopic asthma ***(Gao et al., 2000),*** a higher age of tolerance to cow's milk ***(Yavuz et al., 2013),*** local eosinophilia ***(Negoro et al., 2006)*** and when combined with a repeat homozygosity in STAT6, was significantly associated with atopic dermatitis, bronchial asthma, and food-related anaphylaxis ***(Tamura et al., 2003).***

With respect to rs1059513, it was found to be associated with nut allergy ***(van Ginkel et al., 2018),*** total IgE dysregulation ***(Duetsch et al., 2002; Schedel et al., 2004; Sharma et al., 2014; Granada et al., 2012)*** and increased concentrations of GM-CSF and TNF-α which altered immune responses at birth and caused the development of allergic diseases during childhood ***(Casaca et al., 2014).*** Moreover, an interaction between in IL13 rs20541 and STAT6 rs1059513 SNPs was found to cause a 1.52-fold increased risk of eczema ***(Ziyab et al., 2013).***

The genetic constitution relevant to the development of FA is largely unknown and differs with differing ethnicities. There are as yet no reports on the nature and role of genetic polymorphisms contributing to FA among Egyptians.

# AIM OF THE WORK

This work aimed to investigate the association of two selected SNPs in the STAT6 gene, rs324015, and rs1059513, with IgE mediated food allergy (FA) for identifying some of the genes incriminated in FA in Egyptian children. Learning about the roots of the problem will help design therapeutic approaches for FA.