The *COL5A3* and *MMP9* genes interact in eczema susceptibility

Patricia Margaritte-Jeannin 1,2*, Marie-Claude Babron 1,2, Catherine Laprise 3, Chloé Sarnowski 1,2, Myriam Brossard 1,2, Miriam Moffatt 4, William O. Cookson 4, Emmanuelle Bouzigon 1,2, Florence Demenais 1,2, Marie-Hélène Dizier 1,2 **

1 Inserm, UMR-946, Genetic Variation and Human Diseases unit, F-75010, Paris, France; 2 Univ Paris Diderot, Sorbonne Paris Cité, Institut Universitaire d’Hématologie, F-75010, Paris, France; 3 Université du Québec, Chicoutimi, Canada; 4 National Heart Lung Institute, Imperial College, London, UK.

*: these authors contributed equally

**: presenting author

Genetic studies of eczema have identified many genes, which explain only 14% of the heritability of this trait. Missing heritability may be partly due to ignored Gene–Gene (G-G) interactions. Our aim was to detect new interacting genes involved in eczema.

The search for G-G interaction in eczema was conducted using a two-step approach, which included a first step of gene selection based on biological knowledge related to eczema, and a second-step of interaction analysis of the selected genes. Analyses were carried out at both SNP and gene levels in three asthma-ascertained family samples: the discovery dataset of 388 French EGEA (Epidemiological study on the Genetics and Environment of Asthma) families and the two replication datasets of 253 French-Canadian SLSJ (Saguenay-Lac-Saint-Jean) families and 207 UK MRCA (Medical Research Council) families.

One pair of SNPs, rs2287807 in *COL5A3* and rs17576 in *MMP9*, that was detected in EGEA at $P_{\text{int-SNP}} \leq 10^{-5}$ showed significant interaction after meta-analysis of interactive effects estimated in EGEA, SLSJ and MRCA ($P_{\text{int-SNP}}=10^{-8}$ under the significant threshold of $10^{-7}$). Gene-based analysis confirmed strong interaction between *COL5A3* and *MMP9* ($P_{\text{int-gene}}=4x10^{-8}$ under the significant threshold of $4x10^{-6}$) by meta-analysis of the three datasets. When stratifying the data on asthma, this interaction remained in both groups of asthmatic and non-asthmatic subjects.

This study identified two new genes, *COL5A3* and *MMP9*, interacting on eczema susceptibility, independently from asthma. Further confirmation of this interaction as well as functional studies are needed to better understand the role of these genes in eczema.