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EFP European Federation of Periodontology — Periodontal Health for a Better Life

Scientific release from the European Federation of Periodontology

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Study:

Study: Genome-wide exploration identifies sex-specific genetic effects of alleles upstream NPY to increase the risk of severe periodontitis in men

Freitag-Wolf S, Dommisch H, Graetz C, Jockel-Schneider Y, Harks I, Staufenbiel I, Meyle J, Eickholz P, Noack B, Bruckmann C, Gieger C, Jepsen S, Lieb W, Schreiber S, König IR, Schaefer AS.
J Clin Periodontol 2014; 41: 1115–1121.

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Relevant background to study:

Periodontal disease expression is influenced by a complex interplay between genetics, socio-economic and other factors such as gender. Several epidemiological studies suggest a higher risk for chronic periodontitis in men compared with women. There is, however, no evidence for such a gender bias in aggressive periodontitis (AgP).

Studies investigating the genetic basis of AgP have been relatively small in scale with only a limited number of risk alleles identified. Moreover, characteristics such as gender and its potential influence upon disease expression were rarely analysed.

Study Aims:

To test the hypothesis that for AgP gender interacts with specific single nucleotide polymorphisms (SNPs) and alters disease risk.

Methods:

A genome-wide association study (GWAS) involving 329 German patients with AgP versus 983 controls was performed to investigate genetic constitution including gender as an interaction term for the expression of the disease. The SNP with the strongest gender association in AgP was further tested in an independent replication study of 382 AgP cases against 489 controls.
In the GWAS, whole genomes extracted from frozen blood samples were genotyped using Affymetrix Gene Chip Human Mapping 500K Arrays. The SNP with the strongest gene-gender interaction (SNP rs198712) was then genotyped in the replication study with the TaqMan Assay hCV9946741, using an automated platform. Logistic regression analysis was employed to study potential interactions between eligible SNPs and gender in AgP with a cut-off significance value of $p<0.05$. Gender-specific odds ratios (ORs) were calculated for the GWAS, the replication study and both studies pooled.
In addition, analysis of the annotation of the chromatin elements of different human cell types based upon ENCODE data was performed in order to assess the nature of the associated chromosomal region.

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Results:

- From the 287,224 SNPs analysed, 2,041 SNPs had a significant interaction with gender ($p<0.05$), SNP or the gene–gender interaction term. The most significant findings were for a region on chromosome 7 upstream of the gene neuropeptide Y (NPY) and included 11 SNPs. 10 exhibited p-values <5x10-5 in the gene–gender interaction and were in high linkage disequilibrium.
- The lead SNP was rs198712 with gender-specific Odds Ratios (ORs) of 1.629 for males and 0.689 for females and also showed the strongest interaction effect with gender when the Model-Based Multifactor Dimensionality Reduction (MB-MDR) analysis was performed.
- There was a difference of 12% in the Minor allele frequency (MAF) between the male cases and the controls (48% vs 36%) and a MAF difference of 9% between the female cases and controls (30% vs 39%), whilst there was no difference in the MAF of the controls and the cases overall (males and females, both 37%). These SNPs therefore showed no significant effect upon Aggressive Periodontitis unless gender was taken into account.
- In the replication study of the association on chromosome 7 upstream of NPY SNP rs198712, the gender-specific ORs were 1.304 for males and 0.832 for females. The MAF differences were smaller for males but comparable both for males and females to the initial explorative study.
- In silico analysis of the chromatin state of the NPY region showed that the associated chromosomal region that was tagged by rs198712, showed tissue-specific transcription and possessed a poised "silent" promoter.

Limitations, conclusions and impact:

- AgP cases were identified solely on radiographic criteria and an arbitrary age cut-off point.
- The use of different case definitions of aggressive periodontitis which differ in extent and severity of disease in the exploratory study compared to the replication study may have altered the effect size of the association.
- There is uncertainty as to whether potential confounders were accounted for either at the stage of study design or during statistical analysis.
- Multiple related genes in the same functional pathway may work together to confer disease susceptibility. The sample size in the current study is likely still too small to detect significance for other genes that may also be involved in disease susceptibility.
- Combining the explorative and replication data in order to obtain one pooled interaction p-value may be not always be considered as statistically optimal.

Conclusions:

An associated intergenic region of 140-kb, situated upstream of the gene NPY conferred an increased risk for aggressive periodontitis in men but a decreased risk in women. In a replication study, this region showed strong linkage disequilibrium upstream of NPY and also displayed a gene–gender interaction.

Impact:

The data provide evidence of a gender-dependent role for alleles in the region of the neuropeptide Y (NPY) locus in humans and support previous genome-wide findings for a role for NPY in periodontitis. The introduction of gender-stratified analysis may be important for the analysis of future genome-wide association studies.