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EuroPerio9 press release

Gum disease and coronary artery disease share genetic basis**Meta-analysis explores common molecular pathway to both diseases**

Amsterdam, the NETHERLANDS. 15 June 2018 – Results of a meta-analysis to be presented at EuroPerio9, the world's leading congress in periodontology and implant dentistry, found that gum disease and coronary artery disease (CAD) share a common genetic basis, involving the VAMP8 function (1).

“Knowledge of the shared genetic basis helps to understand the molecular mechanisms that underlie and predispose to the disease,” explained lead author, Dr Arne S Schäfer (Prof. Ph.D.) at the Department of Periodontology and Synoptic Dentistry, Charité University Medicine Berlin, Germany. “This knowledge will guide strategies for therapy but also allow the identification of risk groups for preventive care, before the disease manifests itself,” he said.

Strong evidence of association between CAD and periodontal disease (PD) has already been established. Both are among the most common diseases: CAD affects 110 million people worldwide and is the first cause of death, while PD affects 538 million people (2). Both diseases are frequently diagnosed together and have common risk factors, such as smoking and diabetes. Both are characterised by a chronic inflammatory process but, independent of those shared risk factors, previous studies (3,4) had suggested a few shared genetic variants.

“Our aim in undertaking this study was to further explore the joint genetic basis of CAD and PD. The identification of the shared genetic susceptibility factors will pinpoint relevant molecular pathways for the disease. This knowledge will yield very specific therapeutical targets for precision medicine. We believed that, given the localised nature of periodontitis which is confined to the oral cavity, there would be a small variety of different pathways that had the potential to contribute to both diseases,” said Dr Schäfer.

“What we did in this study, that took over ten years, was to look at every common variant in the entire DNA sequence, these are alternative building blocks called alleles, which are in the millions. We counted if a variant was more common in both CAD and periodontitis cases, compared to healthy controls. To rule out chance findings, which can be caused by random differences of natural variation, we counted all these variants in all patients of CAD and periodontitis that were available to us. This high number of analysed individuals and a replication of the results in an independent sample of cases and controls, allows to generalise our findings,” explained Dr Schäfer.

“In the discovery stage, we used a German sample with aggressive periodontitis (717 cases vs 4,213 controls) and the CARDIoGRAMplusC4D CAD meta-analysis dataset, including 60,801 cases and 123,504 controls. Replication was performed in an independent genome-wide association study (GWAS) meta-analysis dataset consisting of patients with either aggressive periodontitis or with chronic periodontitis,

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from Germany, Austria, The Netherlands and the United States of America (4,423 cases vs 6,219 controls),” said Dr Schäfer.

Researchers identified a variant in the promoter region of the gene VAMP8 (a promoter regulates the activity of a gene in response to other stimuli) to be significantly more frequent in CAD and periodontitis cases than in healthy controls, indicating the involvement of this gene in the aetiology of both diseases.

“VAMP8 is of special interest, because it is involved in the import and export of molecules and other substances into and out of the cells (acting as a sort of door). It is strongly expressed in the epidermis of cellular interfaces of barrier organs of the gastrointestinal tract, which includes the gingiva. We are now looking in detail at which direction the transport is affected in the disease processes and what substances are involved, e.g. microbial substances that get in or antimicrobial substances that get out of the gut,” commented Dr Schäfer.

Two single nucleotide polymorphisms (SNPs) at the known CAD risk loci ADAMTS7 (rs4468572) and VAMP8 (rs7568458) passed the pre-assigned selection criteria (PAgP-Ger <0.05 ; PCAD $<5 \times 10^{-8}$; PMeta $<$ PCAD, PAgP-Ger). SNP rs1561198 ($r^2 = 0.91$ with rs7568458) showed significant association in both disease phenotypes of PD (PD: $P=0.0005$ [1.04-1.17]; AgP: $P=0.005$, OR=1.16, 95%CI=[1.03-1.30]; CP: $P=0.008$, OR=1.09, 95%CI=[1.02-1.16]). For the associated haplotype block, allele specific cis-effects on VAMP8 expression were reported.

Asked for a “take home” message, Dr Schäfer said that it is important to retain that coronary artery disease and gum disease are not linked to lifestyle factors alone. “There are probably risk groups which have a genetic predisposition in response to certain factors. This also means that periodontitis does not increase the risk for CAD in general or vice versa. Nevertheless, a group of individuals may share a genetic predisposition, involving the VAMP8 function, which increases the risk for both diseases. While it is possible that one disease precedes the onset of the other, that does not necessarily mean that the manifestation of one causes the manifestation of the second disease,” highlighted Dr Schäfer.

Regarding a general message for the public, Dr Schäfer added that: “The most efficient way to prevent the onset of both heart and periodontal diseases is to quit smoking and live healthily.”

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Notes to Editors

Meta-analysis: A meta-analysis is an analysis that combines the results of multiple scientific studies in a statistically meaningful way.

Periodontitis: a serious gum inflammation that damages soft tissue and destroys the bone that supports teeth. It can lead to tooth loss. Periodontitis is usually the result of poor oral hygiene and is largely preventable with good habits such as brushing teeth twice a day and cleaning regularly between the teeth

Coronary Artery Disease (CAD): refers to a group of common cardiovascular diseases including angina, myocardial infarction and sudden cardiac death. Complications include heart failure and arrhythmias.

VAMP8: Vesicle associated membrane protein 8: protein encoded by the VAMP8 gene, involved in the fusion of synaptic vesicle

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Genome wide association studies (GWAS): also known as whole genome association studies (WGAS). They are observational studies of a genome-wide set of genetic variants in different individuals, to see if any variant is associated with a trait. When applied to human data, GWA studies compare the DNA of participants having varying phenotypes for a particular trait or disease.

References:

1. EuroPerio9 Abstract O017, Genome wide association meta-analysis of coronary artery disease and periodontitis reveals a novel shared risk locus. Presentation at the Biomarkers session on 21 June 2018, at 14:00.
2. "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". *Lancet*. 388 (10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6.
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4. The large non-coding RNA ANRIL, which is associated with atherosclerosis, periodontitis and several forms of cancer, regulates ADIPOR1, VAMP3 and C11ORF10. Gregor Bochenek et al. *Hum Mol Genet* 2013 Nov 27; 22(22):4516-27. Epub 2013 Jun 27.

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[About the EFP](#)

The European Federation of Periodontology (EFP) is an umbrella organisation of 30 national scientific societies devoted to promoting research, education and awareness of periodontal science and practice. It represents more than 14,000 periodontists and gum-health professionals from Europe, northern Africa, and the Middle East.

[About EuroPerio9](#)

EuroPerio is the world's biggest scientific meeting devoted to periodontology. The most recent of these triennial meetings, EuroPerio8, took place in London in June 2015 and brought together almost 10,000 people. EuroPerio9 will take place from 20 to 23 June 2018 at the [RAI](#), Amsterdam, The Netherlands.

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