CED/NOF-IADR
2024 Oral Health
Research Congress
12 — 14 Sept 2024
Geneva, Switzerland

0056

Prenatal and Genetic Determinants of Third Molar Agenesis

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Objectives Third molar agenesis (M3A) research may provide a better understanding of the etiology of craniofacial and dental development. We aimed at investigating determinants of M3A, including prenatal factors, ancestral background and genetic factors in the context of a genome-wide association study (GWAS).

Methods We included 4487 participants (mean age 13.62 years) from the Generation R study, a multiethnic population-based cohort. Orthopantomographs were assessed for M3A. Maternal smoking and alcohol consumption during pregnancy were assessed using questionnaires. Ancestral background was established using admixture analysis. The association between prenatal factors and M3A was analyzed with binary and multinomial logistic regression corrected for confounders. GWAS was conducted in a subset genotyped using microarrays and imputed to the 1000 Genomes Project panel (N=4192; 825 M3A cases) with a linear mixed modelling approach using SAIGE.

Results The prevalence of M3A was 19.7%; comprising the M3A of only mandible (N=286, 32%), maxilla (N=266, 30.2%) or both jaws (N=333, 37.8%). Maternal smoking (p=0.35) and alcohol consumption (p=0.74) were not significantly associated with M3A. Children of sub-Saharan African ancestry had significantly lower prevalence of M3A (9.3%) compared to European (20.8%) and Asian (19%) ancestries. African ancestry was significantly associated with M3A in the mandible and in both jaws, but not in the maxilla (OR=0.27, 95%CI:0.13-0.58, OR=0.19, 95%CI:0.08-0.44, OR=0.70, 95%CI:0.39-1.23). GWAS identified two variants at genome-wide significant levels (P<5x10-8). The top-associated variants with common minor allele frequency (MAF) mapped in the vicinity of *CACNA1S/ASCL5* (rs10920121, MAF=0.43, OR=1.46, P=3.56×10-11) and *TEX37/FOXI3* (rs6759657, MAF=0.19, OR=1.51, P=3.69x10-9).

Conclusions We found no evidence supporting the involvement of prenatal environmental factors in M3A. The prevalence of M3A is higher in children of European ancestral background. We report two variants in the vicinity of genes previously associated with tooth agenesis, suggesting M3A and hypodontia share a common genetic background.