Genome-wide association study of primary dentition pit-and-fissure and smooth surface caries

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Supplemental Methods

Details on subject recruitment and data collection have been described previously [Shaffer et al., 2011].

PF surfaces included buccal and occlusal surfaces of mandibular molars and lingual and occlusal surfaces of maxillary molars. SM surfaces included all other tooth surfaces. Phenotype assessment has been previously described in detail [Wang et al., 2010; Warren et al., 2002]. Inter- and intra-examiner concordance was high [Warren et al., 2002; Wendell et al., 2010].

All the genotype data are publicly available from dbGap (http://www.ncbi.nlm.nih.gov/gap, study accession designation: phs000095.v2.p1 for COHRA and IFS1; phs000440.v1.p1 for IFS2). Details regarding genotyping quality control can be found online (https://www.genvastudy.org/sites/www/content/files/datacleaning/data_cleaning_reports/Dental_Caries_Marazita_DCR_6-2-2010.pdf for COHRA and IFS1; https://www.genevastudy.org/sites/www/content/files/datacleaning/data_cleaning_reports/marazitaG_qc_report.pdf for IFS2). Imputation of un-genotyped autosomal SNPs and sporadic missing data of genotyped autosomal SNPs was per-formed for COHRA and IFS1 samples using BEAGLE software [Browning and Browning, 2009] and the HapMap Phase III reference panel. Details regarding imputation are available online (https://www.genevastudy.org/sites/www/content/files/datacleaning/imputation/Dental_Caries_Imputation_Report.pdf). In general, genotyping quality and imputation accuracy was excellent.

For association analysis, we filtered out SNPs with minor allele frequency < 0.02, Hardy-Weinberg equilibrium p-value < 0.001, or genotype call rate < 0.1, and also filtered out individuals with genotype call rate < 0.1, in either COHRA or IFS. As a result, 531,025 genotyped SNPs were included for dfs_{SM} scan and 531,230 for dfs_{PF} scan. Including imputed SNPs, the numbers were increased to 1,216,189 and 1,216,074, for smooth and pit-and-fissure scans, respectively.

Because the IFS1 and IFS2 samples were from the same cohort and genotyped using the same platform, they were merged together and mega-analyzed using the participant-level data. Then meta-analysis was used to combine the COHRA and IFS association results. Between-genotyping-center differences were checked by comparing allele frequencies among COHRA, IFS1 and IFS2. Overall, the concordance was excellent.

The threshold for suggestive significance was set at $\alpha = 1.0E\text{-}5$. All tests for genetic association were performed using PLINK [Purcell et al., 2007]. Manhattan plots, quantile-quantile plots and estimates of genomic inflation factor (λ) were generated using the R statistical package (R Foundation for Statistical Computing, Vienna, AU). LocusZoom [Pruim et al., 2010] was used to plot association signals for loci of interest. Cluster plots of observed allelic intensities were examined visually to ensure high genotype-calling quality for the top hit within each reported region. SNPs meeting criteria for suggestive significance were re-analyzed for the COHRA sample using likelihood-based methods that condition on the family-structure of the sample as implemented in SOLAR [Almasy and Blangero, 1998].

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