Association of Low-Frequency Genetic Variants in Regulatory Regions with Non-Syndromic Orofacial Clefts

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Supplemental Material

**Supplemental Figure S1: Results of genetic association tests of variants with MAF less than 5%:** Quantile-quantile plots depict the observed log10-transformed p-values (y-axis) vs. the expected distribution of p-values (x-axis) under the null hypothesis of no association. Each point represents the evidence of genetic association for a specific craniofacial enhancer. The top panels show results for CP and the bottom panels show results for CL/P. Left panels show results of CMC scans, and right panels show results of SKAT scans. Horizontal dashed lines represent the threshold for suggestive association (p-value < 0.004).



CP

CL/P

CMC

CMC

SKAT

SKAT

**Supplemental Figure S2: SNP genotype cluster plot shows evidence of a null allele.** The putative enhancer located on chromosome 1 at base pair position 209663057-209663962 (hg19) showed suggestive evidence of association in the scan of variants with MAF < 5% (SKAT p-value = 0.0011, CMC p-value = 0.017), and the SNP rs141738759 located in this enhancer region individually shows evidence of association (p-value = 0.0002). However, inspection of the cluster plot for this SNP showing missing genotype calls due to a presumed null allele; therefore, we deem this association as potentially spurious.

