Nonsyndromic cleft lip with or without cleft palate (NSCLP) is a common birth defect with a multifactorial etiology. Despite decades of research, the genetic underpinnings of NSCLP still remain largely unexplained. A genome wide association study (GWAS) of a large NSCLP African American family with seven affected individuals across three generations found evidence for linkage at 8q21.3-24.12 (LOD =2.98). This region contained three biologically relevant candidate genes: *Frizzled-6 (FZD6)* (LOD = 2.8), *Matrilin-2 (MATN2)* (LOD = 2.3), and *Solute Carrier Family 25, Member 32 (SLC26A32)* (LOD = 1.6). Sequencing of the coding regions and the 5’ and 3’ UTRs of these genes in two affected family members identified a rare intronic variant, rs138557689 (c.-153+432A>C), in FZD6. The rs138557689/C allele segregated with the NSCLP phenotype; *in silico* analysis predicted and EMSA analysis showed that the 13857689/C allele alters DNA binding. FZD6 is part of the WNT pathway, which is involved in craniofacial development, including midface development and upper lip fusion. Our novel findings suggest that an alteration in FZD6 gene regulation may perturb this tightly controlled biological pathway and in turn contribute to the development of NSCLP in this family. Studies are underway to further define how the rs13857689/C variant affects expression of FZD6.

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