Cleft lip and palate article pdf

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Most orofacial clefts, like most common congenital anomalies, are caused by the interaction between genetic and environmental factors (see the image below). Etiology of cleft lip and palate anomalies. In those instances, genetic factors create a susceptibility for clefts. When environmental factors (ie, triggers) interact with a genetically susceptible genotype, a cleft develops during an early stage of development. The proportion of environmental and genetic factors varies with the sex of the individual affected with cleft. In CL and CP, it also varies with the severity and the unilaterality or bilaterality of the cleft anomaly; the highest proportion of genetic factors are in the subgroup of females with a bilateral cleft, and the smallest proportion is in the subgroup of males with a unilateral cleft. Thus, the classic multifactorial threshold (MFT) model of liability (see the first image below) can be applied to CL/P as the multifactorial model of liability with four different thresholds (see the second image below). Multifactorial threshold model for the distribution of liability for cleft lip and palate. Four-threshold multifactorial threshold model of the liability for cleft lip and palate. This model can facilitate understanding of differences in values of risk of recurrence as well as differences in prevention approaches between different subgroups of clefts. [10] Theoretically, the subgroup of clefts closest to the population average should have the highest population prevalence, the lowest value of heritability, and thus the lowest risk of recurrence. This was confirmed in a large, population-based study of whites with clefts (see the image below). [10] Decreased occurrence of orofacial clefts. The value of heritability expresses a ratio of genetic and nongenetic factors. Heritability is equal to 1 for conditions completely controlled by genetic factors and equal to 0 for conditions completely controlled by environmental factors. A higher proportion of environmental factors indicates a lower risk of recurrence and also gives a better chance to act in prevention, because the only etiologic factors that can be changed are environmental factors. Thus, the subgroup whose average prevalence is closest to the population average represents males affected with a unilateral CL/P. This subgroup is most common among orofacial clefts; the risk of recurrence for siblings and for offspring of an individual with cleft is the lowest, the value of heritability is the lowest, and efficacy of primary prevention is the highest (see Treatment, Prevention). A cleft develops when embryonic parts called processes (which are programmed to grow, move, and join with each other to form an individual part of the embryo) do not reach each other in time and an open space (cleft) between them persists. In the normal situation, the processes grow into an open space by means of cellular migration and multiplication, touch each other, and fuse together. In general, any factor that could prevent the processes from reaching each other—for instance, by slowing down migration or multiplication of neural crest cells, by stopping tissue growth and development for a time, or by killing some cells that are already in that location—would cause a persistence of a cleft. Also, the epithelium that covers the mesenchyme may not undergo programmed cell death, so that fusion of processes cannot take place. [7] Considerable interest has developed in the identification of genes that contribute to the etiology of orofacial clefting. Advances in modern molecular biology, developments in methods of genome manipulation, and availability of complete genome sequences led to an understanding of the roles of particular genes that are associated with embryonic development of the orofacial complex. [11] The first candidate gene was transforming growth factor-α (TGFA), which showed an association with nonsyndromic CLP in a white population. [12] Lidral et al investigated five different genes (TGFA, BCL3, DLX2, MSX1, TGFB3) in a largely white population from Iowa. [13, 14] They found a significant linkage disequilibrium between CL/P and both MSX1 and TGFB3 and between CP and MSX1. The TGFB3 gene was identified as a strong candidate for clefting in humans based on both the mouse model [15] and the linkage disequilibrium studies. [16, 14, 17] Other candidate genes that were described as being associated with nonsyndromic CLP included D4S192, RARA, MTHFR, RFC1, GABRB3, PVRL1, and IRF6. MSX1 was found to be a strong candidate gene involved in orofacial clefts and dental anomalies. Analysis of the MSX1 sequence in a multiplex Dutch family showed that a nonsense mutation (Ser104stop) in exon 1 segregated with the phenotype of nonsyndromic cleft lip and palate. [18] Some have proposed that cleft palate in MSX1 knock-out mice is due to insufficiency of the palatal mesenchyme. [19] Zucchero et al reported that variants of IRF6 may be responsible for 12% of nonsyndromic cleft lip and palate, suggesting that this gene would play a substantial role in the causation of orofacial clefts. [20] A meta-analysis of all-genome scans of subjects with nonsyndromic cleft lip and palate, including Filipino, Chinese, Indian, and Colombian families, found a significant evidence of linkage to the region that contains interferon regulatory factor 6 (IRF6). [21] Also, gene-gene interactions have been examined. A complex interplay of several genes, each making a small contribution to the overall risk, may lead to formation of clefts. Jugessur et al reported a strong effect of the TGFA variant among children homozygous for the MSX1 A4 allele (9 CA repeats). [22] Much remains to be done in the evaluation of gene-environment interactions. Studies of the role of smoking in TGFA and MSX1 as covariates suggested that these loci might be susceptible to detrimental effects of maternal smoking. [17, 23] Folate-metabolizing enzymes such as methylenetetrahydrofolate reductase (MTHFR), which is a key player in etiology of neural tube defects, and RFC1 are considered candidate genes on the basis of data that suggest that folic acid supplementation can reduce incidence of nonsyndromic cleft lip and palate. [24] Of the more than 30 potential candidate loci and candidate genes throughout the human genome have been identified as strong susceptibility genes for orofacial clefts, MSX1 (4p16.1), TGFA (2p13), TGFB1 (19q13.1), TGFB2 (1q41), TGFB3 (14q24), RARA (17q12), and MTHFR (1p36.3) are among the strongest candidates. [21, 25, 26] The TGFB3 gene was identified as a strong candidate for clefting in humans based on a mouse model. Generally, palatogenesis in mice parallels that of humans and shows that comparable genes are involved. [27] Kaartinen demonstrated that mice lacking the TGFB3 peptide exhibit cleft palate. [15] In addition, the exogenous TGFB3 peptide can induce palatal fusion in chicken embryos, although the cleft palate is a normal feature in chickens. [28] In humans, association studies between TGFB3 and nonsyndromic CL/P showed conflicting results. Lidral reported failure to observe an association of a new allelic variant of TGFB3 with nonsyndromic CL/P in a case-control study of the Philippines' population. [13] Another study by Tanabe analyzed DNA samples from 43 Japanese patients and compared results with those from 73 control subjects with respect to four candidate genes, including TGFB3. [29] No significant differences in variants of TGFB3 between case and control populations were observed. On the other hand, subsequent case-control association studies, family-based studies, and genome scans supported a role of TGFB3 in cleft development. Beaty examined markers in five candidate genes in 269 case-parent trios ascertained through a child with nonsyndromic orofacial clefts; [17] 85% of the probands in the study were white. Markers at two of the five candidate genes (TGFB3 and MSX1) showed consistent evidence of linkage and disequilibrium due to linkage. Similarly, Vieira attempted to detect transmission distortion of MSX1 and TGFB3 in 217 South American children from their respective mothers. [30] A joint analysis of MSX1 and TGFB3 suggested a possible interaction between these two genes, increasing cleft susceptibility. These results suggest that MSX1 and TGFB3 mutations make a contribution to clefts in South American populations. In a study of the Korean population, Kim reported that the G allele at the SfaN1 polymorphism of TGFB3 is associated with an increased risk of nonsyndromic CL/P. The population study consisted of 28 patients with nonsyndromic CL with or without CP and 41 healthy controls. [31] In 2004, Marazita performed a meta-analysis of 13 genome scans of 388 extended multiplex families with nonsyndromic CL/P. [21] The families came from seven diverse populations including 2551 genotyped individuals. The meta-analysis revealed multiple genes in 6 chromosomal regions including the region containing TGFB3 (14q24). In the Japanese population, blood samples from 20 families with nonsyndromic CL/P were analyzed by using TGFB3 CA repeat polymorphic marker. On the basis of the results of the study, the investigators concluded that either the TGFB3 gene itself or an adjacent DNA sequence may contribute to the development of cleft lip and palate. [32] A study by Ichikawa et al investigated the relationship between nonsyndromic CL/P and seven candidate genes (TGFB3, DLX3, PAX9, CLPTM1, TBX10, PVRL1, TBX22) in a Japanese population. [33] The sample consisted of 112 patients with their parents and 192 controls. Both population based case-control analysis and family based transmission disequilibrium test (TDT) were used. The results showed significant associations of single-nucleotide polymorphisms (SNPs) in TGFB3 and nonsyndromic CL/P, especially IVS+5321(rs2300607). [33] Although IVS-1572 (rs2268625) alone did not show a significant difference between cases and controls, the haplotype "A/A" for rs2300607- rs2268625 showed significant association. The author concluded that the results demonstrated positive association of TGFB3 with nonsyndromic CL/P in Japanese patients. A study by Bu et al found evidence of an association between nonsyndromic CLP and SNPs in FOXF2 (6p25.3). [34] Several micromanifestations of orofacial clefts have been studied, [35, 36] and additional candidate genes associated with these minimal, clinically less significant anomalies have been suggested. [35, 37] Associations of specific candidate genes with nonsyndromic CL/P have not been found to be consistent across different populations. This may suggest that multiplicative effects of several candidate genes or gene-environmental interactions are noted in different populations. The identification of factors that contribute to the etiology of nonsyndromic CL/P is important for prevention, treatment planning, and education. With an increasing number of couples who seek genetic counseling as a part of their family planning, the knowledge of how specific genes contribute to formation of nonsyndromic CL/P has gained an increased importance.

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