

## **The causes of Cleft Lip and Palate: where have we got to with gene research?**

**Dr Philip Stanier, researcher at Imperial College, London, provides an update.  
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Facial clefts affecting the lip and/or palate (CL/P) are among the most common birth defects worldwide and affect around 1000 newborn babies each year in the UK (5,000 in the US). With this high incidence, it is surprising that so little is known about the underlying cause. Without some knowledge of the underlying cause, it is very difficult to conceive novel treatment or preventative therapy. From both family and twin studies (studies on sets of twins) it has long been known that there is a strong inherited component to the defect but this is complicated by environmental risk factors such as diet. Many studies have attempted to identify the predisposing genes by studying carefully chosen candidate genes in large collections of cleft patients. Unfortunately, due to the complexity of the disorder, most studies have failed to identify major risk factors.

Recently, however, this may have changed, with several important studies finding genes of significance, each using a different approach or model system. A frequent mutation was identified in a gene encoding a cell adhesion molecule (PVRL1) in patients with Margarita Island syndrome (from the Islands population). Cleft lip is a common feature although this is usually associated with ectodermal dysplasia. This mutation was also found to be quite prevalent in CLP patients in the surrounding Venezuelan mainland although its role in patients from other geographical locations has yet to be determined. Another breakthrough came in the identification of the gene (IRF6) that is mutated in a rare condition called van de Woude syndrome. These patients have cleft lip and/or palate in association with lip pits. It is not yet clear whether this gene plays a role in patients with isolated clefts.

Work in my group has concentrated on several unusual families in which cleft palate was inherited in a strong and predictable fashion, suggesting a specific gene was the primary influence. Following a lengthy search, we identified a gene on the X chromosome called TBX22 (for T-box 22). This gene encodes a transcription factor protein, which is responsible for switching on or off other genes in the developing fetus. In this case we found that TBX22 is only active in the fetal palate and is therefore important in regulating genes that are of specific relevance to palate development. The families we studied all had mutations in the TBX22 gene. We have also extended these studies to sporadic cases and found that up to 5% of cleft palate patients have TBX22 mutations. Given the complexity of the disorder, the mutation frequency is a lot higher than would have previously been predicted.

Clearly some significant discoveries have recently been made as to the causation of facial clefts. This is valuable at several levels and gives much hope for the future. For example, a precise knowledge of the genes involved can help in diagnosis and genetic counselling. Identifying the genetic pathways that are involved will lead to the identification of novel genes that are likely to be involved in craniofacial development. Finally, understanding the underlying biology of clefting may ultimately lead to the development of a preventative therapy.