We defined a selection pipeline involving all possible data combinations, and identified those genes specifically involved in the disease and minimizing variations between samples and different cell cultures. The comparison between control and NSCL/P patients yielded 56 genes. Subsequent signaling pathway analyses involving the identified genes, suggested involvement of three different pathways. In particular, we concentrated on the up-regulation of 3 candidates genes (COL15A1, PPT2, ERAP2). All expression results were confirmed by real time PCR.

Our results suggest that expression profile differences in stem cells isolated from normal and CLP patients can identify candidate genes which had not been previously detected in the multitude of association analyses performed to date. Our work is now moving towards functional studies involving these genes. CEPID/FAPESP, CNPq.

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06-P007

Different functional roles of FGF2 and FGF10 signaling in S252W FGFR2 cells: Impact in the Apert phenotype?

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S252W mutation in the ligand binding region of FGF Receptor 2 (FGFR2) causes a severe form of congenital craniosynostosis associated with syndactyly called Apert Syndrome (AS). This mutation leads to prolonged receptor engagement and violation of FGFR2c isoform ligand binding specificity. Moreover studies have suggested an important role of FGF2 and FGF10 in AS pathological process: signaling through FGF2 might be associated to the craniofacial phenotype whereas FGF10 might be involved with syndactily. Therefore, we aimed to investigate if FGF10, that binds to mutant but not to wild-type (WT) FGFR2 and FGF2 lead to different cellular response. We performed transcriptional profiling of FGF-treated fibroblasts from coronal suture periosteum of 3 AS patients and 3 age- and sex-matched controls. Non-stimulated and harvested AS cells compared to WT cells showed 134 differentially expressed genes (DEGs) mainly related to extracellular region process (DAVID Bioinformatics Database Analysis , Enrichment Score = 3.89) and down-regulation of 3 Wnt/β-catenin canonical pathway genes ($p = 0.02$). Mutant FGFR2 signaling by FGF2 had an enrichment of Ribosomal protein genes (ES = 4.95) and up-regulation of 5/134 Oxidative Phosphorylation Pathway genes ($p = 0.004$). FGF10 treatment in mutant fibroblasts showed 100 DEGs, 5 of which were associated to hypoxia response pathways ($p = 0.022$). Extracellular region process (ES = 3.91) was the most enriched GO term in this list. Thus, S252W FGFR2 leads to distinct downstream signaling in response to different FGFs, possibly due to loss of ligand binding specificity.

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06-P008

Loss of *Tbx22* causes submucous cleft palate, ankyloglossia and choanal atresia

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Cleft palate is a common birth defect, with an incidence of approximately 1 in 1500. Mutations in TBX22, which encodes a T-box transcription factor, result in X-linked cleft palate and ankyloglossia. This is known to account for approximately 5% of all cleft palate patients. Although these defects are obvious at birth, the underlying developmental pathogenesis remains unclear.

Here, we have created a $Tbx22^{null}$ mouse, which has a submucous cleft palate (SMCP), similar to the human phenotype, with a small minority showing overt clefts. In addition we find ankyloglossia and oro-nasal defects, including choanal atresia. In the choanae the oro-nasal membrane persists or is only partially ruptured. Each of these defects can cause severe breathing and/or feeding difficulties in the newborn pups, which results in about 50% post-natal lethality. Analysis of the craniofacial skeleton demonstrates a marked reduction in bone formation in the posterior hard palate, resulting in the classic notch associated with SMCP. Our results suggest that Tbx22 plays an important role in the osteogenic patterning of the posterior hard palate. Ossification is severely reduced after condensation of the palatal mesenchyme, resulting from a delay in the maturation of osteoblasts.

Rather than being involved in palatal shelf closure, we show that Tbx22 is a major determinant for intramembranous bone formation in the posterior hard palate, which underpins normal palate development and function. These findings could have important implications for the molecular diagnosis in patients with SMCP and/or in patients with unexplained choanal atresia.

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06-P009

A role for Abca12 in regulating terminal differentiation and lipid balance in the developing epidermis

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