LETTER TO JMG

TBX22 mutations are a frequent cause of cleft palate

A C B Marçano, K Doudney, C Braybrook, R Squires, M A Patton, M M Lees, A Richieri-Costa, A C Lidral, J C Murray, G E Moore, P Stanier


C left lip and/or cleft palate is among the most frequent birth defect seen in humans, with a reported prevalence of 1 in 700 births worldwide. Development of the secondary palate is a complex coordinated sequence of events, beginning with the appearance of palatal shelves from the first branchial arch derived maxillary prominences during the sixth week of embryogenesis. This involves mesenchymal–epithelial interactions, cell differentiation, migration, and transformation, with the interactive role of soluble growth factors, extracellular matrix molecules and their receptors, and programmed cell death. A disruption anywhere in the required sequence may result in a failure of the palate to close.

A genetic involvement in clefts was first recognised by Fogh-Anderson, with the majority of cases thought to display a multifactorial mode of inheritance. Analysis of recurrence risk patterns of cleft lip with or without cleft palate (CLP) indicates that there are likely to be few major loci interacting epistatically with an oligogenic background. As a consequence, there have been numerous studies to identify genetic determinants, either studying individual candidate genes and loci, or screening at the whole genome level. These efforts have been encouraged by the many candidates revealed by mouse mutants that exhibit a cleft as at least part of their phenotype. Nevertheless, the results of many of these studies have not been informative, with only a few candidate genes or loci being strongly implicated in human CL/P or CP only. As a consequence, the mechanisms of interaction, which probably include both genes and the environment, remain poorly understood. Recently, however, significant progress has been made with the identification of gene mutations in several forms of CL/P and CP. These include the cell adhesion molecule PVRL1 and the transcription factors MSX1, IRF6, and TBX22.

TBX22 encodes a T box containing transcription factor that is mutated in families with X-linked cleft palate including ankyloglossia (CPX; OMIM 303400). CPX has been described in a small number of families exhibiting a strong X linked Mendelian inheritance. The cleft phenotype predominantly affects males who show variation ranging from a complete cleft of the secondary palate, submucous cleft, or bifid uvula to high arched palate. Ankyloglossia (tongue tie) is frequently seen in affected patients and carrier females, and has proved to be a useful indicator of CPX. Temporal and spatial studies using in situ hybridisation in both human and mouse has shown that TBX22/Tbx22 is expressed primarily in the palatal shelves and tongue during palatogenesis, indicating a specific role of TBX22 in both palatal and tongue development. In addition to families with well defined X linked inheritance, TBX22 mutations have been identified in several families where pedigree size and/or family history were too limited to predict mode of inheritance. In these cases, ascertainment was largely based on the presence of ankyloglossia as well as cleft palate.

In this study, we investigated the prevalence of TBX22 mutations in a cohort of CP patients from different ethnic backgrounds, who were randomly ascertained and were not selected on the basis of likely X linked inheritance or the co-occurrence of ankyloglossia. We also present several TBX22 mutations in new CPX families as well as an analysis of the phenotype–genotype correlations found in familial cases. Our findings suggest that TBX22 mutations are responsible for a significant proportion of CP cases.

Key points

- Cleft palate is a common birth defect, with a poorly understood molecular aetiology. Cleft palate with X linked inheritance (CPX) has been considered a rare form of the disorder, recently shown to result from mutations in the transcription factor TBX22.
- We analysed TBX22 in a large random sample of cleft palate patients with no pre-selection for inheritance or ankyloglossia, a common associated feature of CPX. We found coding mutations in 5/200 patients in North American and Brazilian cohorts, with an additional four putative splice site mutations.
- We also describe mutations in novel CPX families and present a combined phenotype/genotype analysis of the familial cases described to date. Males frequently exhibit cleft palate and ankyloglossia together (78%), as do a smaller percentage of carrier females. Mutations within families can result in either cleft palate only, ankyloglossia only, or both, indicating that these defects are distinct parts of the phenotypic spectrum.
- We conclude that TBX22 is a significant risk factor for cleft palate. While ankyloglossia is not always present, a diagnosis of CPX is strongly supported by a positive family history and the tongue defect.
- Recognition of CPX in the complex pool of cleft palate patients will offer the potential for greatly improved genetic counselling.

Materials and methods

Patients

Blood samples from 256 random or consecutive consenting CP patients were collected for DNA analysis from three geographically distinct populations: the Philippines, North America, and Brazil. Samples were obtained following informed consent with local ethical approval. The Filipino cohort are principally Asian, while the North American and Brazilian cohorts are principally Caucasian and have a similar ethnic background. A total of 189 patients were randomly ascertained and 67 were selected because of the presence of ankyloglossia as well as cleft palate.

Abbreviations: CL/P, cleft lip or palate; CP, cleft palate; CPX, cleft palate with X linked inheritance
TBX22 mutations are a frequent cause of cleft palate

Brazilian cohorts are of mixed origin, including white European and African descent. For each patient, a detailed phenotype was obtained, taking note of cleft type and associated features such as presence or absence of ankyloglossia and positive or negative family history. Syndromic features were described in 18 of the patients, the majority classified as Pierre-Robin syndrome (table 1). While the frequency of a positive family history is similar in different groups, the strikingly high incidence of ankyloglossia seen in the Brazilian cohort is notable. The general prevalence of ankyloglossia is not well documented, with reports varying from 0.04–5%. Currently, it is not known whether the tongue defect is more common in the Brazilian population than elsewhere. Alternatively, this may reflect differences in diagnostic criteria or simply a regional difference local to the collection/treatment centres, where population frequencies may be skewed.

Two families with the characteristic CPX features of suspected X linked inheritance and/or the presence of ankyloglossia were also analysed for TBX22 mutations. For family K, which is of white European origin, the proband presented with cleft palate only and had a brother with a cleft palate and a cousin with absent uvula. The mother and her sister both have ankyloglossia. The maternal grandfather was reported to have a cleft palate with ankyloglossia unknown. In family W, also of white European origin, the proband presented with cleft palate and ankyloglossia and the family includes a further five affected males; one with absent tonsils (III.2) and two including ankyloglossia. Consistent with a semi-dominant X linked inheritance pattern, ankyloglossia was also observed in all obligate carrier females.

**Mutation analysis**

DNA was extracted from blood samples according to standard procedures. Each patient was examined for TBX22 variants following DNA sequencing of PCR amplified genomic fragments containing the flanking splice site junctions and exons 1–8 as previously described. Sequence was analysed using Sequencher (version 4.1.2; Gene Codes Corporation, Ann Arbor, MI, USA). For each variant, normal controls (including Brazilian, white European, and Filipino) were screened to indicate whether the sequence was likely to represent a non-causative polymorphism. In addition, where DNA samples were available, parents or siblings were also screened for the same variant.

**RESULTS**

To establish whether TBX22 may contribute to the general causation of idiopathic CP, 256 cleft palate patients were screened for DNA mutations. No mutations were detected in any of the 18 syndromic patients within this cohort. In the remaining 238 CP patients and controls, 15 different sequence variants were identified (table 2, fig 1). This included five potentially disease causing mutations affecting the coding region as well as several putative splice site mutations, none of which were present in control individuals. Four of the coding region mutations were found in patients with a positive family history for clefts and/or ankyloglossia and one in a patient with no known family history.

In the Brazilian CP group (n = 102), four patients with mutations that directly affected the coding region were identified. These included a 2 bp deletion in exon 1 (105–106delGC; numbering for all mutations found within the putative transcript starts at the adenine (A) residue of the ATG initiation codon) that results in a frameshift, potentially introducing a premature stop codon (fig 2). This male patient has both cleft palate and ankyloglossia but has no previous family history of clefting or tongue defects. Next, a single base substitution (361A→G) was identified in exon 3 in a familial male patient with ankyloglossia (fig 2). The mother and a maternal aunt both had ankyloglossia, while two maternal male cousins were reported to have cleft palate with ankyloglossia unknown. This resulting missense change (M121V) occurs at a position conserved throughout all T box genes and species. Finally, a 3 bp insertion (581–582insCAG) introducing an additional serine residue was detected in two unrelated male patients (fig 2). One of these has an extended family history for clefts and ankyloglossia and was previously reported as a familial case. The other patient with cleft palate and ankyloglossia has a mother with the same phenotype but no additional family history. There is no known common ancestry between these two families for at least three generations; however, haplotype analysis with closely linked flanking markers demonstrated common alleles, possibly due to a founder effect (data not shown).

In the North American CP group (n = 94), one missense mutation was identified. This was a single base transition 548C→T resulting in an amino acid substitution P183L that was identified in a male patient with cleft palate only (fig 2). While the father of this patient was also reported to have cleft palate only, both the mother and maternal uncle have ankyloglossia. The proband cannot inherit TBX22 from the father and has inherited the mutation from the maternal X chromosome. This position is highly conserved in T box genes and is based on the crystal structure of the Brachyury T domain. This lies within a β barrel and corresponds to the putative site of contact for dimerisation. As is the case for all of the novel missense mutations described in this report, the position is conserved in mouse, rat, and chick Tbx22 (fig 3). It is likely therefore that this maternally inherited mutation significantly contributes to the phenotype of the proband.

In both the North American and Brazilian cohorts, a number of other single nucleotide alterations were detected (table 2). Several of these were identified multiple times either in patients alone, or in both patients and controls. The latter group is most likely to be non-causative polymorphisms, while a functional role of the former group cannot be excluded without further study. Of particular note, however, are two different sequence variants close to splice sites that were not seen in any of the unaffected controls studied. One is a potentially transcribed transversion (→G) that occurs immediately upstream of the translation start (ATG) codon (fig 2). This was present in two unrelated sporadic Brazilian male patients, both with ankyloglossia, but not in any other cleft palate individual or controls (table 2). Interestingly, the location of this change is ambiguous with respect to the transcript owing to the presence of an alternative 5’ exon. From 5’RACE data, this mutation is located in the 5’ UTR, 9 bp upstream of the start ATG. However, both the mouse and human EST databases contain

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**Table 1** Characteristics of cleft palate patients screened for TBX22 mutations

<table>
<thead>
<tr>
<th>Origin of patient</th>
<th>Family history</th>
<th>Male</th>
<th>Female</th>
<th>Syndromic</th>
<th>CPO</th>
<th>CP-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td>60</td>
<td>45</td>
<td>26</td>
<td>77</td>
<td>11</td>
</tr>
<tr>
<td>Brazil</td>
<td></td>
<td>45</td>
<td>57</td>
<td>271</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>Philippines</td>
<td></td>
<td>33</td>
<td>16</td>
<td>201</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>113</td>
<td>143</td>
<td>75</td>
<td>181</td>
<td>18</td>
</tr>
</tbody>
</table>

*Includes putative Pierre-Robin syndrome (12), Stickler syndrome, chromosomal anomalies, Goldenhar-, and campomelic dysplasia-like syndromes; includes CP only probands with first degree relative with ankyloglossia as part of their phenotype; includes two pedigrees with male to male transmission; includes four pedigrees with male to male transmission.

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sequences suggesting the presence of several different isoforms of TBX22 that use different upstream exons. These alternative transcripts utilise a splice site two bp upstream of the ATG, in which the \(-9C\text{--}G\) mutation is intronic and located within five nucleotides of the AG splice sequence. The entire sequence containing the splice site and sequence variant is completely conserved between mouse and human (mouse: CCCCCTCCAGGGATG; human: CCCCCTCAGGGATG) and the mutation was not seen in a total of 445 control chromosomes (table 2). The second variant is present in intron 1, at IVS1-13C\text{--}G and found in two sporadic CP only North American male patients. While the homology between the human and mouse sequence is not so strong as the \(-9C\text{--}G\) variant (mouse: CCCCCTGCTAGCAG; human: TCTGTGTCAGCAG), the sequence was also absent from normal chromosomes (table 2). Functional studies will be required to determine the significance of these changes.

Several coding region variants were identified (table 2), including a G559A transition that causes a missense glutamate to lysine (E187K) change within the T box motif. This amino acid position is variable in different T box genes and amino acid sequence (L24L) and most likely represents an ethnically or geographically restricted origin. Finally, one Filipino patient was heterozygous for a single base transition (1591A\text{--}T) in exon 8, which is 31 bp beyond the stop codon. This 3′UTR sequence is well conserved (human: acaattAcatgtaaaca; mouse: acaatttAcatgtaagca) and was not seen in other patient groups. However, the sequence variant was present in two unaffected Filipino controls (table 2), so while an effect on gene expression has yet to be ruled out, it is most likely a non-functional polymorphism.

In contrast to the genetically heterogeneous North American and Brazilian cohorts, no mutations were identified that were strongly suggestive of causation in the Filipino group. Nevertheless, three different single base substitutions were identified, including a common single base deletion, IVS7+56delC, and two changes that are transcribed but are not predicted to alter the mRNA or protein in an obvious way (table 2). The novel coding region variant 72C\text{--}T was found in three Filipino patients and in Filipino controls (7/149) but not in patients or controls of other ethnicities. This change does not alter the putative amino acid sequence (L24L) and most likely represents an ethnically or geographically restricted origin. Finally, one Filipino patient was heterozygous for a single base transition (1591A\text{--}G) in exon 8, which is 31 bp beyond the stop codon. This 3′UTR sequence is well conserved (human: acaattAcatgtaaaca; mouse: acaatttAcatgtaagca) and was not seen in other patient groups. However, the sequence variant was present in two unaffected Filipino controls (table 2), so while an effect on gene expression has yet to be ruled out, it is most likely a non-functional polymorphism.

In addition to previously reported families and the above patient groups, two new families were identified with possible X linked inheritance and/or presence of ankyloglossia (table 3). In each case, probands were screened for
mutations in TBX22 as described previously. The proband of family K presented with cleft palate only, but the presence of ankyloglossia in the mother was suggestive of the typical semi-dominant X linked inheritance of CPX. An A786T transversion was detected in exon 5, which is predicted to result in the missense mutation N264Y (fig 4). This amino acid position is located in the T box domain at the start of the alpha helix 3. This position recognises the target DNA in the minor groove and bridges the DNA backbone. The position is conserved throughout all T box genes and species available. The family history of family W also strongly indicated CPX and was found to have a G→T transversion at IVS4+1 (fig 4). This affects the invariant GT splice consensus sequence and is precisely the same variant identified in the Brazilian family BR1 reported previously. Haplotype analysis with close flanking markers shows no other common alleles, indicating that these mutations arose independently (data not shown). Neither mutation was detected in 200 control chromosomes.

Ankyloglossia is a commonly associated feature found in X linked cleft palate and is frequently the only phenotype in carrier females. It has been regarded as an important diagnostic sign suggesting CPX in the absence of sufficient evidence for X linked inheritance. We and others have previously shown that TBX22/Tbx22 is specifically expressed both in the developing palatal shelves and future lingual frenulum during the time of palatogenesis.33 As there is a reported correlation with the type and location of mutation within TBX5 and the clinical phenotype,34 we examined the concordance of palate and tongue phenotype with mutation

Figure 2  TBX22 mutations identified in randomly collected cleft palate patients. Sequence electropherograms are from patients' genomic DNA (top panels) amplified with exon specific primers and compared with unaffected control DNA samples (bottom panels). Boxed sequences represent 3' AG splice site sequences. *Represents the site(s) of the sequence variant.
type in familial cases where genotype data were available for multiple family members. Data were collated from 13 unrelated CPX families, including the large Icelandic family,\textsuperscript{18, 28} which is also presented separately to illustrate the phenotypic variability despite a similar genetic background (table 4). Overall, males carrying mutations (96%) exhibited cleft palate or a microform of cleft palate as the primary phenotype regardless of mutation type. Within this group, a range of severity was seen within the larger families, which included complete cleft of the secondary palate, submucous cleft, bifid uvula, absent tonsils, or high vaulted palate. Ankyloglossia is seen in 79% of male patients but is present as the sole phenotype in only 4%. Ankyloglossia is a common phenotype (45%) in female carriers but cleft palate (6%) may also be the sole presenting feature.

**DISCUSSION**

Despite the high degree of heterogeneity responsible for human CP, the sequence changes in \textit{TBX22} reported here provide the first evidence that X linked cleft palate makes an important contribution to the general prevalence of orofacial clefting. The mutation types included frameshift and splice site changes, which resulted either in truncated proteins or rapid removal of transcripts through the mechanism of nonsense mediated decay, but also a number of missense mutations that only affected single amino acids within the DNA binding T box domain. From the predicted three dimensional structure elucidated for both T and TBX3,\textsuperscript{32, 34} it is likely that these variants interfere with the capability of the protein either to bind DNA or to form stable interactions, perhaps as dimers or with other binding proteins in the transcriptional complex. Similar findings have been reported for other T box gene mutations such as those found in \textit{TBX3} and \textit{TBX5} and \textit{TBX19}.\textsuperscript{35–37} In addition, missense mutations in \textit{TBX5} were all shown to result in impaired nuclear localisation and it is thought that this too may contribute to the loss of transcriptional activation function.\textsuperscript{38}

Interestingly, one \textit{TBX22} mutation (G118C) corresponds to the equivalent \textit{TBX5} T box domain amino acid position Gly 80 that is mutated (G80R) in a Holt-Oram syndrome patient.\textsuperscript{33} This position is predicted to interact with the major groove of target DNA and has been shown to result in loss of DNA binding.\textsuperscript{38, 39} This is similar to the majority of \textit{TBX22} missense mutations that occur at points of contact with the

### Table 3

<table>
<thead>
<tr>
<th>Family</th>
<th>Selection*</th>
<th>Mutation</th>
<th>Exon</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>A</td>
<td>166G→T</td>
<td>1</td>
<td>E56X stop codon</td>
<td>18</td>
</tr>
<tr>
<td>Mennonite</td>
<td>X=A</td>
<td>352G→T</td>
<td>2</td>
<td>G118C missense</td>
<td>18</td>
</tr>
<tr>
<td>Family 2 (BR3)</td>
<td>A</td>
<td>581→582insCAG</td>
<td>4</td>
<td>S195→196ins</td>
<td>19+text</td>
</tr>
<tr>
<td>BR1</td>
<td>X=A</td>
<td>IVS4+1G→A</td>
<td>4</td>
<td>Splice site</td>
<td>18</td>
</tr>
<tr>
<td>Family W</td>
<td>A</td>
<td>IVS4+1G→A</td>
<td>4</td>
<td>Splice site</td>
<td>See text</td>
</tr>
<tr>
<td>Family 1</td>
<td>A</td>
<td>641T→C</td>
<td>5</td>
<td>L214P missense</td>
<td>19</td>
</tr>
<tr>
<td>BR2</td>
<td>X=A</td>
<td>664delC</td>
<td>5</td>
<td>Frame shift</td>
<td>18</td>
</tr>
<tr>
<td>Native American</td>
<td>A</td>
<td>779C→T</td>
<td>5</td>
<td>T260M missense</td>
<td>18</td>
</tr>
<tr>
<td>Family K</td>
<td>A</td>
<td>790A→T</td>
<td>5</td>
<td>N264Y See text</td>
<td></td>
</tr>
<tr>
<td>Icelandic</td>
<td>X=A</td>
<td>IVS6+1G→C</td>
<td>6</td>
<td>Splice site</td>
<td>18</td>
</tr>
</tbody>
</table>

*Selection criteria: cleft palate with (X), X linkage; (A), presence of ankyloglossia

### Table 4

<table>
<thead>
<tr>
<th>Gender</th>
<th>CPA*</th>
<th>CPO*</th>
<th>AO</th>
<th>Unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icelandic male (n = 28)</td>
<td>21 (75%)</td>
<td>6 (21%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total male (n = 87)</td>
<td>69 (79%)</td>
<td>14 (17%)</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Icelandic female (n = 37)</td>
<td>3 (8%)</td>
<td>1 (3%)</td>
<td>23 (62%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Total female (n = 101)</td>
<td>11 (11%)</td>
<td>5 (6%)</td>
<td>45 (45%)</td>
<td>38 (38%)</td>
</tr>
</tbody>
</table>

*CPA includes cleft of the hard and soft palate, cleft of the soft palate, bifid or absent uvula, or high arched palate.
†Data obtained from individuals carrying mutations in 13 independent families.
DNA backbone. In contrast, one TBX5 missense mutation G169R, found within the T box domain does not affect DNA binding but causes diminished interaction between TBX5 and NKX2.5, reducing synergy during transcriptional activation. This position is within four residues of the previously described Leu214 mutation and may also be involved in forming essential molecular interactions within the transcriptional complex. In addition, the P183L TBX22 mutation described in this report has the potential for a role in protein–protein interaction rather than protein–DNA contact. This position is equivalent to the Pro128 in Xenopus Brachyury, which forms part of a small hydrophobic region thought to be the interface for dimerisation. There is currently debate as to whether T box genes actually do dimerise in vivo, as they are stable as monomers in solution and the palindromic binding sequence elucidated for Brachyury has not been observed in the downstream targets identified so far. Pro183 is highly conserved within T box proteins and between species, although it is interesting to note that an exception is TBX15, which is closely related to TBX22, sharing a common ancestral sequence. TBX15/18/evolutionary perspective, TBX15 is closely related to TBX22, specific T box genes.32 42 The evidence suggests that whether missense or nonsense, the effect of the mutations is most likely to be a loss of functional protein and in males, this is highly penetrant for a cleft. From the families studied, there was no evidence that different types of mutation or location of the missense mutations had a significant role in determining the severity or specificity of the phenotype. The variable expression of CPX is therefore likely to be influenced by modifiers or environmental factors. It is interesting to note that the portion of the CPX family living in the north of Iceland generally has a milder phenotype than those living in the south. Not surprisingly, heterozygous females share greater variability in their phenotype and it is equally likely they will have ankyloglossia only or no phenotype at all. Not all female carriers escape a cleft, however, which affects 16% regardless of tongue phenotype. It is not yet clear whether this variability is the result of non-random X inactivation or due to the later closing of the female palate in human development. The combined male and female data suggest that while ankyloglossia is a common phenotype associated with TBX22 mutations, its occurrence is not a prerequisite for cleft palate and the two features are independent effects of loss of TBX22 function.

TBX22 clearly makes a significant contribution to the prevalence of cleft palate and it will be important to study its biological role in the process of craniofacial development. Owing to its role as a transcription factor that is expressed specifically in tissues related to palatogenesis and its confirmation as a major genetic influence in normal palate development, identification of the downstream target genes remains a priority. Although causative mutations lying outside of the exonic regions screened in this study may play a part, it seems extremely likely that the CPA patients lacking TBX22 mutations will harbour mutations in other genes that function in the same transcriptional pathway. Characterisation of the gene networks in which TBX22 participates will therefore identify novel candidate genes and provide important insights into the mechanisms involved during palatogenesis.

As more and more of the genes contributing to facial clefting disorders become characterised, the ability to make informed counselling decisions is greatly improved. There is often a very fine division between orofacial clefts that can be truly categorised as non-syndromic and those that are syndromic, particularly where associated features are often mild and variable in their expression. As is shown in this report, the elucidation of single gene disorders will show increasing overlap between the two. While in general, DNA sequencing of unselected CP patients may not yet be a realistic option, screening of patients with a positive family history and/or ankyloglossia may be worthwhile. Our experience shows that the majority of familial cases with suspected CPX and up to 4% of unselected CP cases have TBX22 mutations. For each patient harbouring a mutation, recurrence risk assessment is substantially enhanced from an empiric 3–5% to a more informative 25–50%. In combination with a better understanding of the cellular biology, this will lead to appropriate advice, therapy, and ultimately prevention.

ACKNOWLEDGEMENTS

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Authors’ affiliations

A C B Marcéu, K Doudney, C Braybrook*, G E Moore, P Stanier, Institute of Reproductive and Developmental Biology, Imperial College London, Du Cane Road, London W12 ONN, UK

R Squires, M A Patton, M M Lees, Medical Genetics Unit, St George’s Hospital Medical School, Tooting, London SW17 0RE, UK

A C B Marcéu, A Richieri-Costa, Hospital de Reabilitação de Anomalias Craniofaciais, Universidade de São Paulo, Bauru, São Paulo, Brazil

A C Lidral, Department of Orthodontics, University of Iowa, IA, USA

J C Murray, Department of Pediatrics, University of Iowa, IA, USA

*Present address: Molecular Medicine Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

Correspondence to: Dr P Stanier, 4th Floor, Institute of Reproductive and Developmental Biology, Imperial College London, Du Cane Road, London, W12 ONN, UK; pstanier@imperial.ac.uk

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REFERENCES


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CORRECTION

We would like to apologise for a number of errors that were published online in the paper by Kohlhase et al. (J Med Genet 2003;40:e127). R276X was incorrectly referred to as ArgR276X throughout the first page of the article. In addition, the first sentence of the second paragraph of the paper should read: Twenty three of 24 SALL1 mutations known to date are located in exon 2 (2-3), and unpublished results.

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