Tooth agenesis is a clinically heterogeneous disorder affecting various teeth at different rates, and is strongly influenced by ethnicity. Evidence confirms the role of genetic heterogeneity in this common dental anomaly, and alterations in two genes have been identified as causing this condition namely, \textit{MSX1} and \textit{PAX9}. Interestingly, our understanding of the genetic aetiology of human tooth agenesis is still largely based on the selective agenesis of predominantly posterior teeth. Specifically, mutations in the transcription factor \textit{PAX9} were shown to be responsible for “molar oligodontia” in three independent families, and a large deletion of \textit{PAX9} in one nuclear family led to the absence of all posterior teeth. Moreover, point mutations in the transcription factor \textit{MSX1} have been identified in families affected with selective posterior tooth agenesis predominantly involving premolars and occasionally molars.

Although recent studies of human tooth agenesis have greatly advanced our knowledge of the genetic basis of this disorder, very few studies have specifically considered the genetic aetiology of anterior tooth agenesis. In one study, a mutation in the \textit{SHH} gene was identified in association with a solitary maxillary incisor; however, this pattern of tooth agenesis presents as a clinical variation of the holoprosencephaly syndrome. Interestingly, in certain Asian populations (including Japanese, Chinese, and Malaysian people), the incidence of non-syndromic anterior tooth agenesis has been reported to be 2%, which contrasts with the 0.08%–0.23% occurrence rate in a white population. Despite the high prevalence of incisor hypodontia, there is little known about the genetic aetiology in this pattern of tooth agenesis.

Previous studies have increased our current understanding of the biology of tooth development, specifically concerning the roles of \textit{PAX9} and \textit{MSX1}. Moreover, human genetic studies have provided interesting data that allow us to infer a genotype/phenotype correlation. Several affected people in previous human studies present with classical patterns of premolar or molar agenesis, but many also lack mandibular incisors. Furthermore, expression studies in mice show that \textit{Pax9} is present in early odontogenic mesenchyme where incisors and molars first develop. Taken together, these data suggest that \textit{Pax9} may be associated with a temporal event, thus controlling the development of molars and mandibular incisors. This may begin to explain the presence of mandibular incisor agenesis that occurs with molar agenesis.

In the study presented here, we describe the clinical features, inheritance, and mutational analysis of familial mandibular incisor agenesis in people of Vietnamese descent located in the Houston area. Mutational analysis of \textit{PAX9} and \textit{MSX1} has excluded these genes as the cause of mandibular incisor agenesis in this population. Further, pedigree analyses suggest that mandibular incisor agenesis is inherited in an autosomal dominant manner with incomplete penetrance. Taken together, these studies strongly suggest that this pattern of tooth agenesis in this population is the result of mutations in a gene other than \textit{PAX9} or \textit{MSX1}.

**MATERIALS AND METHODS**

**Patient recruitment and clinical diagnosis**

Seven hundred sequential dental records from consenting and participating dental offices were reviewed, and screenings at health fairs were performed to identify affected people of Vietnamese descent. Affected people were also identified through referrals from dentists. Patients screened for this study ranged in age from 5 to 40 years, with roughly equal numbers of male and female patients (table 1). Pedigrees were extended laterally and vertically for six of 20 identified families, and are designated families 1 to 6 (fig 1A–F). The diagnosis of mandibular incisor hypodontia (fig 2A and B) for all patients was based on a clinical examination and either panoramic or periapical/bite wing dental radiographs. For this study, mandibular incisor agenesis includes those involving central or lateral incisors as it is difficult to distinguish definitively between these two teeth. Cephalometric analysis was performed to determine the presence of skeletal or dental malocclusion in those patients who were receiving orthodontic care. This study was approved by the University of Texas Health Science Center at Houston committee for the protection of human subjects. Consent to participate in this study (including release of dental records) was obtained from every adult participant, or a parental guardian in the case of minors.

**Pedigree construction and power analysis**

A pedigree analysis by inspection was performed for six families to determine the mode of inheritance of the hypodontia phenotype. This analysis suggested an autosomal dominant mode of inheritance with incomplete penetrance. Power

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**Key points**

- Several families of Vietnamese descent were identified with mandibular incisor hypodontia that was transmitted as an autosomal dominant trait with incomplete penetrance.
- Mutational analysis was performed using the candidate gene approach to determine whether mutations in the coding regions of two genes known to cause tooth agenesis, namely \textit{MSX1} and \textit{PAX9}, are responsible for this unique pattern of incisor hypodontia.
- Direct sequencing of the coding regions of \textit{PAX9} and \textit{MSX1} excluded the involvement of these genes in mandibular incisor hypodontia.

*The first two authors contributed equally to this work.*
calculations (table 2) were performed with the program Simlink assuming an autosomal dominant model with 90% penetrance.

**Polymerase chain reaction and sequencing**

Peripheral blood samples or buccal swabs were obtained from probands and family members, and DNA extractions were performed for affected probands and one affected relative for three independent families (families 1, 2, and 3) using a Puregene DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). DNA was amplified by polymerase chain reaction (PCR) with primer sets for exons 1 and 2 of human PAX9, and with primer sets for exons 1 and 2 of MSX1 (described previously). The PCR and purification were carried out as described previously for PAX9 and for MSX1. Amplified products were subsequently sequenced in both directions using ABI Big Dye terminator reagents (Applied Biosystems, Foster City, CA) using an ABI PRISM 377 DNA sequencer.

**RESULTS**

**Clinical diagnosis**

We found a unique form of incisor hypodontia that occurs as an isolated pattern, predominantly in Vietnamese people. All patients were otherwise medically healthy, and reported no syndromic involvement. Initially, 20 cases of incisor agenesis were identified, comprising 12 female and eight male patients. In 19 of the 20 Vietnamese patients with mandibular incisor hypodontia, all the remaining teeth were present, including the third molars. The only exception was a patient who was missing maxillary third molars (table 1). Ten out of 19 patients showed bilateral incisor agenesis. For 16 of 20 patients, at least one first degree relative was also affected with mandibular incisor hypodontia. Clinical examination further disclosed that the remaining teeth of affected patients seemed morphologically normal with the following exception: 12 patients had “shovel shaped incisors” (fig 3), and one patient had a fusion of primary teeth B and C in the left lower quadrant (fig 4). Finally, cephalometric and occlusal analysis disclosed that 15 patients had a class III dental relationship, possibly resulting from mesial migration of the mandibular posterior teeth subsequent to the missing anterior teeth.

Previous studies have established the hereditary basis of tooth agenesis. We therefore questioned whether mandibular incisor hypodontia in this population was transmitted as an inherited trait. Extension of six pedigrees and analysis of these pedigrees by visual inspection suggest that mandibular incisor hypodontia is inherited in an autosomal dominant manner with incomplete penetrance, although we could not exclude a pseudodominant pattern of inheritance.

**Mutational analysis**

The coding regions and exon splice boundaries of MSX1 and PAX9 were sequenced using DNA from affected probands and unaffected relatives in three unrelated families. No alterations were identified in the genes (data not shown).

**Power calculations**

We used Simlink to estimate the amount of power for linkage which was available with this set of families. Based on the

### Table 1: Twenty cases of lower incisor agenesis in Vietnamese people

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Missing permanent tooth</th>
<th>Dental findings</th>
<th>Skeletal classification</th>
<th>Presence of agenesis in family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Class III molars, class II cuspsids, shovel shaped maxillary incisors</td>
<td>Skeletal class II</td>
<td>Yes: maternal cousin</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Full molar class III, class III cuspsids, shovel shaped maxillary incisors</td>
<td>Skeletal class I</td>
<td>Yes: mother</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>F</td>
<td>One mandibular incisor</td>
<td>Class III molar relationship, cuspsids not erupted yet, shovel shaped incisors</td>
<td>Skeletal class III</td>
<td>Yes: brother</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Class III molar, class III cuspsids, anterior open bite</td>
<td>Skeletal class II</td>
<td>Yes: daughter, son</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>F</td>
<td>One mandibular incisor</td>
<td>Class III molar subdivision right, class III cuspsids, shovel shaped incisors</td>
<td>skeletal class I</td>
<td>Yes, mother missing 1 lower incisor</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>F</td>
<td>One mandibular incisor</td>
<td>Class III molar, block out left maxillary cuspid, right peg lateral maxillary incisor</td>
<td>Skeletal class II</td>
<td>Yes: father</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Class III molar, minimal, shovel shaped incisors</td>
<td>No cephal</td>
<td>Yes: brother</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Class III molar, moderate, shovel shaped incisor</td>
<td>No cephal</td>
<td>Yes: brother</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Class III molar, class III cuspsids arch, shovel shaped incisor</td>
<td>No cephal</td>
<td>Yes: father</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Class I molar, class III cuspid, shovel shaped incisors</td>
<td>Skeletal class I</td>
<td>No, brother has congenitally 1 missing maxillary lateral incisor</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Class III molar, class III cuspsids, shovel shaped incisors</td>
<td>Skeletal class I</td>
<td>None from immediate family</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>M</td>
<td>Two mandibular incisors</td>
<td>Class III molar, class III cuspsids, shovel shaped incisors</td>
<td>Skeletal class I</td>
<td>None from immediate family</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>F</td>
<td>One mandibular permanent incisor</td>
<td>Distal step of primary molars, fusion of primary B and C</td>
<td>No cephal</td>
<td>Yes: mother</td>
</tr>
<tr>
<td>14</td>
<td>12</td>
<td>F</td>
<td>Two mandibular incisors, upper 3rd molars</td>
<td>Class I molar, blocked out cuspsids, shovel shaped incisor</td>
<td>Skeletal class I</td>
<td>Yes: 2 of 3 sisters</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>M</td>
<td>Two mandibular incisors</td>
<td>Class III molar, extraction of lower right 1st molar, lower left 3rd molar</td>
<td>Skeletal class I</td>
<td>Yes: mother and sister</td>
</tr>
<tr>
<td>16</td>
<td>11</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Full molar class III, class III cuspid, block out maxillary cuspsids</td>
<td>Skeletal class III</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>32</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Class I molar</td>
<td>No cephal</td>
<td>Yes: son, daughter</td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>M</td>
<td>One mandibular incisor</td>
<td>Class I molar</td>
<td>No cephal</td>
<td>Yes: father</td>
</tr>
<tr>
<td>19</td>
<td>30</td>
<td>F</td>
<td>Two mandibular incisors</td>
<td>Class III molar</td>
<td>No cephal</td>
<td>Yes: both mother and father, 3 of 4 sibs</td>
</tr>
<tr>
<td>20</td>
<td>27</td>
<td>F</td>
<td>One mandibular incisor</td>
<td>Class I molar, minimal crowding in maxillary and mandibular arches</td>
<td>No cephal</td>
<td>Yes: two aunts</td>
</tr>
</tbody>
</table>

Summary of affected people with congenitally missing teeth, other dental findings, cephalometric analysis, and family history of lower incisor agenesis. No cephal (cephalometric analysis), no lateral head film available. Yes, the subject has an affected relative.
pedigree inspection, we assumed an autosomal dominant pattern of inheritance. We considered a 90% penetrance rate, and based on the clinical information, we did not consider the penetrance to be age dependent. We simulated with equal frequencies of biallelic marker alleles and found that the estimated mean lod score was 1.96, with family 2 providing the largest contribution of the overall lod score.

**DISCUSSION**

Previous epidemiological studies have shown that tooth agenesis varies with each class of tooth and for ethnic groups. The most commonly missing teeth in the white population are the third molars (wisdom teeth), followed by the maxillary lateral incisor or mandibular second premolar. In our study, we identify a unique pattern of missing teeth that occurs at a much higher rate in the Asian population (including Vietnamese, Japanese, Chinese, and Malaysian people) compared with white or black populations. Interestingly, the third molar, which is typically absent in association with missing molars or premolars of the same quadrant, is seen to develop normally in patients with congenitally missing mandibular incisors in the Vietnamese population. We explored the question of whether this very unique pattern of familial tooth agenesis is

![Figure 1](image_url)

**Table 2** Power analysis of six pedigrees based on an autosomal dominant model confirms that summed pedigrees provide sufficient power to detect linkage

<table>
<thead>
<tr>
<th>II Model*</th>
<th>III Marker type</th>
<th>Theta</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biallelic</td>
<td>0.0</td>
<td>1.926</td>
<td>0.905</td>
</tr>
<tr>
<td>Autosomal dominant, 90% Penetrance</td>
<td>Biallelic</td>
<td>0.1</td>
<td>0.845</td>
<td>0.405</td>
</tr>
</tbody>
</table>

*Assumes no effect of sex.
caused by similar mutations in two genes known to cause other forms of tooth agenesis. Our analysis failed to identify mutations in the coding regions of either MSX1 or PAX9. Moreover, the power calculations show that our families, although underpowered for conclusive findings, were of sufficient power to determine a suggestion of linkage. Because only the power calculations show that our families, although underpowered for conclusive findings, were of sufficient power to determine a suggestion of linkage. Because only

The studies define and describe a unique form of hypodontia present in people of Vietnamese descent, and excluded genes known to cause other forms of hypodontia as the cause of this condition. Future studies will identify the genes responsible for various forms of tooth agenesis, we will further our understanding of the genes that control the patterning and formation of teeth.

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