Familial Aggregation of Maxillary Lateral Incisor Agenesis

INTRODUCTION

Agenesis of maxillary lateral incisors (MLIA) and mandibular second premolars is the most frequent form of hypodontia, its frequency varying across populations (Grahnén, 1956; Horowitz, 1966; Alvesalo and Portin, 1969; Muller et al., 1970; Thilander and Myrberg, 1973; Magnusson, 1977; Rolling, 1980; Aasheim and Øgaard, 1993; Johannsdottir et al., 1996; Arte et al., 2001). Woolf’s study (1971) focused only on MLIA.

In spite of recent progress, the etiopathogenesis of hypodontia is largely unknown, although there is strong support for the hypothesis of a genetic etiology. There is evidence showing that congenital tooth absence can be the result of environmental or hereditary causes, or their interaction (Vastardis, 2000). Grahnén’s study (1956) in the Swedish population confirmed the hypothesis of a genetic component for hypodontia and attempted to clarify its modes of inheritance. Familial segregation studies suggested that hypodontia showed an autosomal-dominant inheritance in some families, with incomplete penetrance and variable expressivity (Grahnén, 1956; Svinhufvud et al., 1988; Vastardis et al., 1996; Arte et al., 2001); however, modes of transmission linked to the X-chromosome and of polygenic or multifactorial type have also been proposed (Chosack et al., 1975). Grahnén (1956) and Alvesalo and Portin (1969), among others, strongly suggested that peg-shaped incisors are a variable expression of the gene responsible for MLIA, an argument also presented by Arte et al. (2001). Woolf’s study (1971) focused only on MLIA.

The identification of phenotypes of tooth absence and hypoplasia in mouse lines null-zygous for different genes, together with the identification of mutations causing hypodontia in a relatively small number of human families (Vastardis et al., 1996; Stockon et al., 2000; van den Boogaard et al., 2000; Nieminen et al., 2001; Frazier-Bowers et al., 2002; Mostowska et al., 2006; Kapadia et al., 2006; Tao et al., 2006; Tarpey et al., 2007), confirmed the relevance of genetic determination of tooth agenesis. However, the role of genes in sporadic and less severe forms of hypodontia has not yet been clarified. Additionally, there is evidence for an extensive clinical and genetic heterogeneity within the “hypodontia” phenotype. Further definition of clinical and genetic subtypes within hypodontia is thus required, and familial aggregation studies are needed to establish a measure of the genetic contribution to different subtypes of congenital tooth absence, as well as their modes of inheritance—a first step toward the identification of causative genes.

KEY WORDS: hypodontia, microdontia, maxillary lateral incisors, relative risk, familial aggregation.

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In a previous population-based study of hypodontia in Portugal (Pinho et al., 2005), we found that 87% of MLIA subjects had no other form of agenesis. In accordance with Woolf (1971), we hypothesized that MLIA is a separate genetic entity within the hypodontia phenotype. In addition, 57.1% of the 121 subjects with unilateral MLIA also showed microdontia of the contralateral maxillary lateral incisor.

Our strategy was (1) to investigate the degree of familial aggregation for MLIA, (2) to assess which other forms of agenesis segregate in these families, and (3) to test the hypothesis that microdontia of maxillary lateral incisors is a milder form of the MLIA phenotype. We obtained novel data regarding MLIA in the Portuguese population, and re-assessed data published by Grahnén (1956) for the Swedish population, by Woolf (1971) for the Utah population, and by Chosack et al. (1975) from Israel. For the first time, relative risk was estimated in MLIA families. Estimates derived from four populations are presented and discussed.

### Table 1. Frequency of Agenesis of Maxillary Lateral Incisors (MLIA) in Relatives of Probands Compared with General Population

<table>
<thead>
<tr>
<th>Population</th>
<th>No. Examined</th>
<th>No. Affected</th>
<th>% of Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portuguese MLIA + other agenesis (62 probands)</td>
<td>General population 16,771</td>
<td>219</td>
<td>1.3</td>
</tr>
<tr>
<td>Parents of probands 81</td>
<td>14</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td>Sibs of probands 61</td>
<td>11</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>Parents + Sibs 142</td>
<td>25</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>Portuguese MLIA only (54 probands)</td>
<td>Parents of probands 71</td>
<td>14</td>
<td>19.7</td>
</tr>
<tr>
<td>Sibs of probands 51</td>
<td>10</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>Parents + Sibs 122</td>
<td>24</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Grahnén MLIA + other agenesis (82 probands)</td>
<td>General population 1006</td>
<td>16</td>
<td>1.6</td>
</tr>
<tr>
<td>Parents + Sibs 162</td>
<td>47</td>
<td>29.0</td>
<td></td>
</tr>
<tr>
<td>Portuguese MLIA only (55 probands)</td>
<td>Parents + Sibs 92</td>
<td>23</td>
<td>25.0</td>
</tr>
<tr>
<td>Grahnén MLIA only (153 probands)</td>
<td>General population 21,384</td>
<td>451</td>
<td>2.1</td>
</tr>
<tr>
<td>Parents + Sibs 426</td>
<td>44</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Woolf MLIA + other agenesis (103 probands)</td>
<td>General population 918</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Parents + Sibs 462</td>
<td>66</td>
<td>14.3</td>
<td></td>
</tr>
</tbody>
</table>

In comparisons between our data and data from Sweden, Utah, or Israel, only RR for parents and sibs (altogether) were considered microdontic when their mesiodistal dimensions were smaller than those of the lower lateral incisors.

The study was approved by the Ethics Committee of the Medical Dentistry School. Patient or parental written informed consent was obtained in all cases.

### Data from Sweden, Utah, and Israel

We re-assessed the data published by Grahnén (1956), focusing only on MLIA. Of those 171 families, 82 had probands with MLIA, and we then analyzed the occurrence of the same phenotype in their parents and sibs (Table 1). Woolf’s study (1971) consisted of 103 probands with MLIA and 187 control families from Utah and their parents and sibs (Table 1). Chosack et al. (1975) studied families of 153 probands with MLIA (Table 1).

### Methods

#### Measuring Familial Aggregation

Relative risk (RR) represents the ratio between the frequency of the disease in relatives of probands and its prevalence in the population (Cantor and Rotter, 1992) and was used as a measure of familial aggregation. We estimated RR for probands’ relatives also to be affected with MLIA when compared with the general population, using a prevalence rate of 1.3% for the Portuguese (Pinho et al., 2005), 1.6% for the Swedish (Grahnén, 1956), 1.2% for Utah (Woolf, 1971), and 2.1% for Israel (Chosack et al., 1975) (Table 1).

In comparisons between our data and data from Sweden, Utah, or Israel, only RR for parents and sibs (altogether) were considered (Table 2).

Probands and relatives were classified as affected when they showed only MLIA, and as unaffected when having no dental agenesis; relatives with MLIA together with other forms of hypodontia were excluded from the RR calculations (Table 2).

Since Woolf’s study did not provide data on MLIA only, and for the purpose of comparisons of our data with those data, we...
performed a second analysis in which probands and relatives were classified as affected when showing MLIA (whether isolated or together with other agenesis), and as unaffected when having no MLIA (Table 2).

**Further Analysis of Portuguese Data**

To test the hypothesis that MLIA is a separate clinical and genetic entity, we analyzed the type of agenesis and the occurrence of microdontia in parents and sibs of probands with MLIA only or with MLIA plus other ageneses (Table 3). We also assessed if, in parents and sibs, MLIA was bilateral, unilateral with microdontia of the contralateral tooth, or unilateral.

We further analyzed 54 Portuguese families whose proband had MLIA only. First, we investigated whether the frequency of affected first-degree relatives differed according to severity in the proband, *i.e.*, whether MLIA in the proband was bilateral, unilateral with microdontia of the contralateral tooth, or unilateral. We then looked for patterns of transmission of MLIA (and microdontia) in those families.

**Statistical Analysis**

We assessed comparisons between and among categorical variables using chi-square tests. We made comparisons between and among RR using the ratio of relative risks (RRR) (Altman and Bland, 2003). Values of RR are given with 95% confidence intervals. A 5% significance level was used in all analyses. Statistical analyses were performed with SPSS (version 14.0 for Windows).

**RESULTS**

**New and Re-assessed Evidence for Familial Aggregation of MLIA**

**Portuguese Data**

Among 122 first-degree relatives of probands with MLIA only, 24 (19.7%) also had MLIA (Table 1); therefore, the risk for a relative of a proband with MLIA to have the same kind of agenesis was about 15 times greater (Table 2) than for an individual from the general population. For the purpose of comparison with Woolf’s data, a second estimate of 14 for RR was obtained (Table 2), including as affected both probands (62) and relatives (142) with MLIA together with other forms of agenesis.

**Comparing Portuguese and Swedish Data**

Grahnén’s data consisted of 92 parents or sibs of 55 probands with MLIA (23 affected; Table 1), leading to a RR of 15.72 (Table 2). RRR showed no significant differences between this data set and ours (Table 2).

**Comparing Data from Portugal and Utah**

Woolf’s data consisted of 462 parents or sibs of 103 MLIA cases (66 affected; Table 1). RR for first-degree relatives of MLIA probands was 11.9 (Table 2). RRR showed no significant differences between this data set and ours (Table 2). Since data from Utah were not stratified according to the pure MLIA phenotype, it was not possible to establish this other comparison.

**Comparing Portuguese and Israeli Data**

Chosack’s data consisted of 426 parents or sibs of 153 MLIA probands, of whom 44 were also affected (Table 1), leading to a RR of 4.9 (Table 2). In spite of being lower than RR derived from the other three populations, the RR is still considerably high.

**Further Analysis of Portuguese Data**

MLIA is a Distinct Clinical and Genetic Entity

All forms of agenesis or microdontia found in relatives of both groups of probands are described (Table 3). The most frequent phenotype by far was MLIA only, followed by microdontia of contralateral incisors. Other types of ageneses were found in only four out of 142 first-degree relatives (Table 3) and were associated either with MLIA (two cases) or with microdontia (two cases) (Table 3). No other form of agenesis was found on its own.
Severity in Proband Correlates with Frequency of Affected Relatives

Frequency of affected relatives with MLIA was 22.5% when the proband had bilateral MLIA, 18.2% when the proband had both unilateral MLIA and microdontia of the contralateral tooth, and 12.5% when the proband had only unilateral MLIA (not shown), indicating a gradient of affected relatives according to severity in the proband.

Our probands showed bilateral MLIA in 52% of the cases, and unilateral with microdontia of the contralateral tooth in 34%; only 14% of probands displayed unilateral MLIA alone. In relatives, the same gradient of frequencies could be observed (Table 3), adding evidence that microdontia forms an intermediate phenotype.

Mode of Transmission of MLIA

Our analysis of 54 families whose probands had pure MLIA revealed that, in 19, vertical transmission was observed, which was compatible with autosomal-dominant transmission (in three of these, there was evidence of incomplete penetrance). In 18 other families, although transmission was also compatible with AD inheritance with incomplete penetrance, autosomal-recessive inheritance could not be ruled out, mostly due to small family size or lack of information. Pedigrees of these 37 families are included in the Appendix. The remaining 17 families were not informative (neither parent could be observed).

We observed similar frequencies of affected parents (19.7%) and affected sibs (19.6%) of MLIA probands (Table 1), which is counter to the hypothesis of recessive inheritance. Since father-son transmission was also observed in several pedigrees, analysis of our data suggests that autosomal-dominance with incomplete penetrance plays an important (although not exclusive) role in MLIA transmission.

When we included microdontia in relatives as part of the same phenotype (not shown), the frequencies of affected parents and sibs of MLIA probands were 24 and 32%, respectively, not significantly different at this sample size.

Three families where cases of MLIA and microdontia segregated in the same pedigree, often occurring in the same individual, are depicted in the Fig.

DISCUSSION

In this work, we studied familial aggregation of MLIA in an attempt to investigate the hypothesis of a genetic basis for this subtype of hypodontia. As in previous studies, we found strong familial aggregation of MLIA, as derived from a higher frequency of affected individuals among affected probands’ relatives than in the general population.

Results from Portuguese data showed that risk for a first-degree relative of an individual with MLIA to have the same kind of agenesis was about 15 times higher than that of the general population. Comparisons between our estimates and RR derived from Grahnén and Woolf’s series showed that, in all three populations, RR were not significantly different from each other. Although the estimate from Chosack’s data was lower than the other three, RR was consistently high in the four populations, and their magnitude was too high to be due to environmental factors only (Khoury et al., 1988). Analysis of our data also showed that the presence of other forms of agenesis in relatives of MLIA probands is residual and always associated with MLIA or with microdontia, which is also consistent with previously published results (Pinho et al., 2005), where 87% of patients with MLIA had no other form of agenesis. In our opinion, these results show that it is worth concentrating on MLIA as a separate clinical entity.

Moreover, phenotype definition should include microdontia of lateral incisors, which should be considered a milder form of the MLIA phenotype, as suggested previously (Alvesalo and Portin, 1969) in peg-shaped incisors. In our data, bilateral MLIA or MLIA, together with microdontia, was more frequent than unilateral MLIA (in both probands and relatives), a result in accordance with the meta-analysis performed by Polder et al. (2004). When the epidemiological data were re-assessed (Pinho et al., 2005), 78% of individuals displayed a bilateral phenotype (bilateral agenesis or unilateral agenesis with contralateral microdontia), which is in accordance with the hypothesis of a developmental disturbance.
In spite of recent developments in the genetics of hypodontia, data regarding the genes responsible for MLIA are still scarce and controversial. The search for genes associated with anterior hypodontia has been largely unsuccessful so far, and several of the known hypodontia candidate genes, including MSX1 (Niemenen et al., 1995; Vastardis et al., 1996; Scarel et al., 2000; Vastardis, 2000; Lidral and Reising, 2002) and PAX9 (Stockton et al., 2000; Niemenen et al., 2001; Frazier-Bowers et al., 2002; Mostowska et al., 2006; Kapadia et al., 2006), seem to have an important role mostly in posterior tooth odontogenesis. A plausible hypothesis is that the various hypodontia patterns are the result of different types of mutations in different genes, as suggested by Vastardis (2000), possibly also involving gene-gene and gene-environment interactions.

It is thus probable that different genes are involved in different phenotypes. The consistently high RR for MLIA across four different populations also indicates that it is worth looking for genes specifically within this phenotype.

Analysis of our data suggests that the pattern of segregation of MLIA (including microdontia of maxillary lateral incisors) is compatible with an autosomal-dominant trait with incomplete penetrance (although in some families recessive inheritance could not be excluded); further studies are needed that will allow us to proceed to the mapping and identification of genes that play a role in the determination of this phenotypic trait.

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