Regional Dispersion of Non-Syndromic Cleft Lip With/without Palate Turkish Children Patients and Possible Geographical Effects

Korkut Ulucan¹, Arzu Akçay², Burak Ersoy³, Deniz Kiraç⁴, Teoman Akçay⁵, Deniz Ergeç⁶, Ahmet İlter Güney⁷

¹Department of Molecular Biology and Genetics, Faculty of Engineering and Natural Sciences, Uskudar University, Istanbul - Turkey
²Department of Pediatric Hematology and Oncology, Kanuni Sultan Suleyman Education and Research Hospital, Istanbul - Turkey
³Department of Plastic, Reconstructive and Aesthetic Surgery, Faculty of Medicine, Marmara University, Istanbul - Turkey
⁴Department of Medical Biology, Faculty of Medicine, Yeditepe University, Istanbul - Turkey
⁵Department of Pediatric Endocrinology, Dr. Sadi Konuk Education and Research Hospital, Istanbul - Turkey
⁶Department of Molecular Biology and Genetics, Faculty of Arts and Science, Yeni Yüzyıl University, Istanbul - Turkey
⁷Department of Medical Genetics, Faculty of Medicine, Marmara University, Istanbul - Turkey

ÖZET
İzole dudak-damak yarıkı Türk çocuk hastaların bölgesel dağılımı ve olası bölgesel etkiler


Yöntem: Temmuz 2006-Haziran 2010 yılları arasında doğum yapan yarık dudak-damaklı çocukların annelerinden; kökenleri, vitamin almımı dahil beslenme alışkanlıkları, iş ve yaşam biçimleri hakkında bilgi toplanmıştır.


Anahtar sözcükler: Cleft lip, cleft palate, nutritional habits, life style, geographical dispersion

INTRODUCTION
Non-syndromic Cleft Lip and Palate (NSCL/P) is a common structural birth malformation affecting up to 1/700 live births (1). It has a rather complex etiology where major and minor genetic influences are held responsible as the major determinant of its occurrence (2). Although several loci were identified to have an effect on the cleft

ABS TRACT
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Objective: Non-syndromic cleft lip with/without palate (NSCL/P) takes part in multifactorial anomalies. In the present retrospective-descriptive study, we aimed to evaluate the distribution of Turkish children patients with non-syndromic cleft lip with/without palate according to the geographic regions and analyse the possible geographic and environmental effects which can be considered in the aetiology of the anomaly.

Method: Information about the origin, nutritional habits including vitamin intake, occupational and lifetime status were obtained from mothers of NSCL/P patients who gave birth between July 2006 and June 2010.

Results: When regional status was investigated, it was found that the eastern parts of Turkey have a relatively higher number of NSCL/P patients than other regions. The ratio of the affected boys to affected girls was found as 154/136. Also, the average age of the mothers at the time of delivery was found to be 24.7. None of the mothers used alcohol or smoked during their lives.

Conclusions: Regional differences in nutritional habits and life style have various effects on NSCL/P occurrence, nevertheless more detailed studies are needed to specify the major differences that are responsible.

Key words: Cleft lip, cleft palate, nutritional habits, life style, geographical dispersion
formations of lip and palate, studies including the family and case-control studies have exhibited inconsistent results (3). The multifactorial nature of the malformation can be accepted as the main reason of these findings. The lack of a 100% concordance in monozygotic twins and the occasional findings of non-syndromic cases in large family groups suggest the environmental factors as the responsible factor for the formation of the orofacial clefts (4).

In addition to the genetic determinants, environmental factors like eating and drinking habits, having a sedentary life style, and even the socioeconomic status can play role on cleft lip and palate formation (5,6). The most thoroughly studied environmental factors are smoking and alcohol consumption of pregnant women. There are several reports indicating that maternal and infantile gene variations in conjunction with maternal smoking may contribute to the orofacial cleft formation in the developing embryo (7,8). On the other hand, alcohol consumption has controversial effects on NSCL/P occurrence, which indicates the complexity of alcohol metabolism and its side effects on both mother and infant (9,10).

Turkey, a gate between the continents of Europe and Asia, has a heterogeneous ethnic background. It is divided into seven geographic divisions, each with different abiomic and geographic properties. Socioeconomic status varies with the division and has an important effect on overall nutritional status. Occupational preferences differ in these regions as well, thus the eastern part of Turkey is mainly based on agriculture and animal husbandry, whereas the working population in western part of Turkey predominantly has industrial jobs (11). Due to the occupational differences, people are exposed to different chemicals which can have various influences on the health of the general population. Some areas tend to consume mostly vegetable dishes whereas others rely more on meat products (12). These nutritional differences can exert various effects on the metabolism as well as the mineral and vitamin ratio. Following the rural-urban migration to western part of Turkey in search of better life conditions, most of these individuals manage to preserve their original life style in their new habitat. In this retrospective study, we aimed to analyze the distribution and the geographical origin of NSCL/P Turkish children patients and possible geographical effect mechanisms on the onset of orofacial clefting.

**MATERIAL AND METHODS**

290 NSCL/P patients who were born between July 2006 and June 2010 were recruited to the study. Those patients, whose parents had immigrated to Istanbul from other cities in Turkey and lived in Istanbul for more than 10 years are excluded from the study. Only patients with both parents belonging to the same geographical region were selected for the retrospective analysis. Likewise, in order to confine the results to the Turkish borders, those patients having a parent who had resided in another country for longer than 2 years were also excluded from the study. Thus, 290 out of 367 newborn patients with NSCL/P deformity were analyzed for the geographical origin of their parents and the age of their mothers. The subjects were asked about their occupational and social life styles including medication, eating habits, alcohol consumption, vitamin supplement.

**RESULTS**

The ages of mothers at the time of delivery were between 19 and 37, the average age was 24.7 years. Of the examined children patients, Eastern Anatolia Region had the most quantity and percentage whereas Marmara Region had the lowest values (Table 1). Eastern parts of

<table>
<thead>
<tr>
<th>Geographic regions</th>
<th>Number of children with NSCL/P</th>
<th>Boys</th>
<th>Girls</th>
<th>Percentage of Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marmara Region</td>
<td>29</td>
<td>16</td>
<td>13</td>
<td>10.0</td>
</tr>
<tr>
<td>Aegean Region</td>
<td>34</td>
<td>18</td>
<td>16</td>
<td>11.7</td>
</tr>
<tr>
<td>Mediterranean Region</td>
<td>32</td>
<td>14</td>
<td>18</td>
<td>11.1</td>
</tr>
<tr>
<td>Black Sea Region</td>
<td>42</td>
<td>20</td>
<td>22</td>
<td>14.5</td>
</tr>
<tr>
<td>Central Anatolia Region</td>
<td>39</td>
<td>20</td>
<td>19</td>
<td>13.5</td>
</tr>
<tr>
<td>Eastern Anatolia Region</td>
<td>59</td>
<td>34</td>
<td>25</td>
<td>20.3</td>
</tr>
<tr>
<td>Southeastern Anatolia Region</td>
<td>55</td>
<td>32</td>
<td>23</td>
<td>19.0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>290</td>
<td>154</td>
<td>136</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Turkey had higher percentages in terms of NSCL/P. The ratio of boys to girls was found as 154/136.

Eating and drinking habits did not differ in individuals living in the same region, and they showed similar habits related to their geographical region, like individuals in eastern parts commonly ate animal products whereas others in western parts stabilized their nutrition with herbal nutrition. None of the mothers enrolled in this study used alcohol or smoked during their lives.

Consanguinity numbers and percentages of the mothers in their regions were as follows: 6 (10%) in Eastern Anatolia, 7 (12.7%) in Southeastern Anatolia, 2 (5%) in Central Anatolia and 1 (2%) in Black Sea. All of the parents that have consanguinity did not have any other genetically affected child.

**DISCUSSION**

The results of the present study revealed that the eastern part of Turkey has a relatively higher number of NSCL/P patients. This finding is very similar to the results of previous studies indicating high prevalence of CL/P formation in the eastern countries (2,13). It is very difficult to find out whether the main reason of this result is genetic determinants or environmental factors.

As mentioned before, agriculture and animal husbandry are the main sources of income in the eastern parts of Turkey. The people living in this region are presumably exposed to a greater cumulative burden of pesticides and chemicals from the soil or from the animals feeding in these regions. Exposure to certain chemicals like glycol ether, which is a compound found in domestic and industrial products, organic solvents like xylene, toluene, pesticides and lead has been reported to increase the orofacial cleft (14-16). This difference might partially explain the high number of NSCL/P patients in the eastern regions.

On the other hand, the average educational level of the general population is significantly higher in western regions (17). As a direct consequence of higher educational input, the individuals living in the western regions tend to be more aware of their nutritional status and the need for any vitamins or mineral supplement and this awareness in turn can have beneficial effects on their offspring. Nutrition also plays a major role in the development of a cleft lip and/or palate. In our study, all the individuals showed similarity in terms of nutrition. They all complied the nutrition list advised by their clinicians. An adequate supply of vitamins, whether included in the regular diet or as an additional multivitamin supplement has a protective role against cleft formation. Zinc is yet another important mineral whose effect on cleft formation was previously examined; it is considered to be an additional protective factor which reduces cleft formation (18). The overall rate of routine medical check-ups and compliance to the medical treatment appear to be substantially higher in the western regions which can be argued as a possible reason for low CL/P occurrence.

Similar to many other genetic diseases, maternal age does also play a crucial role in cleft formation. The relation between age of the mother and NSCL/P occurrence is a controversial issue. Some studies reported a positive correlation between advanced maternal age and increased orofacial cleft risk (19), whereas other studies failed to demonstrate any relation (20). In another study, the risk for cleft lip formation was found to be increased at younger mothers (21). The average age of pregnancy in Turkey is quite low; in 2009, almost 30% of the women who gave birth to a child were between 20-24 years and 25% of them were between 25-29 years of age (22). In our study, the average age of mothers was 24.7. There are only a few reports in the literature dealing with the effect of the age of pregnancy on the occurrence of CL/P; thus it is rather difficult to comment on this issue. Yet, it can be stated that the average age of the mothers in the present study constitutes no exception for the general tendency.

Maternal exposure to tobacco smoke, either passive smokers (mothers that do not smoke) or smokers, is a point of discussion in terms of NSCL/P. Wyszynski et al. (23) reported a meta-analysis including 11 different reports, in which half of the studies significantly associated maternal smoking. There are also some reports that associate maternal smoking with an increased risk of CL/P (24-26). Our results are not in agreement with the previous results. Sample size, other factors playing role in the pathogenesis of NSCL/P and the study design may explain why our results failed to support previous findings.

Consanguinity is reported to be an important factor which affects the formation of CL/P (27). This was supported with other studies in different populations, and all share the common idea, as consanguinity is an effective factor in
NSCL/P formation (28,29). Consanguinity generally gave rise to syndromic diseases and single gene defects. The low number of consanguinity between the parents of NSCL/P may be due to the study design. In the present study, only the mothers of children with NSCL/P, but not with other genetically transmitted diseases were included. The number of consanguinity would have been much higher if we had included the mothers who had other children with congenital anomalies.

In our study population, boys were more affected than girls. The ratio of boys to girls was 154/136, greater than 1. There are some other studies indicating male to female ratio greater than 1 and reporting that NSCL/P is more common in boys (30,31). But Elliot et al.(32) could not find any gender difference for orofacial clefts in the Zambia population and Suleiman et al. (33) reported a higher incidence of girls in the Sudan population. More studies are necessary to illuminate the molecular mechanisms underlying the gender difference in NSCL/P as these mechanisms have not been fully explained yet.

**REFERENCES**


**CONCLUSION**

The clarification of the etiology of complex and multifactorial diseases such as the non-syndromic cleft lip and palate is never easy. However, it is well known that various environmental factors as well as genetic determinants have important influences on the fetal development. According to the results of our retrospective-informative study, nutritional habits and life style are broad subjects embracing many variables and their infinite combinations. Yet, with help of descriptive studies similar to the presented one, regional tendencies for NSCL/P occurrence and its correlation with some of the main determinants of various nutritional habits and life style characteristics can be detected. One limitation of the present study was the lack of the nutritional habits of participants therefore more detailed investigations including the nutritional habits will help researchers make more precise comments about the effect of nutrition on NSCL/P formation.


