Familial Aggregates in Obstructive Sleep Apnea Syndrome*

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Obstructive sleep apnea syndrome (OSAS) was diagnosed in 157 subjects based on clinical symptoms, physical evaluation, cephalometric x-ray films, and polysomnography. These index cases identified 844 living first-degree relatives. Mailings were sent to 792 (94%). The mailing consisted of two identical questionnaires, one for the family member of the index case and one to be given to a friend (not a relative) of approximately the same age. In response, we received 531 (63%) questionnaires from relatives and 195 (25%) questionnaires from age-matched nonrelated friends, which were used as a control group. A more extensive investigation was performed on first-degree relatives of the index group living in the San Francisco Bay Area or vicinity. Two hundred seventy-nine relatives (100%) were identified. One hundred sixty-six subjects (59%) as well as 69 age-matched friends (ie, 41% of the 166 relatives and 25% of the potential total group) agreed to participate in further studies. These subjects had interviews, clinical investigations, and nonattended ambulatory monitoring. Cephalometric x-ray films could be obtained on only 22 of 166 participating relatives and 6 of 69 friends. Body mass index was not a differentiating measure between relatives and friends. Odds ratios (ORs) were calculated from the questionnaire data. The report of tiredness, fatigue, and sleepiness did not distinguish family members from friends. The OR, however, progressively increases when there is a positive history of near nightly loud snoring (OR=1.78; 95% confidence interval [CI] 1.25-2.54) or a positive history of daytime sleepiness in conjunction with near nightly loud snoring (OR=3.11; 95% CI=1.94-4.99). The investigation in the Bay Area indicated that, when first-degree relatives were compared with friends, the complaint of daytime tiredness, sleepiness, or both with the presence of a high and narrow (ogival) hard palate sharply differentiated between friends and relatives (OR=10.9, 95%, CI=5.31-22.5). An Epworth Sleepiness Scale score of 9 or greater with the presence of another symptom associated with OSAS, and a respiratory disturbance index greater than 5 (number of apneas and hypopneas per hour of sleep ≥5) gave an OR of 45.6 (95% CI=18.8-11.0). Disproportionate craniofacial anatomy was common in familial groups with OSAS. Craniofacial familial features can be a strong indicator of risk for the development of OSAS. (CHEST 1995; 107:1545-51)

Key words: Cephalometric x-rays; craniofacial abnormalities; familial traits; genetics; sleep apnea; snoring

| BMI=body mass index; CI=confidence interval; EDS=excessive daytime sleepiness; ESS=Epworth Sleepiness Scale; H=hyoid bone; MP=mandibular plane; NSBA=nasion to sella to basion; OR=odds ratio; OSAS=obstructive sleep apnea syndrome; P=soft palate; PNS=posterior nasal spine; RDI=respiratory disturbance index; SaO2=oxygen saturation; SNA=sella to nasion to subspinal A; SNB=sella to nasion to supramentale B |

In 1979, Strohl et al1 presented a family with obstructive sleep apnea syndrome (OSAS). Several authors2-5 have reported subsequently families with OSAS. In a recent review chapter, Redline and Tishler6 emphasized that several risk factors for obstructive sleep apnea have been reported to have a genetic basis. These risk factors include obesity, central control of ventilation (particularly ventilatory responsiveness to hypoxemia and hypercapnia) and craniofacial morphology. Our group previously found that OSAS patients have some mild craniofacial disproportions. In a study published in 1986, Guilleminault et al7 also found that infants with apparently life-threatening events and sleep apnea typically have family members with obstructive sleep apneas and that small upper airways, indicated by cephalometric roentgenograms and volume computer tomographic scans, were a common familial feature. In order to further investigate the possible genetic basis of obstructive sleep apnea, we performed a study based on a large index case population.

METHODS

Population

Index Case Identification: We identified obstructive sleep apneic patients (index cases) from subjects seen consecutively at the Stanford Sleep Disorders Clinic. All index cases had a complaint of daytime sleepiness, tiredness, or fatigue. All were reported to be loud, chronic snorers during sleep and presented, to varying degrees, with clinical symptoms associated with OSAS. All subjects underwent nocturnal polysomnography, which was conducted according to American Sleep Disorders Association guide-
lines. It included an EEG (C3/A1-C4/A2), electro-oculogram, a chin and leg electromyogram, an ECG (one modified V2 lead), airflow (naso-oral thermistors), uncalibrated inductive respiratory plethysmography, esophageal pressure monitoring using a 6-mm diameter supple esophageal catheter, a microphone taped to the frontal region of the neck, and pulse oximetry. The sleep/wake cycle was scored according to the international criteria of Rechtschaffen and Kales\(^8\) and the American Sleep Disorders Association Atlas Task Force criteria were used for the scoring of transient arousals.\(^9\) Respiratory events were subdivided into apneas and hypopneas according to the published international criteria.\(^10\) Total sleep time, sleep stages and state, wake after sleep onset, number of leg movements, number and type of respiratory events, oxygen saturation ($\text{SaO}_2$) fluctuation, and presence and type of cardiac arrhythmias were evaluated in relationship to sleeping position and time during the night. All subjects must have had more than 5 apneas and hypopneas per hour of sleep (respiratory disturbance index [RD]) $>$5) to be included in the study. All had cephalometric x-ray films.

Index cases must have had clinical complaints, clinical symptoms, and polygraphic monitoring results supporting the diagnosis of OSAS. The OSAS must not have been related to an associated syndrome (e.g. acromegaly, neuromuscular disorder, a congenital craniofacial syndrome, such as Pierre Robin, Hurler’s).

**Questionnaires:** For this study, we used a questionnaire that has been used for the past 3 years in the clinical arena and previously tested against polysomnography. This questionnaire investigates snoring, daytime sleepiness, tiredness, obesity, alcohol intake, and symptoms associated with OSAS. It incorporates the Epworth Sleepiness Scale (ESS), an 8-item instrument which has been validated in previous studies,\(^11\)\(^12\) among its 30 questions. We sent two questionnaires to each family member and asked that each member complete one of the questionnaires (or if the relative was too young that a parent assist him or her) and that the second questionnaire be given to a friend of about the same age, living near by and having no blood relationship whatsoever to the family member. A stamped envelope was included with each questionnaire, and a short letter of introduction explaining the study and signed by the index case also was included.

In addition to the questionnaires, a second form was sent to all subjects living in the San Francisco Bay Area. This form invited the subjects: (1) to submit to an interview and clinical examination; (2) to submit to ambulatory nocturnal recording of sleep and breathing using equipment (Edentrace; EdenTec; Eden Prairie, Minn) whose sensitivity and specificity for recognition of sleep-disordered breathing has been calculated previously against polysomnography;\(^13\) and (3) to have cephalometric x-ray films taken.\(^14\) Each test was described in detail in the form. This request offered volunteers the possibility of participating in only one part of the study and not in others if they so desired. The form also indicated that there would be no financial compensation for participation in the study, but that the investigating team was willing to set up the monitoring equipment at the subject’s home or to reimburse for travel expenses when coming to Stanford.

**List Interests:** This part of the study was limited to subjects living in the San Francisco Bay Area for obvious geographical and financial reasons. All subjects volunteering for the investigation were expected to have responded to the questionnaire survey. This geographically limited investigation was planned (1) to confirm the responses to the questionnaire with live interviews and (2) to eliminate any doubts about the presence of a “secondary” sleep-disordered breathing problem associated with obstructive sleep apnea. These two elements were only to confirm the questionnaire responses, and to further check on the subjects’ understanding of the questions.

The three new features identified in the second form sent to Bay Area residents were clinical investigations focusing on the upper airway, Edentrace recordings and monitored variables, and cephalometrics.

**Clinical Investigations Focusing on the Upper Airway:** This evaluation was performed following a protocol used on our patients systematically for the past 6 years. The investigator trained to perform this evaluation and who performed all examinations, however, was blinded to whether or not each subject was related to an index case. The protocol called for clinical evaluation of the nose, pharyngeal region, and craniofacial features. Subjects were placed supine and requested to take a deep inspiration with evaluation of movements and possible collapse of each ala nasi. The presence of narrowing by 50% or more of the width of the nares during inspiration compared with end expiration, a sign which may suggest the presence of upper airway resistance, was scored as “present” or “absent.” In a seated position, with the patient at rest and relaxed, presence of an overjet was determined. This observational measure was determined on a 2-point scale (present/absent) and was quoted as “present” when the upper to lower incisive distance was more than 2.5 mm. The hard palate was classified as one of the following: (1) high arch and narrow or “ovigal” (±30 mm from tongue); (2) mid-placed; or (3) low placed (±15 mm from tongue). Distances were measured from the highest point of the hard palate to the tongue in a relaxed position with the mouth open at a 20-degree angle. The presence or absence of tonsils, with the size scored on a scale from 0 (absent) to 4 (“kissing tonsils”), was evaluated. The size of the uvula was evaluated by length on a scale of 1 to 3 (short to long) and by width on a scale of 1 to 3 (narrow to wide). A general score of the size of the pharynx also was recorded on a scale of 1 to 4 (very narrow to very wide).

An overall rating was derived from these analyses and scores. Subjects were classified as having either a normal or abnormal upper airway. Those with an “abnormal” upper airway were further classified as having a high placed, mid-placed, or low-placed hard palate.

As general information, height and weight were measured and used to derive the body mass index (BMI).\(^15\)

**Edentrace Recordings and Monitored Variables:** Variables monitored with the Edentrace included naso-oral airflow studies with thermistors, chest wall impedance, $\text{SaO}_2$ (finger pulse oximetry), heart rate, snoring, body position (supine vs others), and movements (detected by comparison of ECG and oximetry recordings with artifacts on different channels). Total time in bed, time spent in supine vs other sleeping positions, number and type of apneas and hypopneas, changes of $\text{SaO}_2$, temporal distribution of breathing events, and the presence of cardiac arrhythmias also were tabulated. The number of transient arousals and long awakenings were calculated from heart rate and artifact analyses, as already described in published works.\(^15\)\(^16\) Estimated wake after sleep onset and estimated total sleep time also were derived following the example of previously published works.\(^15\)\(^16\) A diary kept by the subject on the night of ambulatory non-attended recording confirmed lights-out time, lights-on time, and long nocturnal awakenings. Scoring was performed by a single research assistant blind to the subject’s classification. If a recording appeared inappropriate as a result of a malfunction of the equipment, all efforts were made to obtain a second recording. In addition, polysomnography was performed on 19 subjects after Edentrace recording.

**Cephalometrics:** Lateral cephalometric roentgenograms and cephalometric x-ray films were done with a cephalometric x-ray device (Cephalostat unit; B.F. Werner, Franklin Park, Ill.) using the technique of Riley et al.\(^14\) Tracings were made on acetate sheets by a single investigator, again blind to the subject’s grouping, following the published rules of Edentrace for the interpretation of these x-ray films. Measured quantities included the sella to nasion to subspinal (A [SNA]) angle, the sella to nasion to suprana...
(B [SNB]) angle, the nasion to sella to basion (NSBA) angle, the distance from mandibular plane (MP) to hyoid bone (H), the distance from posterior nasal spine (PNS) to the tip of the soft palate (P), and the posterior airway space (PAS), defined as the space behind the base of the tongue and limited by the soft tissues, and therefore more difficult than bony landmarks to clearly delineate.

**Statistical Analyses**

Descriptive statistics were calculated and SDs were used to analyze the total population and subgroups. Nonparametric statistics and logarithmic transformations were used for non-normally distributed variables. The odds ratio (OR) and 95% confidence intervals (CI) were calculated as indicated by Kahn and Schoenberg.21

**Results**

Two different studies were performed. One was a questionnaire survey on a large population; the second one was a more extensive investigation with specific testing on a geographically defined population which was also part of the initial large population. The latter study shall be discussed first here.

**Population Responses and Subgroups Obtained: Index Cases**

The index cases were individuals seen successively in a well-known sleep disorders clinic with a large referral network that includes among its many sources of referral 3 major internal medicine groups with a minimum of 5,000 clinic visits a year, 2 large pulmonary clinics, 3 large otolaryngologic clinics, 2 craniofacial clinics, and 3 major orthodontic practices. A mean of 600 in-laboratory polygraphic recordings with a positive diagnosis of sleep-disordered breathing have been performed each year over the past 4 years in this center. The index cases represent, thus, the overall spectrum of patients with upper airway OSAS and not a population biased by a more specialized recruitment base, eg, pulmonary medicine or otolaryngology-based patient recruitment. The clinic’s ability to offer any therapeutic approach for OSAS currently available also assured a very diverse, multiethnic recruitment.

One hundred fifty-seven successively monitored index cases (136 men; mean age, 51.3 ± 8.5 years) were identified for the study. The mean number of apneas and hypopneas during sleep (ie, RDI) was 40 ± 19.5. The mean BMI was 26.8 ± 4.1 kg/m².

The cephalometric measurements were as follows. The mean SNA angle was 81.3 ± 4 degrees; the mean SNB angle was 77.3 ± 4.1 degrees; the mean MP-H distance was 23 ± 8 mm; the PNS-P distance was 36 ± 6.8 mm; and the PAS was 5.4 ± 3.5 mm. Ninety-three (59%) subjects were classified as having a high arched-hard palate (ogival palate), while only 17 (11%) subjects were classified as having a midplaced (ie, normal) palate. All subjects underwent appropriate treatment for their OSAS, had posttreatment follow-up, and demonstrated control of both symptoms and polygraphic abnormalities.

**Questionnaire Survey**

**Family Members:** We identified a total of 844 living family members of the index group. They were subdivided into 91 parents, 471 siblings, and 282 children. From this total first-degree relative population, we obtained the mailing addresses of 792 (94%) relatives. We mailed two identical questionnaires to these relatives (one to be given to an age-matched friend) with a letter countersigned by the index case. In return, we received 531 questionnaires (63% of the contacted population) from the relatives and 198 (25%) from the friends.

Based on the questionnaire survey, 202 subjects from the group of relatives presented complaint of daytime sleepiness or fatigue or both. Subjects who reported “daytime fatigue” and scored 9 or above on the ESS were considered to present “excessive” sleepiness in association with daytime tiredness or fatigue or both, even if the subject only mentioned the latter in the questionnaire. Two hundred nineteen subjects admitted to snoring “nearly nightly” or “nightly,” but only 154 (18.2% of the total possible population, 19.4% of the total contacted population, and 50% of the responding population) subjects presented both daytime sleepiness and “near nightly” or “nightly” snoring.

At the initial interview, 95 index cases identified 177 relatives (21% of the total possible population) with a problem similar to theirs, namely, heavy snoring and inappropriate sleep episodes and levels of alertness. The other 62 index cases either did not know enough about their relatives to respond or did not believe that any of their first-degree relatives had a problem similar to theirs. By comparison, the questionnaire survey with only a 63% response rate (531 questionnaires) identified 154 relatives with similar problems. This finding suggests that index cases may be helpful in identifying relatives presenting problems similar to theirs.

Table 1 presents the OR obtained when we compared the responses of questionnaires from relatives with those of friends. As can be seen, “snoring” associated with excessive daytime sleepiness (EDS), ie, with Epworth Sleepiness Scale (ESS) score of 9 or more, was significantly more reported by relatives than by friends. Complaint of daytime sleepiness alone (ie, without taking into consideration ESS scores) did not dissociate the two groups, but report of frequent snoring was already significantly more common among relatives.

The BMI was never a significant variable for dissociating friends from relatives, and there was always
a large standard deviation for this variable.

Investigation Performed on San Francisco Bay Area Relatives: We obtained clinical evaluations and non-attended nocturnal monitorings from 166 (59.5%) of a group of 279 identified family members living in the San Francisco Bay Area. Sixty-nine friends (41.6%) from a group of 166 potential subjects agreed to have simultaneous clinical evaluation and Edentrace recordings.

Three families, with many members over several generations reportedly affected, had 19 first-degree relatives among the 166 subjects. These 19 subjects agreed to undergo not only Edentrace recording but also nocturnal polysomnography in the laboratory following the same protocol as the index cases.

Overall Family Distribution: There were 16 index probands with 3 or more affected relatives (affected was defined as the presence of symptoms associated with OSAS and RDI ≥5). Forty index cases had parents, offspring, or both affected, and 7 index cases had only affected siblings. Sixteen index cases had relatives with offspring, parents, and siblings affected.

Odds Ratio and Confidence Intervals: The clinical symptoms reported by the relatives and friends are indicated in Table 2. There was no significant difference between questionnaire-reported symptoms and complaints and those verified with interviews. One hundred thirty-nine (83.7%) related subjects presented with an RDI of 5 or more vs 7 (10%) friends. When presence of at least two different clinical symptoms (one of them must have been an ESS score ≥9) with RDI of 5 or more was requested, there was a very significant difference between relatives and friends. The OR, as seen in Table 3, was very highly significant. Also when presence of a complaint of daytime tiredness/sleepiness (without taking ESS score into consideration) was associated with the presence of high and narrow (orival) hard palate, the OR again showed a significant difference between relatives and control subjects (Table 3). The significance was less, however, than when RDI and

Table 2—Number of Subjects Reporting Clinical Symptoms and Complaints

<table>
<thead>
<tr>
<th>Clinical Symptoms*</th>
<th>% of Investigated Population</th>
<th>% of Potential Population</th>
<th>Relatives</th>
<th>No.</th>
<th></th>
<th></th>
<th>% of Investigated Population</th>
<th>% of Potential Population</th>
<th>Friends</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime fatigue/sleepiness</td>
<td>131</td>
<td>78.9</td>
<td>135</td>
<td>81.3</td>
<td>48.3</td>
<td></td>
<td>67</td>
<td>40.4</td>
<td>23</td>
<td>111</td>
</tr>
<tr>
<td>ESS ≥9</td>
<td>129</td>
<td>77.7</td>
<td>19</td>
<td>30.4</td>
<td>12.6</td>
<td></td>
<td>111</td>
<td>66.8</td>
<td>33.3</td>
<td>23</td>
</tr>
<tr>
<td>Heavy chronic snoring (score 4 or 5)</td>
<td>111</td>
<td>66.8</td>
<td>19</td>
<td>30.4</td>
<td>12.6</td>
<td></td>
<td>111</td>
<td>66.8</td>
<td>33.3</td>
<td>23</td>
</tr>
<tr>
<td>Nocturnal dryness of mouth or throat (score 4 or 5)</td>
<td>67</td>
<td>40.4</td>
<td>6</td>
<td>8.7</td>
<td>3.6</td>
<td></td>
<td>6</td>
<td>8.7</td>
<td>3.6</td>
<td>6</td>
</tr>
<tr>
<td>Nocturnal bruxism (presence/absence)</td>
<td>78</td>
<td>46.9</td>
<td>2</td>
<td>2.9</td>
<td>1.2</td>
<td></td>
<td>4</td>
<td>5.8</td>
<td>2.4</td>
<td>4</td>
</tr>
<tr>
<td>Nocturnal drooling (score 4 or 5)</td>
<td>51</td>
<td>30.7</td>
<td>4</td>
<td>5.8</td>
<td>2.4</td>
<td></td>
<td>5</td>
<td>5.8</td>
<td>2.4</td>
<td>4</td>
</tr>
<tr>
<td>Mouth breathing (score 4 or 5)</td>
<td>49</td>
<td>29.5</td>
<td>8</td>
<td>11.5</td>
<td>4.8</td>
<td></td>
<td>5</td>
<td>1.4</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Morning headaches (score 4 or 5)</td>
<td>57</td>
<td>34.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>34.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Score is based on a scale: 1=never; 2=exceptional; 3=rarely; 4=frequently; 5=nightly.
clinical symptoms of OSAS were considered together (OR = 10.9 vs 45.6).

The BMI was once again not a significant variable. There was a large SD in both groups and this may again explain the lack of significance: the mean BMI was 26.1 ± 4 kg/m<sup>2</sup> vs 25.8 ± 6 kg/m<sup>2</sup> in the adult population.

**Cephalometric Investigation:** Twenty-two (13%) family members and six (3.6%) friends (out of 166 potential subjects in each set) agreed to undergo these measurements. Their ages ranged from 16 to 68 years old (mean, 51 ± 18.1 years). The very low number of friends (6) who agreed to undergo cephalometric x-ray screening precluded OR calculations. The 22 family members were different from control subjects previously accumulated in our laboratory and from normative data in the literature,<sup>14,17-19</sup> as shown in Table 4, and from the few friends investigated. There was a significantly smaller SNB angle, a longer MPH bone distance and decreased PAS in these family members. These cephalometric findings reinforced the clinical findings. They indicate a mild craniofacial “disproportionate anatomy” similar to that described by Rojewski et al<sup>22</sup> and Jamieson et al.<sup>23</sup> Self-selection bias must be suspected here, considering the refusal rate of other volunteers to participate in this test.

**Specific Families:** Three families who lived in the Bay Area were affected over 3 successive generations, comprising 27 living first-degree relatives. We obtained questionnaires from 26 and performed nocturnal polysomnography on 19 (Fig 1). A subject was labeled “affected” if she or he had clinical symptoms associated with OSAS and an RDI of more than 5 on polysomnography. Family 1 was of particular interest because in the middle-age adult generation both parents were affected and treated with nasal continuous positive airway pressure. Five out of six offspring of these parents were affected as was the paternal “grandfather.” The grandparents on the maternal side were deceased. All affected subjects presented high, narrow, arched ogival hard palates associated with an overjet, a moderate retroposition of the mandible, and an abnormally small upper airway. Families 2 and 3 also showed a “disproportionate anatomy” in their affected members with similar high “ogival” hard palates and retroposition of the mandible. Figure 1 presents family trees constructed for each of these families.

**COMMENT**

The study reported here considered only first-degree relatives. Considering the number of potential subjects, a 63% response rate, particularly in the US environment, is large enough to bring valuable information. The risk of self-selection of affected individuals is always present and cannot be avoided completely in studies with this type of design, but the large database reduces the probability of selection bias. The study would have benefited if we had succeeded in obtaining a similar response rate from our control group. Once again, however, 198 responses allow for a meaningful comparison. In most cases, monitoring was performed with ambulatory, non-attended equipment, an approach which has been shown sometimes to deviate from polysomnographically determined RDI, since determination of total sleep time may not be as accurate as with polysomnography. Several studies have been performed using Edentrace, however, that reported reasonable comparative results with polysomnography.<sup>13,16,24,25</sup> We
also previously had performed a study with this equipment. We agree with prior findings: it is possible to have a reasonable calculation of total sleep time and of RDI with Edentrace. In our prior studies, the maximum deviation of Edentrace calculated RDI and polysomnographically calculated RDI was 11%. These differences had no impact on the classification of any subject and modified the RDI scores in only a very moderate way. Edentrace may not, however, be appropriate to evaluate arousal indices, particularly if transient EEG arousals are considered.

Acknowledging these limitations, several conclusions can be drawn from this study that assessed the OR of having OSAS.

The Issue of Body Mass Index

Often it is emphasized, at least in pulmonary literature, that OSAS occurs in very obese patients. Otolaryngologists have nearly as large a patient recruitment but much less morbid obesity. It is obvious that there are population recruitment biases depending on the clinical setting in which an investigation is performed. We have tried to avoid this bias and have a very large multidisciplinary referral network. This may explain why BMI was never a significant variable in our calculations. One has to analyze carefully the sleep-disordered breathing of obese patients. First, as well demonstrated by now, neck circumference is a better indicator of OSAS than is BMI. We acknowledge that this information is lacking in most large familial investigations, including ours, because this measure is difficult to obtain in questionnaire surveys. Second, obese patients usually present a complex syndrome, combining a chest bellows problem with an upper airway problem. The chest bellows problem may lead to sleepiness, hypoxemia, and cardiovascular complications. The upper airway problem, when it exists, can be related to a disproportionate anatomy, to fatty deposits in and around the upper airway, or to both.22,23,26-29 One must remember, however, that the upper airway impairment is by far not always present in obese subjects. None of the most overweight index cases (10 subjects with BMI >33 kg/m²) had “disproportionate” craniofacial anatomy. Interestingly, our investigation indicated that the 20 most overweight index cases had no familial aggregate of OSAS.

Craniofacial Features and Obstructive Sleep Apnea Syndrome

Previously, we have indicated, as have many others, that craniofacial abnormalities are common in OSAS.22,23,26-29 The OR for the presence of a high narrow “ogival” hard palate and complaints of daytime tiredness, EDS, or both in the relatives of our index cases in the San Francisco Bay Area study is high (OR=10.9; 95%, CI=5.31–22.5). This supports the notion that certain facial anatomical features (more particularly disproportionate anatomy), which seem to be familial traits, are risk factors for the development of OSAS. Undoubtedly, OSAS occurs in familial aggregates. The high number of index cases presenting intergenerational (parents or offspring) affected relatives indicates the presence of an inter-

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**Figure 1.** Three family trees demonstrating intergenerational and intragenerational transmission of OSAS. PSG=polysomnography; nasal CPAP=nasal continuous positive airway pressure.
generational transmission. Similarly, the number of affected siblings of index cases suggests an intragenerational occurrence. Both findings support a genetic basis for OSAS.

**Familial and Genetic Factors**

The fact that none of the very obese patients had any familial aggregate of OSAS while patients with specific craniofacial features (mostly involving the maxillomandibular growth) did have a familial aggregate is an interesting finding. The anatomic features that we have identified are, most probably, only indicative of risk of development of sleep-disordered breathing. It is unclear from this and other studies, however, whether the risk factors are associated with the bones (their development and anatomical relationship) or with the mucosa and soft tissues attached to these bone structures or with a combination of both. Many genes are involved in the development of the region, from genes that induce migration of specific cellular groups at a given time to genes leading to the structural organization during fetal life, for example. There is a continuous interaction in the structural development of the region at the time of early infancy between genetic and environmental factors. It will be important to determine the potential role of these environmental factors. This search will bring a better understanding of the development of sleep-disordered breathing syndromes in individuals with a familial aggregate. Hopefully, identification of these families and the presence in children of the facial anatomical features we have described may in the long run help in making adult OSAS more preventable.30

ACKNOWLEDGMENT: The authors thank Michael Gulevich for editing the manuscript.

**REFERENCES**


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