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HERITABILITY OF MAXILLARY MIDLINE DIASTEMA

By

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Submitted in partial fulfillment of the requirements

for the Degree of Master of Science in Dentistry

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ABSTRACT

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The purpose of this study was to calculate an estimate of the heritability of a common dental trait; maxillary midline diastema (MMD). The sample consisted of thirty families, fifteen African American (AA), fourteen Caucasian (CA), and one mixed race family. Families were selected from the Case Western Reserve University, Department of Orthodontics using a single ascertainment scheme. Familial data was collected using a seven-point survey. A pedigree constructed for each family indicated the relationship between affected and unaffected individuals. In all, the sample of 430 subjects consisted of 220 female, 210 male, 99 nuclear families, 534 sibling pairs, 422 avuncular pairs, 318 grandparental pairs, and 27 cousin pairs. Data was analyzed using the Statistical Analysis for Genetic Epidemiology© software. An estimate of heritability was

calculated as 0.44 for the Caucasian sample and 0.16 for the African American sample. Heritability was calculated using three familial correlations; spousal, parent-offspring, and sib-Sib, allowing for ascertainment correction. Relative risk for siblings, calculated following correction for ascertainment bias, was indicative of an autosomal dominant mode of transmission. The results suggested a genetic basis for maxillary midline diastema in the Caucasian sample, and a significant risk of recurrence of the trait in affected Caucasian families.

DEDICATION

To my mother, Carol, for your unconditional love and support, for believing in me and allowing me to believe in myself. I could not have become the person I am without your guidance.

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INTRODUCTION

Taber's Medical Cyclopedic Dictionary defines diastema as "a space between two adjacent teeth,"(1993). Angle (1907) described the midline diastema as a relatively common form of malocclusion characterized by a space between the upper and less commonly lower central incisors, and recognized that there were functional and esthetic consequences with midline spacing. He stated that diastema "always presented with an unpleasing appearance and that it interfered with speech in proportion to its width." However, Angle did not elaborate on the specific speech sounds that were affected. Similarly, Andrews (1972) in his classic article, "The Six Keys to a Normal Occlusion," stated that there should be no spaces between teeth and that all contact areas should be tight if a patient is to be viewed as having teeth that are "straight and pleasing in appearance as well as a bite that is considered generally correct".

Broadbent (1941) described the unaesthetic appearance of normal developmental maxillary midline spacing in growing children as the "ugly duckling stage" of dental development. This stage was characterized as a transitory state of spacing between the anterior incisors, which was indicative of the space available for the erupting permanent dentition. Broadbent described closure of the diastema space with the full eruption of lateral incisors and canine teeth as a normal part of occlusal development.

It is clear that midline spacing does not always close as a consequence of dental development. Persistent maxillary midline diastema is seen frequently by dental professionals in individuals who are seeking esthetic correction. Keresuo et al. (1995), in a study from Finland, demonstrated the importance of the esthetic component of anterior dental relationships. This study compared the modified facial photographs of six different individuals. Each individual's photographs were modified to portray four different dental arrangements and were shown to 1,007 Finnish students who estimated social and personal characteristics of the individual. The results

demonstrated that the dental arrangements had a significant effect on the perceived attractiveness and success of the persons portrayed. The study reported that faces which displayed incisal crowding or midline diastema were rated as significantly less intelligent, beautiful, and sexually attractive, and were judged to be in a lower social class than the same faces with ideal occlusion.

If the clinician is to successfully treat maxillary midline diastema for the esthetic and functional benefit of the patient, then a thorough understanding of the malocclusion is necessary for optimal results. There have been numerous causative factors suggested for midline diastema in the literature, most of which are related to environmental factors (Oesterle and Shellhart 1999; Nainar and Gnanasunderam 1997). There is a clear void in the literature with regard to the genetic contribution or cause for persistent maxillary midline diastema. The reported evidence for a genetic basis of this trait is largely anecdotal.

From a clinical standpoint, it appears that genetics can play a significant role in the persistence of

maxillary midline diastema. The trait is often seen in siblings and in other family members of affected individuals. If a significant genetic contribution could be established for this dental trait, it would aid the clinician in the estimation of risk to future generations and help to improve diagnosis and treatment protocols for the patient. Also of significance to the orthodontist, is the inherent instability of the orthodontic treatment result. The literature shows that a high familial prevalence of midline diastema is one of only two significant factors associated with post-orthodontic treatment relapse for this trait, (Shashua and Artun 1999). The orthodontist might better develop alternate treatment protocols for retention and stability when patients are found to be at risk of relapse given a family history of diastema.

LITERATURE REVIEW

Etiology of the Maxillary Midline Diastema

Numerous etiologies have been proposed and studied in the literature. A consensus has not been reached on a single causative factor for midline spacing, but rather, the prevailing opinion seems to be that the trait is multifactorial in origin, (Nainar and Gnanasundaram 1997; Oesterle and Shellhart 1999). The multifactorial basis of midline spacing is suggested to be largely of environmental causes, with very little reported on a genetic contribution.

Genetic Basis of Maxillary Midline Diastema

There is little mention of genetics or inheritance in the etiology of maxillary midline diastema in the dental literature. Gardiner (1969) pointed out that in the etiology of persistent midline space there is:

> "...almost no end to the conditions which could contribute to this (midline diastema). Undoubtedly congenital causes rank high on the list, and we have all seen parents and offspring with this characteristic."

Shasua and Artun (1997) mentioned that genetic predisposition was a possible contributing condition to maxillary midline space. The authors examined ninety-six post-orthodontically treated cases, a mean period of 6.3 years after treatment, to assess stability and retention of corrected maxillary midline space. The authors concluded that a family history of diastema was one of only two significant risk factors for diastema relapse. The other factor was pre-treatment diastema size.

Nainar and Gnanasunderam (1997), in a study of midline diastema in a population in South India, examined 9,774 patients aged thirteen to thirty-five, to determine incidence and possible etiological factors of the trait. Familial incidence, derived from history taking, was one of many factors studied in relation to midline diastema in the purified research sample. Other factors included parafunctional habits, mouth breathing, Bolton tooth size discrepancy, high frenal attachment, axial inclination of incisor teeth, spacing in the anterior region, class of occlusion, type of overbite, and maxillary suture type. They found that no single etiological factor was attributable to midline diastema, and that one patient

could have two or more of factors. The authors concluded that spacing in the anterior region (51.8%) was the most significant factor associated with midline diastema, but that also significant were familial incidence (32.5%) and parafunctional habits (29.5%). The relatively high percentage of familial incidence of maxillary midline diastema led the authors to suggest that there was a possible genetic factor at work in the expression of the trait.

Schmitt et al. (1982) described a family in which eight members over a span of three generations had a syndrome that included bilateral triphalangeal thumbs, radial hypoplasia, hypospadias, and maxillary midline diastema. All affected individuals had a maxillary midline diastema and the authors concluded, based on the pattern of inheritance, that the syndrome was autosomal dominant. The authors did not expand on the role or association of maxillary midline diastema in the syndrome, or the genetic contribution that might have been responsible for the expression of the dental trait.

There are other developmental defects of orofacial midline structures that are not necessarily associated

with syndromes. Neville et al. (1995) described the thyroglossal duct cyst as a remnant of thyroglosal duct epithelium that normally undergoes atrophy and is obliterated, but occasionally persists to form a cyst. They reported that thyroglossal duct cysts developed in the midline and could occur anywhere from the foramen cecum area of the tongue to the supracrestal notch. The median palatal cyst is another midline structure that is described by Neville et al. as a rare fissural cyst that develops from epithelium entrapped along the line of fusion of the lateral palatal shelves of the maxilla during development. Incomplete palatal fusion was proposed as an etiology for persistent midline diastema, and there was evidence that these cystic formations had a familial occurrence, which indicated a possible genetic contribution (Neville et al. 1995).

Other authors have examined the role of genetics in malocclusion without specifically looking at midline diastema. Stein et al. (1956) examined 150 families in a cephalometric study that compared facial angle and Angle molar relationship. Data obtained from family members of the 150 index cases was analyzed to determine the

proportion of index cases with affected and unaffected relatives. The authors defined malocclusion as "any deviation from the normal, with regard to missing, transposed or malformed teeth," as well as anterior posterior relationships of the teeth as defined by Angle. The authors reported that 33% of the normal group had parents or siblings with malocclusion, compared to 77% of the affected group. The authors also established pedigree to analyze the transmission of class II molar occlusion within families and reported an apparent recessive mode of inheritance.

Lundsstrom (1948) as reported by Smith and Bailit (1977) analyzed tooth size and dental occlusion in over two hundred sets of twins. All characteristics in Lundstrom's study were considered as quantitative continuous variables, so that the sagittal molar relationship, as an example, was measured rather than divided into Angle's categories. Lundstrom did not specifically look at maxillary midline diastema but did indicate that all variables examined had a larger genetic than environmental component of variation.

Chung and Niswander (1975), in similar study, examined occlusal characteristics on sixteen hundred pairs of siblings. The traits studied were buccal segment relationship, malalignment, overjet, overbite, crowding, crossbites and incisor width. The authors did not specifically look at midline diastema but found that intra-family correlations adjusted for age, sex, and other variables suggested the highest degree of genetic determination to be associated with incisor width and the lowest degree with buccal segment relation. This was also shown to be true in Lundstrom's study (1948). The authors concluded that the differences in the intra-family correlations were inversely related to the degree that environmental factors intervened in the formation of the dental traits.

Harris and Johnson (1991) also examined the role of heritability in malocclusion. The authors examined both craniometric and occlusal variables in a longitudinal sib analysis. The study was based on serial assessments of untreated persons in thirty sibships from 4-20 years of age in the Bolton-Brush Growth Studies. The intent of the study was to assess the contribution of heredity to a

variety of craniofacial skeletal and occlusal variables. The authors concluded that craniometric variables have high heritabities, while almost all occlusal variability was acquired rather than inherited.

Environmental Basis of Maxillary Midline Diastema

In looking at the causes of maxillary midline diastema, the majority of literature focuses primarily on environmental factors. One factor commonly implicated in the etiology of midline diastema was an enlarged labial frenum. Angle (1907) suggested that the maxillary midline diastema was caused by the superior labial frenum. Angle contended that the orthodontic stability of diastema closure was dependent on the removal of the tissues of the frenum. Sicher (1952), Gardiner (1967), and others have supported this reasoning.

Popovich et al. (1977) argued that where diastema persisted, the frenum was not a cause of the diastema, as many clinicians had previously concluded, but rather, that a contrary relationship existed. Popovich proposed that the maxillary labial frenum persisted as a consequence of the existing diastema, that because the

dentition exerted little or no pressure on the frenum, it therefore produced little or no atrophy of the frenum.

Edwards (1977), in his investigation into the frenum and the midline diastema, examined 308 patients who demonstrated a maxillary midline diastema and/or a clinically abnormal appearing maxillary labial frenum. The sample was categorized as having one of the following: a diastema (2mm or more) with an abnormal frenum; a diastema (2mm or more) with a normal frenum; or no diastema but an abnormal frenum. Edwards also examined 162 diastema subjects who had been orthodontically treated and whose diastema had been retained for 11-22 months. Edwards found that the pretreatment relationship between a clinically abnormal appearing maxillary labial frenum and midline diastema showed a strong, but not absolute correlation. A certain portion of subjects showed diastema without an abnormal frenum and others showed no diastema but had an abnormal frenum. In addition, in those subjects in which there were abnormal pretreatment frenums, the subjects demonstrated a decidedly stronger potential for relapse following orthodontic closure.

Tait (1924) stated that the frenum has no function and its action, if any, in relation to the upper incisors, was purely passive, that of resisting mesial pressure. Tait contented that the frenum was sometimes associated, but not the cause of spacing between the maxillary central incisors.

Ceremello (1953) studied thirty-four patients, half with midline diastema and the other half without, and concluded that the position and appearance of the frenum did not correlate with the presence, or width, of the diastema.

James (1967) surgically removed enlarged superior labial frenum from ten human subjects, all of whom had a maxillary midline diastema and who had achieved a full adult dentition prior to the operation. After a one-year post-operative period, and without orthodontic treatment, 80% of the subjects showed some degree of closure of the midline diastema space. James concluded that this was a specific indication for frenectomy in association with orthodontic treatment for a stable result.

Another etiological factor for maxillary midline diastema often cited in the literature is tooth size

discrepancy. Oesterle and Shellhart (1999) described tooth size discrepancy as being a major cause of maxillary midline diastema. They contended that the most common tooth size discrepancy, manifested in the form of peg shaped lateral incisors, allowed distal drifting of the maxillary central incisors, thus creating midline diastema.

Tooth size discrepancy is one manifestation of what could be considered a generalized dento-alveolar disproportion. Other factors that can contribute to maxillary midline spacing under this general heading, include missing teeth from trauma or pathosis, extra teeth as with a mesiodens, and displaced teeth in the maxillary anterior segment. Oesterle and Shellhart (1999) outlined the sequelae on the dento-alveolar complex, and reported that, in all cases, generalized spacing and specifically maxillary midline diastema could result. The authors reported that endocrine imbalances resulting in increased growth hormone, as in acromegaly, and that weakness in orofacial muscle tonicity could also contribute to spacing problems. Individuals with acromegaly could have abnormally large jaws relative to

their tooth size, causing spacing. In addition, individuals with weakened oral facial muscles and flaccid lips can have an outward migration of the dentoalveolar complex with labial or buccal movement of the teeth. These patients can exhibit wide ovoid arches with a lack of interproximal contact.

Excessive anterior vertical overlap or overbite, has also been suggested by Oesterle and Shellhart (1999) as being a contributing factor in the etiology of maxillary midline diastema. When there is no Bolton discrepancy and the individual has an anterior-posterior Angle class I occlusion, significant vertical overlap of the anterior teeth results in an increase in the circumference of the maxillary arch. This circumferential increase leads to maxillary spacing or mandibular anterior crowding. This phenomenon is the result of the wedge-shaped lingual surface of the maxillary central incisors.

Oral habits in individuals are an important etiologic component of the expression of midline diastemas. Gardiner (1967) pointed out that thumb sucking and/or the activity or size of the tongue can result in spacing of the maxillary central incisors.

Proffit and Fields (1993) discounted tongue thrusting as a possible etiological factor for midline diastema, due to the short time the tongue was in contact with the lingual surface of the anterior teeth, but suggested that tongue position at rest can have a large effect on tooth position. Many others have implicated habits such as thumb or finger sucking as an etiological factor in the expression of maxillary midline diastema. Oesterle and Shellhart (1999) suggested that any habit that resulted in a long- term protrusion or separation force on the maxillary anterior teeth should be considered a potential causative factor for midline diastema.

Diastema and Normal Dental Development

Broadbent (1941) described midline spacing in the developing dentition as a normal occurrence in growing children. This has been widely supported in the literature. Taylor (1939), in a study of 516 children ranging in age from 5.5-11 years of age, found that 98% of six year olds observed showed spacing between the incisor teeth. In another study by Taylor (1939), a group aged 6-7 years showed that 88.7% had midline diastemas. As age increased, the percentage of children

displaying maxillary midline diastema decreased significantly. In a group aged 10-11 years, the percentage of midline diastema was 48.7%, and in a sample of 1,067 high school students aged 12-18 years, the percentage displaying midline diastema fell to 7%. Taylor's survey represented children with any type of midline space without regard to contributory factors.

Gardiner (1967) studied one thousand school children in Sheffield, England who ranged in age from 5-15 years. He found that as age increased, the prevalence of midline diastema decreased correspondingly from 46% at 6 years of age to 7% at 15 years of age. Others such as Weyman (1967) and Richardson et al. (1973) had similar findings.

Clearly, the literature shows that midline diastema is a consequence of age and normal development. In an effort to predict whether, or not, a diastema space would close on its own with time, Sanin et al. (1969) developed a method whereby they could predict, with a reported 88% accuracy, if a diastema space would be self-correcting. The prediction was based on millimeter measurement in the early mixed dentition, with the probability of the space closing without treatment as an inverse proportion to the

diastema size. Early in the mixed dentition, a diastema space measurement of 1.0 mm had a 99% probability of closing by itself. For 1.5 mm the probability of natural closure was 85%, at 1.85 millimeters, 50%, and at 2.7 millimeters the probability of the space closing without treatment falls to one percent. The authors pointed out that the measurement must be made at a time when the lateral incisors are fully erupted. Attempts of prediction at an earlier age had proven to be highly inaccurate.

Incidence/Prevalence of Maxillary Midline Diastema

There have been numerous studies on the incidence or prevalence of maxillary midline diastema. These studies have reported a wide range of findings (Table I). Differences in these epidemiological studies can be attributed to the large number of factors that contribute to midline diastema, the definition used to define diastema, and the racial and gender differences in the distribution of the trait. (Sullivan et al. 1997)

Table 1.--Summary of Reported Incidence/Prevalence Values for Maxillary Midline Diastema

Authors	Total Sample (n)	Age	Gender	Race	% With Diastema and Conclusions
Keene (1963)	183	17-25 y	Male	Caucasian	8.3%
Lavelle (1970)	656	18-25 y	Male> Female	Caucasian Black Asian	3.5% Caucasian 5.2% Black 3.4% Asian
Richardson et al (1973)	5307	6-14 y	Male> Female	Caucasian Black	14.1% Caucasian 22.8% Black
McVay (1984)	5970 Panorex Radiographs	18+ y	Male> Female	Caucasian Black Asian	19.9% Caucasian 29.1% Black 19.9% Asian
Steigman and Weissberg (1985)	1269	12-18 y	Male> Female	Jewish	25.4% w/ other spacing in arch 1.4% w/o other spacing in arch
Brunelle et al (1991)	7000	8-50 y	Male> Female	Caucasian Black Hispanic	4.9% Caucasian 16.2% Blacks 6.6% Hispanic
Nainar and Gnanasundaram (1997)	9774	13-35 y	Male> Female	Indian	1.6%
Weyman (1967)	751	14-16		Caucasian	5.7%

In their study, Nainar and Gnanasundaram (1997) found that in South India, of 9,774 patients aged 13-35 years, 166 patients (1.6%) displayed true maxillary midline diastema. True maxillary midline diastema was defined as "one without periodontal/periapical involvement and with the presence of all anterior teeth in the arch."

Keene (1963) studied 641 white, male United States Naval recruits aged 17-25 years and found a prevalence of

maxillary midline diastema of 8.3%. The original sample of 641 was purified based on exclusion criteria. Of the original 641, 458 were excluded leaving a sample of 183. Subjects were excluded if they were missing one or more teeth, had pronounced malformations of the teeth or jaws, previous orthodontic treatment, or gross destruction of the crowns of the teeth.

Steigman and Weissberg (1985) examined the dentitions of 1,279 Israeli high school students aged 12-18 years. The authors found the incidence of maxillary midline diastema to be 0.9% in males, and 1.4% in females, when no other spacing in the arch existed. However, when other spacing existed, the incidence rate was 25.8% for males and 25.4% for females.

McVay and Latta (1984), in a random sampling of 5,970 Panorex radiographs of individuals ranging in age from eighteen years and up, found the incidence of maxillary midline diastema to be 22.33%. The subjects were stratified by age, sex, race, and size of diastema. The definition of midline diastema for this study was "any space larger than 0.5 mm". McVay and Latta found that there was no difference in number or size of the

midline diastema assignable to sex. Blacks exhibited a greater number and size of diastemas when compared to either Whites or Orientals. There were also differences in the number and size of diastemas with regard to age; specifically, the number decreased with age while the width increased with age.

In a report on oral traits as part of the oral health component of the Third National Health and Nutrition Examination Survey, Phase 1, 1988-1991, Brunelle et al. assessed the presence of maxillary midline diastema in a sample of over 7,000 people. The survey sample consisted of non-institutionalized individuals aged 8-50 from across the United States. The authors defined maxillary midline diastema as "a space between the central incisors greater than two millimeters in width." No assessment was made if the individual had one or both central incisors missing or crowned. Space that had been closed with dental restorative material was also excluded. The authors found the prevalence of maxillary midline diastema to be 6.5% for all persons studied. As supported by previous studies, children aged 8-11 years showed a higher prevalence rate of midline

diastema (19.0%) when compared to older age groups 12-17 years (6.0%), and 18-50 years (4.8%). More males than females exhibited midline diastema in all age groups. When prevalence of midline diastema was examined by race-ethnicity, a greater percentage of non-Hispanic Blacks (16.2%) had a midline diastema than non-Hispanic Whites (4.9%) or Mexican Americans (6.6%).

Lavelle (1970) studied the distribution of midline diastemas in a population of 656 subjects in the United Kingdom. The sample was broken down into three different racial groups that consisted of 266 Caucasians, 218 Blacks, and 172 Asians ranging in age from 18-25 years. The sample included roughly the same number of male and female subjects. The percentages of maxillary midline diastema in the three different races were found to be 3.5% in Caucasians, 5.2% in Blacks, and 3.4% in Asians.

Richardson et al. (1973), in a biracial study of maxillary midline diastema, sampled 5,307 elementary school children in Jackson, Tennessee. The children's ages ranged from 6-14 years and the sample was divided into 2,554 Blacks, and 2,753 Whites. The sample was further broken down according to gender with 1,253 Black

males, 1,301 Black females, 1,288 White males and 1,465 White females. Diastema was defined as "a space between the central incisors greater than 0.5 millimeter." Subjects were included in the sample if they had no history of previous orthodontic treatment, no obvious dental or dentofacial abnormality, and no loss of anterior tooth material. The authors found that the highest prevalence of the maxillary midline diastema was at age eight. The prevalence in both races, and the total group, increased between six years of age and eight years of age and then gradually decreased between ages eight and fourteen. Blacks showed higher prevalence of midline diastema than Whites at all age levels except at age eight.

Weyman (1963) found the incidence of midline diastema in a sample of 751 children, to be 56.8% after the eruption of permanent central incisors, 38.0% after the eruption of lateral incisors, 7.4% after the eruption of permanent canines, and 5.7% at ages 14-16 years. The author concluded that the eruptive stage of the dentition was a more accurate point on which to base treatment planning than the actual age.

Treatment and Stability of Midline Diastema

A number of treatment strategies have been proposed for the management of maxillary midline diastema. Treatment strategies that have been suggested include orthodontic correction with fixed appliances, orthodontic correction with removable appliances, surgical orthodontic correction, and prosthetic correction with composite resin bonding, veneers, or full jacket crowns.

Sullivan et al. (1997) studied a sample of thirty-five patients with pre-treatment diastemas ranging from 0.9-3.0 mm following the eruption of the maxillary canines. They examined post-retention stability of maxillary midline closure, searched for predictors of relapse, and tested for an association between relapse and post-retention changes. The post-retention data ranged from 1-26 years with a mean of 11.4 years. The authors found that measurable diastema relapse was evident in twelve of thirty-five cases and that the majority of the relapse was 0.6 mm or less, with a maximum relapse reported of 3.0 mm. The authors concluded that abnormal frenums and/or intermaxillary osseous clefts did not appear to be risk factors for

relapse as had been previously reported in the literature (Edwards 1977). Furthermore, the authors concluded that no pre-treatment predictors of relapse could be established, and that the only post-treatment change associated with diastema was proclination of the maxillary incisors.

Shashua and Artun (1999) had similar findings to Sullivan et al. in their study of ninety-six orthodontically treated patients with maxillary midline diastema that ranged from 0.5-5.62 mm. Post-retention data was examined for the sample four to nine years after the completion of active treatment. The authors found that the incidence of relapse was 49% when defined as "the presence of a measurable space at follow-up, a history of prosthetic treatment to close a space that had re-opened, or the prolonged use of a retainer to control the tendency for relapse." As in the study of Sullivan et al., Shashua and Artun found that there was no association between relapse and the presence of an abnormal frenum or an osseous intermaxillary cleft. However, the authors did find that those with an abnormal frenum had a wider post-treatment diastema than those

with a normal frenum. The authors also concluded that pre-treatment diastema size and presence of a family member with a similar condition were the only significant risk factors for relapse.

The literature supports the notion that the etiology and distribution of midline spacing is varied and complex. It is also clear that there has been a broad focus on the environmental causes of the trait with minimal attention paid to a possible genetic influence in the expression of midline diastema. The ability of the clinician to assess the heritability of maxillary midline diastema as a means of prediction of risk to future generations should be valuable in the formulation of diagnoses and treatment protocols for patients.

STATEMENT OF THESIS

The aim of the present study is to determine the heritability of a common dental trait, maxillary midline diastema. In addition, the study is intended to determine the risk of recurrence of the trait within affected families.

Specifically, data will be collected on thirty families, stratified by race, using a seven-point survey. Pedigrees will be constructed for each family to demonstrate relationships between affected and unaffected individuals. Heritability will be calculated using three familial correlations including spousal, parent-offspring, and sib-sib, allowing for ascertainment correction. Sibling relative risk will be calculated, following correction for the ascertainment bias, to estimate the mode of inheritance, and to determine the risk of recurrence within affected families.

MATERIALS AND METHODS

Study Population

Fifty-two sample subjects from the Case Western Reserve University, Department of Orthodontics, School of Dentistry were selected as probands for the present study. Selection criteria for the probands was the presence of a clinically visible maxillary midline diastema of 0.5 mm or more. Subjects under the age of twelve years, or missing maxillary anterior teeth were excluded from the study. In addition, the probands had to have maxillary canines erupted past the height of contour of the clinical crown. Recruitment of proband subjects followed clinical examination, an assessment of plaster study models and by examination of existing photographs of the face and teeth.

Data Collection--Family Questionnaire

Proband subjects were mailed fifteen copies of a seven-question survey for their biological family members to complete and return. The questionnaires were sent

with a self-addressed, stamped envelope, a letter of consent, and instructions for completing the survey. Biological family members over the age of twelve were asked to complete the survey, answering biographical data including their name, gender, ethnicity, and specific relationship to the proband. Sample subjects were asked questions as to the presence or absence of maxillary midline diastema after the age of twelve, presently or in the past. The subjects were also asked about any current medical conditions.

Subjects were requested to complete the survey for family members unable to fill them out due to geographic location, or in the event that the family member was deceased. Subjects were encouraged to refer to old photographs, and to contact family members. The completed surveys were returned to the Department of Orthodontics. The returned surveys were coded by assigning a family identification number (1-30), and each individual family member was given a personal identification number, with the proband number being the first digit.

Data on some of the familial members was obtained by telephone interview, or in person. Questions asked were identical to those of the questionnaire. This process assisted in familial data collection and increased sample size. In all, thirty families participated in the study; fourteen Caucasian, fifteen African American and, one mixed-race family. Data was collected on 430 individuals within these families.

Family Pedigrees

The information obtained on the questionnaires was organized by family identification number and by individual identification number. A pedigree for each family was constructed based on the relationships reported in the returned surveys. When reported the affected status of each individual, in each family, was indicated by black fill. Males were designated "squares" and females "circles" in the constructed pedigrees. Unaffected subjects were designated in white; subjects whose status was unknown were depicted with a question mark, and deceased individuals were indicated by a slash mark. An example of a family pedigree is shown in Figure 1.

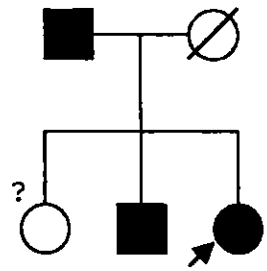


Figure 1.--Family pedigree example; squares represent males, circles represent females, filled represents affected, unfilled represents unaffected, slash mark represents deceased, question mark represents unknown, and arrow indicates proband.

Data Analysis

Data for the subjects in each family was entered in the spreadsheet program Microsoft Excel (Microsoft, Seattle, WA). The presence of a maxillary midline diastema was recorded as "1" and unaffected by "0". In addition, the family identification number (1-30), individual identification number (beginning with 1), gender, proband identification, ethnicity, mother's and father's individual identification number and observable phenotype were recorded. Observable phenotype represented those sample subjects willing to provide blood or cheek swab material for future molecular studies. General descriptive statistics, including prevalence of the trait by race and sex, as well as

number and affected status of sib, brother, sister, brother-sister, avuncular, grandparental, and cousin pairs, and number of nuclear families, founders and non-founders were determined. Data was analyzed using the REG C program of the software package Statistical Analysis for Genetic Epidemiology (S.A.G.E.©, B.Elston, Cleveland, OH 1998). Data analysis by the REG C program included an estimation of heritability using calculation of three familial correlations, including spousal, parent-offspring, and sib-sib relationships, while allowing for ascertainment correction. As a model for the heritability calculation, an assumption of parent-offspring covariance equaling ½ genetic variance, sib-sib covariance equaling ½ genetic variance + ½ common environment variance, and spouse-spouse covariance equaling common environment variance was made. The equation used to estimate heritability was:

$$h^2 = [w_1 \cdot r(PO) + w_2 \cdot r(diff)]$$

where,

$$w_1 = \frac{(1/\sigma^2_{r(PO)})}{(1/\sigma^2_{r(PO)} + 1/\sigma^2_{r(diff)})}$$

and,

$$w_2 = \frac{(1/\sigma^2_{r(diff)})}{(1/\sigma^2_{r(PO)} + 1/\sigma^2_{r(diff)})},$$

The correlations were designated by r(PO)= parent-offspring, r(Sibs)= Sib-Sib, r(Spouse)= Spouse-Spouse, and r(diff)= r(Sibs)-r(Spouse). From the available data, $\sigma^2_{r(PO)}$, $\sigma^2_{r(diff)}$, and $\sigma^2{}_h{}^2$ could be estimated from the REG C program in the S.A.G.E.© (1998) software package. The analysis of data was carried out on fifteen African American and fourteen Caucasian pedigrees, excluding one mixed race pedigree. The pedigrees were corrected for input into the REG C program by eliminating a portion of the pedigrees that provided the least amount of information. In this way, complex bilineal pedigrees were analyzed as a single set of founders.

Sibling relative risk was calculated from the data, correcting for ascertainment bias, using the equation relative risk= recurrence risk/prevalence. Recurrence risk was calculated for the Overall, Caucasian, and African American populations as the sum of affected siblings minus one and divided by the sum of the total

siblings minus one. Prevalence was estimated at 0.05 based on previously reported values in the literature (Brunelle et al. 1996).

RESULTS

Overall Sample Population Statistics

A sample of thirty families was analyzed for the presence of maxillary midline diastema (MMD). Family pedigrees were constructed showing the relationship of affected and unaffected family members (Appendix 3). The sample consisted of 430 subjects, 220 females, 210 males, 99 nuclear families, 534 sibling pairs, 132 brother pairs, 148 sister pairs, 254 brother-sister pairs, 422 avuncular pairs, 318 grandparental pairs, 27 cousin pairs, 129 founders, and 301 non-founders. The minimum pedigree size was 7 individuals and the maximum pedigree size was 26 individuals.

Of these groups, it was determined that 230 individuals, 133 females, 97 males, 159 sibling pairs, 36 brother pairs, 47 sister pairs, 76 brother-sister pairs, 178 avuncular pairs, 104 grandparental pairs, and 19 cousin pairs were affected with maxillary midline diastema. The overall sample data is summarized in Table 2.

Table 2.--General Statistics-Overall Sample Population

Category	Total Number	Total Affected with Diastema
Pedigrees	30	
Individuals	430	230
Females	220	133
Males	210	97
Sibling pairs	534	159
Brother pairs	132	36
Sister pairs	148	47
Brother-sister pairs	254	76
Avuncular pairs	422	178
Grandparental pairs	318	104
Cousin pairs	27	19
Nuclear families	99	
Founders	129	
Non-founders	301	
Minimum pedigree size	7	
Maximum pedigree size	26	

African American Sample Population Statistics

A total of fifteen of the thirty families sampled were of African American decent. Family data was stratified by race due to a greater prevalence of MMD among African Americans reported in the literature (Brunelle et al. 1996; Richardson et al. 1973; McVay 1984), and that racial predilections for various phenotypes have been well established.

In the African American subject population, 15 pedigrees comprised of 238 individuals, 119 females, 119

males, 333 sibling pairs, 87 brother pairs, 91 sister pairs, 155 brother-sister pairs, 244 avuncular pairs, 178 grandparental pairs, 18 cousin pairs, 55 nuclear families, 70 founders, and 168 non-founders. The minimum pedigree size was 8 individuals and the maximum pedigree size was 26 individuals.

In this population, 125 individuals were affected with MMD. The affected population included 72 females, 53 males, 92 sibling pairs, 22 brother pairs, 29 sister pairs, 41 brother-sister pairs, 109 avuncular pairs, 56 grandparental pairs, and 10 cousin pairs. African American sample population statistics are summarized in Table 3.

Pedigree size was adjusted from complex to simple for each of the pedigrees in the African American sample. This was achieved by excluding a lineal branch, the least informative side of the family. The resulting population numbers and affected status for each of the groups is summarized in Table 4.

Table 3.--General Statistics-African American Sample Population

Category	Total Number	Total Affected with Diastema
Pedigrees	15	
Individuals	238	125
Females	119	72
Males	119	53
Sibling pairs	333	92
Brother pairs	87	22
Sister pairs	91	29
Brother-sister pairs	155	41
Avuncular pairs	244	109
Grandparental pairs	178	56
Cousin pairs	18	10
Nuclear families	55	
Founders	70	
Non-founders	168	
Minimum pedigree size	8	
Maximum pedigree size	26	

Table 4.--General Statistics-African American Sample Population, After Pedigree Correction

Category	Total Number	Total Affected with Diastema
Pedigrees	15	
Individuals	212	115
Females	103	68
Males	107	47
Sibling pairs	303	88
Brother pairs	85	22
Sister pairs	74	26
Brother-sister pairs	144	40
Avuncular pairs	218	101
Grandparental pairs	152	45
Cousin pairs	18	10
Nuclear families	49	
Founders	64	
Non-founders	148	
Minimum pedigree size	8	
Maximum pedigree size	26	

Caucasian Sample Population Statistics

The Caucasian sample was comprised of 14 family pedigrees and 184 individuals. There were 97 females, 87 males, 200 sibling pairs, 45 brother pairs, 56 sister pairs, 99 brother-sister pairs, 177 avuncular pairs, 134 grandparental pairs, 9 cousin pairs, 41 nuclear families, 55 founders, and 129 non-founders. The minimum pedigree size in the Caucasian population was 7 individuals and the maximum pedigree size was 18 individuals.

There were 101 individuals affected with MMD in this population including, 59 females, 42 males, 67 sibling pairs, 14 brother pairs, 18 sister pairs, 35 brother-sister pairs, 69 avuncular pairs, 46 grandparental pairs, and 9 cousin pairs. Caucasian sample population statistics are summarized in Table 5.

Table 5.--General Statistics-Caucasian Sample Population

Category	Total Number	Total Affected with Diastema
Pedigrees	14	
Individuals	184	101
Females	97	59
Males	87	42
Sibling pairs	200	67
Brother pairs	45	14
Sister pairs	56	18
Brother-sister pairs	99	35
Avuncular pairs	177	69
Grandparental pairs	134	46
Cousin pairs	9	9
Nuclear families	41	
Founders	55	
Non-founders	129	
Minimum pedigree size	7	
Maximum pedigree size	18	

After correction of the Caucasian sample, by removing a lineal branch of the pedigrees, the resulting

population statistics and affected status of the sample are summarized in Table 6.

Table 6.--General Statistics-Caucasian Sample Population, After Pedigree Correction

Category	Total Number	Total Affected with Diastema
Pedigrees	14	
Individuals	150	85
Females	80	51
Males	70	34
Sibling pairs	172	58
Brother pairs	34	10
Sister pairs	53	18
Brother-sister pairs	85	30
Avuncular pairs	138	50
Grandparental pairs	90	33
Cousin pairs	9	9
Nuclear families	32	
Founders	46	
Non-founders	104	
Minimum pedigree size	7	
Maximum pedigree size	16	

One family pedigree in the overall sample was of a mixed-race heritage. This family included 8 individuals, including 4 females, 4 males, 1 sibling pair, which was a sister pair, 1 avuncular pair, 6 grandparental pairs, 3 nuclear families, 4 founders and 4 non-founders. Those affected with MMD in this group included 4 individuals, 2

females, 2 males, and 1 grandparental pair. Data for this family is summarized in Table 7.

Table 7.--General Statistics-Mixed Race Sample Population

Category	Total Number	Total Affected with Diastema
Pedigrees	1	
Individuals	8	4
Females	4	2
Males	4	2
Sibling pairs	1	0
Brother pairs	0	0
Sister pairs	1	0
Brother-sister pairs	0	0
Avuncular pairs	1	0
Grandparental pairs	6	1
Cousin pairs	0	0
Nuclear families	3	
Founders	4	
Non-founders	4	

Heritability Calculation

Heritability was calculated for the African American and Caucasian populations using familial correlations with the REG C portion of the Statistical Analysis for Genetic Epidemiology software program. Heritabilty was calculated using the adjusted pedigree data and found to be 0.44 with a standard deviation of 0.14 in the Caucasian population. Heritability was found to be 0.16

with a standard deviation of 0.14 in the African American population. The results suggest that the dental phenotype in the African American population may, to a greater extent, be due to environmental factors.

Sibling Relative Risk

Sibling relative risk was calculated for the Overall, African American, and Caucasian populations. Sibling relative risk was the ratio of sibling recurrence risk to the prevalence rate for the dental phenotype in the general population, estimated to be 0.05 (Brunelle et al. 1996). The sibling risk of recurrence was found to be 0.55 for the overall population, 0.67 for the Caucasian population, and 0.46 for the African American population. The sibling relative risk was found to be 11.0 for the Overall total sample population, 9.2 for the African American sample population and 13.4 for the Caucasian sample population. From the calculated relative risk, and the family pedigree data, an autosomal dominant mode of inheritance was determined.

DISCUSSION

This study examined the heritability of maxillary midline diastema, sibling recurrence risk and sibling relative risk within African American and Caucasian sample populations. Data was collected via questionnaire and organized into family pedigree format with affected and unaffected individuals indicated.

Family Questionnaire

The families of proband subjects selected from a patient population at the Case Western Reserve University Department of Orthodontics were sent questionnaires to determine the phenotypic status of related family members. The questionnaires, as sent, included information as to the presence or absence of maxillary midline diastema, any current medical conditions, an estimation of diastema size on an ordinal scale, relationship to proband, previous dental treatment to close diastema, and biographical data including name and gender.

The self-reporting of diastema size on an ordinal scale proved to be unreliable. Many of the sample subjects were unable to understand the scale as written, and it was, therefore, removed from the questionnaire. The resultant data was based on a dichotomous scale of affected or unaffected. Self-reporting of the diastema trait was considered to be reliable because the trait was so easily identifiable.

Heritability of Maxillary Midline Diastema in the Caucasian Sample Population

The results suggest that maxillary midline diastema is heritable in the Caucasian sample population. Heritability was estimated at 0.44 for this sample with a standard deviation of 0.14. Heritability was calculated using intra-family correlations including spousal, sib-sib, and parent-offspring.

Heritability was defined as the ratio of total genotypic variance to the total phenotypic variance. In the Caucasian sample, which showed a relatively high heritability for maxillary midline diastema, it is plausible that the Caucasian sample population had a fairly uniform etiology for the trait. This study examined the heritabilty of midline diastema in a general

sense without stratification of the sample by potential cause for the diastema. If the Caucasian sample had many affected individuals, and the underlying cause of the diastemas was highly heritable, then this would be reflected in a higher heritability for the trait. For example, if tooth size discrepancy was largely responsible for the reported midline diastemas in the Caucasian sample, and tooth size is highly heritable, as supported by Chung and Niswander (1975), this may account for the result. In summary, the Caucasian population may have had fewer causes for the trait, with those causes having a higher heritability.

Heritability in the African American Sample Population

Heritability, as measured by a heritability index of maxillary midline diastema, was found to be lower for the African American sample when compared to the Caucasian sample. Heritability for this sample was found to be 0.16, with a standard deviation of 0.14.

The literature reports a higher prevalence of maxillary midline diastema in the African American population. The disparity of heritability between the African American and Caucasian races might have been due to sporatic environmental factors, a greater number of

less heritable causes in the African American sample, or inaccurate reporting of diastema presence. A higher prevalence of midline diastema in this population could have affected the heritability calculation by increasing the spousal correlation. Spouses had a greater likelihood of sharing the diastema phenotype because the phenotype was more common in the population. The spousal correlation was assumed to contribute zero genetic variance to the calculated heritability. If the spousal correlation increased, as it did in the African American sample, then the resulting heritability would correspondingly decrease. The spousal correlation, for the purposes of the heritability calculation, was considered common environmental variance only.

Phenotypic variance is the common genetic variance plus the common environmental variance. If there were a greater number environmental influences in the African American group, such as periodontal drift, unreported habits, missing teeth etc., then heritability would be correspondingly lower. In addition, with a smaller sample size, any inaccuracy in the reporting of diastemas could amplify the intra-family correlation calculations. Indeed, in this study, the parent-offspring correlation

in the African-American sample was much lower than in the Caucasian sample.

As another explanation, there could simply be other causes for maxillary midline diastema in the African American population, such as increased incisor angulation and increased maxillo-mandibular jaw size. If this is true, and those causes have lower heritability, then a correspondingly lower overall heritability for the trait would result.

Regardless of the lower calculated heritability in the African American sample, the pedigree data was still suggestive of a genetic influence in the expression of maxillary midline diastema.

Analysis of Heritability

Heritability was calculated based on familial correlations derived from the REGC portion of the Statistical Analysis of Genetic Epidemiology software program. Statistical significance was determined using a t-statistic. Clearly, a quantitative study measuring diastema space would have allowed for more powerful statistical analysis, but was beyond the scope of this research project.

Sibling Relative Risk

Sibling risk of recurrence is an estimate of the likelihood of one sibling being affected if another sibling is affected, and was found to be 0.46 for the African American sample and 0.67 for the Caucasian sample. A 50% chance of parent-offspring transmission of the trait in question is expected with an autosomal dominant mode of inheritance. It must be clear that genetic transmission cannot be verified unless molecular level studies are undertaken to determine specific gene transmission.

Sibling relative risk is the risk to siblings within an affected family compared to the risk to siblings in the general population. The results suggested that a person in an affected African American family was 9.2 times more likely to be affected than the general population risk. In the Caucasian sample, the risk was 13.4 times greater if there was a family history of diastema. These results were consistent with a seemingly autosomal dominant mode of transmission, evident in the family pedigrees. These numbers are indicative of a genetic contribution in the expression of maxillary

midline diastema in both African American and Caucasian sample populations.

Limitations

The present study relied on the self-reporting of maxillary midline diastema. Although the trait was easily identified, reporting errors could have occurred. Verification of the diastema space with models or photos could have avoided potential errors in reporting. The difficulting in obtaining photos and/or models of sample subjects spread out geographically across the state and country prevented this more reliable method of data collection.

Another limitation of this study was related to the analysis of data as a dichotomous variable. Measuring the variable quantitatively would have allowed for more powerful statistical analysis. Again, the inability to physically reach sample subjects around the country prevented accurate measurement of diastema space.

Future Studies

The logical next step in the study of the heritability of maxillary midline diastema is to quantify diastema space and to collect biological material for molecular level studies and gene identification. Marker

genes should be sought in large families that show high heritability for the maxillary midline diastema trait. Caucasian families showed a higher heritability than African American families and might prove more valuable in gene isolation and identification.

SUMMARY AND CONCLUSIONS

Thirty families, selected by proband, consisting of 430 individuals of Caucasian, African American, and mixed African American/Asian race were screened for maxillary midline diastema. Data was organized into pedigree format, and intra-familial correlations were used to estimate heritability. Sibling risk of recurrence and sibling relative risk was also calculated. Analysis of the data led to the following conclusions:

1) In the Caucasian sample, the heritability of maxillary midline diastema was 0.44 with a standard deviation of 0.14.

2) In the African American sample, the heritability of maxillary midline diastema was 0.16 with a standard deviation of 0.14.

3) There was a significant sibling risk of recurrence in both the African American and Caucasian Sample populations.

4) Sibling relative risk was high for both the African American and Caucasian sample populations. This finding was consistant with an autosomal dominant mode of inheritance.

5) The data suggests a strong genetic influence in the expression of maxillary midline diastema in both African American and Caucasian sample populations.

APPENDIX 1

Consent Form

CONSENT FORM

Heritability of Maxillary Midline Diastema

You are being asked to participate in a research study examining spacing or gaps between the upper two front teeth within families. You were selected for this study as a possible participant because two or more family members of yours have been identified from existing x-rays, as currently having, or having had a space or gap between the upper front teeth. We ask that you read this form and ask any questions that you may have before agreeing to be in the study.

Researchers at Case Western Reserve University, Department of Orthodontics are conducting this study.

Background Information:

The purpose of this study is to analyze families and identify people within families who currently have a space, or had a space that was closed, between the upper two front teeth. This information can be used to determine if a space between the upper teeth is inherited, and can give clues as to how the space is passed on within families. This information might also be used to predict the likelihood of future generations within the family having a space between their two front teeth.

Procedures:

If you agree to be in this study we would ask that you fill out a brief questionnaire and return it to our department.

Risks and Benefits to being in the study:

There are potential benefits of increasing dentist's understanding of the genetic basis of the dental trait being studied.

Confidentiality:

The information gathered from this study will be kept private. In any sort of report that we might publish, we will not include any information that will make it possible to identify a participant. Research records will be kept in a locked file and only researchers will have access to the records.

Voluntary Nature of the Study:

Your participation is voluntary and your refusal to participate will not affect your current or future relations with the University or with University Hospitals. If you decide to participate, you are free to withdraw at any time.

Any significant new findings that develop during the course of the research, which may relate to your willingness to continue participation, will be provided to you.

Contacts and Questions:

The researcher conducting this study is Jedidiah Gass. The research advisor for this study is Manish Valiathan. You may ask any questions that you may have by contacting Jedidiah Gass at (216) 368-3249 ext. 1061, or Manish Valiathan at (216) 368-3249.

If you would like to talk to someone other than the researcher about ; 1) concerns regarding this study, 2) research participants rights, 3) research-related injuries, or 4) other human subject issues, please contact Case Western Reserve University's Office of Research Administration at (216) 368-4510 or write:

Case Western Reserve University
Office of Research Administration
4 Adelbert Hall
10900 Euclid Ave.
Cleveland, OH 44106

You will be given a copy of this form to keep for your records.

Statement of consent:
I have read the above information. I have received answers to the questions I have asked. I consent to participate in the study.

Signature of Participant:
Date:

Signature of Parent or Guardian (if subject under 18):
Date:

Signature of Person Obtaining Consent:
Date:

APPENDIX 2

Questionnaire

Family Questionnaire

Family Identification Number: *To be filled in by the investigator*

Subject Number: *To be filled in by the investigator*

First Name: **Last Name:**

What is your relationship to *(proband's name)*
(be specific, indicate mother or fathers side of the family if you are an aunt, uncle, grandmother, grandfather etc.)

Gender (circle): Male Female

Ethnic Background /Race (you may circle more than one if necessary):

White

African American/Black

Hispanic

Asian

American Indian or Alaska Native

Native Hawaiian or other Pacific Islander

1.) Do you have a space between your upper two front teeth? (circle) Yes No

2.) Have you ever had dental treatment (braces, caps/crowns, veneers, or bonding) to close a space between your upper two front teeth. (circle) Yes No

3.) If you are missing any of your top teeth, did you have a space between your upper front teeth before you lost the teeth. (circle) Yes No

4.) Does anyone, or has anyone in your family, who is not available to fill out this survey, have a space/gap between their two front teeth. (circle)
Yes No

5.) If you answered Yes to the above question, is their relationship to you on your mothers or fathers side? How are they related to you?

6.) Have you been diagnosed with, or are you currently being treated for a medical condition? If so please briefly elaborate.

APPENDIX 3

Pedigree Data

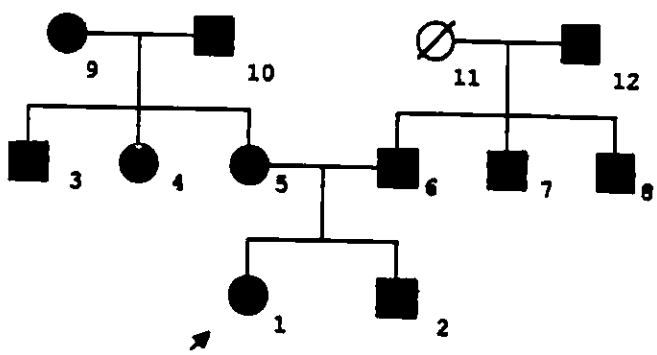


Figure 2. Family pedigree data for family number 1. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

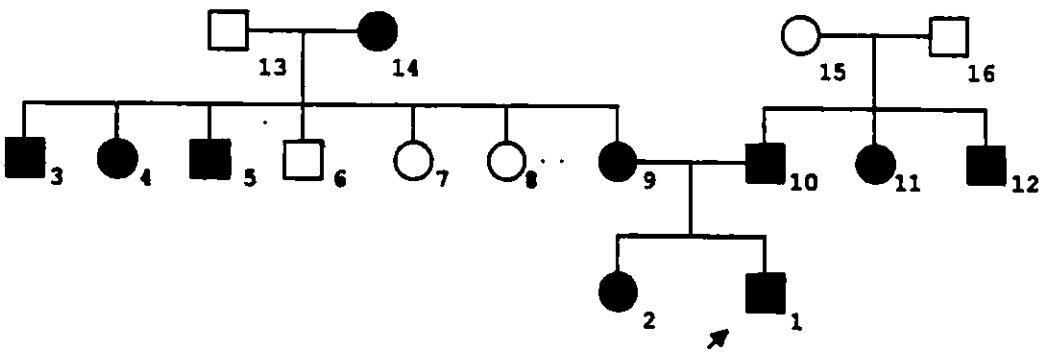


Figure 3. Family pedigree data for family number 2. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

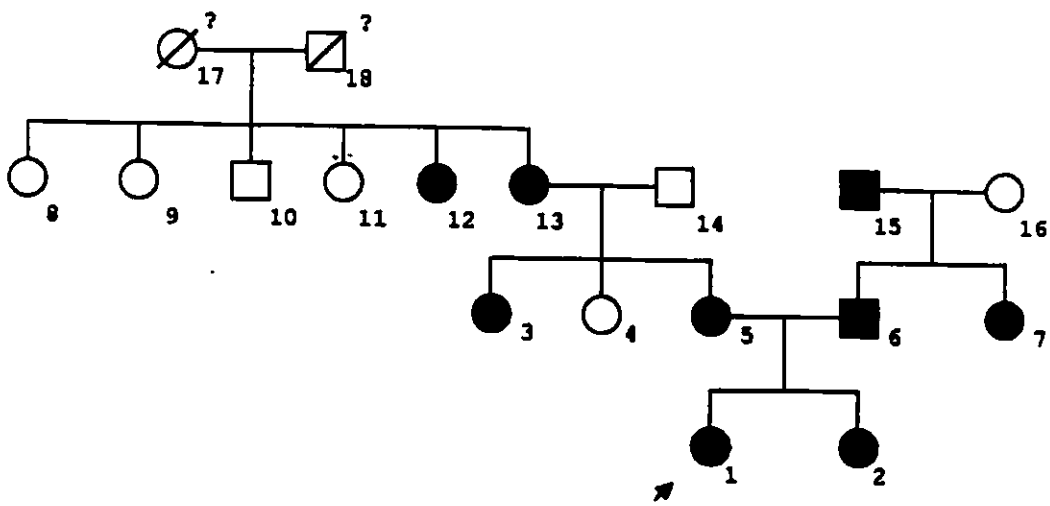


Figure 4. Family pedigree data for family number 3. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

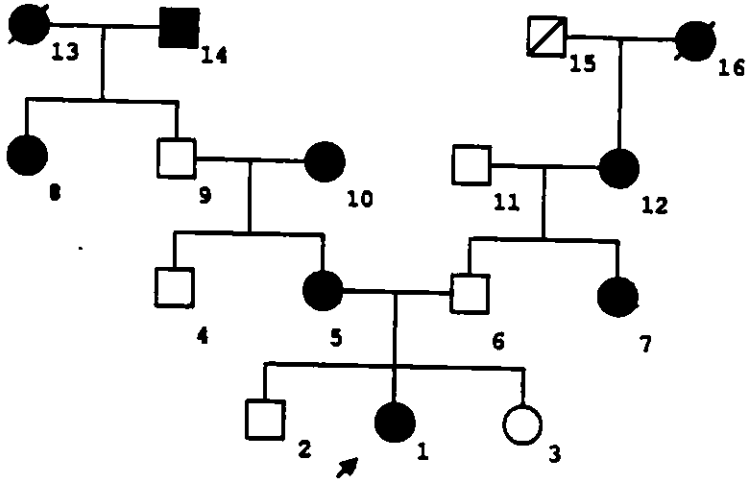


Figure 5. Family pedigree data for family number 4. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

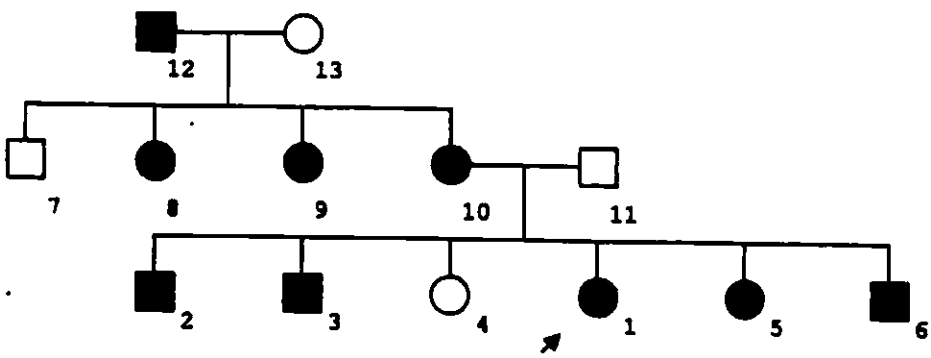


Figure 6. Family pedigree data for family number 5. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

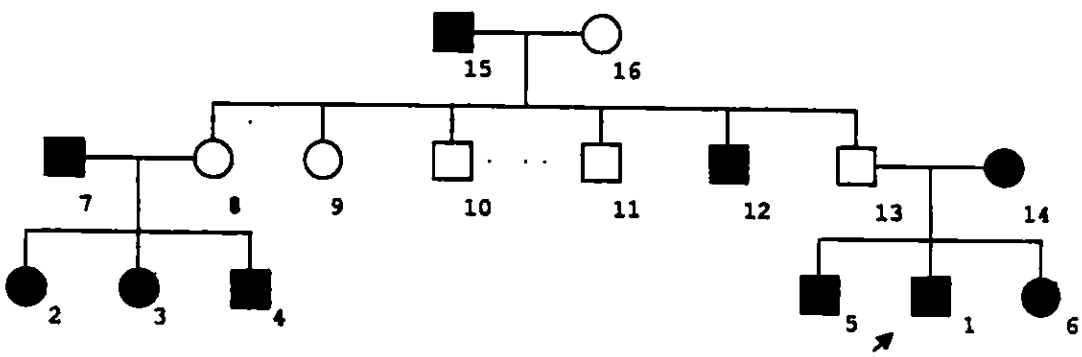


Figure 7. Family pedigree data for family number 6. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

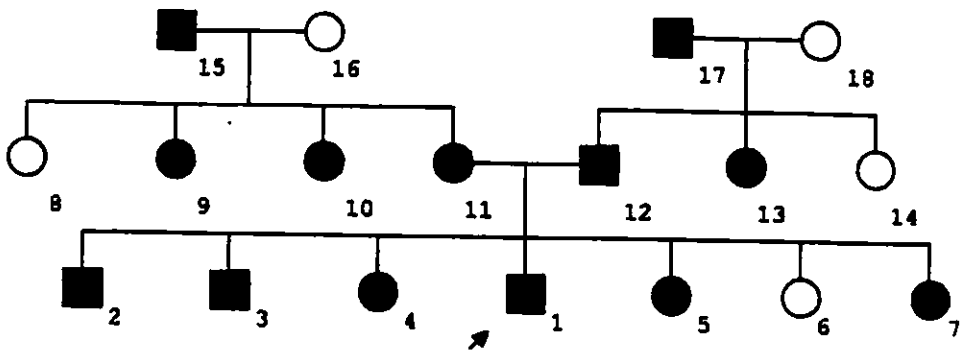


Figure 8. Family pedigree data for family number 7. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

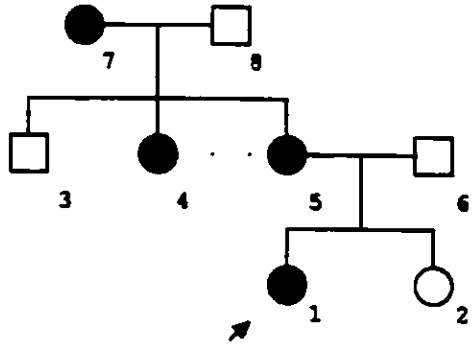


Figure 9. Family pedigree data for family number 8. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

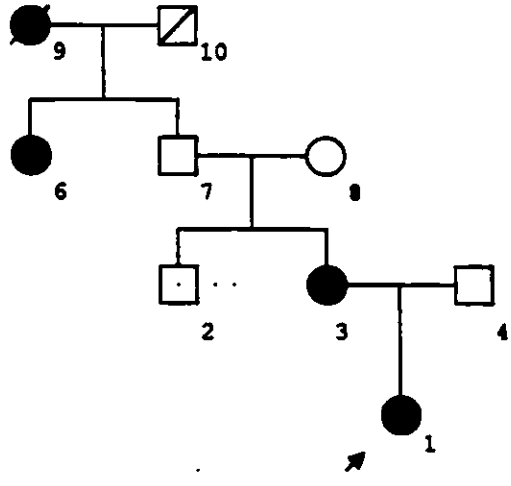


Figure 10. Family pedigree data for family number 9. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

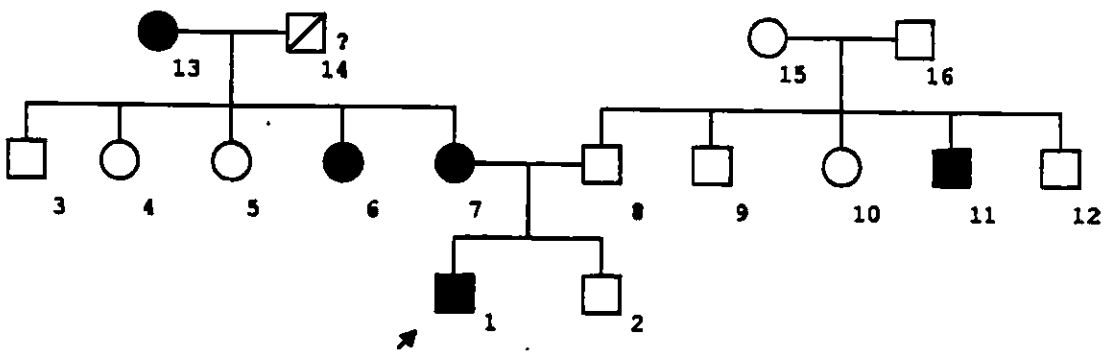


Figure 11. Family pedigree data for family number 10. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

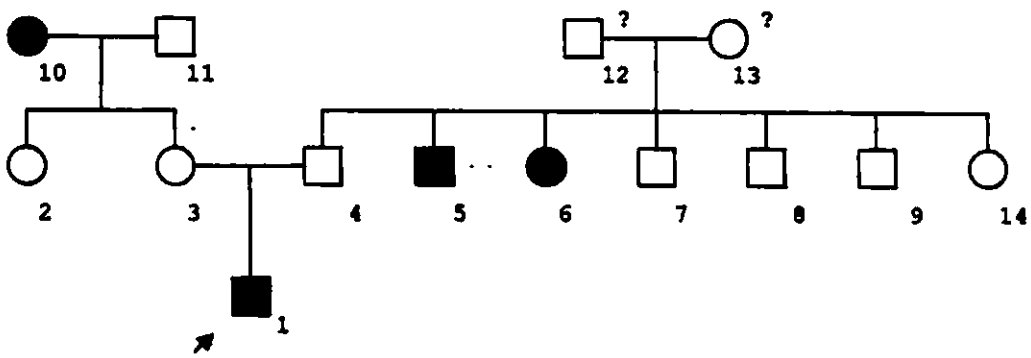


Figure 12. Family pedigree data for family number 11. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

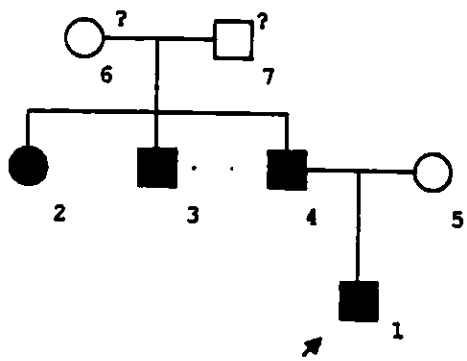


Figure 13. Family pedigree data for family number 12. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

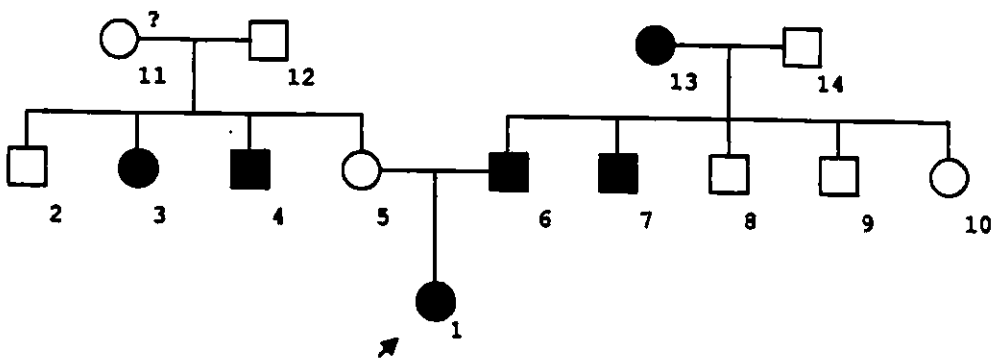


Figure 14. Family pedigree data for family number 13. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

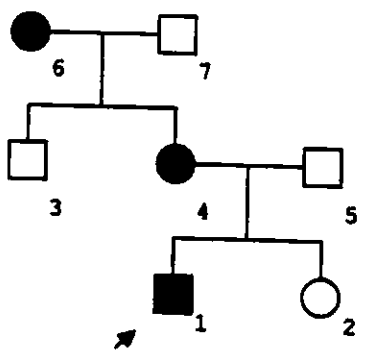


Figure 15. Family pedigree data for family number 14. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

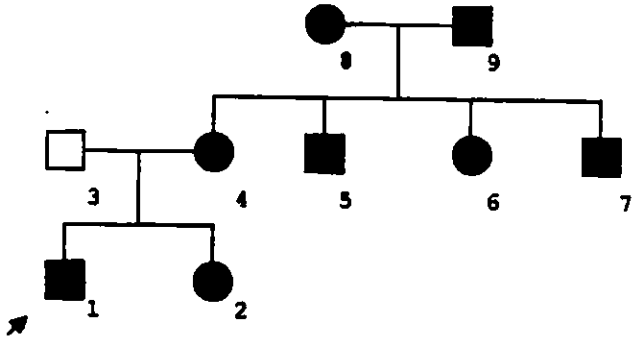


Figure 16. Family pedigree data for family number 15. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

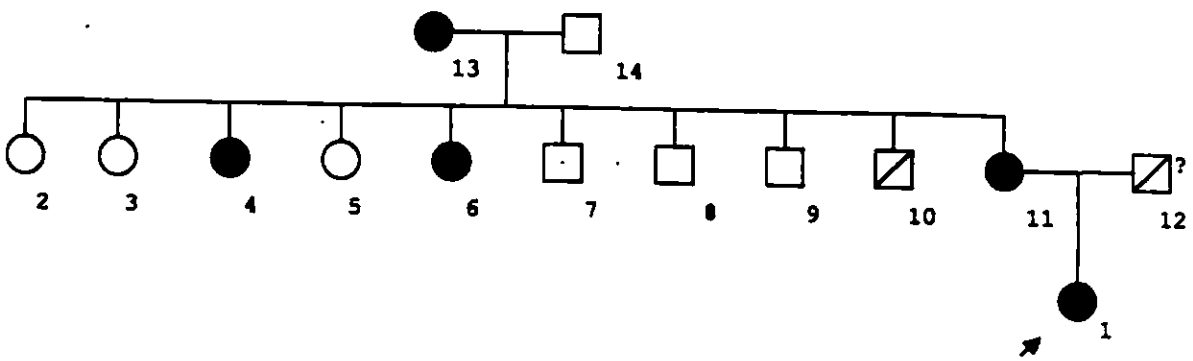


Figure 17. Family pedigree data for family number 16. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

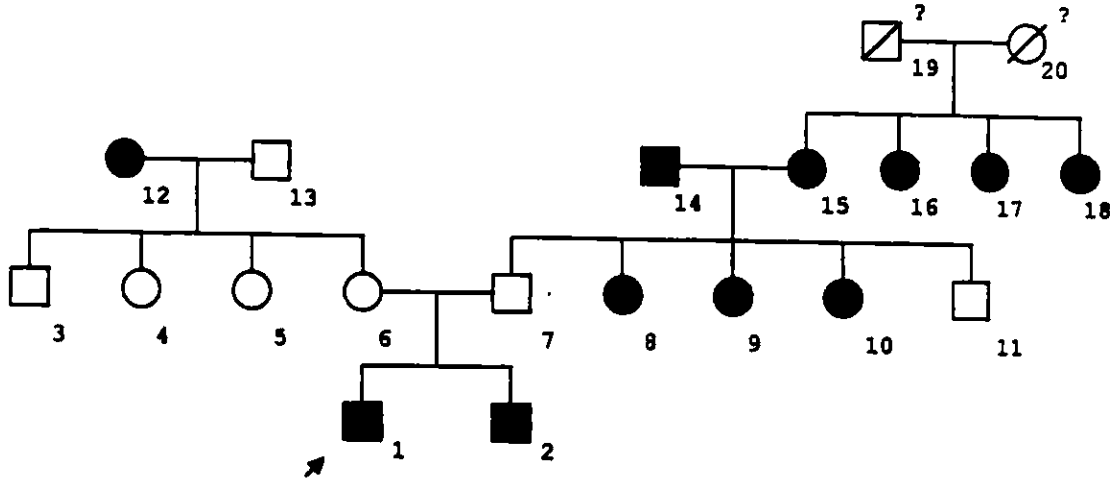


Figure 18. Family pedigree data for family number 17. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

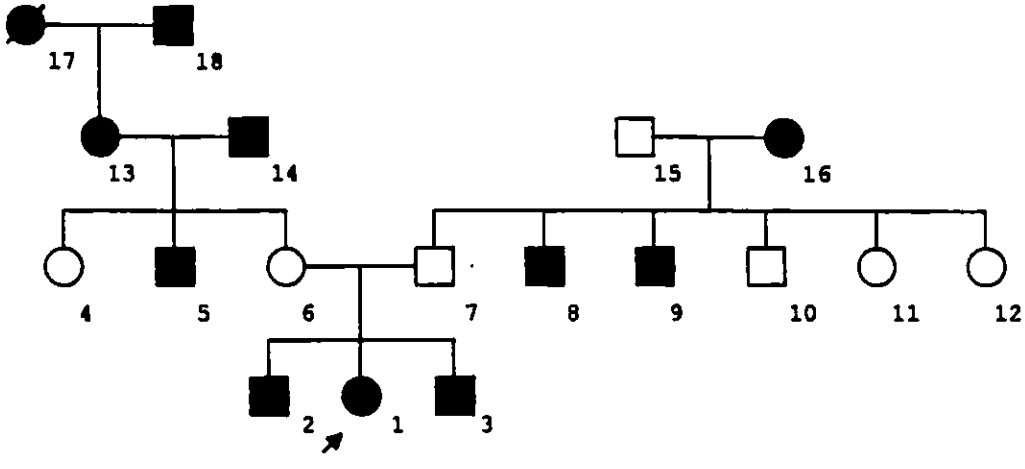


Figure 19. Family pedigree data for family number 18. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

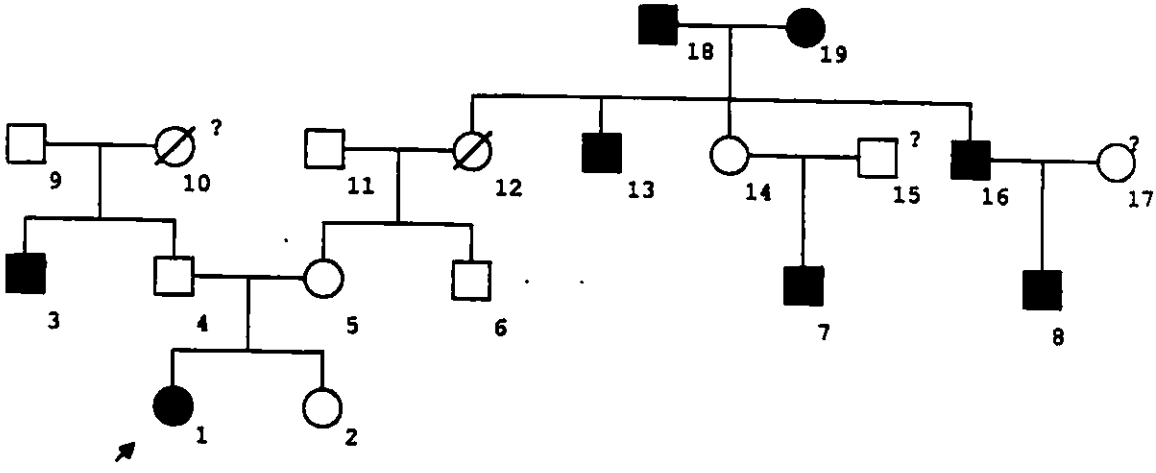


Figure 20. Family pedigree data for family number 19. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

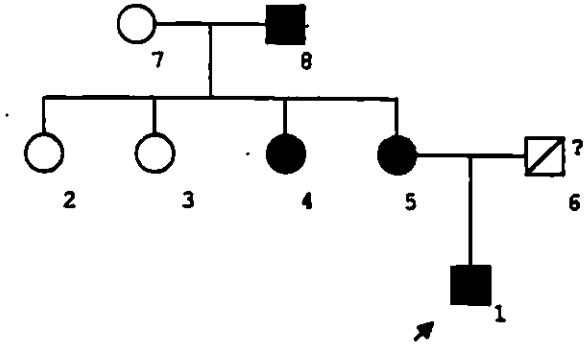


Figure 21. Family pedigree data for family number 20. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

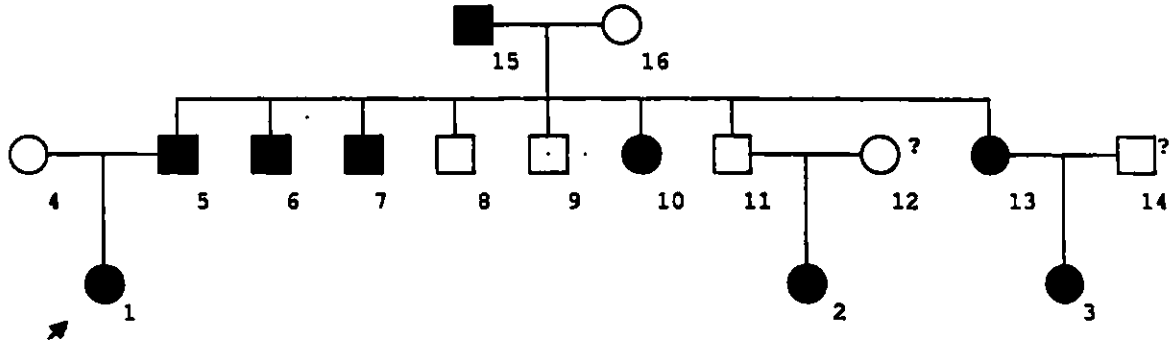


Figure 22. Family pedigree data for family number 21. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

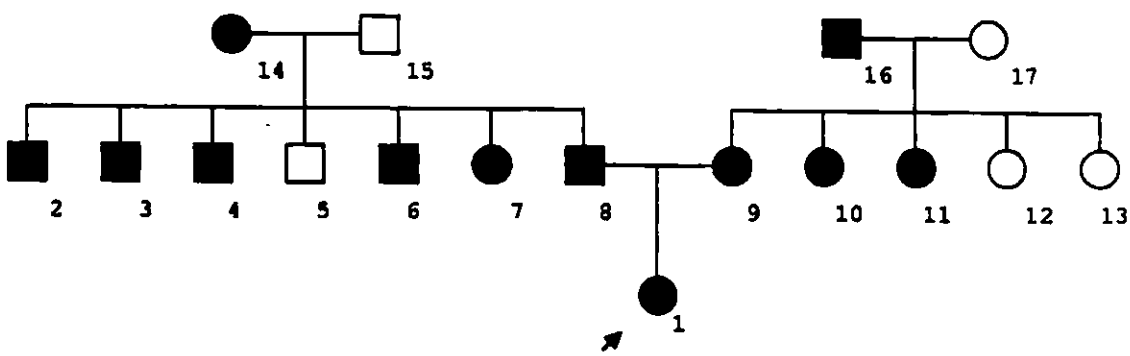


Figure 23. Family pedigree data for family number 22. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

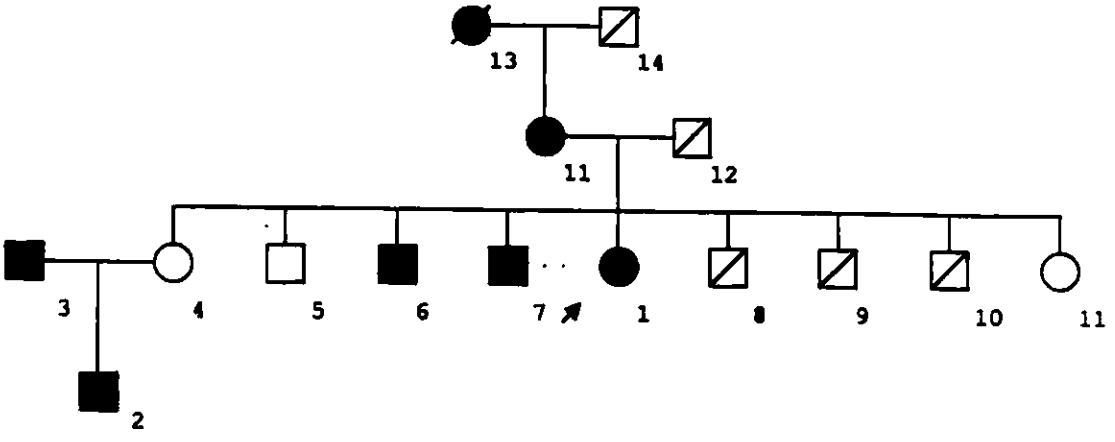


Figure 24. Family pedigree data for family number 23. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

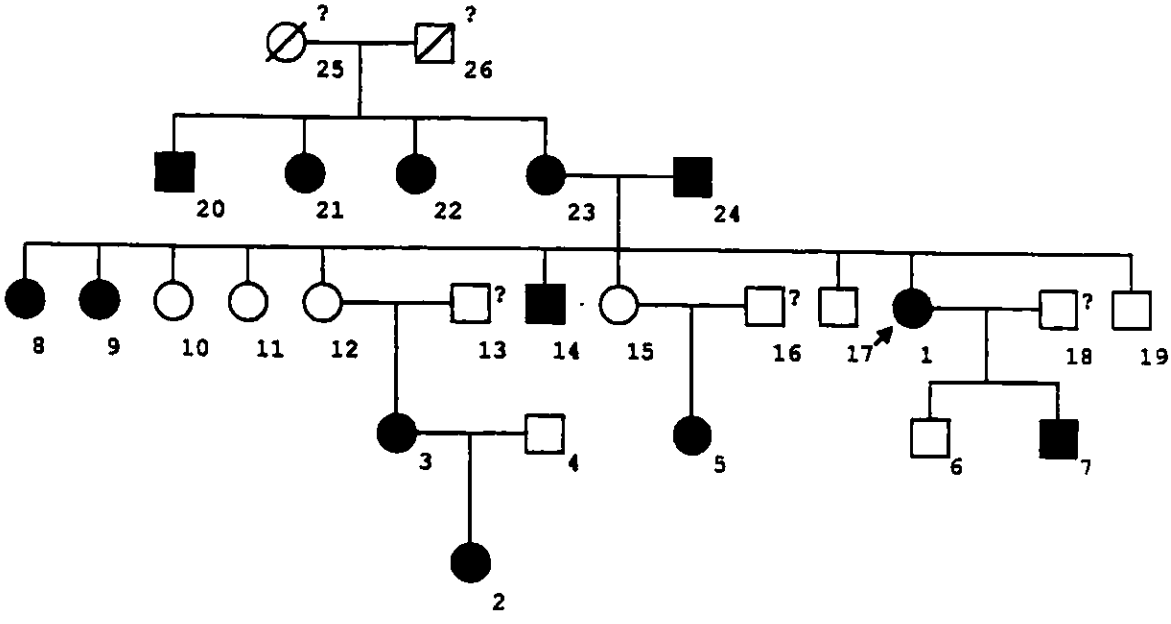


Figure 25. Family pedigree data for family number 24. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

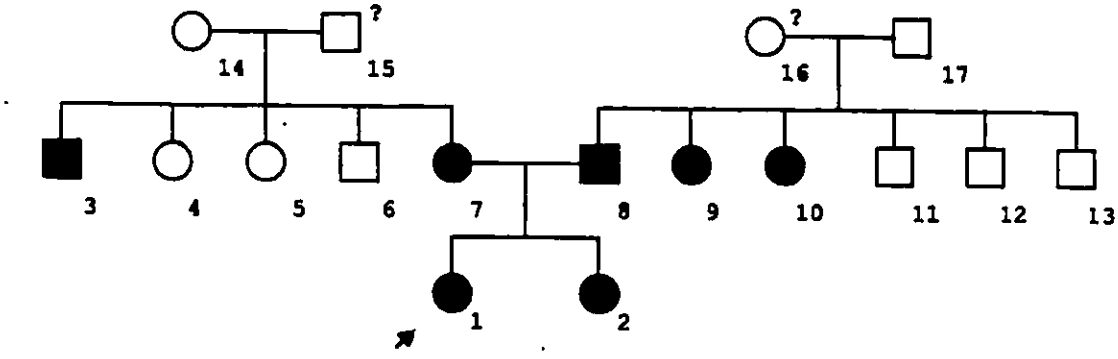


Figure 26. Family pedigree data for family number 25. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

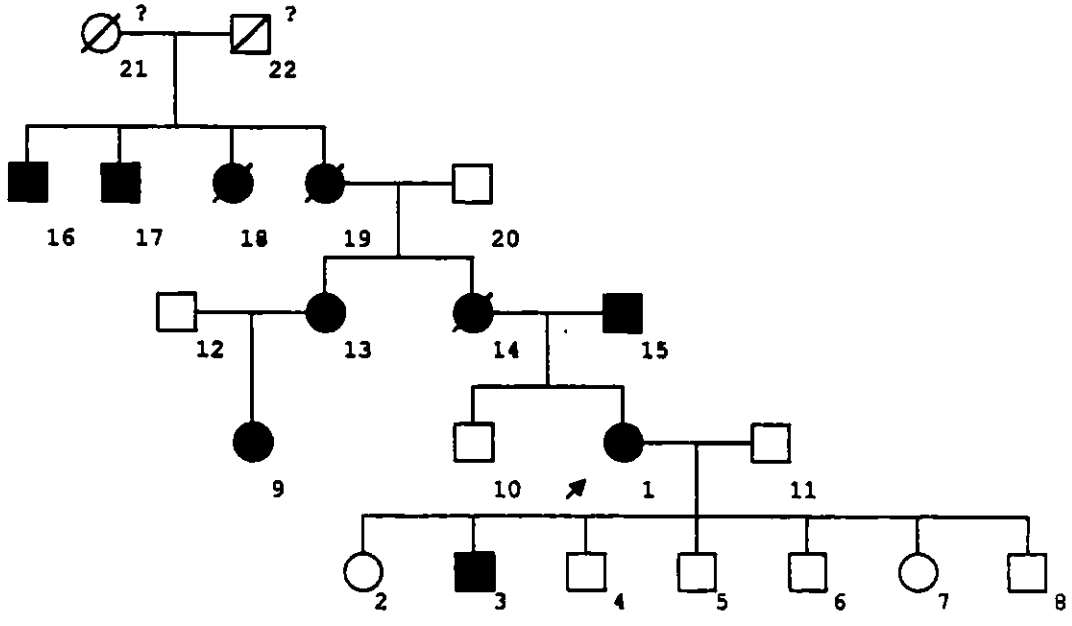


Figure 27. Family pedigree data for family number 26. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

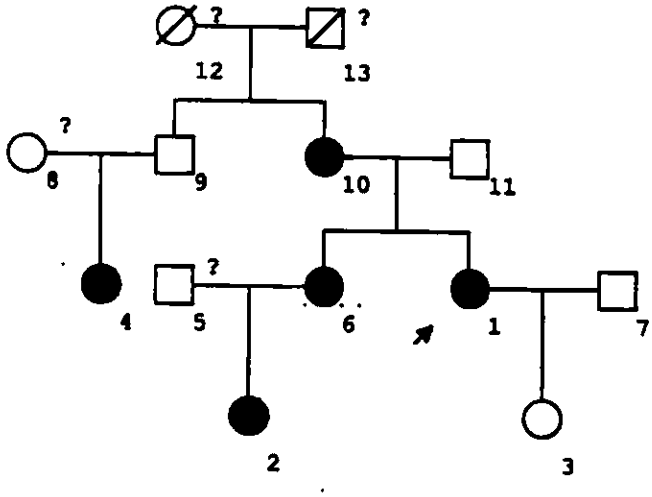


Figure 28. Family pedigree data for family number 27. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

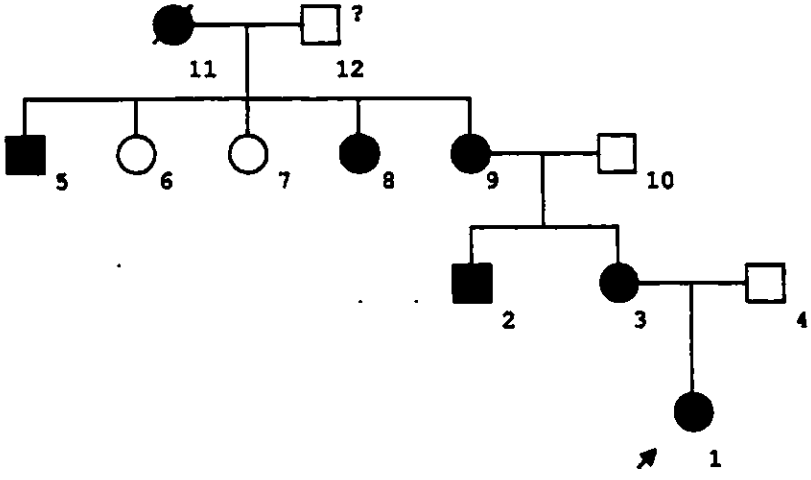


Figure 29. Family pedigree data for family number 28. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

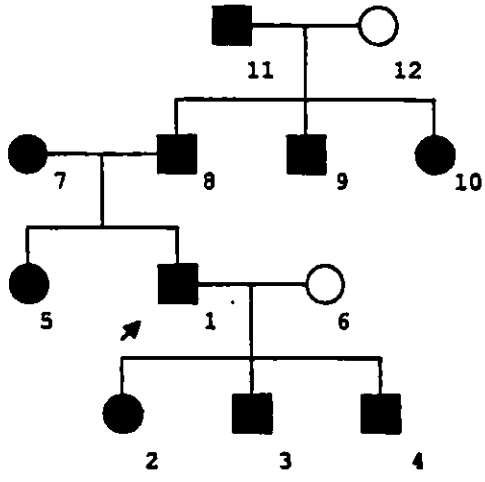


Figure 30. Family pedigree data for family number 29. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

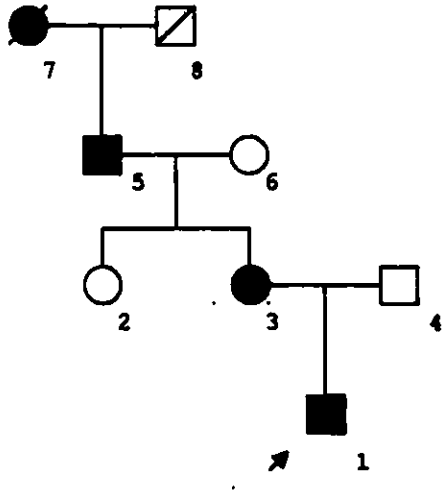


Figure 31. Family pedigree data for family number 30. Circles represent females, squares represent males, filled represents affected, unfilled represents unaffected, question marks represent unknown, and arrow represents proband.

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