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Skewed sex ratios in familial holoprosencephaly and in people with isolated single maxillary central incisor

Graeme Suthers, Scott Smith, Sue Springbett

Abstract

Autosomal dominant holoprosencephaly is a rare but well documented entity and it can be the result of mutations in the Sonic Hedgehog gene (*SHH*). The transmitting parent may be normal or have a single maxillary central incisor.

We describe a skewed sex ratio among the transmitting parents with *SHH* mutations, with more mothers than fathers having the mutation ($p=0.002$). The mechanism underlying this skewed sex ratio is not clear; the *SHH* mutations do not involve triplet repeats, imprinting is plausible but untested, and there is no evidence that the risk of holoprosencephaly is greater among males carrying such a mutation ($p=0.15$). We considered the possibility that males with such a mutation are at greater risk of other malformations outside the central nervous system, which could reduce their reproductive fitness.

To avoid ascertainment bias in identifying children with various malformations in kindreds with familial holoprosencephaly, we reviewed the reports of people with single maxillary central incisor and no other congenital malformations. Of the 16 cases identified, 13 were female ($p=0.0085$).

We suggest that boys with mutations associated with autosomal dominant holoprosencephaly may be at greater risk of major malformations outside the central nervous system than girls.

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Keywords holoprosencephaly; single central maxillary incisor; sex ratio

Holoprosencephaly represents the partial or complete failure of the cephalic neural tube to divide into right and left lobes. It can be chromosomal, multifactorial, or monogenic in origin and may be associated with other midline malformations.

Autosomal dominant (AD) holoprosencephaly is uncommon but well documented. The transmitting parent may have a single central maxillary incisor as the only manifestation of a midline abnormality. There are at least 12 genetic loci responsible for holoprosencephaly¹ and the Sonic Hedgehog gene (*SHH*) at 7q36 has been identified as one of the genes responsible.^{2,3}

AD holoprosencephaly resulting from mutations in *SHH* exhibits preferential maternal transmission. In nine families with documented *SHH* mutations^{2,3} there were 16 transmitting parents, 14 of whom were female ($p=0.002$). Preferential maternal transmission was not evident in one large kindred with AD holoprosencephaly that is not linked to 7q36 (pedigree 1 in reference 4) or in four families that have not been genotyped (pedigrees f, l, n, and o in reference 5); of the total of 12 transmitting parents, four were female ($p=0.12$).

What could account for the skewed sex ratio among parents who are carriers of documented or presumptive *SHH* mutations? There are a number of possibilities.

First, triplet repeat mutations can show sex specific preferential expansion during transmission, but the *SHH* mutations identified were missense, nonsense, and deletions.^{2,3}

Second, imprinting of 7q36 could account for the skewed ratio. There is indirect evidence that portions of chromosome 7 are imprinted. Maternal uniparental disomy of this chromosome is associated with short stature and the Russell-Silver syndrome.⁶ In particular, the region 7q35-qter is probably imprinted and this would encompass the *SHH* gene. There are limited data to explore this possibility in relation to AD holoprosencephaly. In one family with a documented *SHH* mutation, a man and his sister each had a child with holoprosencephaly (pedigree 3 in reference 4; see also reference 7). This would argue against imprinting of the *SHH* gene.

A third possibility is that the expression of *SHH* mutations in the developing brain is more severe in males than females and hence the reproductive fitness is selectively reduced in males. In the seven families with documented *SHH* mutations and published phenotypes,⁴ nine of the 15 children with holoprosencephaly were male ($p=0.15$). These data do not support the suggestion that there is a sex specific effect of *SHH* mutations on the developing brain. This conclusion is reinforced by the general observation that the sex ratio for non-chromosomal holoprosencephaly is close to one.⁸

A fourth possibility is that males with mutations causing AD holoprosencephaly are more likely than females to have other midline malformations outside the central nervous system. As a result, males with the mutation would have reduced reproductive fitness. It is difficult to assess this reliably in the families described.

South Australian Clinical Genetics Service, Centre for Medical Genetics, Women's & Children's Hospital, North Adelaide, SA 5006, Australia
G Suthers

Dental Clinic, Women's & Children's Hospital, North Adelaide, SA 5006, Australia
S Smith

Adelaide Dental Hospital, University of Adelaide, SA, Australia
S Springbett

Correspondence to:
Dr Suthers

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The process of identifying the families introduces an ascertainment bias and there were usually insufficient data reported to determine whether the reproductive fitness of males carrying a presumptive or proven mutation was indeed reduced.

In view of the difficulty of testing this hypothesis directly by examining families with AD holoprosencephaly, we took an alternative approach. A single central maxillary incisor is a rare finding, occurring in approximately 1:50 000 people,⁹ but it is well documented in some carriers of AD holoprosencephaly.^{7 10} The presence of a single maxillary central incisor as an isolated finding would not affect reproductive fitness, and such a feature in the absence of any family history of midline congenital malformations could represent mild expression of an AD holoprosencephaly mutation or be the result of some other mechanism. If males with mutations causing AD holoprosencephaly are more likely than females to have midline malformations outside the central nervous system that reduce their reproductive fitness, one might expect to find more females with an isolated single maxillary central incisor than males. In other words, are single maxillary central incisors in otherwise healthy people more common in men or women? A skewed sex ratio in favour of women would suggest that there is a link between isolated single maxillary central incisor and being a carrier of AD holoprosencephaly.

We defined a single maxillary central incisor as a maxillary tooth that was symmetrical in the midline and which lacked a clearly defined central notch which is often used to infer a double tooth. We excluded reports of people with agenesis of one central incisor and associated asymmetry of the dental arch, holoprosencephaly or other congenital malformations (including choanal atresia) that would compromise reproductive fitness, short stature, Mendelian disorders, or chromosome abnormalities. We avoided an ascertainment bias by excluding people with a family history of holoprosencephaly. We also excluded cases described in population surveys of oligodontia as insufficient detail was presented.

We identified articles describing 15 people with an isolated single maxillary central incisor and no other congenital abnormalities that would have reduced their reproductive fitness (table 1). We also identified a child with isolated single maxillary central incisor through our Dental Clinic. Of the 16 cases identified, 13 were female ($p=0.0085$), indicating a skewed sex ratio among those with isolated single maxillary central incisor. It is intriguing to note that the only published familial cases we noted were a mother and daughter, and that two of the girls were reported to have sibs with cleft lip; one sib was male and the gender of the other was not stated.

It is clear that transmitting carriers of AD holoprosencephaly resulting from *SHH* mutations are more likely to be female than male. A similar skewed sex ratio is evident among healthy people with a single maxillary central incisor. This concordance suggests that such

Table 1 Reported cases of isolated single central maxillary incisor

Year	Reference	Case No	Gender	Additional clinical data
1970	16	5	Male	
1986	17	1	Male	
1991	18*	1	Male	
1958	19	1	Female	
1967	20	1	Female	Daughter of next case
1967	20	2	Female	Mother of preceding case
1970	16	1	Female	
1970	16	2	Female	
1974	21	1	Female	
1977	22	5	Female	Also had Graves' disease
1978	23	2	Female	Also had unilateral absent cochlea
1979	24	1	Female	Had sib with cleft lip
1983	25	1	Female	
1991	18*	2	Female	Had brother with cleft lip
1991	18*	3	Female	
		1	Female	Present case

*These cases were described as having single maxillary central incisors that were morphologically right (or left) maxillary central incisors. These teeth were centred in the midline with no distortion of the maxillary arch or gaps in the maxillary dentition.

people might represent the mildest phenotype of an *SHH* mutation; this possibility could only be evaluated by examining the *SHH* gene in people with a single maxillary central incisor. It also raises the possibility that the preferential maternal transmission of *SHH* mutations in families with AD holoprosencephaly may be because of milder expression of the causative mutation outside the central nervous system in women. This is not to suggest that all males with such mutations are phenotypically abnormal; two clinically normal males with *SHH* mutations have been identified.^{2 3}

We have some anecdotal evidence consistent with the suggestion that the reproductive fitness of boys with a single maxillary central incisor may be less than that of girls. We identified two boys with single maxillary central incisors through our Dental Clinic in addition to the girl mentioned above. The boys were of normal height and intelligence, lacked dysmorphic features, and had been ascertained through the Dental Clinic rather than through a medical service. However, both boys had had correction of major midline malformations in infancy, imperforate anus in one and double outlet right ventricle in the other.

There is a slight female excess among children with the syndrome of solitary maxillary central incisor, short stature, and choanal atresia (F:M=1.6).⁹ The female excess is less marked than among people with isolated single maxillary central incisor, and this is similar to the loss of sex ratio distortion with more severe expression of the AD holoprosencephaly phenotype.

Skewed sex ratios have been observed in other midline malformations as well. Neural tube defects occur in male and female babies with equal frequency, but in kindreds with two or more affected children there are more transmitting mothers than fathers.^{11 12} It is well documented that cleft lip occurs more frequently in boys,^{11 13} with a predominance of fathers among normal transmitting parents. On the other hand, the schisis association occurs more commonly in female babies,¹⁴ but it is not

clear if this reflects more severe expression in females or a higher risk of early prenatal loss among males.

The underlying reasons for these various sex ratios are not known. On the other hand, there are some preliminary data that implicate abnormal *SHH* expression in the formation of a single central incisor. A number of genes in the Sonic Hedgehog signalling pathway (including *SHH* itself) are expressed in specific temporal and spatial patterns during early tooth development in the mouse.¹⁵

In preparing this report we struggled with the terminology. The term "central incisor" usually refers to paired teeth that are in paramedian locations and are morphologically right and left sided. The same term is also used (as we have in this report) for a single abnormal tooth that is symmetrical about the midline. As a small step towards more precise nomenclature, we would follow Hall⁹ and suggest that a "single maxillary central incisor" as defined for this study would be described more appropriately as a "single maxillary median incisor".

Finally, this analysis raises the possibility that a healthy woman with a single maxillary median incisor and no family history of midline malformations may be at increased risk of having a baby with holoprosencephaly. There are no data to suggest the magnitude of this risk and, as noted above, it would be interesting to examine the *SHH* genes of such people for evidence of mutations.

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