A family showing apparent X linked inheritance of both anencephaly and spina bifida

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SUMMARY A family is reported which includes five males, two with spina bifida, two sibs with anencephaly, and one with both high and low spinal lesions. The affected subjects came from four sibships in three generations. The mode of inheritance of these neural tube defects is consistent with X linkage.

A few families show apparent autosomal recessive or dominant inheritance of anencephaly and spina bifida (ASB), a pair of conditions included in the term neural tube defects (NTD). More rarely there has been apparent X linked transmission. We report a family in which various males had either spina bifida or anencephaly, including one with both a high and a low spinal lesion, in which inheritance was consistent with X linkage (figure).

Material and methods

Iceland had a population of approximately 240 000 in 1986. During the last 40 years living conditions and health services in Iceland have been comparable to those in other Scandinavian countries. Genetic and neonatal services are centralised in the National Hospital in Reykjavik. In 1972, a new birth registration form came into use, allowing the registration of all visible birth defects. The number of births, including stillbirths, with ASB in 1972 to 1981 was obtained from this registry and the frequency calculated from the reported births. Clinical data were obtained from records of the National Hospital (table 1).

Case reports

The proband (IV.13, figure) was born to a healthy 21 year old mother. The infant had a large occipital encephalocele and a thoracolumbar meningo-myelocele. No therapeutic measures were taken and the infant died. The mother has also had a normal boy (IV.14). Subsequent family studies showed the following. A maternal uncle (III.25),
aged 16, had a lumbosacral meningomyelocele, but no other defect. The maternal grandmother’s brother (II.1), who died at the age of 56 from lung cancer, had a cystic tumour over the lumbar region and had not walked until the age of seven because of club feet. One of his three daughters (III.2), a monozygotic twin, had delivered two male stillbirths (IV.3 and IV.4) with anencephaly. She also had a normal son.

Two sisters in the family (III.20 and III.21) had signs of hydrocephalus at 23 and 19 years. The latter died at 20 years of age from a cerebral tumour. One male member (II.6) had a pilonidal sinus.

Other members of the family appear to be normal either by history or on examination. There was no known consanguinity. Information obtained from the family did not suggest the presence of ASB in earlier generations.

**Genetic markers**

Blood groups, HLA-A, B, and C antigens (table 2), and several protein genetic marker systems were studied for the influence of autosomal loci and possible discrepancies in paternity.

**Results**

The main clinical findings are summarised in table 1. Transmission of an X linked gene causing ASB is suggested in two branches of the family. Genetic marker system studies, including HLA haplotypes (table 2), showed no discrepancy in paternity in informative branches of the family.
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Discussion

THE FAMILY

In this family, there have been five males with ASB including two who survived. There was no affected female member. One of the affected males (II.1) is the father of three normal daughters (III.1, 2, and 3), one of whom has had two anencephalic sons and one normal son. The phenotypical variation present in the five affected members indicates that the presumed X linked recessive gene of large effect is markedly influenced by other genes or by the environment. Family members classified as unaffected have not been examined radiologically for occult spina bifida, with the exception of two brothers (II.23 and 24) who were normal. The hydrocephalus in the two adult sisters is probably linked recessive with the exception of two male siblings (II.9 and 10) who were normal. In the five affected members indicates that the normal male (III.25) and his sister (III.22), who is probably an obligatory carrier, share the HLA-A2 allele. The mother (III.2) of two affected sons (IV.3 and 4) has, on the other hand, two different alleles at the HLA-A locus (table 2). Sharing of alleles at the HLA loci was present in one branch of the family (II.7 and 7a) (table 2). However, there was no apparent association between transferrin and ASB in this family.

AUTOSOMAL INFLUENCE

Influence of certain autosomal genes on the development of neural tube defects has been suggested. No HLA haplotype association with ASB was detected in this family, which agrees with results of others. One affected son (III.25) and his sister (III.22), who is probably an obligatory carrier, share the HLA-A2 allele. The mother (III.2) of two affected sons (IV.3 and 4) has, on the other hand, two different alleles at the HLA-A locus (table 2). Sharing of alleles at the HLA loci was present in one branch of the family (II.7 and 7a) (table 2). However, there was no apparent association between transferrin and ASB in this family.

FREQUENCY

The frequencies of ASB in Iceland are shown in table 3. The percentage of males with spina bifida (40%) deviates little from the average (44%) in 17 population studies. In contrast, a notable male preponderance of 60% is present among Icelandic anencephalics. This deviation is considered fortuitous and the majority of ASB in Iceland, as elsewhere, is probably due to environmental and polygenic causes. Two of five affected males have spina bifida in the lumbar and lumbosacral region and a striking threefold male excess has been found associated with these sites. A particular type of X linked cleft palate and ankyloglossia has caused an unusual sex ratio in this condition also in the small population of Iceland. Retrospective study of the offspring of ASB male probands has not yet been undertaken in Iceland and this would reveal whether X linked transmission is involved in other ASB families than the present one.

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References


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