LETTERS TO THE EDITOR

Genes for intelligence on the X chromosome

Some 20 years ago Robert Lehrke, a psychologist from Minnesota working in a state hospital for the mentally retarded, suggested that genes that determine the major intellectual traits are carried on the X chromosome.^{1 2} At that time Lehrke was severely criticised on the grounds that his hypothesis was inherently improbable,³ and that the evidence was meagre and could be interpreted in other ways.^{4 5} Since then more medical evidence has accumulated to support two of the steps in Lehrke's argument.

(1) "The well documented excess of males among the mentally retarded (25-50%)". Two further studies^{6 7} have shown that this male excess results from mutations on the X chromosome, using as evidence the excess of affected brothers over affected sisters and calculating this as a gene frequency for X linked forms of mental retardation.

(2) "A review of families published at that time with mental retardation showing an X linked pattern of inheritance—which only numbered 5, together with 5 new families that he had identified". In the former group three were shown later to have the fragile X syndrome and this we now know is very common. A further two had specific features, one spasticity and the other obesity, and in the remainder, as best as can be judged, the clinical description fell into the non-specific group. As we can see in this issue, this is the most common form. There are now three separate gene localisations, *MRX1*, *MRX2*, and *MRX3*, and it seems likely that more loci will be defined in the future. His suggestion, therefore, that X linkage may be important, is being cemented by fact.

Lehrke's two other arguments were the lesser variability and reduced extremes of intelligence in the female when compared with the male, which he suggested resulted from the averaging out of the effects at different

alleles through Lyonisation. He also noted that mental retardation was transmitted more often from mother to child than from father to child.

If there are genes which directly determine intellectual traits, then one would expect that mutations of such genes would produce phenotypes showing only effects on intelligence, perhaps with secondary effects on behaviour and personality. If so, there should also be no somatic changes, no recognisable metabolic abnormalities, no other neurological signs, and no progression with age, although the effects of the mutations would be less obvious in infancy than in childhood when intellectual thought becomes evident. This is the clinical picture of non-specific mental retardation. Clinical descriptions of autosomal dominant and recessive forms of non-specific mental retardation are rare, ill defined, and found mainly in older publications. The X linked forms are common and are now being mapped on the X chromosome. We would like to reawaken Lehrke's hypothesis and suggest that the mutations that we are now locating associated with non-specific mental retardation are those that have determined the higher intelligence of homo sapiens.

Why should intelligence be coded primarily on the X chromosome? Although, as Ohno⁸ and others have stressed, genes on the X chromosome have been conserved throughout mammalian evolution we have to suppose that, in man, additional genes for intelligence have arisen there. Once they had appeared their advantage in a hunter-gatherer society would assure male dominance and rapid dissemination throughout the group.⁹ In recent correspondence on this subject Ohno philosophised: "Most mammalian species, including our own, are noticeably sexually dimorphic. As a rule such species practice the polygamous, more precisely the polygynous, mating system; after exhaustive combat between adult males, only the victor gains possession of a large number of females. Is it not ironic if the reward of a victor has been to transmit his intelligence only to his daughters and never to his sons. If the main genetic source of intelligence resides on the X chromosome, man, at least, should have organised the matriarchal society with the polyandrous mating system.

Perhaps we are still paying for the mistake of organising the patriarchal society of kings and dukes."

GILLIAN TURNER
Department of Medical Genetics,
Prince of Wales Children's
Hospital, Sydney,
NSW 2031, Australia.

MICHAEL W PARTINGTON
Regional Medical Genetics Unit,
Western Suburbs Hospital,
Newcastle, NSW, Australia.

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X linked complicated spastic paraplegia, MASA syndrome, and X linked hydrocephalus owing to congenital stenosis of the aqueduct of Sylvius: variable expression of the same mutation at Xq28

Hereditary 'pure' spastic paraplegia is a disorder characterised by progressive spasticity of the legs in otherwise normal subjects. In the majority of families pedigree data are in accordance with autosomal dominant inheritance, but X linked recessive transmission has also been documented.¹ In the 'complicated' form the spasticity may be combined with a variety of one or more symptoms, such as mental retardation, micro- and macrocephaly, epilepsy, and ocular symptoms.^{2 3}

In 1974 Blanchine and Lewis⁴ delineated, on the basis of clinical and

neurological symptoms, a clinically distinct X linked complicated form: affected males show the combination of Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs (MASA syndrome). No more than five other families have been reported up to now⁵⁻⁹ and in three of them linkage analysis located the gene in the region of Xq28.⁷⁻⁹ In the family reported by Schrander-Stumpel *et al*⁹ the two affected males had extensive widening (dilatation) of the lateral ventricles and one male relative died at a young age from progressive hydrocephalus. In the family reported by Winter *et al*⁸ affected males had true macrocephaly.

X linked hydrocephalus with aqueductal stenosis and short, flexed thumbs was first described by Bickers and Adams¹⁰ and Edwards.¹¹ In families with X linked hydrocephalus surviving male relatives have been

documented with non-specific mental retardation with or without spastic paraplegia¹² and preliminary results of genetic linkage analysis¹³ have assigned X linked hydrocephalus to Xq28. The results of linkage analysis together with the available pedigree data and clinical and neurological findings in the affected males therefore suggested that MASA syndrome and X linked hydrocephalus may be allelic variants.⁹

Recently, we had the occasion to perform clinical and DNA linkage studies in another large, four generation family (figure). Five males had a mental retardation syndrome with neurological abnormalities which varied greatly in severity and clinical expression. Two male sibs died at a young age and had hydrocephalus with aqueductal stenosis. One moderately mentally retarded maternal uncle had clinical and neurological abnormalities

compatible with the diagnosis of MASA syndrome, and two other borderline intelligent to slightly mentally retarded maternal uncles presented severe complicated spastic paraplegia. The findings in the five affected males of the present family support the evidence that the three X linked conditions (X linked complicated spastic paraplegia (SPPXI, McKusick 31290¹), MASA syndrome (McKusick 30925¹), and X linked hydrocephalus owing to congenital stenosis of the aqueduct of Sylvius (McKusick 30700¹) are variable clinical manifestations of the same mutation at Xq28, that is, the spectrum of the MASA syndrome/X linked hydrocephalus apparently also includes X linked complicated spastic paraplegia. Moreover, a relationship between the degree of mental retardation and the neurological symptoms is observed: severe spastic paresis is

Pedigree of the family with informative DNA markers. The side of the shaded region in the female carriers' symbols corresponds to the parental origin of the haplotypes.

present in the more severely mentally impaired males.

FAMILY DATA (FIGURE)

Clinical findings

A 22 year old normal female (IV.5) was seen for genetic counselling. She was the youngest child, and the only daughter, in a family with five children. Her oldest brother (IV.1) is normal. The second brother (IV.2) died in the neonatal period and was hydrocephalic. The third brother (IV.3) was prematurely born (26 weeks). No necropsy was performed and no further data are available. The fourth brother (IV.4) had progressive hydrocephalus from the age of 6 weeks onwards. A ventriculocardiac shunt was inserted. He died at the age of 2.5 years from septicaemia. Necropsy confirmed the presence of massive dilatation of the lateral ventricles with aqueductal stenosis. Her mother (III.1) was the first born in a sibship of eight children. One (III.4) died at the age of 6 months from pneumonia. One normal sister (III.8) has three daughters (IV.6, IV.7, IV.8); one of them (IV.7) died suddenly at the age of 9 months. Three brothers (III.3, III.5, III.6) are normal, but two other brothers (III.2 and III.7) are mentally retarded.

III.2 is a 52 year old, moderately mentally retarded male living in an occupational centre. Weight is 76 kg, height 161 cm, and head circumference 53 cm. Severe spastic paresis of the legs with hyperreflexia, hypertonia, and clonus makes walking even short distances difficult without support. The thumbs are flexed and adducted. He has simple speech, but cannot read or write.

III.7 is a 42 year old, slightly mentally retarded male working in a sheltered workshop. He has spastic paresis of the legs, but much less pronounced than III.2. He has normal thumbs and hands, and no dysarthria. Weight is 68 kg, height 165 cm, and head circumference 52 cm.

The maternal grandmother (II.3) was the third born in a family of nine children. Two older brothers (II.1 and II.2) died at a young age and there is no further information about them. Three brothers are normal (II.5, II.8, II.9). One normal sister (II.7) has two normal sons. One sister (II.6) died at a young age from pneumonia. One brother (II.4) is 77 years old with borderline intelligence. He worked in a

factory and was unmarried. He had a spastic gait and walking without help became impossible after the age of 50 years. Thumbs and hands are normal. Height is 160 cm, weight 60 kg, and head circumference 53 cm. CT scan of the brain could not be performed in the surviving mentally retarded males.

DNA studies

DNA was extracted from peripheral blood. After restriction enzyme digestion the resulting fragments were separated by agarose gel electrophoresis and alkali blotted onto Hybrid N-plus membranes. The membranes were hybridised with probes pERT87.1 and XJ1.2 on the short arm of the X chromosome and with VK21C (DXS296), U6.2 (DXS304), and St14.1 (DXS52) on the long arm. The disease clearly segregated with the Xq27.28 markers without recombination, confirming our previous findings of linkage of the MASA locus with the Xq27-28 markers.⁹

J P FRYNS,
A SPAEPEN,
J J CASSIMAN,
H VAN DEN BERGHE
*Centre for Human Genetics,
University of Leuven,
Herestraat 49,
B-3000 Leuven,
Belgium.*

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BOOK REVIEWS

Genetic Approaches in the Prevention of Mental Disorders. Ed V Bulzyhenkov, Y Christen, L Prilipko. (Pp 119.) Berlin: Springer-Verlag. 1990.

This slim, but informative volume summarises the proceedings of a meeting organised by the World Health Organization and Fondation Ipsen held in Paris in May 1989. Despite its title, most of the book is not about prevention of mental disorders but rather focuses on recent developments in genetic epidemiology, linkage strategies, and the application of molecular biology to complex disorders such as schizophrenia and manic depression, as well as 'simple' diseases of psychiatric relevance such as Huntington's disease.

The range of topics covered is wide, from methods of diagnosis and classification of mental illness in relation to molecular genetic research to the genetic basis of brain development and neurocellular differentiation. In between, there are important theoretical papers, for example, Clerget-Darpoux on methodological issues in linkage analysis and McGue and Gottesman on the feasibility of applying single gene models in studies of schizophrenia. The sceptical stance and weighty statistical arguments here provide a useful counterbalance to the more upbeat and optimistic approach of, for example, Williamson and Goate who discuss the range of molecular genetic