Medical genetics: advances in brief

Epilepsy and mental retardation limited to females: an X-linked dominant disorder with male sparing

Ryan S, Chance P, Zou C-H, Spinner N, Golden J, Smietana S. *Nat Genet* 1997;17:1:92-5.

Ryan *et al* describe a large pedigree with epilepsy and mental retardation expressed exclusively in females, but with male transmission. Sixteen out of 17 daughters of asymptomatic transmitting males are affected suggesting high penetrance only in females. Linkage analysis shows the gene responsible to lie in Xq22. The authors suggest four possible explanations for this unusual mode of inheritance. (1) The mutation may be recessive with a Y chromosome homologue rendering males heterozygous but females functionally hemizygous owing to X inactivation, the X with the mutation being active in a proportion of cells. (2) Hemizygosity for the mutation has no effect but heterozygosity may result in metabolic interference between the normal and mutant protein products. (3) The mutation may cause the gene to escape X inactivation in females, functional disomy causing the phenotype. (4) The gene may not be necessary for male brain development or the hormonal status of males protects them from deleterious effects. An X linked condition with male sparing has not previously been described; however, Ryan *et al* stress that the distinguishing feature of this disease is its inheritance pattern and not the neurological symptoms. The recognition of such an inheritance pattern requires a large pedigree which would be rare because of low reproductive fitness in affected females. The expression of an X linked disorder predominantly in females is usually the result of male lethality, but it is of interest to note that for some such diseases, for example, Aicardi syndrome, Rett syndrome, and microphthalmia with linear skin defects, there is little evidence of male lethality.

DAVID O ROBINSON

High incidence of Down's syndrome in infants of diabetic mothers

Narchi H, Kulayat N. *Arch Dis Child* 1997;77:242-4.

The incidence of Down's syndrome was studied in 22 300 neonates born at the Al-Hasa Hospital in Saudi Arabia between January 1987 and April 1994. A retrospective review of possible relevant factors in the maternal medical histories of these infants was undertaken, including maternal age and presence of diabetes mellitus or other endocrine or autoimmune disease. The presence of diabetes was screened for by a glucose tolerance test in all pregnancies, at 24 weeks' gestation in low risk situations, but earlier if indicated. The diagnosis of gestational diabetes was made in a total of 1870 mothers. The diagnosis of Down's syndrome was made on clinical grounds and confirmed by chromosomal analysis of lymphocytes in 35 infants during the time period of the study.

All affected infants had trisomy 21. Of these 35 infants, seven were born to mothers with gestational diabetes (only one requiring insulin) and 28 were born to non-diabetic mothers. The diabetic mothers had no evidence of other autoimmune disease. The authors concluded that the incidence of Down's syndrome was higher in the former group (3.75 per 1000 compared with 1.36 per 1000) and the relative risk in mothers with gestational diabetes was 2.75. There was no difference in the maternal age in the two groups. This report suggests that Down's syndrome should be considered as one of the malformations known to occur more frequently in infants of diabetic mothers. This association has been shown previously in relation to Klinefelter's syndrome and Turner's syndrome as well as Down's syndrome. However, it remains unknown whether fetal trisomies predispose to the development of gestational diabetes or vice versa. These authors suggest that patients should be counselled specifically about the increased risk of Down's syndrome if diabetes is diagnosed in pregnancy.

SARAH SLANEY

Screening of newborn babies for familial ureteric reflux

Scott JES, Swallow V, Coulthard MG, Lambert HJ, Lee REJ. *Lancet* 1997;350:396-400.

Reflux nephropathy is a major cause of end stage renal failure necessitating either long term dialysis or transplantation in both adults and children. It can be clinically silent while damage is occurring. A genetic role in the aetiology has long been recognised with probable autosomal dominant inheritance with reduced penetrance. Population screening at present is avoided because of the invasive nature of cystography as a screening test. This study was an attempt to use the familial nature of this disorder to identify neonates at high risk who were then screened. The study was carried out over a three year period; 211 women were included as having a family history of assumed or confirmed reflux. The total number of deliveries at risk was estimated to be 34 555; only 60% of this number completed a preliminary questionnaire, of whom 1341 were interviewed further. Forty-eight had a family history of reflux but declined to be studied further. The person with reflux was most commonly (in 57% of the cases) either the mother herself or a sib to the pregnancy. Renal ultrasound and cystography were planned within two weeks on the infants delivered from the identified pregnancies. This proved to be difficult and the median time for both investigations was around 30 days. Two babies were identified to have frank urinary tract infection. A total of 186 babies had cystography, of whom 20.4% were shown to have reflux (compared to 1 to 2% of the general population). Renal ultrasound was carried out on 196 babies and three had renal pelvis dilatation with reflux. A further two babies had dilatation without reflux. DMSA scans were carried out at 3 months of age on those babies with docu-

mented reflux. Only one DMSA was abnormal. Where reflux was identified, the mother or a sib was more often the affected relative with reflux (in 71% of cases). The study clearly shows the importance of genetic traits in the development of reflux, but how much identification of infants with reflux at birth will modify the outcome awaits evaluation. The difficulties of implementing such a screening programme even in high risk pregnancies is shown by the study, as even with a dedicated research team 12% of babies shown to be at risk were not investigated.

ANGELA BARNICOAT

Prevalence of Pro250Arg mutation of fibroblast growth factor receptor 3 in coronal craniosynostosis

Moloney DM, Wall SA, Ashworth GJ, *et al*. *Lancet* 1997;349:1059-62.

Patients presenting with coronal craniosynostosis (both unilateral and bilateral) but without other syndromic features are frequent in craniofacial centres. Twenty-six such patients were studied for the Pro250Arg mutation in FGFR3 (fibroblast growth factor receptor 3 gene), which has been identified both in a small number of patients with a Pfeiffer-like phenotype and in patients with a variety of other diagnoses but including craniosynostosis as a feature. The mutation was identified in eight (31%) of their patients. In six cases it was shown to have arisen *de novo* and in the other two it was familial. Relatives who had the mutation showed a range in phenotypes mostly milder than the presenting person. A mother and a sib of two separate probands with the mutation showed no evidence of craniosynostosis, although both of them had the mutation; the mother had facial asymmetry and the sib had macrocephaly with an elongated skull. Two other relatives did have craniosynostosis; a mother had bilateral coronal craniosynostosis which had not been treated and was shown to be heterozygous for the mutation and a sib of an unrelated patient had unilateral craniosynostosis but has not been tested for the mutation. The authors calculate that (given the frequency of this form of craniosynostosis and 95% confidence intervals for the proportion caused by this particular mutation), this nucleotide shows the highest rate of transversion in the human genome. Six of the patients who did not show this genetic change had unusual features such as first cousin parents or other dysmorphic features. The Pro250Arg mutation is in the linker region between immunoglobulin-like domains of FGFR3 in a similar position to mutations in FGFR1 seen in Pfeiffer and FGFR2 in Apert. Much remains to be learned about the molecular pathology of these conditions. This report allows genetic counselling for some families with isolated coronal craniosynostosis to be given with greater confidence.

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