Medical genetics: advances in brief

Phenotypic diversity in siblings with partial androgen insensitivity syndrome

The androgen insensitivity syndrome results from mutations in the androgen receptor gene. The mutant receptors have reduced androgen binding causing impaired virilisation. A wide spectrum of phenotypic abnormalities result, ranging from complete female to ambiguous genitalia more closely resembling males. The authors describe two maternal half-sibs who had the same arrhythmia 840 to cycsteine mutation in the androgen receptor gene, also carried by their mother (who was phenotypically normal). The first sib had ambiguous genitalia with a microopenos, penoscrotal hypospadia with chordee, and a bifid scrotum. The second sib, 46,XY, but it was decided that the child should be raised as a girl and at 21 months she underwent plastic surgery. At the age of 9 years she was reported to have normal external female genitalia. The mother’s half-brother of this child was born with a relatively normal penis, mild penoscrotal hypospadia, and a bifid scrotum. His karyotype was 46,XY and as he was substantially more virilised than the older sib, he was raised as a boy. At the age of 7 years he still had a normal sized penis but the testes were present in the inguinal canal. The authors discuss the variable phenotypic presentations of this point mutation in the androgen receptor gene, which in previous reports has usually been associated with ambiguous genitalia. The reported family is atypical as sibs are usually similarly affected. This is particularly true of families in which there is complete absence of virilisation. They conclude that the cause of the phenotypic variation in this family remains unclear, but postulate that environmental factors such as fluctuating androgen levels during critical stages of embryonic development may account for the differences. This report highlights that intrafamilial variance in phenotypic expression of an identical gene mutation can occur in the androgen insensitivity syndrome. Caution is required in genetic counselling for this condition, especially for partial androgen insensitivity.

SARAH SLANEY

Simultaneous, multilocus FISH analysis for detection of microdeletions in the diagnostic evaluation of developmental delay and mental retardation

Many syndromes caused by chromosomal microdeletions are associated with learning difficulties and developmental delay, and these clinical features are a frequent indication for karyotyping. As the majority of these deletions are submicroscopic, laboratory confirmations of a suspected clinical diagnosis has only become possible in some cases since the development of FISH (fluorescent in situ hybridisation) techniques. Unique physical characteristics are associated with some microdeletion syndromes, and scoring systems to facilitate clinical diagnosis have been developed; however, the increasing availability of FISH tests means that some mild clinical cases with only a few clinical signs are now being diagnosed. The authors of this paper have combined probes for the commonly deleted regions of Prader-Willi, Angelman, Williams, Smith-Magenis, and DiGeorge/velocardiofacial syndromes in a single hybridisation. The probes were differentially labelled, allowing multicolour detection, and samples referred from 200 people with developmental delay were screened. Eleven were found to have a microdeletion. When the referral forms were reviewed, however, the request was withdrawn from all 11 postnatal cases were specifically for FISH analysis, so the use of the multiFISH cocktail picked up only one case (with deletion of chromosome 22) out of 200 screened which would otherwise have been missed. Deletions of chromosome 22 are often inherited (unlike deletions of chromosome 7 in Williams syndrome, for example), the significance of this case is considerable; however, the cost per case found is not stated. The authors acknowledge that experienced clinicians will be able to suggest which clinical diagnoses are possible and exclude others, but they justify consideration of a panel of probes as an approach because (1) even the best clinicians may miss a diagnosis, (2) currently atypical cases may be missed so the full clinical spectrum of some disorders may be unknown, (3) many clinicians are not dysmorphologists, (4) some syndromes have a very variable and inconsistent phenotype (for example, Smith-Magenis syndrome), and (5) if multiple probes can be tested for a single patient, the incremental cost relative to testing with a single probe, a higher quality of diagnostic evaluation can be offered.

FRANCES FLINTER

Occurrence of myeloproliferative disorder in patients with Noonan syndrome

Haematological abnormalities, particularly involving coagulation pathways, are now a well recognised feature of Noonan syndrome. This report and an accompanying editorial (Side LE, Shannon KM. J Pediatr 1997;130:857-9) suggest a possible association with childhood myelodysplasia. Fifty-one children with myelodysplasia who were under 15 years of age at diagnosis were recruited retrospectively between 1986 and 1994 from 13 participating centres in France. The bone marrow specimens were reviewed by three independent haematologists and met conventional diagnostic criteria. Three of these children had Noonan syndrome and a fourth child born before 1986 but known to the authors was also included. No phenotypic illustrations are provided but the diagnosis of Noonan syndrome was made at between 6 months and 10 years of age on the basis of characteristic facial dysmorphism (4/4), developmental delay (4/4), pulmonary stenosis (3/4), pectus carinatum (3/4), cryptorchidism (3/3 males), impaired growth (2/4), congenital hylotherax (1/4), and pulmonary hypertension (1/4). Features of neurofibromatosis type 1 were specifically sought and not found. Phenotypic findings in the parents were not discussed. All four children had presented early with thrombocytopenia and splenomegaly at 1-2 months of age and were classified as having the chronic myelomonocytic leukaemia (CMML) form of myelodysplasia. The initial bone marrow karyotype was normal in all four, as were their constitutional karyotypes, and X inactivation studies in the one female patient indicated a polyclonal origin. Three children had a benign clinical course while one progressed to acute type M1 myeloblastic leukaemia with emergence of a cytogenetically abnormal cell line following chemotherapy. Although the incidence of childhood myelodysplasia in France is not known, it is rare, and the finding of four patients with Noonan syndrome among this group was unexpected. Myelodysplasia has been associated with other genetic disorders including Fanconi anaemia, ataxia-telangiectasia, and Bloom, Dubowitz, and Shwachman syndromes. Neurofibromatosis type 1 is associated with the CMML form in particular. The authors hypothesise that the underlying genetic heterogeneity in Noonan syndrome and suggest that an association with CMML might be a feature of one subtype.

L WILSON

Factor V Leiden mutation: an unrecognised cause of hemiplegic cerebral palsy, neonatal stroke and placental thrombosis

The Arg->Gly factor V Leiden mutation is present in 2-7% of the western European population. Its association with venous thrombosis is well known. It is not implicated in arterial thromboembolic disease in adults, although it is associated with stroke in children. This report suggests that the factor V Leiden mutation may also have a role in neonatal cerebrovascular disorders. Three infants are described, the first presenting at 6 months of age with hemiplegia and a left middle cerebral artery distribution of encephalomalacia on MRI, the second presenting with neonatal cerebral infarction confirmed by MRI scanning, and the last presenting with neonatal seizures and haemorrhagic periventricular leucomalacia on MRI. All three cases were heterozygous for the factor V Leiden mutation. We will have gained significant insight into the cause of these common and potentially very disabling vascular events if further carefully conducted trials determine that there is a genuine association with the factor V Leiden mutation.

Evan REID