Medical genetics: advances in brief

Novel molecular variants of the Na-K-2Cl cotransporter gene are responsible for antenatal Bartter syndrome

Vargas-Poussou R, Feldmann D, Vollmer M, *et al.* *Am J Hum Genet* 1998;62:1332-40.

The antenatal hypercalciuric variant of Bartter syndrome (known as hyperprostaglandin E syndrome) is rare but shares common features (hypokalaemia, metabolic alkalosis, and hyperreninaemic hyperaldosteronism with normal blood pressure) with the two other types of Bartter syndrome, that is, the classical variant originally described by Bartter, and the hypocalciuric-hypomagnesaemic variant described by Gitelman. In all three types the mode of inheritance is autosomal recessive. The antenatal variant may present in utero, with marked fetal polyuria causing polyhydramnios and premature delivery. Neonatally, there is severe salt wasting, hyposthenuria, hypokalaemic metabolic alkalosis, hyperprostaglandinuria, and failure to thrive. The hallmark of this variant is hypercalciuria with nephrocalcinosis and osteopenia. The molecular pathogenesis of Bartter syndrome involves a defect in one of the molecules primarily or secondarily involved in transepithelial chloride transport across the thick ascending limb. Antenatal Bartter syndrome is genetically heterogeneous, and mutations have been found in both the gene encoding the luminal bumetanide sensitive Na-L-2Cl cotransporter (NKCC2) and the gene encoding the luminal ATP regulated potassium channel, ROMK (KCNJ1). Recently mutations in the CLCNKB gene, which codes for the basolateral renal chloride channel, were identified in patients with the severe neonatal phenotype, but also in those with milder forms of Bartter syndrome (but although many cases in the latter group had hypercalciuria, none had nephrocalcinosis). In this study, DNA from 15 probands belonging to 13 families of different ethnic origin was analysed, and 14 novel mutations are described which lead to either the absence or a dramatic alteration of the protein product. All NKCC2 exons were screened by SSCP, but in four patients only one heterozygous disease causing mutation was identified, giving an overall mutation detection rate of 79%. These patients were also

screened for mutations in KCNJ1 and CLCNKB but none was found. In addition, the authors identified alternative isoforms of human NKCC2. In situ hybridisation studies will be necessary to determine the nephron segment localisation of these three isoforms of the Na-K-2Cl cotransporter, but it is postulated that mutations involving these human isoforms may cause disease of varying severity.

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Role of the region 3' to Xist exon 6 in the counting process of X-chromosome inactivation

Clerc P, Avner P. *Nat Genet* 1998;19:3:249-53.

In female mammals the X inactivation centre (Xic) (a 450 kb region in the mouse) controls the X inactivation process. In cells with only one X chromosome the single X remains active, whereas in cells with two or more X chromosomes all except one are inactivated, indicating the presence of a counting mechanism. The Xist gene within the Xic is necessary for X inactivation to take place and Clerc and Avner have attempted to identify functional elements in Xist by constructing a deletion of 65 kb of DNA 3' to exon 6. In differentiating cultured ES cells with one normal and one deleted X chromosome, even though the level of truncated Xist transcript was reduced, X inactivation was exclusive to the deleted X chromosome. The deletion of sequences 3' to exon 6 was therefore insufficient to negate the ability of Xist to initiate X inactivation. However, in cells with essentially an XO karyotype, X inactivation still occurred exclusively on the deleted X even in the absence of a second Xic. This indicates a role for the deleted area in the counting mechanism. The authors suggest that counting is mediated by a repressive mechanism preventing inactivation of a single X in diploid cells and involving elements within the 65 kb deleted region. This work is an interesting addition to previous deletion analysis of the Xist gene which has identified a 5' deletion resulting in the X chromosome being unable to achieve inactivation once being chosen as the elected inactive X, and a knockout of exons 1-4 resulting in the inability

of the mutated X to be chosen as the elected inactive X. It is also of interest to note that Xce, a controlling element which influences the ability of an X chromosome to inactivate, has been mapped immediately downstream of Xist.

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Linkage-disequilibrium mapping of autistic disorder with 15q11-13 markers

Cook EH Jr, Courchesne RY, Cox NJ, *et al.* *Am J Hum Genet* 1998;62:1077-83.

Patients who have a communication disorder which falls within the autistic spectrum have a complex multifactorial condition with a significant genetic component. There is higher MZ than DZ twin concordance and an increased risk for sibs. Cytogenetic clues as to gene localisations are often helpful when trying to identify disease susceptibility loci and, recently, several patients with autism have been described who have a duplication within the Prader-Willi/Angelman syndrome locus at 15q11-13, all of maternal origin. In this study, 140 affected children and their parents were studied and genotyped for markers between D15S128 and D15S156. Two children had interstitial chromosome 15 duplications and were excluded from further linkage analysis. A multiallelic transmission disequilibrium test was used for nine loci on 15q11-13 and showed linkage disequilibrium between autism and a marker in the γ -aminobutyric acid receptor subunit gene. The gene is a potential candidate gene for autism because of the role of the receptor agonist benzodiazepine in the treatment of seizures and anxiety disorders. (Rates of anxiety disorder are higher in the first degree relatives of probands with autism compared with the first degree relatives of probands with Down syndrome. First degree relatives of patients with autism also show a 10-fold increase in social phobia, a specific anxiety disorder.) There was no evidence for a parent of origin effect on allelic transmission. The convergence of GABRB3 as a potential and functional candidate suggests the need for further investigations in its role in the aetiology of autism.

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