

Medical genetics: advances in brief

Amyoplasia, the most common type of arthrogyriposis: the potential for good outcome

Sells JM, Jaffe KM, Hall JG. *Pediatrics* 1996;97:225-31.

Arthrogyriposis is the term used to describe multiple congenital joint contractures. It is not a single diagnosis, but a descriptive term encompassing a wide variety of distinct conditions. Amyoplasia, in which there is fatty and fibrous tissue replacement of the muscles accounts for about one third of cases of arthrogyriposis. There is a characteristic posture in affected subjects with internally rotated shoulders, extended elbows, flexed wrists, and deformities of the hips and knees. The feet usually show a severe equinovarus deformity. Amyoplasia is a sporadic condition. The aetiology is unknown but vascular compromise is thought to play a part because of the frequent occurrence of associated abnormalities such as gastroschisis and bowel atresias. This paper describes the clinical findings and natural history of 38 patients, ranging from birth to 16 years in age, with a firm diagnosis of amyoplasia. Thirty two cases had involvement of all four limbs. There was an increased incidence of reduced fetal movements, breech presentation, and caesarean section rate. Eight patients had perinatal fractures and 45% had congenital dislocation of the hips. Overall, 87% of patients required orthopaedic surgery, mainly to release contractures, and 94% were having regular physiotherapy. These therapeutic interventions did appear to help the children to become mobile and improved the function of their joints. Considering the degree of their deformities at birth, the overall prognosis for this group as regards functional skills was good; 25/38 were able to walk unaided at the time of examination, with an average age at walking of 6.9 years. Scoliosis, which was apparent in eight children at birth only continued to cause a problem in three. All the patients remained living with their parents; 75% were independent at feeding, but they had more difficulty with dressing and bathing. Twenty five children were in school, the majority attending the age appropriate class in a mainstream school. Some were still pre-school. These data on functional outcome for amyoplasia are much more optimistic than those previously reported and will be useful in counselling parents of newborn babies with amyoplasia. It appears that this condition, which appears so severe at birth, can

improve considerably with appropriate interventions, with many of those affected having an independent life.

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Altered growth and branching patterns in synpolydactyly caused by mutations in HOXD13

Muragaki Y, Mundlos S, Upton J, Olsen B. *Science* 1996;272:548-51.

Synpolydactyly (SPD) is an autosomal dominant condition in which an extra digit in the middle of the hand occurs simultaneously with a variable degree of fusion between the third and fourth fingers. Similarly, in the feet, postaxial polydactyly is accompanied by fusion of at least two of the third, fourth, and fifth toes. These authors first established linkage in two families between SPD and the *HOXD* (homeobox) gene cluster already mapped to the 2q31-32 chromosome region. *HOX* genes are well known for having homeobox DNA binding domains which have been highly conserved in evolution and for being sequentially expressed during embryogenesis, such that genes located at the beginning of the cluster are expressed early and those at the end later in development. As a result the authors chose three candidate genes whose homologues were known to be expressed in the distal limb bud in *Drosophila*, but found no evidence of point mutations within any of the three homeodomains. However, PCR and sequencing across a stretch of repeated alanine GCG codons outside the homeodomain of *HOXD13* showed an amplification from 15 to 22 codons in one family, from 15 to 25 in another, and from 15 to 23 in a sporadic patient. The expansions cosegregated with the SPD phenotype in 21 subjects including a more severely affected homozygote and was apparently non-penetrant in one other family member. Normal numbers of alanine codons were found in 56 controls. These results bear out predictions that homeobox genes would be involved in limb defects but are surprising for both the nature of the mutation and its location in the unconserved NH₂-terminal region of the gene. Alanine tracts are necessary for the function of a number of transcriptional repressors in *Drosophila* and the large number of *HOX* genes in humans may provide a rich source of molecular pathology if similar mechanisms are found to be common among them. It is also interesting that a single base frameshift

would convert the alanine GCG to the CGG triplet repeat whose expansion is responsible for fragile X syndrome and other human conditions. While the resulting phenotype and size of the expansion in fragile X is very different from SPD, it is tempting to speculate that there might be a common underlying mutational mechanism connected with DNA replication.

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Genetic variation in bilirubin UDP-glucuronosyltransferase gene promoter and Gilbert's syndrome

Monaghan G, Ryan M, Seddon R, Hume R, Burchell B. *Lancet* 1996;347:578-81.

Gilbert's syndrome is diagnosed by a consistent but mild increase in serum bilirubin level in non-fasting patients. Missense mutations in the gene coding for bilirubin UDP-glucuronosyltransferase have been shown by other authors in affected patients, but in these patients the increase in serum bilirubin is quite marked (above 52 µmol/l). In the homozygous state these missense mutations are associated with the more severe Crigler-Najjar syndrome. Identification of carriers of such mutations in the heterozygous state has important implications for genetic counselling. Monaghan *et al* examined the molecular changes in a group of more mildly affected patients with serum bilirubin levels of 25-50 µmol/l. These patients were shown to have differing genotypes in the upstream promoter region for the gene. In a group of 16 subjects there was a homozygous 2 bp insertion documented which was associated with mildly increased serum bilirubin levels. The frequency of this genotype in the Scottish population studied is estimated to be 10-13%. One male heterozygous for this insertion had an increase in bilirubin level similar to those with the homozygous insertion and the authors suggest he may have a further genetic change within the coding sequence, or other abnormality in bilirubin metabolism. This study provides further support for the differentiation of a mild and more severe form of Gilbert's syndrome. The findings are interesting in understanding the interaction of differing defects of bilirubin metabolism, but more importantly, although the clinical effects of the mild increase in serum bilirubin are small, they may be determinants of sensitivity to certain drugs.

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