

A Cluster of Sulfatase Genes on Xp22.3: Mutations in Chondrodysplasia Punctata (CDPX) and Implications for Warfarin Embryopathy

Chondrodysplasia punctata (CDP) refers to a group of skeletal dysplasias characterized by abnormal calcium deposition in regions of enchondral bone formation. This results in the "stippling" of epiphyses, which tends to disappear within the first few years of life. One type of chondrodysplasia punctata is X-linked recessive (CDPX). It is characterized by aberrant bone mineralization, severe underdevelopment of nasal cartilage, and distal phalangeal hypoplasia. The authors demonstrated that some of these patients have an inherited deficiency of a novel sulfatase (arylsulfatase E, or ARSE). However, not all patients with the clinical syndrome have this defect. Other patients have a recessive form of CDP. CDPX shows remarkable phenotypic similarities to 2 well-characterized disease entities involving vitamin K metabolism: warfarin embryopathy and a congenital metabolic error of vitamin K epoxide reductase deficiency. Warfarin embryopathy is caused by the administration of warfarin, an anticoagulant drug, during a critical period of pregnancy: the sixth through ninth weeks. The vitamin K epoxide reductase deficiency disease, also known as pseudowarfarin embryopathy, is a rare autosomal recessive disorder affecting the recycling of vitamin K. By extensively analyzing DNA from overlapping yeast artificial chromosome clones that spanned the critical Xp22.3 region, Franco et al identified 3 adjacent genes that encoded previously unrecognized sulfatase enzymes. Because of predicted structural similarities to arylsulfatases A, B, and C, the novel sulfatase genes were named ARSD, ARSE, and ARSF. The authors concluded that mutations of the ARSE gene account for many cases of CDPX and that the phenotype results from reduced ARSE enzyme activity. Warfarin probably produces a CDPX-like syndrome because it inhibits ARSE activity. The authors demonstrated a significant decrease of ARSE activity and postulated that ARSE activity is

inhibited by warfarin. Patients with CDPX had demonstrably deficient ARSE activity. The ARSE gene is mutated in some cases of CDPX. Intriguingly, the congenital deficiency of vitamin K epoxide reductase, the enzyme recycling vitamin K epoxide to vitamin K, produces an identical picture. The striking similarities among CDPX, warfarin embryopathy, and vitamin K epoxide reductase deficiency phenotypes and the evidence that warfarin inhibits ARSE suggest that these disorders are due to abnormalities in the same metabolic pathway but are of different etiologies.

Franco B, et al. *Cell* 1995;81:15-25.

Editor's comment: *This paper begins to tie together a number of loose ends for biochemists interested in the arylsulfatase family of enzymes, clinicians interested in sorting out the different forms of CPDX and related conditions, and for geneticists interested in the ancestry of the pseudoautosomal region of the X chromosome, which is where not only the gene for ARSE but also the genes for ARSC and ARSD exist. The patients themselves have underdevelopment of nasal cartilage and distal phalangeal hypoplasia, as well as short stature.*

William A. Horton, MD

2nd Editor's comment: *The saying that if it looks like an elephant and walks like an elephant, then it is an elephant may apply to elephants but does not apply to patients with CPD. Drugs obviously can induce enzymatic deficiencies identical to those induced by genetic mutations or the absence of genes.*

Robert M. Blizzard, MD

Trisomy 18, Molecular Studies, Parental Origin and Cell Division in the Extra Chromosome 18 Material

Trisomy 18, or Edwards syndrome, was first described in 1960. It is the second most common autosomal trisomy. Individuals with trisomy 18 present with characteristic facial features, growth retardation, severe mental retardation, clenched hands with

overlapping fingers, and renal and cardiac anomalies. Trisomy 18 has an incidence of 0.18% in all clinically recognized pregnancies and, like other autosomal trisomies, is associated with advanced maternal age. The majority of pregnancies with trisomy 18 abort spontaneously, and only 5% survive to birth. The mean survival after birth is 1 to 3 months, and 95% of those born alive die within the first year of life.

The gene or genes responsible for the trisomy 18 phenotype are not known. While the features of trisomy 18 are most often associated with duplication of the entire chromosome, there are a number of cases in which individuals with a partial duplication of chromosome 18 present with the same or similar features. An effort to identify the regions of chromosome 18 that are critical in producing the phenotype was reported by Boghosian-Sell et al, who analyzed 6 patients with partial duplications of chromosome 18. Fluorescent in situ hybridization with DNA-specific probes to chromosome 18 was used to determine the precise duplication in these patients. The clinical features and the extent of the duplication were compared with 4 previously reported partial trisomy 18 patients. This

Editorial Board

Chairman

Robert M. Blizzard, MD
Charlottesville, Virginia

Associate Editors

William L. Clarke, MD Charlottesville, Virginia	William A. Horton, MD Portland, Oregon
Judith G. Hall, MD Vancouver, BC, Canada	Fima Lifshitz, MD Brooklyn, New York

Allen W. Root, MD
St. Petersburg, Florida