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Long deletions of the Williams syndrome region on chromosome 7 result in more severe mental retardation. Colleen A. Morris, M.D.[1], C.B. Mervis, Ph. D.[2], B.F. Robinson, M.A.[2], M. T. Keating, M.D.[3], X. Lu, Ph. D.[3], X. Meng, Ph. D.[3], P. Spallone[4], T.R. Dennis[4], and A. D. Stock, Ph. D.[4]. [1]Department of Pediatrics, Genetics, University of Nevada School of Medicine, Las Vegas, NV; [2]Department of Psychology, University of Louisville, Louisville, KY; [3]Department of Human Genetics, Eccles Program in Human Molecular Biology and Genetics, University of Utah, Salt Lake City, UT; [4] Department of Pathology, University of Nevada School of Medicine, Reno, NV.

Williams syndrome (WS) is characterized by dysmorphic facial features, mental retardation, elastin arteriopathy, a specific cognitive profile, and a unique personality. It is caused by a ~ 1.5 Mb deletion in chromosome 7q11.23, bounded by markers D7S1778 and D7S489A. We report four individuals with WS who have longer deletions in the telomeric direction. The individuals with longer deletions had the classic WS phenotype, but had more severe mental retardation than those with the common WS deletion. The mean (Kaufman Brief Intelligence Test) IQ for 47 individuals with WS (age range 5 years - 47 years) with the classic deletion was 71.13 (SD=14.02), while the mean IQ for those with longer deletions was 47.0 (SD=5.48). the difference between the two groups was significant, $t=3.39$ ($p=.001$). These findings suggest that gene(s) telomeric to the classic WS region may play an important role in normal cognitive development.

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Parental mosaicism for a point mutation in a type III collagen (COL3A1) allele produces Ehlers-Danlos type IV (EDS4) in heterozygous offspring

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We describe a family with EDS type IV in which the clinically unaffected mother of two affected children is mosaic for the mutation in the *COL3A1* gene. The proband, a 27 year old male, presented with a spontaneous retroperitoneal hemorrhage and multiple arterial pseudoaneurysms. At the age of 20, he had a spontaneous colonic perforation. His sister had a cerebral hemorrhage at 23, spontaneous splenic rupture at 26, recurrent patellar dislocations and delayed wound healing. Skin fibroblasts from the proband secreted diminished amounts of type III collagen precursors and retained overmodified proα1(III) chains, consistent with a defect in one *COL3A1* allele. SSCP screening and sequence analysis of cDNA identified a point mutation resulting in a substitution of Asp for Gly at amino acid 493 within the triple helical domain of the proα1(III) chain of type III collagen. The mutation eliminated an *Ava*II restriction site. Amplification and digestion of DNA from the proband's sister showed the identical mutation. Paternal mosaicism was initially suspected as the father had a history or spontaneous rupture of a pancreatic duct cyst. However, digestion of paternal white blood cell DNA with *Ava*II revealed a normal restriction pattern in the father, but evidence for the presence of the mutation in a population of cells in the mother. A small number of families have now been identified in which one asymptomatic parent was mosaic which indicates that this risk must be considered in counseling parents after the identification of an affected child.

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Clinical, cytogenetic and epidemiological approaches to the genetic heterogeneity of holoprosencephaly :Buenos Aires, 1988-1997.
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Introduction :Holoprosencephaly (HPE) is a midline developmental field defect of prosencephalon and craniofacial structures that presents great clinical variability and etiologic heterogeneity. The epidemiology is poorly known due to the paucity of population-based studies. Aims :1) To describe clinical, cytogenetic and epidemiological aspects of this malformation using cases identified through the Garrahan Hospital Genetic Registry from 1988 to 1997 ; 2) To evaluate the predictive value of the facial anomalies for the detection of HPE ; 3) To compare all these data with those previously reported in other populations. Results : We describe the craniofacial abnormalities, present their relative frequencies, coocurrence and their correlation with the severity of the brain defects including the presence of midline porencephalic cysts.
The facial abnormalities allowed the prediction of the brain defect in 85,7% of our cases, being hipotelorism the most reliable clinical sing. Among the different etiologies of HPE, from a total of 35 cases, we found that : 34,3% had isolated HPE ; 45,7% presented a named syndrome, 8,6% were due to the exposure to teratogenic agents and 11,4% had a chromosomal abnormality including trisomy of chromosome 13 and structural rearrangements of chromosome 7. Prevalence among girls was nearly double that of boys in concordance with previous reports.
Also, there was no maternal or paternal age effect. Conclusions : 1) The prevalence of named syndromes in our population is unusually higher ; 2) The predictive value of the facial anomalies is extremely high ; 3) The frequent coocurrence of neural tube defects NTDs and HPE and the high rates of NTDs among relatives of our cases suggest that this is more than the association of two common malformations ; 4) The midline porencephalic cysts have to be considered as a part of the holoprosencephaly spectrum. This is, to our knowledge, the first clinical, cytogenetic and epidemiological study of this malformation in our population. Our results highlight the need for a thorough assessment of the patient and family, realizing the clinical variability and etiologic heterogeneity of HPE.

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A unique X-linked syndrome characterized by congenital deafness, mild dysmorphic features, mid-phalangeal hypoplasia, hernias, and late-onset pancytopenia.

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Three males ranging from 54 to 12 years of age in one kindred were evaluated for a syndrome associated with hearing loss at the request of a female relative desiring preconception counseling. Review of their pedigree was consistent with X-linked recessive inheritance as the males spanned 3 generations and were related through female relatives. No consanguinity was noted. Features in 3 of 3 of the affected males included bilateral congenital severe-profound sensorineural hearing loss (SNHL); mild facial dysmorphisms with telecanthus and unusual ears; mild to moderate mental retardation; telangiectasis; umbilical hernias; dermatoglyphics characterized by a high number of arches; small hypoplastic nipples; and shortening of the mid-phalanges. In addition, the two older males (ages 31 and 54) had microcephaly, short stature and pancytopenia, which was most severe in the 54-year-old man. Both men had normal cytogenetic studies. The clinical course of the 54 year old man was complicated by hypothyroidism diagnosed at 16 years of age, chronic glomerular nephritis diagnosed at 50 years of age resulting in renal failure, and a cataract. Peripheral blood chromosome analysis of the 12-year-old boy revealed a mosaic karyotype of 46XY/45X at birth. He had additional urogenital abnormalities consisting of a bifid scrotum, small testicles and phallus, and absence of the vas deferens and epididymis. Review of the literature, search of the dysmorphology databases, and curbside consultation at a previous American Society of Human Genetics Meeting did not suggest a recognized syndrome. Thus, it seems likely that this is a new X-linked syndrome of SNHL associated with mild dysmorphic features, mid-phalangeal hypoplasia, umbilical hernias, and late-onset pancytopenia. The underlying molecular basis of this syndrome is unclear but it is hoped that analysis of candidate deafness genes on the X chromosome will be revealing.