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Early clinical features of Angelman Syndrome in infants with chromosomal deletion of 15q11-q13. C.H. Tsai[1], M. Taylor[1], J. Siegel-Bartelt[2]. [1]Division of Genetics Service, Department of Pediatrics, The Children's Hospital, Denver, University of Colorado Health Science Center, CO, and [2]Alfagen Genetics, CA.

Angelman Syndrome (AS) is characterized by severe developmental handicap, broad based and ataxic gait, communication disorder with affected children remaining largely pre-verbal, seizure disorders and episodes of spontaneous laughter. Clinical diagnosis may be difficult below age 2, as the clinical phenotype becomes more distinctive in early childhood. We report 2 infants (aged 4 months and 1 week) with chromosomal anomalies involving chromosome 15q11-13 who were subsequently diagnosed to have Angelman syndrome by fluorescent in situ hybridization (FISH) and methylation analysis. Both patients had cleft palate, feeding difficulty, fair skin and hair color compared to siblings, hypertonia since birth and small for gestational age. Patient one also had prominent nose, U-shaped cleft palate with micrognathia, consistent with Robin sequence, tapering fingers, bilateral inguinal hernias, hypogonadism and failure to thrive. FISH did not identify a deletion of the critical region associated with VCFS/DiGeorge syndrome. High resolution karyotype revealed a deletion of chromosome 15: 46,XY,del(15)(q11.2q13). Methylaltion test confirmed the deleted fragment was of maternal origin. Maternal karyotype is pending. Patient two had a rare chromosomal rearrangement as an unusual etiology of Angelman Syndrome. This baby had 46, XY, -15, + der(16), t(15;16)(q13;q13) mat, resulting in duplication 16p and Angelman Syndrome. FISH confirmed that the breakpoint was in the 15q11-q13 region. He presented with dysmorphic features including hypertelorism, cleft soft palate, malformed ears, campto-clinodactaly and hypospadias. Severe intractable seizures began by day 2. Family history revealed that this translocation appeared to be inherited over 4 generations from the proband's maternal great grandmother. It was recognized in the literature, poor feeding and hypotonia are the early clinical signs of Angelman syndrome. Of note, both our patients were hypertonic and both with cleft palate which was initially thought to be the cause of poor feeding. Our patients may provide information for clinical suspicion in infants with Angelman Syndrome from chromosomal anomalies.

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Spondyloepimetaphyseal dysplasia with multiple joint dislocations. S. Unger[1], R. Savarirayan[2], V. Cormier-Daire[3], D. Cohn[1], W. Wilcox[1], R.S. Lachman[1], and D.L. Rimoin[1]. 1) Division of Medical Genetics, Cedars Sinai Medical Ctr, LA, CA; 2)Victorian Clinical Genetics Services Parkville, VIC, Australia; 3) Department of Genetics, Hopital Necker-Enfants-Malades, Paris, France.

We report four cases of a spondyloepimetaphyseal dysplasia (SEMD) characterized by joint laxity and large joint dislocations, especially hips and knees. This condition was first reported as a distinct entity by Hall et al., (J Med Genet 1998; 35:566-572). They described three apparently sporadic patients. We present four unrelated patients (three males and one female) with similar radiographic and clinical findings. Usually, this disorder is manifest in the neonatal period by joint dislocations but normal birth length. The children go on to have significant short stature by the time they are toddlers, as well as scoliosis and progressive joint deformities. They have normal psychomotor development. Three of our four patients also had laryngo/tracheomalacia. The radiographic findings include small irregular epiphyses and metaphyseal abnormalities of the long bones. The changes seen on hand x-rays are unique to this form of SEMD and consist of the characteristic finding of gracile metacarpals and the frequent finding of distal ulnar hypoplasia. As the radiographic findings overlapped somewhat with a severe form of multiple epiphyseal dysplasia (MED), mutation detection was undertaken in one proband. This child had normal sequence of previously established MED loci (COMP, exon 3 of COL9A2, exon 3 of COL9A3) as well as exons 8,9, and, 10 of COL9A1 and COL2A1. Histology of a cartilage sample on this patient was mildly abnormal but not diagnostic. These four cases aid in confirming that SEMD with multiple joint dislocations is a discrete entity which is most likely inherited as an autosomal dominant trait.

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An infant with trisomy 9 mosaicism and features of CHARGE association. M.E. Walker, R.I. Blough, K.E.Bove, and R.J. Hopkin. Children's Hospital Medical Center, Cincinnati, OH.

A range of phenotypic features has been reported in infants and children with trisomy 9 mosaicism. This chromosome abnormality typically involves growth and mental retardation, dysmorphic facial features, skeletal anomalies, cardiac and brain defects, and other malformations. We describe a female infant with trisomy 9 mosaicism who was born at 41 weeks gestation to a gravida 6, para 4, Ab 2, 44 year old white female who had an unremarkable prenatal course. The delivery was by C-section because there was failure of progression of labor. The infant had intrauterine growth retardation, single umbilical artery, iris coloboma, primary pulmonary hypertension, cardiac malposition, asymmetric labia and small clitoris, clinical choanal stenosis, and dysmorphic features of micrognathia, posteriorly rotated lowset ears, and single palmar crease. Because of these findings, she was initially thought to have CHARGE association. However, her blood karyotype was 47,XX,+9[10]/46,XX[10] and she was given the diagnosis of trisomy 9 mosaicism. A policy of comfort care was invoked upon conferring with her parents, and the infant died at age 7 days. At autopsy the clinical findings were confirmed. Also diagnosed post mortem were right ventricular hypertrophy, atrial septal defect, muscularization of pulmonary peripheral arterioles, and absent corpus callosum. The features seen in this infant are consistent with the phenotype described in other published cases of trisomy 9 mosaicism. This case is interesting and important to report because it provides evidence of the need for chromosome mosaicism studies in patients who appear to have CHARGE association.

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A third Prader-Willi syndrome phenotype due to maternal uniparental disomy 15 with mosaic trisomy 15. E. A. Wulfsberg[1] E. Olander,[2] J. Stamberg[1], L. Steinberg[1], [1]University of Maryland School of Medicine, Baltimore, Maryland and the [2]Center for Developmental Medicine and Genetics, Albert Einstein Medical Center.

We report a boy with hypotonia, a Prader-Willi syndrome (PWS) facial phenotype, a large muscular VSD and a PDA due to maternal isodisomy for chromosome 15 with mosaic trisomy 15. At 18 months of age, his height, weight and head circumference are below the 5th %tile and his development is in the moderate mental retardation range. While our patient is unusual in having maternal isodisomy rather than the more common maternal heterodisomy, we believe, based on a review of other cases of trisomy 15 mosiacism, that his more severe PWS phenotype is due to his trisomy 15 mosaicism rather than to homozygosity for deleterious chromosome 15 genes. We propose that individuals with the PWS can have one of three similar but distinctive phenotypes depending on the etiology of their condition. Patients with paternal deletions have the typical PWS phenotype with mild to moderate mental retardation and significant behavioral problems; patients with maternal UPD have a milder physical phenotype, better cognitive function and fewer behavioral abnormalities; and patients with maternal UPD and mosaic trisomy 15 have the most severe phenotype with a high incidence of congenital heart disease, severe growth and development delays. We propose that incomplete "trisomic rescue" with residual mosaic trisomy 15 leads to this third and most "severe" Prader-Willi phenotype. Thus the phenotypic spectrum of the Prader-Willi syndrome is at least in part explainable by the varying molecular etiologies. These phenotype/genotype differences are useful both to guide the evaluation of patients with suspected PWS and to provide prognostic counseling for families.