74

Mutation in the *CSB* gene in a patient with Cerebro-Oculo-Facio-Skeletal syndrome. C.M. Powell[1], L.B. Meira[2] and E.C. Friedberg[2]. [1]Univ. of North Carolina at Chapel Hill and [2]Univ. of Texas Southwestern Medical Center, Dallas.

Cerebro-Oculo-Facio-Skeletal (COFS) syndrome is an autosomal recessive multiple malformation syndrome with congenital microcephaly, microphthalmia and cataracts, characteristic facial features, camptodactyly and rocker-bottom feet. Survival is usually less than 5 years. Cockayne syndrome is an autosomal recessive condition with dwarfism, precocious senile appearance, eye abnormalities and mental retardation. Features are usually not apparent until 2-4 years of age. Two complementation groups have been identified (CS-A and CS-B) and both genes have been characterized. There is an early onset form of Cockayne syndrome (EOCS) and it has been suggested that EOCS and COFS may be the same condition. Recently a mutation in the *CSB* gene has been reported in two related patients with the COFS phenotype.

We describe a patient with congenital microcephaly, microphthalmia, prominent nose, micrognathia, large ears, small mouth with upper lip overlapping lower lip, joint contractures, rockerbottom feet, congenital cataracts, and profound growth and developmental retardation. At age 2 years 10 months she developed seizures, proteinuria, and acute renal failure and died. The family history is notable for a female sibling with identical clinical features who died at age 3 of nephrotic syndrome. There is no reported consanguinity. DNA sequence analysis of the *CSB* gene in fibroblasts from this patient revealed a homozygous 177 bp deletion in exon 10.

This is a different mutation than that previously reported in COFS syndrome and provides further evidence that COFS syndrome is caused by mutations in the *CSB* gene. Patients identified with the COFS phenotype should have UV sensitivity studies and analysis of the *CSB* gene; identification of a mutation would provide a method for prenatal diagnosis in subsequent pregnancies and for carrier testing.

75

Craniosynostosis, ectopia lentis and congenital heart defect: further delineation of an autosomal dominant syndrome with reduced penetrance. N. L. Quercia and A. Teebi. The Hospital for Sick Children, Division of Clinical and Metabolic Genetics, Toronto, Ontario, Canada.

The association of craniosynostosis with ectopia lentis is rare. A review of the literature revealed that most reported cases of craniosynostosis with ectopia lentis are sporadic in nature. Recently, Cruysberg et al [AJMG 82:201-205 (1999)] reported on monozygotic twin sisters with craniosynostosis and ectopia lentis, supporting a genetic etiology for this association. The authors hypothesized that the occurrence of craniosynostosis and ectopia lentis in their case was most likely due to an autosomal dominant new mutation. We report on female first cousins once-removed who were born with a constellation of findings similar to those reported by Cruysberg et al. One cousin was born with unilateral coronal synostosis, and peripheral pulmonic branch stenosis. At 3 months of age she was found to have ectopia lentis. The other cousin was also born with unilateral coronal synostosis, an atrial septal defect and mitral valve prolapse. She has only mild myopia. Both females are of normal intelligence. There is no other family history of craniosynostosis, ectopia lentis or congenital heart defect. There is no consanguinity. The family is of German/English descent. Mutation analysis for the FGFR2, FGFR3, and TWIST genes was negative. Chromosome analysis was normal. Homocystinuria was also ruled out.

We believe this case supports an autosomal dominant etiology for the association of craniosynostosis and ectopia lentis and further defines this syndrome to include congenital heart defects. The additional finding of congenital heart defects in our case has not been previously reported in association with craniosynostosis and ectopia lentis. Furthermore, the presence of coronal synostosis in first cousins once-removed in this family supports the notion that this is an autosomal dominant condition with reduced penetrance. These findings will have important implications for genetic counselling.

76

Oral clefting, cartilaginous auricular malformations and other anomalies: A provisionally unique autosomal dominant syndrome. E.R. Roeder[1], Z. Ali Khan-Catts[1],J.H. Fisher[1], S.Daack-Hirsch[2], J.C. Murray[2], C.J.R. Curry[1]. [1]Valley Children's Hospital, Madera, CA and [2]University of Iowa, Iowa City, IA.

We describe a provisionally unique autosomal dominant syndrome characterized by cleft lip and palate (CL/P) and unusual cartilaginous ear malformations. This is a four-generation family without male to male transmission. The proband is a five year old boy who has bilateral complete CL/P and auricular abnormalities consisting of protruding cartilaginous abnormalities located within the concha of the ear and an abnormal crus of the helix which bridges across to the anti helix. Other distinctive features include bilateral sixth nerve palsy, synophrys, broad nasal tip and mild developmental delay. There are no lip pits or branchial defects. The proband's younger brother has a bilateral CL/P and auricular abnormalities with cartilaginous protrusions in the concha, a prominent crus and pits within the concha. The mother of these children does not have a cleft, but has minor facial dysmorphism. We have examined three other affected family members, including the maternal half-aunt, who has only anosmia. Her two sons have CL/P and auricular abnormalities. One son also has bilateral sixth nerve palsy and mildly short distal phalanges of the fingers. The affected individuals have similar minor dysmorphic features. The grandfather has bilateral CL/P, ear abnormalities and anosmia. Another maternal aunt has a unilateral CL/P and anosmia. Additional studies are under way to rule out abnormalities in other organ systems. Linkage is currently being evaluated for a series of candidate genes thought to be involved in craniofacial development.

In summary, we present a probable new autosomal dominant oral clefting syndrome that has distinctive cartilaginous ear abnormalities. This condition exhibits marked variability in expression and reduced penetrance. There is variable cranial nerve involvement, mild cognitive delay, as well as some minor skeletal abnormalities in some family members. This condition appears to be distinct from other autosomal dominant oral clefting syndromes.

77

Incidence and severity of pain in Stickler and Ehlers-Danlos syndromes. P. Rose, J. Davis, T. Magyari, H. Levy, C. Francomano. National Human Genome Research Institute, NIH, Bethesda, MD.

Although chronic pain is increasingly recognized as a complication of hereditary connective tissue disorders, the incidence and severity of symptoms is poorly characterized. We systematically assessed pain symptoms in 25 patients with Ehlers-Danlos syndrome (EDS) and 21 patients with Stickler syndrome (hereditary arthroophthalmopathy) seen at the National Institutes of Health. Eighteen of 25 EDS patients (72%) and 16 of 21 Stickler syndrome patients (76%) reported mean worst pain ratings of 7.3±1.5 and 5.7±2.2 respectively (0-10 scale, p=0.017 comparing EDS and Stickler syndrome). In the 7 activity indices measured by the Wisconsin Brief Pain Inventory, patients with EDS and Stickler syndrome reported mean interference with activities due to pain of 5.5±2.6 and 3.6±2.0 respectively (p=0.024). EDS patients with pain were significantly older than those without (mean 37.0±15.0 vs 18.1±13.1, p=0.008), but no significant correlation was observed between pain severity and age. An age difference was not seen in Stickler syndrome patients with and without pain (36.6±16.1 vs. 29.0±18.8, p=0.44), and in those with pain there was no correlation of severity with age. These results support the hypothesis that musculoskeletal pain is a common manifestation of both Stickler syndrome and Ehlers-Danlos syndrome and significantly affects quality of life in both disorders.