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Seckel syndrome phenotype in a live-born with ring 4 / monosomy 4 chromosomal mosaicism. M.R.G. Taylor and E. Sujansky, Department of Pediatrics, University of Colorado School of Medicine, Denver.

This is the second report of the Seckel syndrome phenotype in a patient with a ring 4 chromosome. The proband was identified through prenatal growth restriction at 34 weeks gestation, which prompted an amniocentesis. The karyotype was 46,XX, r(p?q?35) [8] / 45,XX, -4 [12] . At 38 weeks gestation a female infant was born, after an otherwise uncomplicated pregnancy. She was severely SGA in all parameters, with a weight of 1030 grams. The Apgar scores were low, and respiratory problems required endotracheal intubation. She had significant hypotonia and microcephaly with a sloping forehead and bitemporal narrowing. The facial features were characteristic of Seckel syndrome, including down-slanted palpebral fissures, a prominent nose with a broad nasal tip, a small mouth with a thin upper lip, and micro-retrognathia. The ears were small, low set, and posteriorly rotated. She also had abnormal palmar creases, a cleft palate, and hypoplastic labia. Postnatal study of peripheral blood lymphocytes confirmed the karyotype as 46,XX,r(4)(p16q35) [24] / 45,X,-4 [4]. After discontinuation of the ventilator at age 18 days, she remained tachypneic on supplemental oxygen. Feeding difficulties were encountered and nasogastric feeds were instituted. Her weight gain was modest and at 33 days of life her weight was 1332 grams.

According to the literature, r(4) patients phenotypically resemble Wolf-Hirschhorn syndrome. Co-existence of a r(4) chromosome with the Seckel syndrome phenotype was reported only once previously (Anderson CE et al: Am.J.Med.Genet. 72:281-5,1997). To explain this association, we are postulating that the locus of the Seckel syndrome gene might be on the distal arm of chromosome 4. In this scenario, a mutation of the gene on the normal chromosome 4, combined with the deletion of a normal allele on the r(4), could explain the co-existence of Seckel syndrome and r(4) in these 2 cases. Molecular analyses of the deleted regions of chromosome 4 in classical Seckel syndrome patients may be warranted to prove that the association is not coincidental. Alternatively, the mosaic monosomy 4 (which has not been described previously in a livebom infant) could be causing the severe growth retardation. It is less likely that this could explain the typical facial features of Seckel syndrome.

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Clinical manifestations of NF1 in African-Americans and Caucasians. M.Tekin[1], J.Bodurtha[1], B. Korf[2],V.Riccardi[3].[1]Virginia Commonwealth University/Medical College of Virginia Hospitals, Richmond, VA, [2]Children's Hospital and Partners Health Care, Boston, MA, and [3]Neurofibromatosis Institute, La Crescenta, CA.

Most of the clinical manifestations of NF1are thought to occur in similar frequencies in different ethnic groups. One exception to this assumption may be optic glioma, which has been reported to be less common in African-Americans. We have compared the manifestations of NF1 in a retrospective analysis of 55 individuals with NF1, including 39 Caucasians and 16 African-Americans in the first part of the study. All patients met the NIH consensus criteria for NF1. The diagnosis of NF1 was established at the mean age of 11.1 years in African-Americans and 8.3 years in Caucasians (±SD 6.9 years for African-Americans and 12.3 years for Caucasians; $p<0.01$). The results revealed that most of the findings were seen in similar frequencies in African-Americans and Caucasians. However, the following manifestations were found to be different: 3 of 16 African-Americans and 3 of 39 Caucasians were noted to have plexiform neuroma. None of the African-Americans were found to develop renal artery stenosis, although it was noted in 2 Caucasians. Three patients from the African-American group were found to develop intracranial tumors other than optic glioma, although none of the Caucasians were noted to have similar tumors in our sample. One explanation for these differences would be that African-Americans might be getting medical attention only if they have significant problems such as plexiform neuroma or intracranial tumors. To better evaluate the previously reported difference on the frequency of optic glioma, we are collecting a larger sample currently including 84 African-Americans and 880 Caucasians. Thus far optic glioma has been diagnosed in 4 of the 84 (4.8%) patients whose both parents were African-Americans and in 144 of the 880 (16.4%) Caucasians (further analysis is continuing). Our results thus far suggest that the manifestations of NF-1 are somewhat different in African-Americans, a lower frequency of optic glioma being the most significant difference. Better understanding of clinical differences in patients with NF-1 from different ethnic groups will help to identify modifying genetic factors and to establish appropriate individualized diagnostic and management plans.

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Chiari I malformation associated with a P250R mutation of *FGFR3*. L. Terry[1], W. Allen[2], F. Schaefer[3], and T. Jewett[1]. [1]Wake Forest Univ., Winston Salem, NC, [2]Fullerton Genetics Center, Asheville, NC, [3]H.A. Chapman Institute, Tulsa, OK.

Advances in molecular studies have shown that mutations in the fibroblast growth factor receptor (*FGFR*) genes are responsible for six autosomal dominant craniosynostosis syndromes. Each FGFR has a common structure which includes a conserved sequence that is thought to be critical for FGF binding. Mutations in this conserved region have been identified in *FGFR1, 2,* and *3* and have been associated with classic craniosynostosis syndromes, such as Pfeiffer and Apert syndromes. Recently, a new craniosynostosis syndrome has been described. This new syndrome is associated with a P250R mutation within the conserved region of *FGFR3*. This syndrome is characterized by synostosis (bilateral and unilateral); macrocephaly in the absence of synostosis; abnormalities of hands and feet, including broad big toes, brachydactyly, thimble-like middle phalanges, coned epiphyses, and carpal and tarsal fusions; sensorineural hearing loss; and developmental delay and/or mental retardation. To further expand the phenotype of this specific mutation, we describe a six-month-old male infant with a P250R *FGFR3* mutation and Chiari I malformation.

Our patient was born at 37 weeks gestation with a birth weight of 5 lb. 9 oz. (15th percentile for 37 weeks) and length of 18.75 inches (50$^{th}$ percentile for 37 weeks). By six months of age, the patient's height and weight were below the 5$^{th}$ percentile, while his OFC remained in the normal range. The patient's features include FTT; hypotonia; a large, patent anterior fontanelle; generous thumbs and great toes; high arched palate; right parieto-occipital plagiocephaly; prominent occiput; asymmetric mandible; low set and posteriorly rotated ears; and flat nasal bridge. A skeletal survey was normal. Head MRI revealed flattening of the right occipital skull with no evidence of definite synostosis (CT scan of head has not been performed). The MRI study also revealed a Chiari I malformation. Subsequent molecular testing for the *FGFRs* indicated a P250R mutation of *FGFR3*. The patient's mother had congenital hydrocephalus and placement of a V-P shunt. She also had learning problems in school. Molecular testing on the mother also indicated a P250R mutation of *FGFR3*. In addition, the patient's maternal grandmother is reported to have a large head size with hydrocephalus.

Our case serves to further broaden the spectrum of the newly described craniosynostosis syndrome associated with the P250R mutation of *FGFR3*. Although many of the features present in this case have already been documented, to our knowledge, the finding of Chiari I malformation has not been described and further expands the phenotype of this syndrome.

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Acampomelic campomelic dysplasia with SOX9 mutation. M.K.Thong[1], G. Scherer[2], K.Kozlowski[3], E.Haan[1], L.Morris[4] [1]South Australian Clinical Genetics Service, Women's and Children's Hospital, North Adelaide 5006, Australia, [2]Institute of Human Genetics, University of Freiburg, Germany, [3]New Children's Hospital, Parramatta NSW 2124,Australia, [4]Department of Medical Imaging, Women's and Children's Hospital, North Adelaide 5006, Australia.

Campomelic dysplasia (CMPD; MIM 114290) is a rare disorder characterised by a distinctive pattern of abnormal skeletal features and a generally lethal outcome as a result of respiratory distress. Mutations in the SOX9 gene are reported in affected children with CMPD. Acampomelic CMPD is a clinical variant of the more commonly encountered CMPD but is characterised by absence of long bone curvature (acampomelia). We report a one-year-old boy who presented at birth with a flat facial profile with depressed nasal bridge, micrognathia, cleft palate and microstomia; genital findings consisting of bifid scrotum, perineal hypospadias and undescended testes and tracheomalacia. Other abnormalities include a bifid kidney, deep plantar creases and limited elbow extension. Skeletal survey showed typical CMPD changes such as bilateral hypoplastic scapulae, 11 pairs of ribs, delayed bone age but without campomelia. The patient's condition gradually improved over time. Both his parents are well and not related. Genomic analysis showed a de novo heterozygous missense mutation K173E (AAG→GAG; nucleotide position 889) located within the DNA binding HMG (high mobility group) domain of SOX9 gene. We postulated that this mutation is associated with residual activity of SOX9 protein leading to a milder phenotype or acampomelic CMPD.