AJHG, Volume *86*

Supplemental Data

Identification of a Recurrent Microdeletion at 17q23.1q23.2 Flanked by Segmental Duplications Associated with Heart Defects and Limb Abnormalities

Blake C. Ballif, Aaron Theisen, Jill A. Rosenfeld, Ryan Traylor, Julie Gastier-Foster, Devon Lamb Thrush, Caroline Astbury, Dennis Bartholomew, Kim McBride, Robert Pyatt, Kate Shane, Wendy E. Smith, Valerie Banks, William B. Gallentine, Pamela Brock, M. Katharine Rudd, Margaret P. Adam, Julia A. Keene, John A. Phillips III, Jean P. Pfotenhauer, Gordon C. Gowans, Pawel Stankiewicz, Bassem A. Bejjani, and Lisa G. Shaffer

Supplemental Discussion

Patient 1 is a 3-year-old female with developmental delay, microcephaly, failure to thrive, hearing loss, behavioral abnormalities, intention tremors, familial 2-3 toe syndactyly, asthma, and mild gastrointestinal reflux. She was born to a 28-year-old mother via cesarean section at 36 weeks' gestation following a pregnancy complicated by gestational diabetes, preterm labor, and a controlled maternal seizure disorder. Birth weight, length, and OFC were all at the 25th percentile. Neonatal course was significant for respiratory distress necessitating intubation, pneumothorax, a large patent ductus arteriosus (PDA) that resolved with Indocin, a need for phototherapy, and NG tube feedings. She had failure to thrive and the emergence of microcephaly in the first year of life. All growth parameters have remained below the 3rd percentile. She had a chalazion at 1 year of age but has normal vision. MRI at 2 years showed incomplete myelination. Intention tremors in arms and feet were noted at 3 years of age. She also has a history of chronic ear infections and moderate bilateral hearing loss diagnosed at 2 years of age. Developmentally, she learned to walk at 21 months and had delays with her speech and poor articulation that improved upon using hearing aids. Behavior problems include sensory abnormalities, smearing feces, obsessive picking, and aggression with biting and pulling hair. The only dysmorphic features noted are high eyebrows, right epicanthal fold, slender fingers, and a wide, deeply grooved space between the first and second toes. Family history is significant for psychiatric disorders in both parents, including Asperger syndrome in the patient's mother, and apparent autosomal dominant 2-3 toe syndactyly in the maternal family.

Patient 2 is a 5-year-old female with developmental delays, significant expressive speech delay, microcephaly, atrial septal defect (ASD), strabismus, and mild dysmorphisms. She was born at 36 weeks' gestation via cesarean section following a pregnancy complicated by pre-eclampsia.

Birth weight was between the 3rd-10th percentile, and the placenta was thin and the umbilical cord small. There were no other neonatal complications. She has an ASD secundum and left-sided esotropia. Concerns arose with delayed development; she rolled over at 9 months, sat at 13 months, walked at 18 months, and ran at 3 years. Fine motor development was also delayed. Her first words were at 15 months, and she has only 20 words at 5 years. Her receptive speech is at a higher functioning level than expressive. There are no behavior concerns; she is social with good eye contact, interacts with her peers (sometimes inappropriately), does not have self-stimulating behavior or inappropriate play, and is flexible in her routine. Creatine phosphokinase was mildly elevated at 359. At 5 years, her height is at the 75th percentile, weight is at the 90th percentile, and OFC is less than -2 SD (47 cm). She has slightly decreased axial tone. Her gait is wide-based. Her dysmorphic features include hypertelorism, flattened nasal bridge and midface, simple right ear, and long and thin fingers and feet.

Patient 3 is a 4-year-old male with skeletal abnormalities, history of tethered cord, speech delay, and minor dysmorphic features. He was born to a 26-year-old primagravida mother at term via spontaneous vaginal delivery following an uncomplicated pregnancy. Birth weight was 4.05 kg (75th-90th percentile), and length was 48.3 cm (10th percentile). Neonatal complications included pulmonary hypertension, infection, and the use of a ventilator and feeding tube. He reached early milestones on time but regressed, apparently following a severe RSV infection at 7 months. He was subsequently mildly slow in obtaining his milestones, although he walked at 13 months and had a vocabulary of 20 words by 18 months. His speech can be hard to understand, and he receives speech therapy. A tethered cord was diagnosed at 2 years of age due to bilateral hamstring contractures and constipation. Following the release of the tethered cord he continued to have a mild crouched gait and inability to straighten his legs. He also has a mild flatfoot deformity while standing. Early radiographs showed underossification of the femoral heads and hips deeply seated in the acetabulae. Radiographs at 47 months showed small and abnormal epiphyses throughout the legs, with mottling of the left proximal femoral metaphysis and right proximal femoral epiphysis. At 4 years of age, his height is 107 cm (50th percentile), his weight is 22.0 kg (90th-95th percentile), and his OFC is 48.5 cm (5th percentile). He has plagiocephaly, bilateral inner epicanthal folds, long eyelashes, a bulbous/bifid nose, posteriorly rotated/prominent ears, bilateral single palmar transverse creases, two sacral dimples, shawl scrotum and second toes that are longer than the great toes.

Patient 4 is a 16 ½-year-old female. She was born at term to a 31-year-old G2P1 mother via induced vaginal deliver following a pregnancy complicated by shingles at 6 months and gestational diabetes that was treated initially with diet control but required insulin in the last month of pregnancy. Birth weight was 2.75 kg (3rd-10th percentile). She had meconium aspiration at birth and required suction and bag valve mask resuscitation. As a complication of the resuscitation, she had bilateral chest tubes but did not require intubation and ventilation after resuscitation. At 18 months a murmur was noted, and subsequent evaluation discovered a PDA with elevated right ventricle and pulmonary artery pressures. She develops dyspnea only with moderate exertion. She has bilateral esotropia and has had one eye muscle surgery. She has prism glasses to maintain conjugate gaze. She was diagnosed with hearing loss at 15 years and uses hearing aids. She has short stature with a left leg 2 cm shorter than right. Lower extremity spasticity was first noted at a young age and has persisted unchanged. Her only other medical problems are migraine headaches.

She was diagnosed with visual-motor perceptual delay and has required assistance or special education throughout school, including occupational and physical therapies in the past; she is doing well in 9th grade at a career center at age 16. She has never had any behavior problems. At age 16 ½ years her height is 146 cm (<3rd percentile), weight is 48.6 kg (15th percentile) and head circumference is 52.5 cm (40th percentile). With the exception of some prominence of the forehead, she is not dysmorphic. Oral examination revealed dental crowding. She had small patellae with lateral subluxation. There was pes planus bilaterally. Cardiovascular exam revealed a right ventricular heave and loud P2 sound, no murmur, and clubbing and mild cyanosis of the distal hands and feet. The heel cords were tight bilaterally, with 3+/4 deep tendon reflexes in the legs and 3/4 in the arms. Skeletal survey at age 13 was notable for hypoplasia of the lateral tibial epiphyses, hypoplasia of both patellae, shallow acetabulae with some uncovering of the femoral heads, and on the right coxa vara, foreshortened femoral neck and coxa magna. She also had mild scoliosis with narrowing of the interpeduncle distances in the lumbar spine. MRI of the brain at age 10 was normal. The most recent echocardiogram at age 16 demonstrated right ventricular hypertrophy and dilation, and a PDA. The last cardiac catheterization was at age 14. She had the following pressures (typical systolic/diastolic pressures are indicated in parentheses): right ventricle 109/7 (25/7); pulmonary artery 110/67 (25/10); descending aorta 112/76 (100/70). These were unchanged from previous studies and are indicative of severe pulmonary hypertension.

Patient 5 is an 8-month-old female. This patient was the product of a multiple pregnancy, born at 32 weeks' gestation via elective cesarean section. Birth weight was 1.4 kg (10th-25th percentile), and Apgar scores were 7 and 8 at minutes 1 and 5, respectively. Birth length was approximately 39.5 cm (3rd-10th percentile), and head circumference was 27 cm (3rd-10th percentile). Genetics consult was requested by the NICU team because she was noted to have a 1 cm posterior sagittal cutis aplasia through the hairline. Neonatal genetics consult noted the following: small ears, bulbous nasal tip, hypoplastic nasal alae, recessed jaw, wide-spaced nipples, and long fingers and toes. An echocardiogram revealed a PDA, patent foramen ovale, and bicuspid aortic valve. Examination at 8 months of age was consistent with a typical neonatal course for prematurity. She has retinopathy of prematurity, bronchopulmonary dysplasia, and vesicoureteral reflux. She was referred to an early intervention program and physical therapy. The cutis aplasia has gradually scarred over. Overall, she is playful and interactive. Her weight is 5.4 kg, length is 60.8 cm, and head circumference is 40.3 cm (all at the 5th percentile when corrected for prematurity). She was also noted to have a box-shaped cranium, an open anterior fontanelle, prominent forehead, wide-set eyes, a small nose with fleshy nasal tip, microstomia, and slightly decreased central tone but with brisk deep-tendon reflexes.

Patient 6 is a 4-year-old female with language delays, behavioral abnormalities, mild dysmorphisms, and a history of failure to thrive. She was born to a 33-year-old G4P2→3 mother at term via spontaneous vaginal delivery following a pregnancy complicated by low placental insertion of the umbilical cord. Birth weight and length were at the 3rd percentile, and OFC was at the 10th percentile. Neonatal course included oxygen administration due to quick labor but was otherwise uncomplicated. She had multiple ear infections and PE tubes placed twice. She also has a history of failure to thrive. Developmentally, she rolled over at 3 months, sat at 6 months, crawled at 7 months, cruised at 10 months, and walked at 15 months. She had her first word at 12

months but did not use short phrases until 3 years. At 4 years, her height is at the 25th-50th percentile, weight is at the 10th percentile, and OFC is at the 10th percentile. Her receptive language is good, but expressive language is difficult to understand. Behaviorally, she has hyperactivity, separation anxiety, is very distractible, and can be aggressive and destructive. Dysmorphic features include mild frontal bossing, an unusual stellate pattern to the irises, rounded nasal tip, a wide gap between her front teeth, long fingers and long, overlapping toes. Strength, tone, and reflexes are all normal. Family history is significant for autism in a paternal first cousin.

Patient 7 is a 22-month-old female with an ASD, limitation of joint extension, scoliosis, microcephaly, developmental delays, and mild dysmorphisms. She was born to a 34-year-old G4P2204 mother at 36 weeks' gestation following a pregnancy complicated by gestational diabetes and a single umbilical artery. Birth weight was < 25th percentile. She required intubation and ventilatory support after birth. She had a pneumothorax and also ASD secundum with pulmonary hypertension noted. Knees and elbows were limited at 20 degrees of full extension. Hematochezia was also noted. Developmentally, she smiled at 2 months, sat at 9 months and walked at 20 months. She used a single word at 12 months but only three words at 22 months. She is receiving occupational and physical therapy. At 22 months, her height is at the 57th percentile, weight is at the 9th percentile, and OFC is <3rd percentile. Dysmorphic features include mild micrognathia, long eyelashes, protuberant ears, small mouth, long neck, somewhat narrow torso, clinodactyly of fifth fingers, long fingers and toes, overlapping toes 4-5, and pes planus. Extension of elbows and knees are improved, showing only mild limitation. Scoliosis is present. Neurological exam was grossly normal, with DTRs measuring 1-2+. Family history is significant for limited elbow mobility and scoliosis in the patient's father, language delays in the patient's sister, and paternal first cousins with retinitis pigmentosum and Usher syndrome.