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Supplemental Data

Variants in HNRNPH2 on the X Chromosome Are Associated with a Neurodevelopmental Disorder in Females

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Supplemental Information: Case Reports

Individual 1 is a 34-year-old female. Her prenatal history was unremarkable but she had a pneumothorax at birth requiring resuscitation. Her head circumference was 32 cm (10^{th} percentile) at birth but by 3 months of age the head circumference fell to the 2^{nd} percentile and remained less than 2^{nd} percentile, measuring 48 cm at 7 years. As an adult with short stature (154 cm, 5-10^{th} percentile) and weight at 56 kg (25-50^{th} percentile). Her development was delayed, as she did not walk until 5 years of age, and she began to speak at 7 years of age. She has autism and speaks in single words and short sentences. She is not toilet trained. She is intellectually disabled, and her intellectual quotient (IQ) is untestable. Her neurological examination is notable for truncal hypotonia, appendicular hypertonia and an abnormal gait. She had rare seizures, both generalized and absence, and co-morbid psychiatric diagnoses including attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder. She has stereotyped behaviors, as well as self-injurious behavior including hand biting. Dysmorphic features include hypotelorism, a wide mouth, full lips, high narrow nasal bridge and curly hair in this photograph taken at 5 years (Figure 2A) and 34 years of age (Figure 2 B,C). She has had orthopedic issues including lordosis, arachnodactyly and bilateral femoral osteotomies. A brain MRI was normal.

Individual 2 is an 8-year-old female with an unremarkable prenatal and perinatal course. Her birth parameters were within normal limits, including a birth weight of 2.6 kg and length 45 cm, both at the 10^{th} percentiles. At 2.5 and 6 years of age, her weight was at the 10^{th} and 48^{th} percentiles respectively. Her head circumference at birth was not available, but at 6.5 years of age was 51 cm at the 50^{th} percentile. Her development was delayed, as she was able to sit

independently at 18 months of age. Currently, she does not walk or talk. She is autistic, intellectually disabled (IQ not testable but estimated as severe) and has epilepsy, which is well controlled on oxcarbazepine. Her neurological examination is significant for hypotonia, weakness and ataxia. Dysmorphic features include bilateral epicanthal folds, midface hypoplasia and almond shaped eyes in a photograph taken at 8 years of age (Figure 2 G). She also has mild hearing loss. Brain MRI showed cerebellar vermis hypoplasia. (Figure 3).

Individual 3 is a 4-year-old female with normal birth and subsequent growth parameters. Her birth weight was 2.7 kg (10-25th percentile) and birth length was 46 cm (10th percentile). She has developmental delay and a history of developmental regression. Abnormal behaviors include hand flapping but Ωno formal diagnosis of ASD. Her neurologic exam is notable for hypotonia and dysmorphic features include small palpebral fissures.

Individual 4 is a 6-year-old female. At birth, growth parameters were within normal limits including both weight of 2.9 kg and length of 48 cm, both at the 25th percentile, and head circumference measured 34.5 cm at the 75th percentile. Her subsequent growth was at <3% for all growth parameters, with weight 11.8 kg, height 104 cm and head circumference 46.5 cm at 6 years of age, thereby with acquired microcephaly. She is developmentally delayed, with a history of developmental regression and an estimated mild degree of intellectual disability. She was using approximately 7 words at 3 years of age, but then stopped consistently using words after a seizure in the setting of a fever at 3.5 years of age. She now has only a few word approximations. Her walking was once steady and unassisted, but she now is less consistent preferring to hold a hand for support while walking. She had previously been finger feeding

independently at 2.5 years old, but now requires full assistance with feeding. She has an anxiety disorder, sensory issues, and has had one convulsion seizure in the setting of fever at 3.5 years of age and one breakthrough seizure at 4.5 years of age, currently on levetiracetam monotherapy. Her neurological exam is remarkable for hypotonia and poor coordination. Dysmorphic features include hypertelorism and fetal finger pads. She has had chronic difficulties with feeding, failure to thrive, and wears orthotics for talus valgus. She also has cardiac abnormalities including an atrial septal defect and mitral valve prolapse. Brain MRI was normal.

Individual 5 is a 21-year-old female. Prenatal care was complicated by advanced maternal age, preeclampsia and gestational diabetes but birth history and perinatal course were unremarkable. Her birth weight was 3.9 kg and length was 53 cm, both above the 90^{th} percentile, and birth head circumference was not available. At 19 years of age, her weight is 42.5 kg (< 5^{th} percentile), height is 159.8 cm (2^{nd} percentile) and head circumference is 55 cm (50^{th} percentile). She was globally developmentally delayed, with walking achieved at 3 years of age and speaking in sentences achieved at 8 years of age. She is intellectually disabled with a full scale IQ of 60; she is able to read and do some addition and subtraction, but functions at a level of about 6 years of age. Her neurological exam is remarkable for hypotonia. She has dysmorphic features including highly arched palate, mild micrognathia and elongated fingers observed at 21 years of age (Figure 2 D-F). She has been diagnosed with both autism and ADHD. She has severe skeletal abnormalities including thoracolumbar scoliosis, joint laxity, pectus carinatum, pes planus and stretchable skin. She also has mitral valve prolapse and mitral regurgitation, but her aorta is within normal limits.

Individual 6 is a 2-year-old female. Her head circumference measured 37 cm at 2 months of age (5^{th} - 10^{th} percentile) and then grew to 46 cm (10^{th} and 25^{th} percentiles) at 2 years of age. She has been developmentally delayed, sitting at 14 months of age and still unable to walk or say any discernible words, although she can babble. Her neurological exam is remarkable for hypotonia, as well as an early right hand preference and abnormal posturing of the left hand suggestive of dystonia. She has dyspraxia, causing difficulty with language and feeding, including handling secretions and solid foods. She has dysmorphic features including concave eyebrows and a fissure in the upper lip. A MRI performed at 4 months of age for hypotonia was suggestive of a distorted cerebellar vermis.

Supplemental Table 1.

Individual #	HNRNPH2 variant	Number of additional *de novo* variants	Non-HNRNPH2 *de novos*
1	c.C616T p.Arg206Trp	2	*HAUS6*:NM_001270890:c.A1943G:p.Q648R; *CHD6*:NM_032221:c.G4229A:p.R1410H
2	c.C616T p.Arg206Trp	2	*B3GNTL1*:NM_001009905:c.A430G:p.R144G
3	c.G617A p.Arg206Gln	3	*COL14A1*:NM_021110:c.A1706G:p.Y569C; *MYO7A*:NM_000260:c.A1373G:p.N458S; *TMEM10*:NM_198563:c.C740T:p.A247V
4	c.C626T p.Pro209Leu	0	none
5	c.C616T p.Arg206Trp	0	none
6	c.C616T p.Arg206Trp	0	none