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Supplemental information

Clustered mutations in the *GRIK2* kainate receptor subunit gene underlie diverse neurodevelopmental disorders

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SUPPLEMENTAL MATERIAL

Supplement Note: Case Reports

Proband A657T.2 was born following a normal pregnancy and delivery but had heavier weight and a taller height than his siblings. He suffered many ear, nose, and throat complications, including ear infections and upper airway infections, and was further diagnosed as having possible hepatomegaly. In addition to the *GRIK2* variant, WES revealed a variant in *RBFOX3*, c.346C>T (p.(Arg116Trp)). This variant has not been described in the literature, but truncating variants of unknown significance (VUS) were proposed to be causative for Childhood Epilepsy with Centrotemporal Spikes (previously rolandic epilepsy).[1] Because the proband in our study does not have epilepsy, this variant is not predicted to contribute to his phenotype.

Proband A657T.3 had irregular breathing while in the neonatal intensive care unit after birth. Ophthalmologic abnormalities were noted in the first week of life. He has had restless sleep with almost constant leg movements and difficulty in hearing in the presence of background noise. Choreiform movements and apraxia were also observed. Clinical notes include obesity and almond-shaped palpebral fissures. In addition to his *GRIK2* variant, a SNP array analysis revealed a 110 kbp deletion at 2q13 that includes the loss of *NPHP1.* An Epilepsy Gene Panel identified VUSs in *PIGQ* (c.157C>T, p.Arg53Trp) and *TSC1* (c.2885T>A, p.Ile962Asn). *PIGQ* is a component of the phosphatidylinositol glycan anchor biosynthetic pathway. Damaging variants cause early infantile epileptic encephalopathy,[2] which is not present in the proband in the current study. Tuberous Sclerosis Complex arising from dysfunction in the *TSC1* gene commonly results in hamartoma formation, a high incidence of early childhood epilepsy, and development of autism spectrum disorder.[3] The proband in our study did not present with these

conditions and therefore it is unlikely that the *TSC1* variant contributed to primary features of his developmental disorder.

Proband A657T.4 was born at term with respiratory distress and possible infection, for which he received continuous positive airway pressure therapy for one day and antibiotics for one week. During pregnancy, his mother used mesalazine to treat Crohn's disease, which was otherwise unremarkable apart from reduced fetal movements. He has no additional genetic variants of note.

Proband A657T.5 had a birthweight of 3.2 kg at 40 weeks. The pregnancy was relatively uneventful except for some significant bleeding at 6 weeks gestation. Birth was complicated by meconium aspiration. She experiences frequent urinary tract infections and constipation and is on Movicol to treat the latter. She has difficulties establishing sleep and takes melatonin for this issue with some success. Her height is below the 0.4th percentile with a Z score of -3.7. Her weight is between the 0.4th and 2nd percentile. Her head circumference is below the 0.4th percentile with a Z score of -2.9.

Proband A657T.6 is an adult of 37 years who was born with the umbilical cord around her neck. At age 33 years she was assessed as overweight (>+2.5 SD from average), has a short stature (<-3 SD from average), and has a high tonus. She has full nose with full columella and upper lip. Her skin is notable for having many naevi, and she exhibits hirsutism. No additional genetic variants were noted.

Probands T660K.1 and T660K.2 do not have any additional clinical information to relate supplementing that in the main text. Proband T660K.3 was born following a pregnancy complicated by diet-controlled gestational diabetes, resulting in early labor induction at 36

weeks. At 3 months of age she exhibited severe oropharyngeal dysphagia and was fed via nasogastric tubing.

Proband T660R.1 suffers from otitis media, gastroesophageal reflux disease, and bronchial hyper-reactivity. She is also hyperflexible and wore supramalleolar orthoses at ~18 months of age. No additional clinical information was reported for proband T660R.2.

No additional clinical information is available for proband I668T.1. This individual also harbors a *de novo* variant in *BMP4* at p.Met383Ile. Aberrant expression of *BMP4* or dysfunction of bone morphogenic protein 4 causes widespread disruptions in embryonic development,[4] which proband I668T.1 does not exhibit.

Supplemental References

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