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Mutation in PQBP1 is associated with Periventricular Heterotopia

Volney L. Sheen, MD, PhD^{1,+}, Alcy R. Torres, MD^{2,+}, Xiang Du, BS¹, Brenda Barry, MS CGC^{1,3}, Christopher A. Walsh, MD, PhD^{1,3}, and Virginia E. Kimonis, MD⁴

¹Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

²Department of Pediatrics, Child Neurology, The Children's Hospital, Boston, MA

³Howard Hughes Medical Institute, Boston, MA

⁴Department of Pediatrics, Division of Genetics, University of California at Irvine School of Medicine, Irvine, CA

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To the Editors

Periventricular heterotopia (PH) is characterized by the ectopic presence of neuronal nodules lining the lateral ventricles. Most genetic causes of PH are due to mutations in the X-linked *filaminA* (*FLNA*) gene [Fox et al., 1998]. Mutations in *FLNA* can also cause an otopalatodigital (OPD) spectrum disorder in the absence of PH [Robertson et al, 2003]. The OPD spectrum results in hearing loss, craniofacial dysmorphism (cleft palate, hypertelorism, prominent suprorbital ridges, ear abnormalities, broad nasal bridge with small mouth, and an anti-mongoloid slant), and skeletal abnormalities of the skull and limbs, leading to shortened digits, limbs and stature. We report a similar phenotype of PH with associated features of OPD, due to a mutation in the *polyglutamine tract binding protein 1* gene (*PQBP1*) on chr.Xp11.

The 20 year-old male proband was followed in the neurogenetics clinic given his early history of developmental delay and mental retardation (Figure). He had microcephaly (HC=55cm, 25th percentile) and short stature (height=164.3 cm, weight 54.3 kg, both below the 5th percentile). He exhibited dysmorphic craniofacial features including a broadened nose with narrow chin, freckled tongue, and low set, cupped ears. Examination of the chest, heart, spine, genitalia, and extremities showed no gross abnormalities except for a chronic cough and flat feet. General neurological evaluation demonstrated impaired hearing and mild cognitive impairment with difficulty reading and forgetfulness with staring spells. Further workup for the respiratory issues revealed numerous sub-centimeter pulmonary nodules on chest computed tomography. Exercise oximetry was normal. Histoplasmosis and coccidiomycosis titers, anti-neutrophil cytoplasmic antibody and angiotensin converting enzyme levels were unremarkable. In preparation for bronchoscopy, the patient had an elevated partial thromboplastin time (39.5), normal prothrombin time, negative lupus

*Correspondence should be addressed to Virginia Kimonis, MD, UC Irvine Medical Center, 101 The City Drive, ZC 4482, Orange, CA 92868, Phone: (714)-456-2942, Fax: (714)-456-5330, vkimonis@uci.edu.

⁺joint co-first authors

anticoagulant, and low-level positive anticardiolipin antibody. Factor XI was low (22%), with normal VIII and IX. Genetic evaluation excluded a peroxisomal disorder. Lactate, pyruvate, acyl carnitine, acyl glycine studies were normal. No mitochondrial mutations were detected. EEG showed no electrographic correlate to the staring episodes. MR imaging demonstrated nodular gray matter heterotopia along the trigones of the lateral ventricles.

The 23 year-old affected brother shared features similar to his sibling, including mental retardation, microcephaly, dysmorphic facies, hearing loss and short stature. In addition, he had a cleft palate, fourth finger camptodactyly, broad distal phalanges of the thumbs and toes, and a curved penis. The mother had a past medical history notable for sarcoidosis, diabetes, hypertension and an aortic aneurysm. MRI of the brain for both sibling and mother did not show PH.

The affected males and carrier mother were found to harbor an AGAG deletion at nucleotide 459–462 in exon four of the *PQBP1* gene. The resultant frameshift predicts early protein truncation, leading to a partially functional proline rich domain and complete absence of the nuclear localization signal and the cell membrane targeting C2 domains in *PQBP1*. Sequencing of the *FLNA* gene in this patient identified no exonic mutations. The mother had normal random X-inactivation studies. Sequencing of the *PQBP1* gene in an additional 41 sporadic cases of PH failed to demonstrate any mutations. The research studies were prospectively reviewed and approved by the IRB at Children's Hospital Boston and the Beth Israel Deaconess Medical Center.

Hearing loss, craniofacial features, and short stature with flattened fingers are consistent with an OPD spectrum disorder. The presence of PH in one male and X-linked inheritance pattern further raised the possibility that *FLNA* might be the causal gene in this pedigree. Screening from a non-syndromic X-linked mental retardation panel (14 genes in total, City of Hope), however, demonstrates that this same phenotype can be associated with mutations in *PQBP1*. Significant overlapping features between *PQBP1* mutations and OPD/PH might suggest that the causal genes may share similar functions.

Mutations in *PQBP1* (including the same deletion observed here) have been reported to cause Renpenning syndrome (RS) [Kalscheuer et al., 2003]. RS is characterized by mental retardation and microcephaly, lean body habitus, facial dysmorphism (including broadened nasal bridge, cupped ears, and triangular face) and short stature; each of these features is present in the current patient. Other more variable features reported with RS, including small testes and midline defects such as anal atresia or imperforate anus, cleft palate and/or uvula, iris coloboma and Tetralogy of Fallot [Kleefstra et al., 2004], were not observed in this case. Finally, this is the first patient of African American descent, as all the mutations for *PQBP1* gene have been reported in Caucasian families.

Aside from cognitive impairment, neurological manifestations in RS are not common and no prior reports have documented PH formation. Seizures, spasticity, blindness and hearing loss have been reported [Stevenson et al., 2005]. Brain imaging with computerized tomography has been described in several males but was either normal or only showed microcephaly, mild dilation of the lateral ventricles secondary to brain atrophy, calcification of the globus pallidus and periventricular frontal white matter. PH, however, can often be missed on computerized tomography and thus may not have been identified on initial characterization.

Genes associated with PH (*FLNA*, *ARFGEF2*, *Mekk4*, *Napa*) regulate vesicle trafficking [Pang et al., 2008]. *FLNA* directs the internalization of cell surface receptors. *ARFGEF2* assists in assembly of coat proteins necessary for vesicle transport. In mice, *mekk4* regulates FlnA expression, while *Napa* is required for vesicle fusion. Similarly, perturbations in vesicle transport are thought to contribute to the pathology of polyglutamine repeat diseases.

Recent studies have shown that individuals with mutations in the *LRP2* gene, like those with *PQBP1* mutations, variably develop PH suggesting incomplete penetrance [Kantarci et al, 2007]. That some affected individuals develop heterotopia while others do not suggests involvement of a stochastic process in causing this malformation. Alternatively, the single affected individual in this case report may be due to some other unidentified genetic cause or external environmental insult.

Collectively, these observations suggest that variable loss of cell adhesion from impaired vesicle trafficking disrupts the neuroepithelial lining or neuronal migration and underlies PH formation.

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Figure 1.

Features of periventricular heterotopia (PH) and otopalatodigital spectrum disorder (OPD) due to mutations in the the *polyglutamine tract binding protein 1* gene (*PQBPI*). (A) Schematic of pedigree. Black squares = affected males, Arrowhead= proband with PH, Circle with dot=obligate female carrier. (B) Axial and coronal MR images of proband II-1 demonstrate bilateral PH (arrows) along the trigones of the lateral ventricles. (C) Photomicrographs of proband shows the broadened nose and low set , cupped ears consistent with OPD. (D) Photomicrographs of flat feet and slightly broadened distal phalanges.