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GPSM2 Mutations in Chudley-McCullough Syndrome

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TO THE EDITOR

Chudley-McCullough syndrome (CMS; MIM 604213) was first described in a Canadian-Mennonite consanguineous family in which two siblings had hydrocephalus due to obstruction at the foramen of Monro and profound bilateral sensorineural deafness [Chudley et al., 1997]. Subsequent case reports further delineated the CMS as an autosomal recessive disorder characterized by congenital or early-onset sensorineural deafness and specific brain anomalies on MRI that include hydrocephalus, hypoplasia of the corpus callosum, enlarged cisterna magna with mild focal cerebellar dysplasia, and nodular heterotopia. Despite these striking brain imaging abnormalities, psychomotor development was generally normal [Alrashdi et al., 2011].

In 2003, we described a non-consanguineous American family of Western European descent in which 3 siblings had profound sensorineural deafness, hydrocephalus secondary to obstruction of the foramen of Monro, arachnoid cysts, partial agenesis of the corpus callosum, and cerebellar dysplasia which were consistent with the CMS [Welch et al., 2003].

The genetic cause of the CMS was unknown until biallelic *GPSM2* (MIM 613557; G protein signaling modulator 2) mutations were identified in a very recent study [Doherty et al., 2012]. We have now sequenced all exons and flanking sequences of *GPSM2* (NM_013296.4) on 1p13.1 in the family we reported in this journal [Welch et al., 2003] using previously reported primers and conditions [Yariz et al., 2011]. Results show compound heterozygous mutations, p.Arg498* and p.Gly249Glufs*32, in the affected members of the family which co-segregate in the family as an autosomal recessive trait (Fig. 1). These data independently confirm that *GPSM2* mutations cause CMS.

GPSM2 is essential for the maintenance of cell polarity and spindle orientation [Yasumi et al., 2005]. Both phenomena are crucial to establishing proper tissue architecture during development. The expression of *GPSM2* is detected at the apical surfaces of hair and supporting cells of the cochlea, utricle, saccule and cristae in the early stages of development of the mouse inner ear [Walsh et al., 2010]. Its expression in these tissues decreases in later stages of development suggesting that GPSM2 is critical for the early development of hearing.

It is of interest that truncating mutations in the same gene were reported to cause non-syndromic hearing loss in two consanguineous families from Palestine and Turkey [Walsh et al., 2010; Yariz et al., 2011]. Brain MRIs were not initially obtained in those families because there were no neurological abnormalities other than hearing loss. Subsequent evaluations with MRIs in the same families showed that affected individuals have brain abnormalities despite no clinical symptoms or abnormal findings [Doherty et al., 2012].

Identification of the responsible gene for CMS now makes molecular diagnosis possible in patients with hearing loss and brain anomalies. Routine brain MRIs during the etiological evaluation of individuals with hearing loss is not warranted until the frequency of *GPSM2* mutations is established. A low threshold for obtaining cranial imaging studies is recommended as patients with CMS may not present with obvious signs of brain dysfunction. Moreover, screening for *GPSM2* mutations may be a part of the standard genetic work-up for hearing loss especially in childhood. If *GPSM2* mutations are detected, a baseline MRI to assess the risk of hydrocephalus due to obstruction of the foramen of Monro and/or arachnoid cysts and regular follow ups are required.

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Figure 1.

Panel A: Abbreviated pedigree of the family. Solid symbols represent subjects with CMS. The genotype is indicated below each symbol. Genomic DNA of the second male with CMS was not available (NA) for sequencing. Panel B: *GPM2* mutations. Electropherograms of forward sequence of *GPM2*: unrelated control (top-left), c.742delC (p.G249EfsX32) in an affected subject (bottom-left), unrelated control (top-right), c.1492C>T (p.R498X) in an affected subject (bottom-right).