Research Letter

Blake’s Pouch Cyst in 13q Deletion Syndrome: ¹
Posterior Fossa Malformations May Occur Due to Disruption of Multiple Genes

Running Title: Blake’s Pouch Cyst with 13q Deletion

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To The Editor: Patients with distal 13q deletion display a wide phenotypic spectrum dependent on the size and location of the deletion. Clinical features may include facial dysmorphism, intellectual disability, growth retardation, microcephaly, distal limb defects, eye anomalies, and malformations of the cardiac, genitourinary and gastrointestinal organs [Kirchhoff et al., 2009]. Nervous system malformations are often described, including holoprosencephaly, neural tube defects, agenesis/dysgenesis of the corpus callosum, cortical dysplasia and posterior fossa malformations [McCormack et al., 2003; Ballarati et al., 2007]. The latter are most commonly reported as Dandy-Walker malformations (DWM) or cerebellar hypoplasia, and based on existing reports, a ~2 Mb critical deleted region at 13q32.2-13q32.3 has been defined [Ballarati et al., 2007; Kirchhoff et al., 2009; Mademont-Soler et al., 2010]. Deletion of two adjacent zinc finger protein genes in the region, ZIC2 (OMIM #603073) and ZIC5, has been proposed as the cause of posterior fossa malformations [Alanay et al., 2005; Ballarati et al., 2007; Mimaki et al., 2015]. Here, we present a patient with a posterior fossa malformation and 13q deletion that does not encompass the previously defined critical region, suggesting that posterior fossa malformations in distal 13q deletion syndrome can occur due to mechanisms other than haploinsufficiency of ZIC2 and ZIC5.

A 31-year-old woman had intellectual disability, microcephaly, von Willebrand disease and a single generalized tonic-clonic seizure at 28 years of age. She reported positive visual symptoms “like fireworks” and electroencephalography showed focal slowing and sharply contoured discharges in the posterior regions suggestive of occipital epilepsy; however, the patient’s symptoms did not improve with anti-epileptic medications. A thorough ophthalmologic examination and work up was normal.
She was born at term via emergency Caesarian section due to breach presentation. She did not feed well in the neonatal period, requiring nasogastric tube for 1-2 weeks. Developmental delay was noted from infancy; she did not walk until two years, and was never able to read or write. During childhood she had frequent respiratory infections. Family history was significant for her mother also having von Willebrand disease and bilateral cataracts.

Physical examination noted microcephaly with OFC 51.5cm (< 2nd centile) and minor dysmorphic facial features including a low-inserted nasal columella, prominent nasal bridge, sloping forehead and upslanted palpebral fissures (Figure 1A). Other physical features included mild shortening of the great toes, narrow hands and feet, sloping narrow shoulders, mild lymphedema of the lower limbs, pedal acrocyanosis, and mild acne. Echocardiogram and renal ultrasound did not reveal any malformations. Comparative genomic hybridization array identified an 11 Mb deletion at the terminal end of the long arm of chromosome 13 (chr13: 103,835,009-115,106,996) (hg 19) affecting an estimated 67 RefSeq genes. Conventional karyotype confirmed an abnormal female karyotype with a recombinant chromosome 13 and did not identify any ring chromosomes. Parental testing identified a maternal balanced pericentric inversion in chromosome 13 between bands p11.2 and q33.1, breakpoint regions consistent with the patient inheriting an unbalanced form of the chromosome 13 rearrangement from her mother. Carriers of such long pericentric inversion segments are generally thought to have a greater risk of producing a viable recombinant gamete [Gardner et al., 2011].

Brain magnetic resonance imaging revealed an enlarged 4th ventricle communicating with a cystic structure located inferior and slightly anterior to the cerebellum (Figure 1B-1D). Vermis and cerebellar hemispheres appeared otherwise normal and the posterior fossa was not enlarged; thus, the malformation was diagnosed as Blake’s pouch cyst (BPC).
Our patient had classic features associated with distal 13q deletion, including microcephaly, intellectual disability, dysmorphic facial features, and posterior fossa malformation. The latter occurred despite the patient’s deletion not encompassing ZIC2, ZIC5, or any other part of the previously proposed 13q critical region for posterior fossa malformations. This finding suggests that not all posterior fossa malformations in 13q deletion syndrome are due to haploinsufficiency of ZIC2 and ZIC5.

Blake’s pouch is a normal embryonic structure formed from the posterior membranous area (PMA) of the roof of the 4th ventricle. By 26 weeks gestation, Blake’s pouch is normally communicating with the subarachnoid space, forming the foramen of Magendie [Azab et al., 2014]. If the latter fails to perforate, a BPC occurs [Tortori-Donati et al., 1996]. The cyst usually remains at least partially attached to the roof of the 4th ventricle, and may result in tetra-ventricular hydrocephalus if obstructive. As long as the anterior membranous area (AMA) is normal, the cerebellar vermis and hemispheres develop appropriately, without maturational arrest of the rhombic lip of His.

The frequency of BPC occurrence is unclear, particularly because some consider it part of the DWM spectrum; however, there is a clear embryologic distinction [Azab et al., 2014]. True DWM involves abnormal AMA development and should include at least enlarged posterior fossa with elevated torcular, vermal hypogenesis/agenesis, and cystic dilation of the 4th ventricle [Barkovich, 2005]. The term “Dandy-Walker variant” is sometimes used to describe posterior fossa malformations that include some, but not all, of these elements; but the term variant is now avoided by most neuroradiologists and neuropathologists because of its ambiguity, lacking precise neuroanatomical criteria. However, other distinct posterior fossa malformations are well-classified, including mega cisterna magna (enlarged posterior fossa due to enlarged cisterna
magna, but normally developed cerebellum), cerebellar hypoplasia (hypogenesia of cerebellum with normally sized posterior fossa and 4th ventricle), and BPC [Barkovich, 2005].

Though distal 13q deletion syndrome is often reported with “DWM”, these reports rarely give radiologic detail. Although this is the first patient with BPC to our knowledge, previous reports may have been misclassified and we suspect the spectrum of posterior fossa malformations that occur is broader than simply DWM and cerebellar hypoplasia. Other brain malformations sometimes co-occur with posterior fossa malformation in distal 13q deletion syndrome, including holoprosencephaly and corpus callosum dysgenesis/agenesis [McCormack et al., 2003; Ballarati et al., 2007; Mimaki et al., 2015].

Figure 2 summarizes the relevant previously published patients that led to definition of the critical region for posterior fossa malformation that includes ZIC2 and ZIC5. We have added our patient and two other relevant reports: a fetus with DWM based on 24-week ultrasound, who carried a 13q33.3-ter deletion as well as 7p triploidy [Chen et al., 2010]; and a patient with vermal agenesis and a 13q33-ter deletion [Bagherizadeh et al., 2014]. In both cases, the reported deletions lie outside the previously defined critical deletion region.

With respect to other candidate genes in the 13q terminal region, mutations in COL4A1 and COL4A2 (OMIM 120130 and 120090; alpha-1 and alpha-2 chains of collagen of basement membrane) cause brain malformation, in addition to multiple other abnormalities, in a rat model; though human mutations have thus far been primarily associated with hereditary angiopathy [Kuo et al., 2014]. There are multiple other genes in this region, however, about which relatively little is known, which might also contribute to nervous system maldevelopment. Another possibility is that deletion of 13q terminal enhancer elements such as hs759 (expression pattern
in hindbrain and neural tube) affects the expression of ZIC2, ZIC5 or other genes nearby, but not within, the deleted region [Visel et al., 2007].

Taken together, these data suggest that there is no single critical region for posterior fossa malformations seen in patients with distal 13q deletion. Haploinsufficiency of one or more genes involved in brain development can lead to a spectrum of phenotypes, including disorders of hindbrain formation (including AMA and/or PMA development), forebrain cleavage and neuroblast migration. ZIC2 and ZIC5 appear to be affected in the majority of cases, and their role is supported by the observations that human ZIC2 mutations cause holoprosencephaly [Brown et al., 1998] and that during murine embryogenesis Zic2 has a dorso-ventral gradient of expression, and plays a key role in hindbrain morphogenesis [Elms et al., 2003; Houtmeyers et al., 2013]. However, haploinsufficiency of one or more other genes in the distal 13q region is clearly sufficient to produce brain malformations in this syndrome. Identifying those genes and clarifying their roles is an important avenue for future research.

References


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Figure Legends

Figure 1 – Clinical Features: (A) Photograph of the patient at 31 years of age. Multiple dysmorphic facial features are seen, including low-inserted nasal columella, prominent nasal bridge, sloping forehead and upslanted palpebral fissures. (B-D) Brain magnetic resonance imaging demonstrates Blake’s pouch cyst. Sagittal T1 (B) shows enlarged 4th ventricle and
cerebrospinal fluid isointense cystic structure inferior and anterior to a normal-appearing cerebellar vermis. Midline structures are otherwise normal. Normal appearing cerebellar hemispheres are seen on axial and coronal T1 views (C, D).

Figure 2 – Distal 13q deletions reported with posterior fossa malformations: Reported malformations included Dandy-Walker malformation (Ballarati patients 8, 11 and 12; Kirchoff patients 12 and 13; Mademont-Soler; and Chen), cerebellar hypoplasia (Ballarati patient 1), cerebellar vermal agenesis (Bagherizadeh) and Blake’s pouch cyst (present patient). In Ballarati patient 12, Dandy-Walker malformation co-occurred with corpus callosum agenesis. The previously proposed critical deletion region at 13q32.2-q32.3 is shown, which is unaffected by the deletion in the present patient, as well as those reported by Chen et al and Bagherizadeh et al. Figure includes a screenshot from UCSC genome browser (http://genome.ucsc.edu).
Figure 2
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