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Research Letter

Deletion of Chromosome 1p36 Is Associated With Periventricular Nodular Heterotopia

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To the Editor:

Periventricular heterotopia (PH) is a malformation of cortical development characterized by the ectopic localization of neuronal nodules along the lateral ventricle. Mutations in X-linked filamin A gene are the most common cause of PH, although a rarer autosomal recessive form of PH with microcephaly due to *ARFGEF2* mutations has been described [Sheen et al., 2001]. Affected individuals generally are of normal intelligence and most often present with adolescent onset seizures.

The 1p36 deletion syndrome is associated with multiple congenital anomalies caused by haploinsufficiency of numerous contiguous genes. This deletion produces specific physical characteristics such as distinctive facial anomalies (pointed chin, flat nose, low set ears) and cardiovascular malformations (atrial septal defect, patent ductus arteriosus, tetralogy of Fallot). Central nervous system (CNS) defects include mental retardation, cranial nerve abnormalities (VI nerve palsies, optic disc anomalies, sensorineural hearing loss), neonatal hypotonia, cortical dysplasia, and seizures [Heilstedt et al., 2003; Kurosawa et al., 2005; Battaglia, 2005]. A reduction in the KCNAB2 potassium channel beta-subunit has been hypothesized to be responsible for the seizures [Hirose et al., 2002]. Affected individuals can display outbursts, tendencies to strike people, and self-injurious behavior, as well as autistic-like behaviors [Slavotinek et al., 1999].

Previous neuroimaging and postmortem studies on individuals with 1p36 deletions have revealed mild CNS structural abnormalities. Deletions involving the most distal p-terminus (*D1S508*, 1p36.23->1pter) have only been associated with microcephaly, mild ventricular asymmetry, and ventricular enlargement [Kurosawa et al., 2005; Slavotinek et al., 1999]. An interstitial deletion (1p36.1->1p36.2) was suggested as causal for the development of neuroblastoma in a single case report [Keppler-Noreuil et al., 1995]. Finally, a series of three patients harboring 1p36.22->1pter deletions was reported to have hydrocephalus by cranial ultrasound but no mention of PH [Keppler-Noreuil et al., 1995]. To date, there have been no reported associations of PH with chromosome 1p36 deletions.

Here, we describe the first case describing PH in an individual with a 1p36.22-> 1pter deletion.

This study was approved by the IRB at the respective institutions in accordance with NIH. Informed consent was obtained from the participating subject's parents. Genomic DNA was extracted from peripheral whole blood lymphocytes using standard blood DNA isolation techniques (Qiagen Inc., Valencia, CA).

Metaphase chromosome analysis of lymphocytes was performed according to standard protocols. Initial routine karyotyping on the child was read as normal, although deletions on 1p36 are commonly missed due to the Giemsa-negative/poor staining in this region. Given the numerous clinical features seen in this subject, FISH analysis utilizing 41 subtelomere probes was performed (Genzyme laboratories (Hawthorne, NY), using Vysis probes (Downers Grove, IL). Results were confirmed with a chromosome 1p subtelomere probe (1pSUBTEL; Vysis) and the D1Z2 midi-satellite probe with repeats in band 1p36 (Oncor). The D1Z2 probe is used for confirmation of a common deletion interval (1p36.3). A chromosome 1 centromere probe (D1Z5; Vysis)

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served as control. Ten metaphase cells were examined for each probe combination.

For exonic sequencing, PCR was performed on genomic DNA using previously published primers for the exons of *FLNA* [Sheen et al., 2001] , the gene responsible for X-linked dominant PH. Greater than 95% of the *FLNA* gene was sequenced. The entire 48 coding exons for the *FLNA* gene were sequenced except for exon 1. Only partial sequence was obtained from exon 2 (75%), and exons 22, 27, 47, and 48 (greater than 50%). All sequenced exons and intron/exon boundaries were compared against the human sequence of *FLNA* (www.genome.ucsc.edu). Sequencing was not performed on the *ARFGEF2* gene given the lack of microcephaly in the affected patient.

For microsatellite analysis, the deletion region (chromosome 1p36.22-1pter) was screened using human MapPairs:*D1S468, D1S2660, D1S214, D1S508, D1S1612, D1S1160, and D1S450*. PCR products using these primers were analyzed on an ABI Prism 3100 and analysis of microsatellite markers was performed using standard software (Genotyper Analysis 3.7, Applied Biosystems, Foster City, CA).

The patient is a 3-year-old female, born to unrelated healthy parents, who was noted to have developmental delay, Duane syndrome anomaly, and hearing loss during her first year of life. Genetic testing at that time showed a de novo chromosome 1p terminal deletion. At 13 months of age, she had a head circumference of 44.5 cm (20th centile), weight of 7.27 kg (<5th centile), and length of 73 cm (25th to 50th centile). On examination at 3 years of age, she has no neurocutaneous stigmata. She has mild dysmorphic features including epicanthal folds bilaterally, posteriorly rotated and slightly low set ears, a broad nasal bridge, thin upper lip, and anteverted nares. Her third digit overrides the second digit in both feet and she has a short fifth digit in the right hand. She has scoliosis. Neurologically, she laughs spontaneously and makes guttural utterances. She visually tracks. She has limited abduction of the left eye. She has good strength but remains hypotonic. Her reflexes are symmetric with no Babinski. She reaches out for objects without ataxia. She only recently is able to sit independently and bear some weight on her feet and stand with help.

MR imaging of the brain revealed several nodular gray matter heterotopia along the wall of the left lateral ventricle (Fig. 1A). The rostrum of the corpus callosum was truncated, the ventricles were slightly enlarged, and patchy areas of hyperintensity were seen in the periventricular and subcortical white matter bilaterally consistent with delayed myelination. Single voxel spectroscopy performed in the left basal ganglia was normal. MR of the spine revealed a T12 to T6 syrinx. CSF neurotransmitters and TSH were normal.

FISH analysis using subtelomere probes detected a deletion of the terminal short arm region of one chromosome 1 (Fig. 1B,C). Hybridization using chromosome 1p subtelomere probe (approximately 200 kB from the telomeric end) and the probe for D1Z2 midi-satellite repeats (approximately 2.3 Mb from the telomeric end) confirmed the terminal deletion and demonstrated that the deletion breakpoint is proximal to this region. For mapping of the minimal deletion interval, a loss of heterozygosity (LOH) was assumed to provide evidence for a possible region of deletion on the chromosome. LOH was observed between microsatellite markers *D1S468* and *D1S450*, indicating at most a 9.6 Mb deletion region on 1p36.22–1pter. The deletion was de novo and not present in either parent.

Mutations in the X-linked filamin A (*FLNA*) gene can cause PH. Sequencing of the *FLNA* gene in this patient, however, did not reveal any alterations in the coding region.

The mapping in this particular patient demonstrates a maximal 9.6 Mb deletion extending from 1p36.22 to the 1p-terminus. Most of the documented 1p36 deletions appear to encompass a 7.4 Mb deletion region (at marker *D1S508*), leaving some 13 genes in the non-overlapping 2.2 Mb region that extends centromeric to the typical 1p36 deletion region. No heterotopia have been reported on radiographic imaging in the typical 7.4 Mb 1p36 deletion region [Slavotinek et al., 1999; Kurosawa et al., 2005]. Several patients have been described as having deletions that extended beyond this region, but no formal imaging was available for these patients to confirm or exclude any radiographic evidence of PH (personal communications, Dr. Keppler-Noreuil) [Keppler-Noreuil et al., 1995].

Several potential candidate genes in this extended 1p36 deletion region (*D1S508-D1S450*) may give rise to PH. The calmodulin-binding transcription activator (*CAMTA1*) has been implicated as a candidate tumor suppressor gene, giving rise to neuroblastoma [Katoh, 2003]. Increased proliferation of neural progenitors along the ventricular lining could potentially lead to PH. Vesicle-associated membrane proteins such as VAMP3 represent one of the main components of a protein complex involved in the docking and/or fusion of synaptic vesicles with the presynaptic membrane [Polgar et al., 2002]. Recent findings demonstrate that alterations in vesicle transport [Lu and Sheen, 2005] can cause PH and suggest that VAMP3 may similarly contribute to PH formation. Alternatively, the mitogen-inducible gene, *MIG6*, is a cytoplasmic protein whose expression is upregulated with cell growth and recent studies have shown an interaction between a highly homologous MIG3 protein to filaminA [Zhang et al., 2005]. Several other genes, while expressed in the CNS, are thought to have other unrelated functions (*PER3* in circadian rhythm

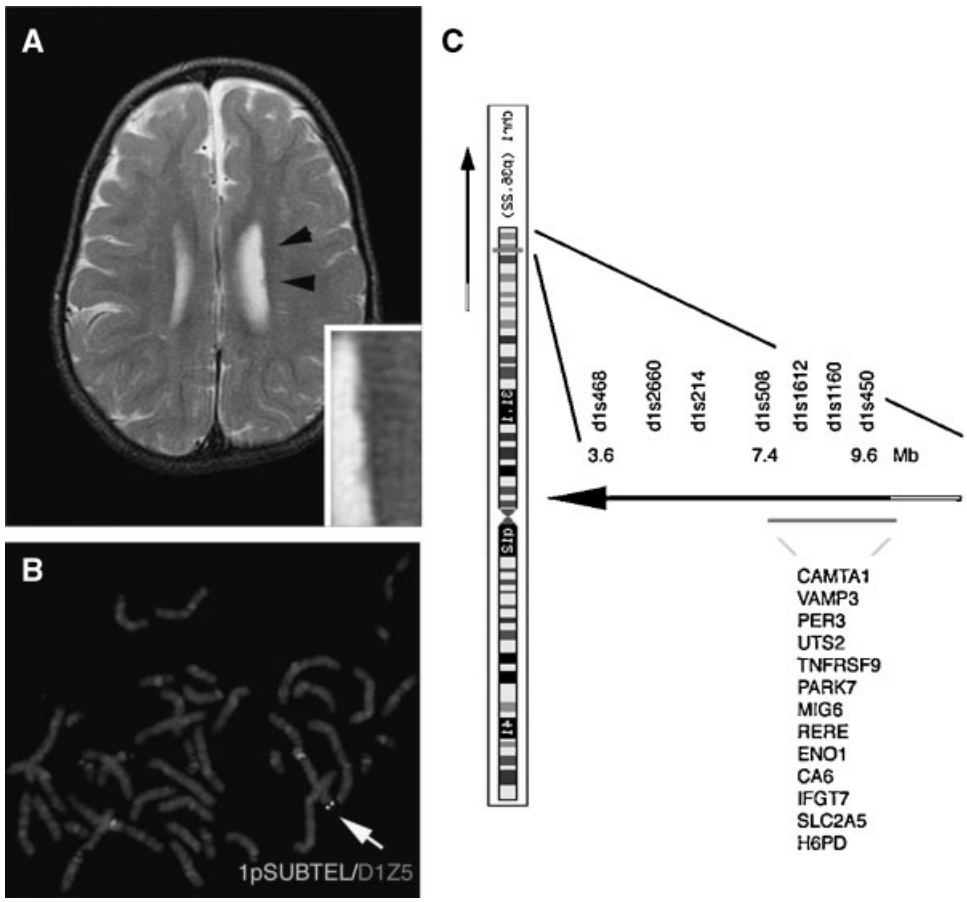

FIG. 1. Periventricular nodular heterotopia (PH) and 1p36 deletion. **A**: Magnetic resonance (MR) images of an individual with PH and harboring a 1p36 deletion. The T2-weighted axial MR image of this individual show bilateral nodular periventricular heterotopias in the anterior aspects of the left lateral ventricles (black arrowheads). The rostrum of the corpus callosum was also truncated, the ventricles were slightly enlarged, and patchy areas of hyperintensity were seen in the periventricular and subcortical white matter bilaterally consistent with delayed myelination. A higher magnification of the left wall of the lateral ventricle (shown in the lower right corner) further illustrates two periventricular heterotopia. **B**: Fluorescence in situ hybridization (FISH) using the 1pSUBTEL probe (green) demonstrates the deletion of one copy of the subtelomeric end along chromosome 1p36 (as indicated by the white arrowhead) in a metaphase spread. The D1Z5 control probe (red) shows the appropriate presence of two copies. **C**: Schematic diagram of chromosome 1 demonstrating the banding pattern for this chromosome. The solid black arrow on the right indicates the 9.6 Mb region on chromosome 1p36.22 to 1pter, containing six microsatellite markers (*D1S1160* to *D1S468*) that demonstrated a loss of heterogeneity (LOH) flanked by the nearest centromeric marker (*D11450*) that did not have LOH. The smaller solid gray bar below represents the 2.2 Mb region that was outside the region, radiographically shown not to have PH. This region is a presumptive region containing a potential gene responsible for PH in our patient. The potential candidate genes for the PH are listed below.

maintenance, *UT2* in brain vasculature, *PARK7* in early onset Parkinson disease). The remainder of the candidate genes do not appear to be expressed in the CNS.

Other potential genetic mechanisms could explain the presence of PH in this case. The phenotype might be due to a gene in the commonly deleted region, which does not give rise to PH in some patients due to variable expressivity and reduced penetrance. That said, a review of the literature reported some 29 cases of 1p36 deletions in individual who have either undergone intracranial imaging by CT, MRI, or ultrasound or postmortem examination [summarized in Keppler-Noreuil et al., 1995; Slavotinek et al., 1999; Kurosawa et al., 2005]. None of these reported findings of PH with the only common findings noted to be ventriculomegaly and cortical atrophy. Alternatively, there may also be another undetected genetic mutation in the patient not on 1p36 that could give rise to PH. Finally, a second undetected mutation may actually exist on the other allele either within the common 1p36 deletion region or the extended region noted in this patient.

Several studies suggest that autosomal dominant mutations in various genes likely lead to PH [Lu and Sheen, 2005]. While the X-linked dominant PH due to mutations in the filamin A (*FLNA*) gene are the most common cause of this cortical malformation, *FLNA* mutations are detected in less than 20% of spontaneous (non-familial) PH cases [Sheen et al., 2001]. An autosomal dominant form of PH has been suggested to localize to chromosomes 5p15 and 7q11 (the William syndrome critical region) [Sheen et al., 2003; Ferland et al., 2006]. Another pedigree with PH

and hydrocephalus, which did not link to the FLNA locus, was also suggestive of a dominant PH disorder [Sheen et al., 2004].

These studies suggest that another gene causal for an autosomal dominant form of PH may lie within the 1p36 deletion region, and more specifically between the 2.2 Mb region spanning *D1S508* and *D1S1450*. Additional cases involving 1p36 deletions in this region will be useful in confirming this association with PH and potentially defining a new gene causal for this cortical malformation.

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