

Clinical Report

Periventricular Nodular Heterotopia and Williams Syndrome

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We report here on the first case of a child with bilateral periventricular nodular heterotopia (PNH) and Williams syndrome. Fluorescent in situ hybridization (FISH) analyses demonstrated a deletion of the *elastin* gene in the Williams syndrome critical region (WSCR). Further mapping by loss of heterozygosity analysis both by microsatellite marker and SNP profiling demonstrated a 1.5 Mb deletion beyond the telomeric end of the typical WSCR. No mutations were

identified in the X-linked *filamin-A* gene (the most common cause of PNH). These findings suggest another dominant PNH disorder along chromosome 7q11.23.

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Key words: periventricular nodular heterotopia; Williams syndrome; cortical malformation

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INTRODUCTION

Periventricular nodular heterotopia (PNH) is a neurodevelopmental disorder of neuronal migration. PNH is characterized by the ectopic presence of neuronal nodules lining the lateral ventricles underlying a normal cerebral cortex [Smith et al., 1988; Kamuro and Tenokuchi, 1993]. Two genes were identified that can cause PNH. Mutations in the X-linked gene *filamin-A* (*FLNA*) result in PNH, but also can give rise to aortic aneurysms, blood abnormalities, and the heritable connective tissue disorder called Ehlers–Danlos syndrome [Sheen et al., 2001, 2005; Gomez-Garre et al., 2006]. In addition, mutations in *FLNA* also can give rise to OPD/Frontotaphyseal spectrum of conditions [Robertson et al., 2003; Zenker et al., 2004; Hehr et al., 2005]. Homozygous mutations in the *ADP-Ribosylation Factor Guanine Nucleotide Exchange Factor 2* gene (*ARFGEF2*) also result in a much rarer form of PNH in addition to microcephaly [Sheen et al., 2004]. These studies not only demonstrate genes directly responsible for PNH formation in the brain, but also point

out that mutations in these two genes can lead to other phenotypes besides PNH.

Williams syndrome is a contiguous gene syndrome caused by a de novo deletion of approximately 20 genes on chromosome 7q [Korenberg et al., 2000]. However, the deletion sizes can vary from just under 1 Mb up to approximately 4 Mb with an average size of 1.5–2.0 Mb [Ewart et al., 1993; Urban et al., 1996; Meng et al., 1998; Wu et al., 1998; Bayes et al., 2003]. From these studies, submicroscopic deletions of 7q11.22, which include the *elastin* gene, have been

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identified in both sporadic and familial cases of Williams syndrome. There have been very few cases of Williams syndrome reported that extend telomerically beyond the Williams syndrome critical region (WSCR) [Wu et al., 1999; Stock et al., 2003].

These deletions on chromosome 7q11.22-23 produce specific physical characteristics that are hallmarks of Williams syndrome such as distinctive facial anomalies, connective tissue abnormalities, vascular malformations, and central nervous system involvement [Morris et al., 1988; Ewart et al., 1993; Bellugi et al., 1999]. Cognitively, individuals with Williams syndrome have increased verbal expression, emotionality, face processing and recognition, and musical abilities, while concomitantly having decreased spatial and visual-motor abilities [Morris et al., 1988; Bellugi et al., 1999].

Previous neuroimaging and postmortem studies of individuals with Williams syndrome have revealed reduced amygdala activation when exposed to threatening faces with increased activation for threatening scenes, decreases in brain volume (sparing cerebellum), decreases in volume and gray matter density in regions of the brain associated with spatial and visual-motor processing with concomitant increases in brain regions associated with face processing and emotion, asymmetric distribution of occipital lobe volume, increased cortical gyrification (right parietal, right occipital, and left frontal regions), and thickness (right perisylvian cortex), and in some instances gyral abnormalities (i.e., polymicrogyria) [Galaburda and Bellugi, 2000; Reiss et al., 2000, 2004; Schmitt et al., 2002; Meyer-Lindenberg et al., 2005; Thompson et al., 2005]. However, to date, there have been no reports of PNH.

Here, we report on the first case describing the radiographic findings of PNH in an individual with Williams syndrome with a deletion of chromosome 7q11.23 that extends beyond the telomeric end of the typical WSCR.

MATERIALS AND METHODS

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

Fluorescent In Situ Hybridization (FISH) Analysis

Metaphase chromosome analysis of lymphocytes was performed according to standard protocols [Brown and Lawce, 1997]. DNA probes for FISH analysis of the Williams syndrome locus (*elastin*

gene) and control region probes (*D7S486* and *D7S522*) were obtained from Vysis (Downers Grove, IL). FISH was performed according to the procedure recommended by the manufacturer.

Sequencing of the *FLNA* Gene

Given that mutations in *FLNA* can cause PNH, we sequenced the coding region (exons) and intron/exon boundaries for this gene. PCR was performed on genomic DNA using previously published primers for the exons of *FLNA* [Sheen et al., 2001]. Greater than 95% of the *FLNA* gene was sequenced. All PCR products were purified using the AMPure system according to the manufacturer's instructions (Agencourt, Beverly, MA) and sequenced by fluorescent dye-terminator chemistry. All sequenced exons and intron/exon boundaries were compared against the human sequence of *FLNA* (www.genome.ucsc.edu).

Mutations in *ARFGEF2* also are known to cause a much rarer form of PNH with severe microcephaly [Sheen et al., 2004]. Clinically, patients are severely affected with profound developmental delay, spastic quadriparesis, and early onset refractory infantile spasms with hypsarrhythmia. Moreover, the MRI shows not only PNH but significant microcephaly, ventriculomegaly, and periventricular white matter changes consistent with delayed myelination. The patient in this case report did not clinically fit the same severity seen in patients with *ARFGEF2* mutations. Moreover, the patient did not fit this disorder radiographically. Aside from the PNH, the MRI did not show the characteristic white matter changes, microcephaly and ventriculomegaly. Given the extremely rare frequency of PNH with microcephaly due to *ARFGEF2* mutations (only described in two families thus far), as well as the inconsistencies in the current case with respect to both radiographic and clinical features associated with this disorder, sequencing was not performed on this gene for this individual.

Microsatellite Analysis of Chromosome 7q11.22-7q11.23

The chromosomal region containing the deletion was screened using the following fluorescently labeled human MapPairs: *D7S502*, *D7S2476*, *D7S1870*, *D7S669*, *D7S630*, and *D7S657*. PCR products using these primers were analyzed on an ABI Prism 3100. Allele sizes were determined using Genotyper 3.7 (Applied Biosystems, Foster City, CA).

100K SNP Chip Analysis of Chromosome 7q11.22-7q11.23

The chromosomal region containing the deletion was further finely mapped using the GeneChip

Mapping 100K set from Affymetrix (GeneChip Human Mapping 50K Arrays (Xba 240 and Hind 240)). All procedures and methods were according to manufacturer's instructions. Analysis of the DNA-chip data was by dChip software [Li and Wong, 2001]. In brief, genomic DNA isolated from the individual is processed with the control genomic DNA provided in the GeneChip Mapping 50K Xba and Hind Assay kits. The protocol uses 250 ng of genomic DNA per array and will generate SNP genotypes for more than 50K SNPs for each array of a two array set. The assay begins with digestion of the genomic DNA with the XbaI or Hind III restriction enzyme and then ligating primer sequences onto the DNA fragments. PCR is then performed on the fragments using a procedure optimized for fragments of a specified size range. Amplification of the products is confirmed by gel electrophoresis (2% TBE agarose gel). The PCR products (amplicons) are fragmented, end-labeled, and hybridized to a GeneChip array. Following washing and staining, the arrays are scanned using the GeneChip scanner 3000.

Given that the parental DNA was not available to conclusively show loss of heterozygosity (LOH), changes in DNA copy number were determined in the proband using the Affymetrix Chromosome Copy Number Analysis Tool (CNAT). The program enables the identification of genome-wide chromosomal gains and losses using the GeneChip Mapping Arrays and Whole Genome Sampling Assay (WGSA) [Huang et al., 2004]. The boundaries for the Williams syndrome region were first determined by examining the areas determined to be either homozygous or heterozygous on the SNP array. The intensity of the perfect match and mismatch probes were then evaluated within this interval region to assess allelic copy number.

RESULTS

Clinical Report

The patient is a 6-year-old female born to unrelated healthy parents after an uneventful pregnancy. At 3 weeks of age, she developed a severe upper respiratory infection and was noted to have a cardiac murmur, consistent with pulmonary artery and mild aortic stenoses. Based on clinical findings and confirmed by genetic testing, the patient was diagnosed with Williams syndrome.

On serial neurological examinations, she has never spoken any words, and her vocalizations consist largely of grunting and cooing. She cannot blow out words, drools, and has difficulty with feeding. Auditory testing failed to detect hearing impairment and the patient can comprehend verbal commands. She has limited abduction of the left eye consistent with Duane syndrome. Adduction of the left eye was normal with full extra-ocular movements on the

right. Facial movements were symmetrical, but notable for hypotonia. Early motor milestones included pulling to stand at 1 year, cruising at 2.5 years, and walking independently at 3 years. Reflexes were brisk and clonus was elicited at both ankles. No dysmetria was appreciated on reaching for objects. Gait was narrow-based and stable.

Due to the presence of this constellation of clinical signs which were not entirely consistent with the Williams syndrome phenotype, MR imaging of the brain was conducted. MR imaging revealed bilateral, up to 1 cm in diameter nodular gray matter heterotopia along the frontal horns of the lateral ventricles (Fig. 1). In this case, as in many other instances of PNH, the heterotopic nodules are contiguous and are often not able to be discerned separately and look blended. The overlying cerebral cortical gray matter appeared normal. MR imaging also demonstrated a Chiari I malformation without significant compression of the brainstem. No other gross structural abnormalities were observed. An overnight EEG showed no evidence of any electrical seizure discharge.

Routine karyotyping in this patient initially was interpreted as normal. Upon further examination, the Geimsa-negative band corresponding to chromosome 7q11.2 (the Williams syndrome locus) on one chromosomal copy appears smaller than in the other chromosome 7 from this patient (Fig. 2). This suggests a deletion within this region. To verify the karyotyping result, we performed FISH analysis using locus specific DNA probes for the WSCR and detected a deletion of the *elastin* gene on one copy of chromosome 7 (Fig. 2).

Mapping of this region on chromosome 7q11.22-7q11.23 was performed using polymorphic microsatellite markers. For mapping of the minimal deletion interval, a LOH was assumed to provide evidence for a possible region of deletion on the chromosome. LOH was observed between microsatellite markers *D7S502* and *D7S669*, indicating at most an 11 Mb deletion region on 7q11.23 (Fig. 2).

To further refine this region, LOH was evaluated within the region using single nucleotide polymorphism (SNP) analyses on the Affymetrix GeneChip arrays. The deletion region spanned a 5 Mb interval on 7q11.23 (Fig. 2). This region overlaps significantly with the published WSCR, but also extends 1.5 Mb beyond the telomeric end of the typical WSCR (Fig. 2). The non-overlapping region contains approximately 16 genes not in the WSCR (Fig. 2), one of which may be responsible for PNH (denoted in Fig. 2—open box with PNH).

Mutations in the X-linked *filamin-A* (*FLNA*) gene can cause PNH [Fox et al., 1998; Sheen et al., 2001]. Sequencing of greater than 95% of the *FLNA* gene in this patient, however, did not reveal any alterations in the coding region. *ARFGF2* is the other known gene associated with PNH, but also includes

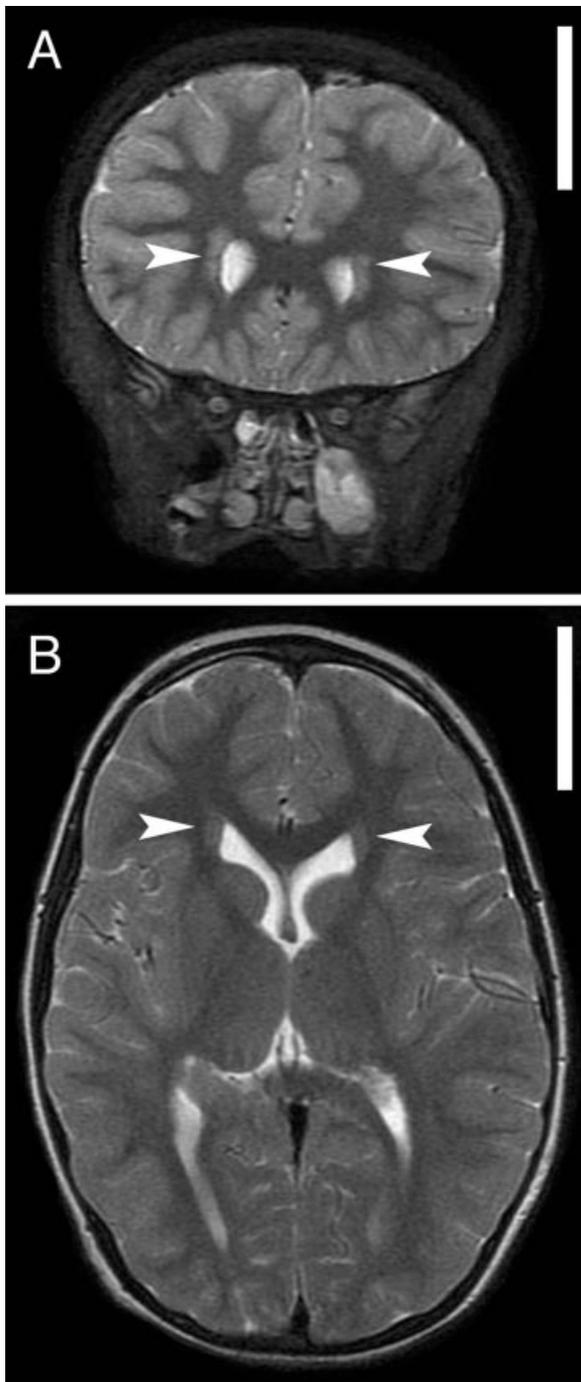


FIG. 1. Magnetic resonance (MR) images of an individual with periventricular nodular heterotopia (PNH) and Williams syndrome. MR images are presented as a FSEIR-weighted coronal image ((A) at the level of the anterior portion of the lateral ventricle and frontal cortex) and as a T2-weighted axial image ((B) at the level of the caudate nucleus). The MR images of this individual were normal except for the presence of contiguous bilateral nodular periventricular heterotopias in the anterior aspects of the lateral ventricles (white arrowheads). Scale bars are 5 cm.

microcephaly as part of the phenotype [Sheen et al., 2004]. Since our subject was not microcephalic, we did not conduct sequencing and mutational analysis on the *ARFGEF2* gene.

DISCUSSION

This study describes the first case of a patient with Williams syndrome and the radiographic findings of PNH. Chromosomal analyses demonstrated a deletion region on chromosome 7q11.23 that extends beyond the typical telomeric end of the standard WSCR. Moreover, no mutations in the *FLNA* gene were found, suggesting that this non-overlapping telomeric region may contain a new causal gene for PNH. Mapping in this particular patient suggests 16 potential candidate genes in the non-overlapping 1.5 Mb region beyond the telomeric end of the WSCR which may give rise to PNH.

Of the 16 genes in the deletion area that extends beyond the typical telomeric end of the standard WSCR, we will discuss four genes (*HSP27*, *HIP1*, *RHBDL7*, and *YWHAG*) as potential candidates for PNH. The *HSP27* gene is located in the deleted region we identified in our patient that extended beyond the telomeric end of the WSCR. *HSP27* is a 27 kDa heat shock protein that was also identified as a p29 estrogen-receptor associated protein and appears to play a crucial role in specific growth stages by regulating the balance between cellular differentiation and apoptosis. *HSP27* is involved in craniofacial development and odontogenesis [Leonardi et al., 2004]. Interestingly, *FLNA* and *ARFGEF2*, the two known genes associated with PNH, are also implicated in control of cell proliferation along the ventricular zone [Fox et al., 1998; Sheen et al., 2002, 2004] and *FLNA* has a known role in craniofacial bone development [Robertson et al., 2003]. The relationship of the *HSP27* gene (*HSPB1* locus) to Williams syndrome was recently described in patients with Williams syndrome with deletions beyond the WSCR (including the deleted region we present) [Stock et al., 2003]. However, it is unknown whether these patients have PNH since no formal imaging was available for these patients [Stock et al., 2003]. In fact, there is no imaging available for other individuals with Williams syndrome that have been identified with deletions telomeric to the WSCR to confirm or exclude any radiographic evidence of PNH [Wu et al., 1999]. Therefore, imaging studies of these patients to determine whether PNH is present will help in determining whether the *HSP27* gene is a potential candidate gene for causing PNH.

The *HIP1* gene encodes for a membrane-associated protein that shares similarities to other cytoskeleton proteins, and interacts with huntingtin in the regulating the cell filament network [Kalchman et al., 1997]. Loss of normal huntingtin-HIP1 interaction in Huntington disease may contribute to a defect in membrane-cytoskeletal integrity in the brain, and a loss of HIP1 in our patient could give rise to PNH through a dysregulation in the membrane-cytoskeletal network.

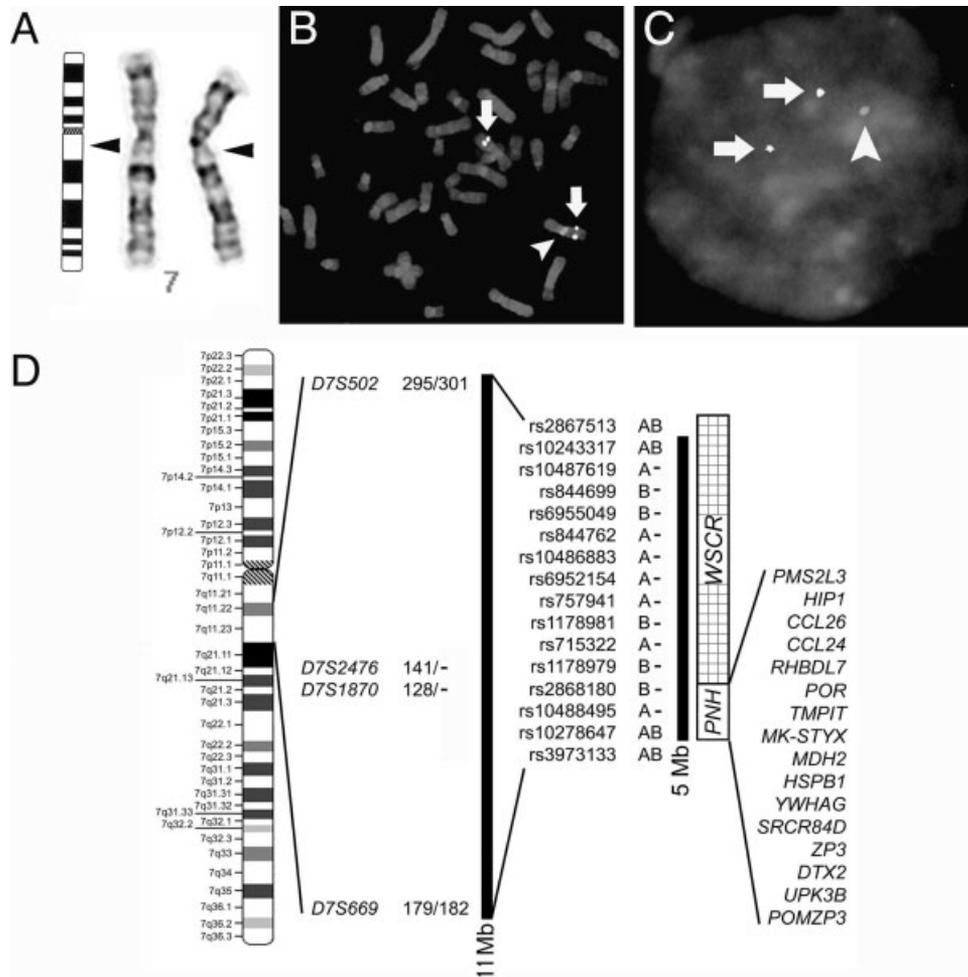


FIG. 2. Genetic analyses of an individual with periventricular nodular heterotopia (PNH) and Williams syndrome. Karyotyping in this patient demonstrates that the Geimsa-negative chromosomal band corresponding to 7q11.2 and the Williams syndrome locus on one chromosome (arrowhead) appears smaller than the one seen in its counterpart, suggesting a deletion within this region (A). Analysis by fluorescence in situ hybridization (FISH) demonstrates the deletion of the *elastin* (*ELN*) gene on one copy of chromosome 7 (as indicated by the white arrowhead) in a metaphase spread (B) and confirmed on an interphase spread (C) as compared to the control probe (as indicated by white arrow). D: Schematic diagram of chromosome 7 demonstrating the banding pattern for this chromosome. The solid black bar on the left indicates the 11 Mb region on chromosome 7q11.22-7q11.23 containing two microsatellite markers (*D7S2476* and *D7S1870*) and their associated alleles that demonstrated a loss of heterogeneity (LOH) flanked by the nearest two markers (*D7S502* and *D7S669*) that did not have LOH. The smaller solid black bar on the right represents the 5 Mb region containing 12 SNPs (rs10487619–rs10488495) and their corresponding alleles that demonstrated a LOH flanked by 4 SNPs (rs2867513, rs10243317, rs10278647, and rs3973133) that did not have LOH. This 5 Mb region was the area on one chromosome 7 that had a heterozygous deletion of part of the Williams syndrome critical region (WSCR—square hatched bar). However, there was an additional region of this chromosome that also was deleted and that was outside of the WSCR. This region is a presumptive region containing a potential gene responsible for PNH (open bar) in our patient. The potential candidate genes for the PNH are listed to the right.

In addition, *RHBDL7* shares homology to the *Drosophila* rhomboid protein, which promotes the cleavage of the membrane-anchored TGF- α -like growth factor Spitz, allowing it to activate the *Drosophila* EGF receptor. This pathway is thought to be involved in both dorsal-ventral axis formation and neurogenesis [Rutledge et al., 1992] and serves as a potential candidate gene for PNH.

Lastly, the *YWHAG* gene encodes a protein belonging to the 14-3-3 family of proteins which are involved in mediating signal transduction by binding to phosphoserine-containing proteins [Horie et al., 1999; Darling et al., 2005]. These transduction events are thought to be important in

regulating such cellular processes as mitosis and cellular proliferation, another potential mechanism involved in PNH formation.

Genetic penetrance of deleted genes may provide an alternative explanation for PNH in Williams syndrome. Part of the Williams syndrome phenotype has been attributed to deletion of *elastin*, one of the components of the extracellular matrix (ECM) that provides elasticity and stretch to structural elements in the body [Ewart et al., 1993; Korenberg et al., 2000]. The associated cardiovascular anomalies including peripheral arterial stenosis and hypertension in Williams syndrome are thought secondary to the role of *elastin* in controlling proliferation of smooth

muscle and stabilization of the arterial wall. Recently, *FLNA* mutations have been shown to cause arterial dilatation, presumably from loss of endothelial integrity and adhesion and weakening of the arterial wall [Sheen et al., 2005]. *FLNA* may regulate the interactions between the ECM and cytoskeleton, and loss of *FLNA* function may impair the structural integrity of the vessel wall. A similar defect in cellular adhesion and ependymal integrity may, therefore, contribute to PNH formation in both the X-linked PNH due to *FLNA* mutations and in the deletion of the *elastin* gene in Williams syndrome. While PNH has not been seen in individuals with Williams syndrome and deletions before, many affected individuals never undergo radiographic imaging of the brain and the genetic penetrance of genes such as *elastin* may vary, making the incidence of detection small.

While the current study suggests that a causative gene for PNH lies within the region extending beyond the WSCR, it is important to consider other potential genetic bases for this malformation. A patient with Williams syndrome was previously found to have a cytogenetically visible and larger deletion than the one described here [Wu et al., 1999]. This individual had a CT scan that was normal. Although MR imaging is more sensitive, PNH has been detected using CT scans. Therefore, it remains a possibility that PNH may not be completely penetrant if it is caused by deletion of gene(s) outside the WSCR. Alternatively, another possibility to account for the presence of PNH in our patient with Williams syndrome is that the heterozygous deletion on one chromosome may have unmasked a recessive mutation on the other chromosome resulting in the appearance of an autosomal recessive PNH. One final alternative is that there may still be another genetic mutation not associated with the deletion on 7q11, which may have led to this disorder.

Although the exact mechanisms involved in the formation of the PNH are largely unknown, it is presumed that some impairment of the initial migration of neurons from the ventricular zone to the cortical plate leads to PNH. Additional PNH loci have been described suggesting that multiple genes will be involved in this initial onset in cortical migration [Leefflang et al., 2003; Sheen et al., 2003]. Identification of additional PNH genes will allow for a better understanding of the mechanisms underlying this cortical malformation.

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