Periventricular Heterotopia in Common Microdeletion Syndromes

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Key Words

Periventricular heterotopia · Microdeletion syndrome · Neuronal migration

Abstract

Periventricular heterotopia (PH) is a brain malformation characterised by heterotopic nodules of neurons lining the walls of the cerebral ventricles. Mutations in *FLNA* account for 20–24% of instances but a majority have no identifiable genetic aetiology. Often the co-occurrence of PH with a chromosomal anomaly is used to infer a new locus for a Mendelian form of PH. This study reports four PH patients with three different microdeletion syndromes, each characterised by high-resolution genomic microarray. In three patients the deletions at 1p36 and 22q11 are conventional in size, whilst a fourth child had a deletion at 7q11.23 that was larger in extent than is typically seen in Williams syndrome. Although some instances of PH associated with chromosomal deletions could be attributed to the unmasking of a recessive

allele or be indicative of more prevalent subclinical migrational anomalies, the rarity of PH in these three microdeletion syndromes and the description of other non-recurrent chromosomal defects do suggest that PH may be a manifestation of multiple different forms of chromosomal imbalance. In many, but possibly not all, instances the co-occurrence of PH with a chromosomal deletion is not necessarily indicative of uncharacterised underlying monogenic loci for this particular neuronal migrational anomaly.

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Periventricular heterotopia (PH) is a genetically heterogeneous neuronal migration disorder characterised by the presence of subependymal heterotopic nodules. These nodules are composed of postmitotic neurons that have failed to initiate migration from the sub-ventricular zone to their proper destination within the cerebral cortex during embryonic and fetal development [Fox et al., 1998]. The clinical presentation of isolated PH includes

Table 1. Cases of chromosomal imbalances in which PH have been described

Segment	Syndromic diagnosis	Balanced, del or dup	n	PH distribution	Reference
t(1;6)(p12;p12.2)	–	apparently balanced	1	Bilateral	Leefflang et al., 2003
1p36	1p36 del syndrome	del	1	Bilateral	Neal et al., 2006 ^a
1p36	1p36 del syndrome	del	1	Unilateral	Saito et al., 2008 ^a
1p36	1p36 del syndrome	del	1	Unilateral	Present case 1
4p14-p15.32 ^d	Proximal 4p del syndrome	del	1	Unilateral	Gawlik-Kuklinska et al., 2008
5p15	–	dup	2	Bilateral	Sheen et al., 2003
mos 46,XX,der(5) ^e	Cri du chat	del	1	Unilateral	Tsao et al., 2005
5q14.3-q15	–	del	3	Bilateral	Cardoso et al., 2009
7q11	Williams syndrome	del	1	Bilateral	Ferland et al., 2006 ^a
7q11	Williams syndrome	del	1	Bilateral	Present case 4 ^a
12q24.3-qter	–	dup	1	Bilateral	Grosso et al., 2008 ^b
17p13.3-pter	–	del	1		Grosso et al., 2008 ^b
der(19)t(X;19)(q11.12;p13.3) ^c	–		1	Bilateral	Balci et al., 2007
22q11	22q11del syndrome	del	1	Bilateral	Kiehl et al., 2008
22q11	22q11del syndrome	del	1	Bilateral	Present case 2
22q11	22q11del syndrome	del	1	Bilateral	Present case 3
Xp22.3	Steroid sulphatase deficiency	del	1	Bilateral	Ozawa et al., 2006
Xq28	BPNH-syndactyly	dup	1	Bilateral	Fink et al., 1997

^a Deletion longer than usually observed in these syndromes.

^b Same case: other brain defects, including lissencephaly.

^c Variant Klinefelter syndrome due to t(X;19).

^d Also inv(9)(p13q13).

^e mos 46,XX,der(5)del(5)(p14) inv(5)(p14q32)[25]/46,XX,del(5)(p15.2)[7] de novo.ish der(5)(5ptel-,D5S23-,wcp5+).

epileptic seizures and often cognitive disability that can range from dyslexia [Chang et al., 2005] to severe mental retardation [Parrini et al., 2006]. Additional extracerebral anomalies include cardiovascular malformations, haematological manifestations, and connective tissue defects [Fox et al., 1998; Sheen et al., 2001, 2005; Parrini et al., 2006]. Although most individuals with PH do not have an assigned aetiology [Parrini et al., 2006], two loci have so far been identified. X-linked PH is due to mutations in the gene encoding filamin A (*FLNA*) [Fox et al., 1998], whereas mutations in *ARFGEF2*, encoding ADP-ribosylation factor guanine nucleotide exchange factor 2, cause a rare autosomal recessive disorder of PH with microcephaly [Sheen et al., 2004]. The majority of familial cases of PH are due to an alteration in *FLNA*, in contrast to sporadic PH cases where only 20–24% have been identified with a mutation in this gene [Sheen et al., 2001; Parrini et al., 2006].

PH is also occasionally observed as a concomitant feature in a small number of syndromes [Sheen et al., 2005; Banerjee et al., 2006; Moro et al., 2006; Ruggieri et al., 2007; Spinoso et al., 2007] and chromosome disorders [Leefflang et al., 2003; Sheen et al., 2003; Ferland et al., 2006; Neal et al., 2006; Balci et al., 2007; Gawlik-Kuklins-

ka et al., 2008; Grosso et al., 2008; Cardoso et al., 2009] including well-delineated conditions such as cri-du-chat syndrome and the 22q11 deletion syndrome [Tsao et al., 2005; Kiehl et al., 2008]. Several of these descriptions have prompted speculation that novel PH loci might lie within these deleted regions, invoking haploinsufficiency for a critical gene as the proposed mechanism [Sheen et al., 2003; Ferland et al., 2006; Neal et al., 2006; Gawlik-Kuklinska et al., 2008], a contention strengthened by the characterisation of deletions that are larger than commonly seen in the 1p36 deletion syndrome and in Williams syndromes [Ferland et al., 2006; Neal et al., 2006; Saito et al., 2008]. With the notable exceptions of anomalies noted on 5p15 [Sheen et al., 2003] and 5q11 [Cardoso et al., 2009], very few of these described chromosomal anomalies have been recurrently and consistently observed in association with PH (table 1).

Extending this experience, this study describes four patients with three commonly encountered microdeletion syndromes. In three cases, one instance of 1p36 deletion and 2 cases with 22q11 deletion syndrome, the deletion size is similar to those commonly reported in these conditions. A fourth individual has a deletion at 7q11.23 that extends beyond the size usually observed in

association with Williams syndrome. Since the size of the 1p36 and 22q11 deletions was typical for these recurrently occurring deletions, we consider the possibility that PH loci may exist nearby (but outside the classic deletion regions) to be unlikely. Rather, and taking note that PH has been reported predominantly in association with a host of non-recurrent chromosomal abnormalities, we propose that PH may be a lowly penetrant and non-specific manifestation of many forms of chromosomal imbalance.

Methods

Ethical Review, Consent and Patient Ascertainment

All subjects were ascertained by physician-initiated referral and consented to participate under an approved institutional protocol. All individuals had a normal G-banded karyotype.

Genomic Copy Number Variation Assay

Copy number variation mapping was performed using Affymetrix 250k *NspI* array, according to the manufacturer's protocol (Affymetrix; Santa Clara, Calif., USA). Copy number estimates were determined automatically in the CNAG 2.0 software package by a hidden Markov model [Nannya et al., 2005].

Quantitative PCR (qPCR)

qPCR was performed on genomic DNA with an ABI 7300 real-time PCR machine (Applied Biosystems, Carlsbad, Calif., USA) using SYBR green for detection. The reaction mix contained 8 μ M of each primer and 12 μ l iQ SYBR Green Supermix (BioRad, Hercules, Calif., USA). Patient DNA was added to a final concentration of 0.25 ng/ μ l, in a total reaction volume of 25 μ l. Each assay included a no-template control and male or female control DNA. All reactions were performed in duplicate. Results were normalised with two autosomal loci (*CFTR* and *TRAF2*) and *SLC16A2* on the X chromosome. $2^{\Delta\Delta CT}$ was calculated as previously described [Livak and Schmittgen, 2001]. Cycling protocols and primer sequences are available on request.

FISH

FISH was performed using RP11-54O7 and p58 BAC clones as probes at 1p36 and the *TUPLE1* probe at 22q11 to confirm deletions at these sites.

Clinical Reports

All patients presented with an apparently normal karyotype, and screening *FLNA* for point mutations was negative.

Patient 1

The patient (fig. 1a, e) is the second child of unrelated healthy parents. He was born at 37 weeks gestation by Caesarean section as a result of fetal distress. Family history was non-contributory. He presented with intractable epileptic seizures from 10 weeks of age. He had severe global developmental delay. Brain MRI at age

11 identified unilateral periventricular nodular heterotopia and bilateral white matter gliosis with under-myelination in the deep white matter of both parietal lobes and a cavum septum pellucidum (fig. 1i). Analysis on the 250k *NspI* array showed a 5.1-Mb telomeric deletion at 1p36 extending from rs2980300 to rs4076635 (fig. 2a, b). FISH and qPCR confirmed the deletion, and examination of parental samples indicated it had occurred as a de novo event.

Patient 2

The patient (fig. 1b, f) is the second child of healthy unrelated parents. There was no notable family disease history. During pregnancy a mega cisterna magna was identified, leading to an MRI scan after birth. The scan revealed symmetrical bilateral PH lining the lateral ventricles, especially the ventricular bodies, with limited extension into the frontal horns (fig. 1j). Epileptic seizures have not been observed. She has mild global developmental delay and joint hypermobility. At 5 months of age she developed febrile neutropenia and pancytopenia; however, bone marrow examination demonstrated normal morphology and haematological indices subsequently returned to normal. Array analysis showed a ~3-Mb deletion at 22q11 extending from rs418623 to rs140390. The qPCR analysis confirmed the extent of the deletion and indicated that it had occurred as a de novo event.

Patient 3

The patient (fig. 1c, g) is the second child born to healthy unrelated parents. The pregnancy was complicated by polyhydramnios, prompting induction of labour at 38 weeks. He initially presented with febrile convulsions, which evolved into non-febrile seizures from 8 months of age. Subsequently, global developmental delay has become evident. Clinical features suggestive of 22q11 deletion syndrome were noted: relative short stature, cupped ears, submucosal cleft palate, long, tapered fingers and generalised joint hypermobility (fig. 1c, g). There was no congenital heart defect present. Brain MRI at age 8 years revealed multiple nodules of heterotopic grey matter lining the bodies of the lateral ventricles and the temporal horns (fig. 1k). FISH analysis showed a deletion at 22q11 which was confirmed to be ~3 Mb in extent by qPCR. Analysis of parental samples using FISH indicated that it had occurred as a de novo event.

Patient 4

The patient (fig. 1d, h) was the child of healthy non-related parents born after an unremarkable pregnancy. There were concerns regarding delayed development from 4 months of age and he developed infrequent generalised seizures from age two years onwards. He had short stature (3rd centile), a wide-based gait, and an intention tremor. Additional dysmorphic features were noted: prominent upper lip with wide-spaced upper incisors and overbite, flexion contractures of elbows, knees, and fingers, thoracic kyphosis, and marked lumbar gibbus; radiology demonstrated lumbar vertebral anomalies. The cardiac examination was normal, and renal function was intact. Brain MRI identified bilateral heterotopic grey matter predominantly located in the frontal horns, mild hypoplasia of the cerebellum, and an enlarged retro-cerebellar space (fig. 1l). Array analysis showed a 3.5-Mb de novo deletion at 7q11.23 from rs12539763 to rs1019096 confirmed by qPCR analysis (fig. 2c, d).

Fig. 1. Clinical presentation of patient 1 (**a, e, i**) with 1p36 deletion syndrome, patient 2 (**b, f, j**) with 22q11 deletion syndrome, patient 3 (**c, g, k**) with 22q11 deletion syndrome, and patient 4 (**d, h, l**) with Williams syndrome. Brain imaging demonstrated nodular heterotopia that was unilateral in patient 1(**i**), bilateral and symmetrical in patient 2 (**j**), lined the bodies of the lateral ventricles in patient 3 (**k**), and was present in the frontal horns in patient 4 (**l**).

Discussion

Previous reports have interpreted the association of PH with a chromosomal anomaly as likely reflecting a causal relationship attributable to disruption of function of a single gene within the deleted interval [Leeftang et al., 2003; Sheen et al., 2003; Neal et al., 2006; Grosso et al., 2008; Cardoso et al., 2009]. However, the description of the association of PH with four well-studied microdeletion syndromes, and with a number of other single instances of rare or unique chromosomal imbalances (table 1), suggests that many chromosomal anomalies have the potential to disrupt neuronal migration and lead to PH, usually with low penetrance. Rather than implicating specific loci that might have a direct effect, these data suggest that PH may be the downstream effect of many

different types of chromosomal imbalance and as such be a final common manifestation of multiple genetic lesions that impair neuronal development. Other manifestations of abnormal neuronal migration such as polymicrogyria, and agenesis of the corpus callosum in 1p36 [Gajecka et al., 2007; Battaglia et al., 2008], 22q11 [Kraynack et al., 1999; Robin et al., 2006], and grey matter anomalies in Williams syndrome [Jernigan and Bellugi, 1990; Mercuri et al., 1997; Boddaert et al., 2006; Chiang et al., 2007] underscore this point.

The rare observation of PH with microdeletions in the patients described in this report, and more broadly in other chromosomal anomalies, may therefore reflect that this sign is a relatively non-specific end result of multiple pathways that impair neuronal migration, rather than the more specific and penetrant effect of an underlying mutated

Fig. 2. Graphic overview of deletions identified in patient 1 and 4. **a** Normalised CNAG data trace from the 250k SNP array with a deletion at 1p36. **b** Diagram of the deleted region in patient 1, the deletion previously reported in association with PH [Neal et al., 2006] and the range of deletion sizes identified in the 1p36 deletion syndrome. **c** Normalised CNAG data trace from the 250k SNP array with a deletion at 7q11. **d** Diagram of the deleted region

in patient 4, a deletion previously described in a patient with PH and Williams syndrome [Ferland et al., 2006], and the region typically deleted in Williams syndrome. The solid black line indicates the extent of the deleted region; the hatched line denotes potentially deleted sequences. * signifies loci for confirmatory FISH and qPCR.

gene such as *FLNA* or *ARFGEF2*. In an analogous fashion several chromosomal loci have been proposed to underlie polymicrogyria [Dobyns et al., 2008] but here, in contrast to the situation with PH, the chromosomal associations have been recurrent and consistent, a finding more in

keeping with a susceptibility conferred by haploinsufficiency for one or a number of underlying genes in those regions. Of the described loci so far associated with PH, only duplications in 5p15 [Sheen et al., 2003] and deletions in 5q11 [Cardoso et al., 2009] may fulfill these criteria.

It was reasonable for Neal et al. [2006] and Saito et al. [2008] to suggest the existence of a PH gene at 1p36 on the grounds that the deletions they described extended further towards the centromere than deletions typically observed in 1p36 deletion syndrome. Now that a patient with PH has been described with a 5-Mb telomeric 1p36 deletion, this proposition is weakened although a lowly penetrant position effect remains a formal possibility and molecular and imaging studies of further individuals with a 1p36 deletion will help clarify this issue.

In contrast to the rare occurrence of PH with deletion sizes commonly encountered at 1p36 and 22q11, the observation of two overlapping atypical deletions leading to PH and Williams syndrome may be indicative of a defined susceptibility locus on 7q11 that predisposes to neuronal migration abnormalities. Williams syndrome is caused by deletions at 7q11.23, typically ~1.55 Mb long and affecting ~28 genes. A small proportion of patients have larger deletions [Stock et al., 2003; Ferland et al., 2006; Marshall et al., 2008]. PH has been previously described in association with Williams syndrome in one patient [Ferland et al., 2006]. A deletion extending 1.5 Mb beyond the telomeric region of the common Williams syndrome deletion interval was defined and affected an additional 16 genes, one or some of which were proposed to be susceptibility genes leading to PH [Ferland et al., 2006]. The atypical 3.6-Mb deletion described here extends telomeric to the common Williams syndrome region, overlapping the 1.5-Mb region described by Ferland et al. [2006], supporting this possibility. Previously described patients with similar or overlapping deletions in the Williams syndrome region [Stock et al., 2003; Marshall et al., 2008] have been reported and neuroimaging of these individuals would be useful to determine the frequency of PH and its relationship to these mapped haploinsufficient regions.

Our hypothesis carries a number of caveats. The number of cases of these classical deletion syndromes – 1p36, 5p, 7q11, and 22q11 – in which PH have been detected is small. However, the true prevalence might well be underestimated, given that MRI brain scanning is not routinely performed in children with established diagnoses of one of these (or of numerous other) chromosome deletion syndromes. Equally, a child manifesting severe seizures (as in case 1), ahead of the chromosome diagnosis, would be more likely to have cerebral imaging, thus leading to a bias in favour of PH detection. Less likely explanations include the potential for a de novo deletion to unmask the presence of a recessive allele in trans or that the phenotype is entirely unrelated to these described microdeletions.

The foregoing observations identified by genome-wide high-resolution copy number variation analysis suggest that some instances of PH may not necessarily have a primarily monogenic aetiology, and that associations with chromosomal anomalies [Leefflang et al., 2003; Sheen et al., 2003; Ferland et al., 2006; Neal et al., 2006; Balci et al., 2007; Gawlik-Kuklinska et al., 2008; Grosso et al., 2008] are not necessarily indicative of underlying uncharacterised loci. These observations of PH in association with multiple different chromosomal rearrangements confirm the aetiologically heterogeneous nature of PH. Although the occurrence of de novo deletions, in association with sporadically arising phenotypic traits, remains a powerful method of identifying highly penetrant disease-causing genes [Vissers et al., 2005], this study suggests that such an inference may be less secure in cases where PH is the phenotypic feature of interest. We suggest that, in selected cases, MRI brain scanning in these and other chromosomal deletion/duplication syndromes may be warranted, in order to cast further light upon this question.

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