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Cerebellar and posterior fossa malformations in patients with autism-associated chromosome 22q13 terminal deletion

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Abstract

The 22q13.3 deletion causes a neurodevelopmental syndrome, also known as Phelan-McDermid syndrome (MIM #606232), characterized by developmental delay and severe delay or absence of expressive speech. Two patients with hemizygous chromosome 22q13.3 telomeric deletion were referred to us when brain-imaging studies revealed cerebellar vermis hypoplasia (CBVH). To determine whether developmental abnormalities of the cerebellum are a consistent feature of the 22q13.3 deletion syndrome, we examined brain-imaging studies for 10 unrelated subjects with 22q13 terminal deletion. In 7 cases where the availability of DNA and array technology allowed, we mapped deletion boundaries using comparative intensity analysis with single nucleotide polymorphism (SNP) microarrays. Approximate deletion boundaries for 3 additional cases were derived from clinical or published molecular data. We also examined brain-imaging studies for a patient with an intragenic *SHANK3* mutation. We report the first brain-imaging data showing that some patients with 22q13 deletions have severe posterior CBVH, and one individual with a *SHANK3* mutation has a normal cerebellum. This genotype-phenotype study suggests that the

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Conflict of Interest.
The authors declare no conflict of interest.

22q13 deletion phenotype includes abnormal posterior fossa structures that are unlikely to be attributed to *SHANK3* disruption. Other genes in the region, including *PLXNB2* and *MAPK8IP2*, display brain expression patterns and mouse mutant phenotypes critical for proper cerebellar development. Future studies of these genes may elucidate their relationship to 22q13.3 deletion phenotypes.

Keywords

cerebellum; chromosome; deletion; SHANK3

INTRODUCTION

Numerous patients with terminal deletions of chromosome 22q13 have been reported [Bonaglia et al., 2011; Dhar et al., 2010; Marshall et al., 2008; Phelan and Rogers 1993; Sarasua et al., 2011; Sebat et al., 2007; Szatmari et al., 2007; Wilson et al., 2003]. The hemizygous terminal chromosome 22q13 deletion syndrome is characterized by neonatal hypotonia, global developmental delay, normal to accelerated growth, absent to severely delayed speech, autistic behavior and minor dysmorphic features [Havens et al., 2004; Phelan and Rogers 1993]. Deletion sizes range from 130 Kb to >9 Mb, with the smallest reported deletion harboring the *SHANK3* gene, which encodes a scaffolding protein that localizes to the postsynaptic density of excitatory synapses [Baron et al., 2006; Bonaglia et al., 2011; Wilson et al., 2003]. *SHANK3* is strongly expressed in the cerebral cortex and cerebellum and has been proposed as the major cause for both the neurological features of the 22q13 deletion syndrome and for a monogenic form of autism [Bonaglia et al., 2001; Durand et al., 2007; Moessner et al., 2007].

Most 22q13 deletion patients have intellectual disability and severe delay or absence of expressive speech, while mixed evidence for correlations between deletion size and observed clinical features have been found [Phelan and Rogers 1993; Sarasua et al., 2011; Wilson et al., 2003]. Here, we report that cerebellar and posterior fossa malformations are underappreciated features of the 22q13 deletion syndrome in some cases. We discuss the potential role for additional genes, including *PLXNB2* and *MAPK8IP2*, within the 22q13 terminal deletion region involved in hindbrain development.

MATERIALS AND METHODS

Subjects

Protocols were approved by Institutional Review Boards at all participating universities, and written informed consent was obtained from all subjects. Three patients (LR04-276, LR07-054 and LR07-144) were referred to us due to abnormal brain imaging. The remaining 7 patients were ascertained due to 22q13 deletion, most identified clinically by fluorescent *in situ* hybridization (FISH). Brain imaging results were reviewed independently and blind to deletion size by A.J.B and W.B.D. Diagnosis of cerebellar vermis hypoplasia (CBVH) was based on qualitative reduced size of the vermis recognized when the top of the vermis was located below the mid-tectum or the bottom above the level of the obex/nucleus gracilis, and enlarged size of the cistern magna [“mega cisterna magna” (MCM)] recognized when it appeared enlarged below and extended behind the cerebellum.

Microarray-based deletion breakpoint analysis

Genomic DNA was isolated from peripheral blood lymphocytes or saliva using standard methods. Genome-wide SNP genotyping was performed for 6 probands (4 with both

parents) using either the Illumina HumanHap550 BeadChip (Illumina, Inc., San Diego, CA) according to the manufacturer's instructions at the Cincinnati Children's Hospital Medical Center or the Illumina Human610-quad BeadChip by the Center for Applied Genomics at the Children's Hospital of Philadelphia. Illumina signal intensity data was initially analyzed using cnvPartition 1.2.1 (Illumina, Inc., San Diego, CA). Signal intensity data for one additional patient previously genotyped using the Affymetrix 500K Array [Moessner et al., 2007] was exported using dchip (http://biosun1.harvard.edu/complab/dchip/) and analyzed together with the other 6 probands. Copy number gains and losses were determined by Nexus 4.0 (BioDiscovery, Inc., El Segundo, CA) using genotyping signal intensity data and thresholds of 0.2 and -0.17, respectively (Suppl. Fig. S1–2). Two patients were analyzed for genomic copy number changes, one using the SignatureChip® (Signature Genomic Laboratories, LLC, Spokane, WA) BAC array (data not shown) and one using an Agilent oligonucleotide array (Agilent Technologies, Santa Clara, CA), as previously described [Klopocki et al., 2011] (Suppl. Fig. S3). Approximate breakpoints were derived from published molecular data for an additional patient [Delahaye et al., 2009]. In total, we obtained 22q13 breakpoint data for 10 probands.

RESULTS

We obtained cross-sectional brain-imaging studies for 10 patients with deletions of 22q13 (Table 1), ascertained because of cerebellar malformation or 22q13 deletion. In general, the brain imaging studies (Figure 1) show abnormalities in all patients. Corpus callosum thinning was observed in 9/10, abnormally thin white matter in 7/10, and enlarged ventricles in 8/10 subjects. We found definite CBVH in 3/10 (including 2 with definite MCM), subtle CBVH in 3/10, and subtle MCM in 3/10 subjects. We found MCM in one patient and normal brain imaging in another patient with reported del 22q13 but no molecular confirmation of deletion size, so these subjects were not included for further analysis (data not shown).

In 7 patients where the availability of DNA and array technology allowed, we mapped the deletion boundaries by using comparative intensity analysis with SNP microarrays (Supplementary Fig. S1–2). Approximate breakpoints for 3 patients were determined from molecular karyotyping (LR08-043, LR08-44) or published report (LR09-60). Deletions ranged in size from ~900 kb to >7 Mb with an average deletion size of 3 Mb (Figure 2). The 3 individuals with the most severe CBVH/MCM phenotypes have intermediate deletions. Surprisingly, the 2 individuals with the largest deletions have normal posterior fossa size and either normal vermis or mild CBVH, while the two individuals with the smallest deletions have normal vermis size and mildly enlarged posterior fossa. These data suggest influence of modifying factors from the undeleted chromosome or elsewhere in the genome.

DISCUSSION

We report brain-imaging studies in 10 patients with deletion 22q13 that show CBVH, enlarged posterior fossa or both in 8/10 patients without features of cerebellar atrophy, and confirm prior reports of thin corpus callosum and ventriculomegaly. While we have only single imaging studies on these patients, comparison of scans from children aged 6 weeks to 18 years (Table 1) showed similar features. In particular, the thin corpus callosum and white matter and enlarged ventricles were not more severe in older patients. While few brain-imaging studies have been reported for individuals with 22q13 deletions, posterior fossa or cerebellar abnormalities were previously noted for seven patients, thin corpus callosum in another seven, and ventriculomegaly in at least three [Bonaglia et al., 2011; Doheny et al., 1997; Lindquist et al., 2005; Philippe et al., 2008; Tabolacci et al., 2005]. However, figures of brain imaging studies were rarely provided. We reviewed the scan available in Fig. 2 of

Tabolacci et al., 2005, and find changes very similar to those observed in our cohort, including mild CBVH and mildly enlarged posterior fossa (Table 1).

SHANK3 is strongly expressed in the cerebral cortex and cerebellum and has been proposed as the major cause for both the neurological features of the 22q13 deletion syndrome and for a monogenic form of autism [Bonaglia et al., 2001; Durand et al., 2007; Moessner et al., 2007]. Cerebellar dysfunction alone may explain many autism symptoms by affecting cognitive and motor behavior, as well as connectivity between the cerebellum and other brain systems [Allen 2006; Allen and Courchesne 2003; Schmahmann 2004; Tavano et al., 2007]. Reports of two neurodevelopmental cerebellar phenotypes in the autistic brain, CBVH and decreased Purkinje cell (PC) number [Bauman and Kemper 2005; Bloss and Courchesne 2007; DiCicco-Bloom et al., 2006], further suggest that genes regulating cerebellar development may also confer autism susceptibility in these patients.

Several *Shank3* mouse mutants have recently been developed [Bangash et al., 2011; Bozdagi et al., 2010; Peca et al., 2011; Wang et al., 2011]. Though no gross cerebellar malformations were reported in these mice, specific investigation of cerebellar development has yet to be performed. We examined one *Shank3* mouse mutant [Bozdagi et al., 2010] using integrated brain-imaging data and head CT scans (data not shown). No obvious cerebellar or posterior fossa phenotypes were detected in adult *Shank3* heterozygous or homozygous mutant mice, suggesting *Shank3* disruption does not impact cerebellar development in mice.

Two other genes in the 22q13 deletion region, *PLXNB2* and *MAPK8IP2*, are strong candidates for cerebellar phenotypes. *Plxnb2* and *Mapk8ip2* are expressed in the mouse hindbrain and abnormal phenotypes of the developing cerebellum are observed in homozygous mutants for each gene (the heterozygous phenotypes were not described). *Plxnb2* is expressed in embryonic mesenchyme and the external granule cell (GC) layer of the postnatal cerebellum [Perala et al., 2005], and is a target of *Atoh1*, a transcription factor critical for GC development [Klisch et al., 2011]. *Plxnb2* knockout mice have a perinatal lethal phenotype that includes reduced cerebellar fissure formation and aberrant granule cell proliferation and differentiation [Friedel et al., 2007]. *Mapk8ip2* encodes the islet brain-2 protein, a scaffolding protein broadly expressed in mouse brain with enrichment at postsynaptic densities, including within the cerebellum [Giza et al., 2010]. *Mapk8ip2* null mice have deficits in PC dendritic aborization and synaptic transmission, but apparent normal cerebellar foliation and PC localization [Giza et al., 2010; Kennedy et al. 2007]. These mice also display behavioral phenotypes proposed to be relevant for autism including deficits in motor, learning, and social interaction paradigms [Giza et al., 2010]. In humans, *PLXNB2* and *MAPK8IP2* are highly expressed in cerebellar vermis [Jones et al., 2009] (http://human.brain-map.org/); their role in human cerebellar phenotypes requires further investigation.

While our series is relatively small, the high rate of cerebellar and/or posterior fossa abnormalities – seen in 8/10 subjects – suggests that developmental abnormalities of the posterior fossa and cerebellum are a common feature of the deletion 22q13 syndrome. We also confirm the high rate of thin corpus callosum and ventriculmegaly. Based on our analysis of the gene content, we propose that MCM-CBVH observed in the Phelan-McDermid syndrome, a contiguous gene deletion syndrome which includes *SHANK3*, are likely due to contributions from two or more genes in the region, possibly including *PLXNB2* and *MAPK8IP2*. Our data in a single patient with an intragenic *SHANK3* mutation suggests that *SHANK3* disruption is not sufficient to produce CBVH, though examination of additional patients is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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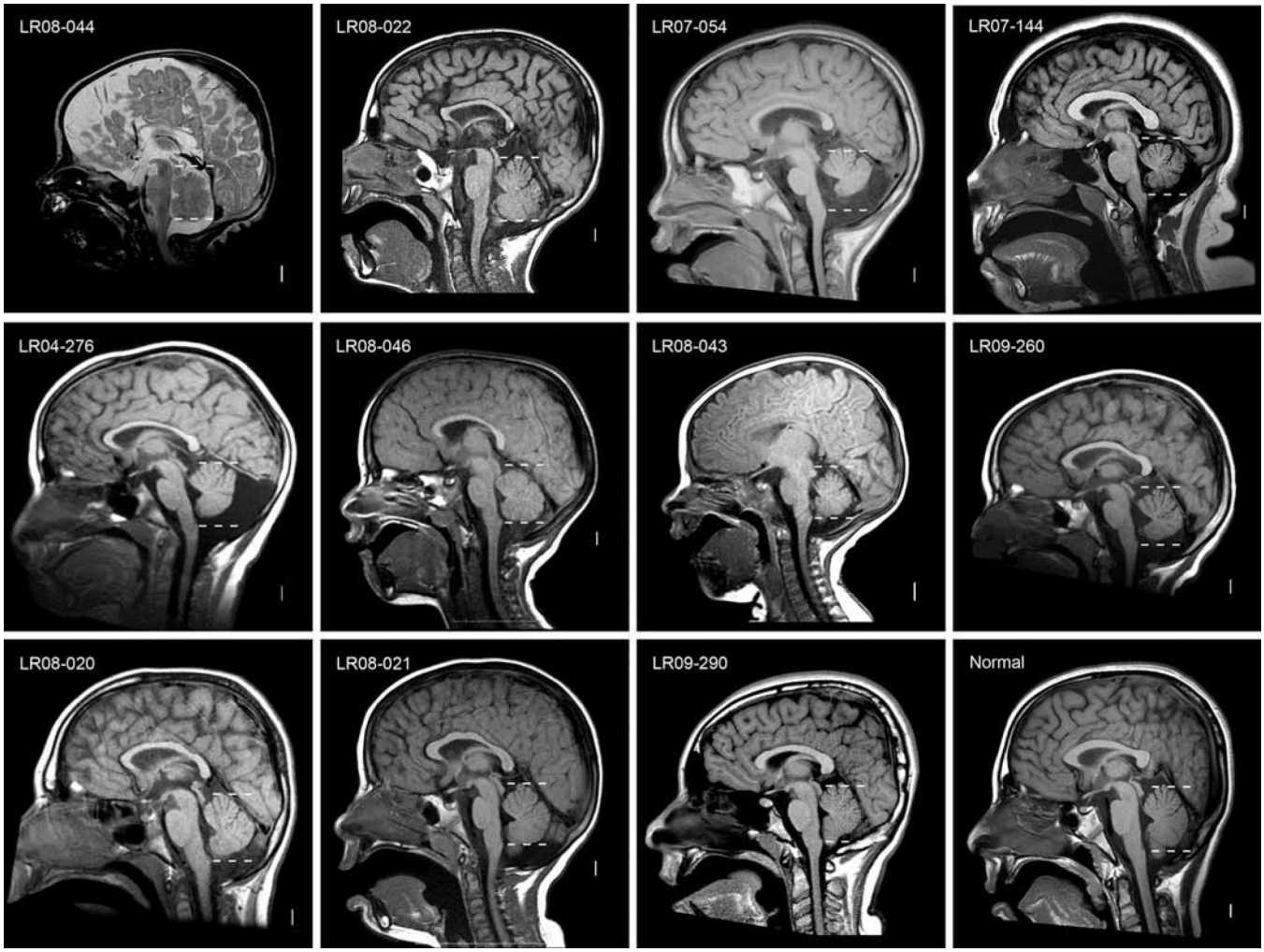

Figure 1. Brain images of patients with 22q13 terminal deletion or *SHANK3* mutation

T1-weighted midsagittal magnetic resonance images in one control subject, 10 subjects with 22q13 deletion, and one subject with an intragenic mutation of *SHANK3* (LR09-90). The upper and lower limits of the vermis are marked by horizontal dashed white lines in each image.

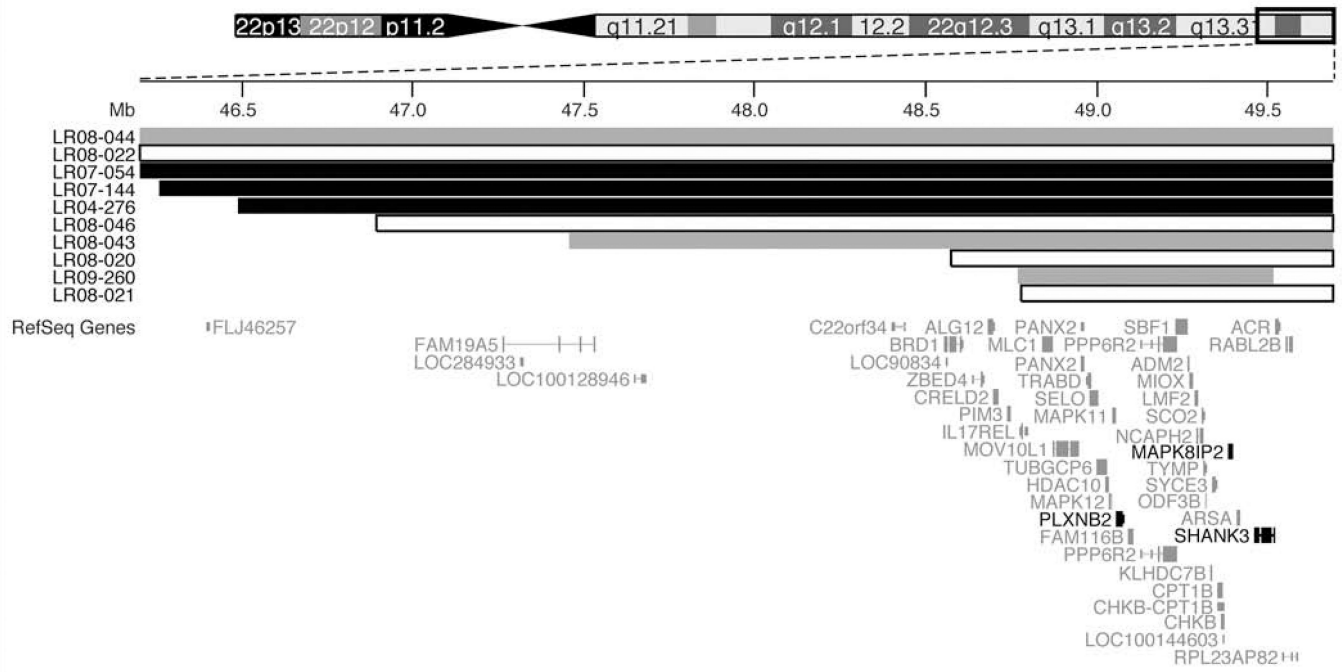

Figure 2. Physical map of the 22q13 deletion locus

Schematic of 22q13.31-qter (UCSC Genome Browser Mar 2006, chr22:46,000,000–49,691,432) drawn to scale shows deletions associated with normal and abnormal posterior fossa brain imaging. Deletions associated with CBVH+MCM (black) or CBVH (grey) are displayed. The deletion in two probands (LR08-44, LR08-22) extends beyond field of view. RefSeq genes are shown. *PLXNB2* or *MAPK8IP2* produce developmental cerebellar phenotypes with homozygous loss in mouse. Mutation or deletion of *SHANK3* has been associated with autism.

Table 1

Summary of clinical features and chromosome 22q13 terminal deletion characterization.

	Brain imaging						Deletion mapping	
	Age[1]	**CC thin[2]**	**WM thin[3]**	**VMEG[4]**	**CBVH[5]**	**PF large[6]**	**Microarray[7]**	**Deletion chr22q13[8]**
LR08-044[9]	6wk	++	+	R>L	+	−	Agilent 244K	40771519–49691432[10]
LR08-022	5.5y	+	++	+	−	−	Illumina Hap550	44616760–49691432
LR07-054	9y	+	+	R>L	++	++	Illumina 610Q	46202165–49691432
LR07-144[11]	18y	−	+	−	++	++	Affymetrix 500K	46260450–49691432
LR04-276	7.5y	+	+	L>R	++	++	Illumina 610Q	46491552–49691432
LR08-046	2.5y	+	+	L>R	−	−	Illumina 610Q	46894487–49691432
LR08-043	3.1y	+	−	−	+	−	Signature BAC	47457855–49691432
LR09-260[12]	NA	+	−	+	+	+	FISH, qPCR	47921342–49518504
LR08-020	10y	+	−	+	−	+	Illumina Hap550	48576196–49691432
LR08-021[13]	5y	+	+	+	−	+	Illumina Hap550	48777410–49691432
LR09-290[14]	14y	−	−	−	−	−	Normal	*SHANK3,* c.962A>G
Normal	11.5y	−	−	−	−	−	NA	NA
Case B[15]	13y	+	+	+	+	+	FISH	44279749–49691432[16]

NA indicates not applicable.

Additional notes:

[1] Age [in weeks (wk) or years (y)] at MRI;

[2] Hypogenesis (thinning) of corpus callosum (CC);

[3] abnormally thin white matter (WM);

[4] enlarged ventricles;

[5] cerebellar vermis hypoplasia (CBVH);

[6] enlarged posterior fossa (PF) consistent with “mega-cisterna magna”;

[7] microarray platform used;

[8] chromosome 22 deletion in NCBI Build 36/hg18;

[9] 46,XX,der(22);t(7;22)(7q36.2;22q13.2)mat, therefore also has dup(7)(q36.2qter);

[10] presumed telomeric because deletion appears to extend past telomeric probe (ch22:49565816–49565875);

[11] also reported in Moessner et al., 2007; Marshall et al., 2008 (NA0039);

[12] also reported in Delahaye et al., 2009;

[13] fragile X premutation carrier with 70 CGG repeats;

[14] 46,XX,der(22);t(14;22)(q32.33;q13.31)pat; also reported in Moessner et al., 2007 (SK0007);

[15] reported in Tabolacci et al., 2005;

[16] proximal deletion boundary reported between FISH probes RP1-102D24 and CTA-1109B5.