A new case of duplication of the MDS region identified by high-density SNP arrays and a review of the literature

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Received: 8 September 2010 / Revised: 10 October 2010 / Accepted: 11 October 2010 / Published online: 3 November 2010
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Introduction

The deletion of the locus 17p13 was associated with Miller–Dieker lissencephaly syndrome (MDLS). Deletion (Delatycki and Leventer 2009) or mutations (Lo Nigro et al. 1997) in the *PAFAH1B1* (601545) gene cause lissencephaly (Gu and Lupski 2008), but facial dysmorphology and other abnormalities in patients with MDLS seem to be the result of the deletion of additional genes distal to *PAFAH1B1* (Cardoso et al. 2003; Saillour et al. 2009). The gene responsible for the greater severity of MDLS compared to isolated lissencephaly is the *YWHAE* (Haverfield et al. 2009) (605066) gene, encoding 14-3-3-epsilon. It was very recently demonstrated that the duplication in 17p13 is a new clinical entity (OMIM 613215), characterized by mental retardation and other variable clinical and radiological findings (Roos et al. 2009; Spalice et al. 2009). There are three different areas within the MDS region containing dosage-sensitive genes. One containing the *PAFAH1B1* gene and the other, more distal, which includes the *TUSC5*, *YWHAE*, *CRK*, and *MYO1C* genes. Until now, few cases have been described with duplication in the MDS region (Mei et al. 2008; Bi et al. 2009) and only two of them show a duplication including only the *PAFAH1B1* area. All patients with duplication in the MDS region have common clinical and phenotypic features. Nevertheless, there are several important differences between those with only duplication in the *PAFAH1B1* area as compared with those who have also (or only) a duplication in the distal area.

Clinical report

The proband, a 6-year-old girl, is the first child of non-consanguineous parents. The family history for mental retardation or congenital disorders was negative. The proband was born at term by dystocia childbirth. At birth, the Apgar was 9/10 at the first and at the fifth minute. Stages of psychomotor development were all delayed. At ten months of life, the proband had not yet acquired a sitting independent position. At 16 months, the proband started to walk, while expressing considerable difficulties. Language was still the worst affected: at about 18 months, the proband started babbling, and she was followed with a support speech therapy. To date, at the age of 6 years, the proband utters only a few isolated words. Further analysis excluded the presence of major malformations of the internal organs and of the skeletal system. The main relevant features of our case are: (A) mental retardation; (B) magnetic resonance imaging (MRI) revealed the presence of an arachnoid cyst (Fig. 2) in the posterior fossa with a consequent asymmetry of cerebellar hemispheres; (C) hypotonia, delayed psychomotor development, especially for expressive language and an autistic spectrum disorder; (D) short stature, despite the fact that the anthropometric values at birth were approximately all around the 50th percentile and a carpus radiography revealed a bone age comparable with the age of the proband; (E) phenotypic features: long face, slight synophrys, long philtrum, thin upper lip, and pointed chin (Table 1).

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Materials and methods

After informed consent, the chromosomal analysis was performed on blood using the standard protocol with 440–550-band resolution. Molecular karyotyping was carried

Table 1 Clinical features of patients with duplication or triplication in the 17p13.3 Miller–Dieker syndrome (MDS) region

	Two distal genes	Four distal genes	All genes	Only the <i>PFAH1B1</i> gene	
Number of patients	1	3	3	2	Our patient
Birth length/weight	Low	Elevated	Normal/elevated	Low	Normal
Current length/weight	Normal	Elevated	Elevated	Low	Low
Head circumference	Low	Elevated	Elevated/low	Low	Low
Head	Normal	Long face/normal	Frontal bossing/normal	Triangular/microcephaly	Long face
Eyes	Deep-set	Mild synophrys/ upslanting	Hypertelorism/downslanting	Normal	Downslanting/mild synophrys
Nose	Broad nasal bridge	Squared/overhanging columella	Broad nasal bridge	Normal	Normal
Mouth	Mild prognathia	Thin upper lip/short philtrum/prominent chin	Normal/small/high palate	Micrognathia/high arched palate	Thin upper lip/long philtrum/pointed chin
Skeletal	Normal	Large hands/scoliosis/ prominent PIP joints	Normal/clinodactyly	Craniosynostosis/ dislocated hips	Normal
Neurological abnormalities	Reduced eye contact	Hypotonia/ADHD/ suspected autism	Hypotonia/autism/ insensitivity to pain	Hypotonia/atrophy/ ADHD/OCD	Autistic spectrum disorder
Delayed psychomotor development	Expressive language	Mild/global/fine motor delay	Mental retardation/moderate	Mental retardation/ development delay	Mental retardation/ expressive language
Magnetic resonance imaging	N/A	Thin corpus callosum/ periventricular leukomalacia	Choroid plexus cysts/ hypo/aplasia of corpus callosum/mild cerebral volume loss	Subarachnoid cyst/ dysgenesis of corpus callosum/mild cerebral volume loss/cerebellar atrophy	Arachnoid cyst/ asymmetry of cerebellar hemispheres

out using single nucleotide polymorphism (SNP) array analysis using the HumanCNV370-Quad array (Illumina, San Diego, CA) according to manufacturer's protocol. This array is characterized by 370,000 SNP markers and covers specifically almost 14,000 CNV regions. Acquired data was visualized and analyzed with GenomeStudio Data Analysis Software v.2008 (Illumina, San Diego, CA).

Results

Chromosomal analysis revealed a 46, XX karyotype. Molecular karyotype analysis by high-resolution SNP arrays performed on the proband DNA revealed a “de novo” duplication of approximately 1.2 megabases in the p13.3 region of chromosome 17 from base 1,558,949 to base 2,787,681 (Figs. 1 and 2), which encompass the *PFAH1B1* gene. No other relevant molecular alterations were detected with a possible relationship with the phenotype.

Discussion

In this report, we describe a case of mental retardation with an autistic spectrum disorder and the presence of specific alterations in the MRI results. The whole-genome study performed with SNP arrays identified a duplication in the critical MDS region. A comparison of our case with those so far described in the literature was carried out. Four cases

present the duplication in the MDS region without *PFAH1B1* gene involvement. Additionally, in four cases, a large duplication involves both areas, while only two cases are duplicated within the *PFAH1B1* area. Although some craniofacial characteristics have been reported among individuals with duplication of the *YWHAE* gene, however, there is no pathognomonic clinical sign of facial dysmorphism or gestalt of the face described in this duplication, and these phenotypic signs may be present even if only the *PFAH1B1* gene is duplicated. Patients primarily carrying only the duplication of the *PFAH1B1* area tend to show growth retardation and microcephaly, whereas the others manifest overgrowth. This macrosomia, as has already been reported by Bi et al. (2009), may be attributed to *CRK*, a gene involved in growth regulation and cell differentiation. Differently from that described by Bi et al. (2009), our patient, who presented a duplicate *PFAH1B1* gene, does not show any internal organ abnormality. Developmental delay, cognitive and speech difficulties, and pervasive developmental disorders were observed in all affected individuals and were the main reason for why they have been studied. The autistic spectrum disorder, present in our proband, is described in two other patients, where the duplication, however, involves different areas. Hypotonia is very frequent in this cohort of patients. MRI was not performed in all patients and, therefore, it is very difficult to perform a correlation between abnormalities detected and the duplicated genes. In any case, it is certainly interesting to note that there are some alterations in the central nervous system (CNS) that frequently recur.

Fig. 1 Ten individuals with duplication and triplication in the MDS region identified by comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays. The MDS region is indicated at the top of the figure. On the bottom are 11 horizontal bars showing the fine-mapping of duplications. *Dark area*, duplication; *gray area*, deletion; *striped area*, triplication. The *asterisk* for subject 7 indicates a ~4-kb deletion

Indeed, in our case, there is the presence of cysts subarachnoid and cerebellar atrophy or asymmetry (Fig. 2), as well as in another case with only the *PAFAH1B1* duplication (Bi et al. 2009). In another patient, there was also described a choroid plexus cyst. However, as already described, the MRI abnormalities are most pronounced with triplication of the *PAFAH1B1* gene as compared to

duplication, an observation which is consistent with a gene dosage effect.

Recently, Bruno et al. (2010) have suggested a new classification characterized by two classes of co-locating microduplications in 17p13.3. Class I involves *YWHA* but not *PAFAH1B1*, and Class II involves *PAFAH1B1* ± several other genes. The clinical spectrum of our patient is in

Fig. 2 **a** Shown is the duplication present in the 17p13.3 region. **b** Facial features of our patient and her magnetic resonance imaging (MRI) scans

agreement with this new classification and overlap with those in Class II. According to Bruno et al. (2010), Class I patients show autistic manifestations, but it is important to highlight also that several patients in Class II, including our case, manifest an autistic spectrum disorder. Moreover, our patient is the only case described so far with autistic spectrum disorder and duplication involving only the *PAFAH1B1* gene.

Finally, we believe that this additional case allows to better define the correlation between the phenotype, the clinical features, the radiological abnormalities, and the area of duplication in the MDS region.

References

- Bi W, Sapir T, Shchelochkov OA et al (2009) Increased *LIS1* expression affects human and mouse brain development. *Nat Genet* 41(2):168–177
- Bruno DL, Anderlid BM, Lindstrand A et al (2010) Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. *J Med Genet* 47(5):299–311
- Cardoso C, Leventer RJ, Ward HL et al (2003) Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller–Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. *Am J Hum Genet* 72(4):918–930
- Delatycki MB, Leventer RJ (2009) Listen carefully: *LIS1* and *DCX* MLPA in lissencephaly and subcortical band heterotopia. *Eur J Hum Genet* 17(6):701–702
- Gu W, Lupski JR (2008) CNV and nervous system diseases—what’s new? *Cytogenet Genome Res* 123(1–4):54–64
- Haverfield EV, Whited AJ, Petras KS et al (2009) Intragenic deletions and duplications of the *LIS1* and *DCX* genes: a major disease-causing mechanism in lissencephaly and subcortical band heterotopia. *Eur J Hum Genet* 17(7):911–918
- Lo Nigro C, Chong CS, Smith AC et al (1997) Point mutations and an intragenic deletion in *LIS1*, the lissencephaly causative gene in isolated lissencephaly sequence and Miller–Dieker syndrome. *Hum Mol Genet* 6(2):157–164
- Mei D, Lewis R, Parrini E et al (2008) High frequency of genomic deletions—and a duplication—in the *LIS1* gene in lissencephaly: implications for molecular diagnosis. *J Med Genet* 45(6):355–361
- Roos L, Jøneh AE, Kjaergaard S et al (2009) A new microduplication syndrome encompassing the region of the Miller–Dieker (17p13 deletion) syndrome. *J Med Genet* 46(10):703–710
- Saillour Y, Carion N, Quelin C et al (2009) *LIS1*-related isolated lissencephaly: spectrum of mutations and relationships with malformation severity. *Arch Neurol* 66(8):1007–1015
- Spalice A, Parisi P, Nicita F et al (2009) Neuronal migration disorders: clinical, neuroradiologic and genetics aspects. *Acta Paediatr* 98(3):421–433