European Journal of Medical Genetics 53 (2010) 303–308

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Short report

Further delineation of the 17p13.3 microdeletion involving *YWHAE* but distal to *PAFAH1B1*: Four additional patients

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ARTICLE INFO

Article history:
Received 8 December 2009
Accepted 26 June 2010
Available online 3 July 2010

Keywords:
17p 13.3 microdeletion
YWHAE
Mental retardation
Coloboma
Chiari type 1 malformation

ABSTRACT

Background: The 17p13.3 deletion syndrome (or Miller-Dieker syndrome, MDS, MIM 247200) is characterized by lissencephaly, mental retardation and facial dysmorphism. The phenotype is attributed to haploinsufficiency of two genes present in the minimal critical region of MDS: *PAFAH1B1* (formerly referred to as *LIS1*) and *YWHAE*. Whereas isolated *PAFAH1B1* deletion causes lissencephaly, *YWHAE* is a candidate for the dysmorphic phenotype associated with MDS.
Objective: We describe clinical, neuroradiological and molecular data in four patients with a 17p13.3 deletion distal to *PAFAH1B1* involving *YWHAE*.
Results: All patients presented with mild or moderate developmental delay and pre and/or post-natal growth retardation. Patients A, B and C had neuro-imaging anomalies: leucoencephalopathy with macrocephaly (patients A and C), Chiari type 1 malformation (patient A) and paraventricular cysts (patient C). Patient B had patent ductus arteriosus and pulmonary arterial hypertension. Patient C had unilateral club foot. Patient D had enlarged Virchow Robin spaces, microcornea, and chorioretinal and lens coloboma. Array-CGH revealed de novo terminal 17p13.3 deletions for patient A and B, and showed interstitial 17p13.3 deletions of 1.4 Mb for patient C and of 0.5 Mb for patient D. In all patients, *PAFAH1B1* was not deleted.
Conclusion: Our patients confirm that 17p deletion distal to *PAFAH1B1* have a distinctive phenotype : mild mental retardation, moderate to severe growth restriction, white matter abnormalities and developmental defects including Chiari type 1 malformation and coloboma. Our patients contribute to the delineation and clinical characterization of 17p13.3 deletion distal to *PAFAH1B1* and highlight the role of the region containing *YWHAE* in brain and eye development and in somatic growth.

1. Introduction

Genomic rearrangements are associated with an increasing number of human developmental disorders [4,5]. Infracytogenetic rearrangements appear to be the pathogenic event in up to 15% of the mentally handicapped children, with a rapidly increasing number of recognizable phenotypes [3,7]. While *PAFAH1B1* haploinsufficiency causes non syndromal lissencephaly, the simultaneous deletion of *YWHAE* and *PAFAH1B1* causes Miller-Dieker

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doi:10.1016/j.ejmg.2010.06.009

syndrome (MDS [MIM 247200]) [11]. Although *YWHAE* (coding the 14-3-3 ε protein) is the candidate gene explaining the more severe phenotype of MDS, the phenotypic effect of *YWHAE* haploinsufficiency without loss of *PAFAH1B* has been recognized very recently in 12 patients [2,8,9]. We report here clinical, neuroradiological and molecular characterization of four patients affected with 17p13.3 deletion distal to *PAFAH1B1*.

2. Patient reports

2.1. Patient A

This young girl was referred for psychomotor delay, macrocephaly and dysmorphism. She was the second child of non consanguineous parents (father of French origin and mother from Madagascar). She was born at 37 weeks of gestation (WG), by cesarean section, for unexplained polyhydramnios. Birth parameters were at −1 SD: birth weight (BW) 2950 g, birth length (BL) 49 cm, birth occipito-frontal circumference (OFC) 33 cm. Minor neonatal feeding difficulties were recorded. She was investigated at 18 months of age for moderate psychomotor delay mainly affecting speech, and dysmorphic features. She weighted 10 kg (−0.5 SD), was 70 cm (−1 SD) tall, and had an OFC of 47.5 cm (+2 SD). She had wide forehead, small nose and coarse facial features (Fig. 1a and b). There was no hepatosplenomegaly, no joint contractures and there were normal deep tendon reflexes. Follow up confirmed progressive macrocephaly (OFC 52 cm, +3 SD at 3 years of age). At age 4 y 4 mo, her verbal IQ was 50, her performance IQ 57; and her total IQ 50, using WPPSI-III. Recurrent hematuria led to the discovery of multiple bilateral urolithiases, which remained unexplained after nephrologic workup. Urography revealed an ectopic ureter behind vena cava, which was operated. At last examination, at age 7 y 9 mo, her weight was 19.7 kg (−1 SD), her height was 111 cm (−2.7 SD) and OFC was 55 cm (+2.7 SD). Full IQ was 54 (VIQ 52, PIQ 57).

Brain MRI performed at age 2 y 9 mo and age 5 y disclosed the same findings: leucoencephalopathy (Fig. 2a, arrow), triventricular dilation (Fig. 2b) with enlargement of subarachnoid spaces (Fig. 2c). There was a Chiari type 1 malformation (Fig. 2d, arrow) but no signal abnormality of the posterior fossa. There was no abnormal lactate or N-acetyl-aspartate peaks on MRI spectroscopy (data not shown). Chiari malformation was successfully operated at age 6 y 8 mo. Motor and sensitive nerve conduction velocities were normal. Metabolic screening, including urinary organic acids was normal, excluding Canavan disease. Activities of hexosaminidases A and B measured in leukocytes were normal, excluding GM2 gangliosidosis.

2.2. Patient B

Patient B was referred at age 22 y. She was the second child of unrelated healthy parents. The pregnancy was uneventful. She was born at 35 WG after normal vaginal delivery. BW was 2320 g, BL was 41.5 cm and birth OFC was 30.5 cm. Feeding difficulties were noted in the first months of life. Persistent ductus arteriosus required surgery at age 3 y. Psychomotor delay was noted with ability to walk at age 2 y, mild speech delay, and moderate mental retardation allowing work in a protected environment. She also had short stature requiring growth hormone supplementation in childhood. At age 22 y, height was 146 cm (−3 SD) and OFC was 53 cm (−2.5 SD). She has dysmorphic features (Fig. 1c and d), short uvula, high arched palate, nasal voice and moderately short limbs. She also has unexplained chronic pulmonary arterial hypertension. Brain MRI showed marked bilateral white matter anomalies, and normal gyration, corpus callosum and posterior fossa (Fig. 2e, arrow).

2.3. Patient C

This girl was the first child of non consanguineous healthy parents, born at 40 WG, after prenatal diagnosis of moderate

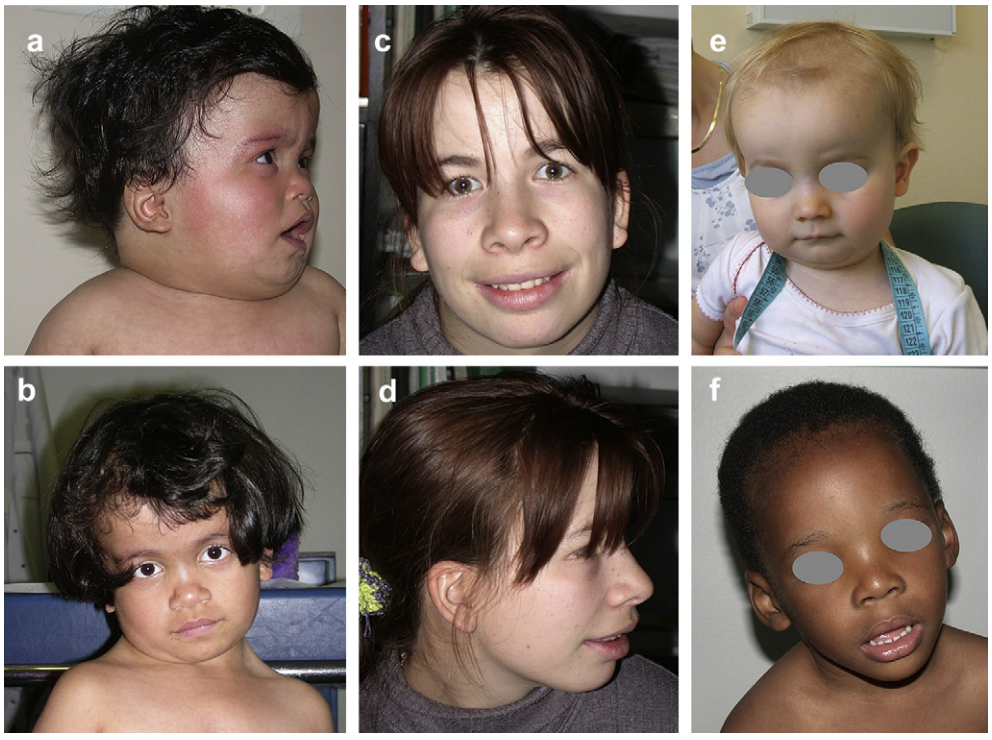

Fig. 1. clinical appearance. Patient A at (a) 9 mo and (b) 5 y-Patient B's front (c) and side (d) views at 22 y- (e) Patient C at 2 y- (f) Patient D at 4 y