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Brain & Development xxx (2017) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

A novel mutation of *WDR62* gene associated with severe phenotype including infantile spasm, microcephaly, and intellectual disability

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Received 16 February 2017; received in revised form 23 May 2017; accepted 11 July 2017

Abstract

The autosomal recessive form of primary microcephaly (MCPH) is a rare disorder characterized by head circumference of at least 3 standard deviation below the mean.

The MCPH exhibits genetic heterogeneity with thirteen loci (MCPH1-MCPH13) identified, and associated with variable degree of intellectual disability. It has been reported that *WDR62* is the second causative gene of autosomal recessive microcephaly (MCPH2) playing a significant role in spindle formation and the proliferation of neuronal progenitor cells.

We report a clinical feature, electroclinical findings, and clinical course of a patient with a severe phenotype of MCPH2 including microcephaly, refractory infantile spasms and intellectual disability. Genetic analysis detected a new homozygous splicing variant c.3335+1G>C in the WD repeat domain 62 (*WDR62*) gene, inherited from both heterozygous healthy parents, and an additional new heterozygous missense mutation c.1706T>A of G protein-coupled receptor 56 (*GPR56*) gene inherited from his healthy father.

The study seeks to broaden the knowledge of clinical and electroclinical findings of MCPH2 and to contribute to a better characterization of the genotype-phenotype correlation.

Keywords: Epilepsy; Infantile spasm; Microcephaly; MCPH; *WDR62*; Intellectual disability

1. Introduction

The autosomal recessive form of primary microcephaly (MCPH) is a rare disorder characterized by head circumference of at least 3 standard deviation below the mean associated with variable degree of intellectual disability [1].

The MCPH exhibits genetic heterogeneity with thirteen loci (MCPH1-MCPH13) identified, nevertheless, the available clinical data do not yet allow the identifying a specific phenotype linked to each MCPH locus [2].

Recent studies, supported by high resolution molecular techniques and neuroimaging data, are broadening the above described phenotype including motor deficit, language impairment, epilepsy, and a wide spectrum of brain malformations in addition to a typical simplified gyration pattern of the brain [3–6].

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http://dx.doi.org/10.1016/j.braindev.2017.07.003

Please cite this article in press as: Nardello R et al. A novel mutation of *WDR62* gene associated with severe phenotype including infantile spasm, microcephaly, and intellectual disability. Brain Dev (2017), http://dx.doi.org/10.1016/j.braindev.2017.07.003

Here, we report a patient with a severe phenotype of MCPH2 resulting from a new homozygous splicing variant c.3335+1G>C in the WD repeat domain 62 gene (*WDR62* – GenBank Accession NM_005682.5), inherited from both heterozygous healthy parents, and an additional new heterozygous missense variant c.1706T>A of G protein-coupled receptor 56 gene (*GPR56* also known as *ADGRG1* – GenBank Accession NM_005682.5) inherited from his healthy father in order to contribute to a better identification of the disorder and improve the detection of the genotype-phenotype correlation.

2. Case report

The detailed clinical evaluation of the patient was performed after obtaining written informed consents from parents.

The patient, a 15-year-old male adolescent, was the second offspring born to healthy Italian unrelated parents. His family history is remarkable for the intellectual disability occurring in a cousin of paternal line. He was born at term following an uneventful pregnancy with APGAR scores 8–10, head circumference 33 cm (10th centile), birth weight 2950 g (10th centile), height 49 cm (50th centile). The clinical postnatal course was uneventful until 7 months of age, when he showed symmetric spasms occurring in clusters associated with diffuse interictal EEG abnormalities suggesting a hypsarrhythmic pattern, and psychomotor development delay.

The electroclinical feature, evocative of Infantile Spasms diagnosis, suggested an antiepileptic treatment including Valproic acid and ACTH that induced a long-term, up to 3 years of age, seizure control and hypsarrhythmia disappearance.

At 3 years of age the spasms relapsed requiring a reassessment of antiepileptic treatment with different drugs, in monotherapy and politherapy, that were unevenly effective.

The brain magnetic resonance imaging (MRI), performed at 3 years of age, showed extensive areas of polymicrogyria in the right frontal lobe (Fig.1A) and abnormal gyration with gray–white matter blurring involving the left parietooccipital cortex (Fig.1B).

From 9 years of age the boy was a inpatient of our Department because of frequent seizure relapses often associated with motor and cognitive deterioration.

On neurological examination, the patient revealed spastic quadriplegia with more impaired left side, poor language development, microcephaly (49,4 cm <3rd centile), and cranio-facial dysmorphism (narrow forehead, prominent nose, large ears, short nasal filter, antiverse nostrils, full lips, microretrognathia and dysodontiasis). His weight and height were kg 33 (80th centile) and 130 cm (30th centile) respectively.

He was unable to be assessed by formal neuropsychological tests because of severe mental and neurological disabilities. He had fine and gross motor difficulties and could walk with support but he was able to fix, follow objects and smile sporadically. The boy did not achieve personal care as night-time toilet training, himself washing, dressing, and eating. He could speak only few meaningful sounds, used in association with restricted conventional repertoire of gestures to communicate with other individuals. The boy understood simple messages involving basic needs, and short phrases with high frequency words. The emotional development seemed less impaired. Because the multiple difficulties the boy followed from early age a programme of neurological and cognitive rehabilitation.

Ictal EEG showed high amplitude slow wave followed by decremental activity associated with spasm (Fig.1D).

Interictal EEG during drowsiness displayed isolated or short series of recurring and generalized irregular slow spikes and spike-waves complex discharges, mainly on frontal-central areas of both hemispheres (Fig.1E).

A comprehensive genetic test performed at 11 years of age showed a normal aCGH analysis (Affymetrix Cytoscan HD Array, hg19, 1Kb resolution) and excluded abnormalities of *TUBA1A* and *TUBB2B* genes. While a directly sequencing analysis of *GPR56* gene showed a new heterozygous missense variant 1706T>A (p.Val569Asp) which was predicted to be "probably deleterious" by the Align-GVGD, Polyphen2 and SIFT algorithms. His father and his sister were healthy carriers of the same variant.

The subsequent step of genetic examination, using target resequencing gene panels by Genome Analyzer IIx (Illumina) revealed a new homozygous variant c.3335+1G>C of the *WDR62* gene not reported in ExAC Database. The variant likely disrupts the splice site and is "likely pathogenic" according to the in silico prediction by HSF (Human Splicing Finder). The variant was detected in heterozygous unaffected both parents and sister.

3. Discussion

In the last years it has been reported that *WDR62* is one causative gene of autosomal recessive microcephaly (MCPH2) playing a significant role in spindle formation and the proliferation of neuronal progenitor cells [3–6]. To date, about 50% of MCPH is caused by *ASPM* and *WDR62* gene mutations [4,7].

The clinical manifestations of MCPH2 are individually variable in severity and include microcephaly, intellectual disability, language impairment, motor deficit and inconstant epilepsy (Table 1) [3–5].

In addition, a wide range of cortical malformations have been reported in patients with *WDR62* gene

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