Molecular and Cellular Probes xxx (2016) 1–6

Contents lists available at ScienceDirect

Molecular and Cellular Probes

journal homepage: www.elsevier.com/locate/ymcpr

WDR45 mutations in Rett (-like) syndrome and developmental delay: Case report and an appraisal of the literature

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form
8 January 2016
Accepted 8 January 2016
Available online xxx

Keywords:
WDR45
NBIA
BPAN
Rett syndrome
Intellectual disability

ABSTRACT

Mutations in the *WDR45* gene have been identified as causative for the only X-linked type of neurodegeneration with brain iron accumulation (NBIA), clinically characterized by global developmental delay in childhood, followed by a secondary neurological decline with parkinsonism and/or dementia in adolescence or early adulthood. Recent reports suggest that *WDR45* mutations are associated with a broader phenotypic spectrum. We identified a novel splice site mutation (c.440-2 A > G) in a 5-year-old Argentinian patient with Rett-like syndrome, exhibiting developmental delay, microcephaly, seizures and stereotypic hand movements, and discuss this finding, together with a review of the literature. Additional patients with a clinical diagnosis of Rett (-like) syndrome were also found to carry *WDR45* mutations before (or without) clinical decline or signs of iron accumulation by magnetic resonance imaging (MRI). This information indicates that *WDR45* mutations should be added to the growing list of genetic alterations linked to Rett-like syndrome. Further, clinical symptoms associated with *WDR45* mutations ranged from early-onset epileptic encephalopathy in a male patient with a deletion of *WDR45* to only mild cognitive delay in a female patient, suggesting that analysis of this gene should be considered more often in patients with developmental delay, regardless of severity. The increasing use of next generation sequencing technologies as well as longitudinal follow-up of patients with an early diagnosis will help to gain additional insight into the phenotypic spectrum associated with *WDR45* mutations.

1. Introduction

Neurodegeneration with brain iron accumulation (NBIA, previously known as Hallervorden-Spatz disease) is a group of neurodegenerative diseases characterized by iron accumulation generally observed in the globus pallidus and substantia nigra, and occasionally in the cortex and cerebellum. The term NBIA was introduced by Hayflick et al. in 2003 for all neurological disorders that lead to progressive extrapyramidal symptoms, intellectual impairment and magnetic resonance imaging (MRI) evidence of abnormal brain iron deposition [1].

To date, mutations in ten genes have been recognised as causative for NBIA subtypes [2]. Most of these subtypes can be diagnosed by MRI, in combination with clinical findings, and can be confirmed by specific mutation analysis. While NBIA1 and NBIA2 and some rarer subtypes have been known for more than a decade, the use of modern next-generation sequencing technologies has led to the discovery of several additional forms in the last years; among them is the only known X-linked NBIA form caused by mutations in the *WDR45* gene [3]. While mutations in this gene were originally identified in a very restricted phenotype, recent studies [4–6] suggest that the phenotypic spectrum may be substantially broader, including Rett- and Rett-like syndrome, epileptic phenotypes and isolated intellectual disability. We present here a 5-year-old Argentinian patient with Rett-like syndrome who carries a novel splice site mutation (c.440-2 A > G) in the *WDR45* gene, and appraise and discuss the current knowledge of the mutational and clinical spectra linked to *WDR45* mutations.

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http://dx.doi.org/10.1016/j.mcp.2016.01.003
0890-8508/

2. Case report

The female patient (Fig. 1A) was born to healthy, unrelated Argentinian parents via Caesarean section after a complicated pregnancy with placental haematoma and abruption in the first trimester. She showed delayed motor milestones with head control at eight months and unassisted walking at 24 months of age as well as acquired microcephaly. The patient had two febrile seizures at the age of two years with later electro-encephalograms (EEGs) revealing abnormal background rhythms. At the time of examination, she was being treated with valproic acid 3 × 125 mg per day. The girl displayed stereotypic movements of the hands, including washing and wringing as well as hand mouthing, starting from six months of age. She also showed intense eye contact, bruxism, permanent drooling and a social smile with unexplained bouts of laughter, smiles or shouts. The patient suffers from chronic constipation, does not reject any kind of food and eats using her hands. Neither the sleep pattern nor breathing appears disturbed. Language development was considerably delayed, starting at four years of age. Currently (at five years), she uses just a few words in Spanish, including “mamá”, “papá” and “agua” (“mom”, “dad”, “water”). She shows a dyspractic walk and runs with her body tilted forward.

MRI scans at three years of age (Fig. 1B) showed no evidence of iron deposits in the substantia nigra or globus pallidus, but a thin corpus callosum and hypoplasia and/or mild atrophy of the pons. Mutational analysis of the *WDR45* gene via high resolution melting analysis [7], followed by direct sequencing, revealed a heterozygous exchange two bases upstream of exon 8, very likely resulting in a splice defect (c.440−2 A > G, Fig. 1C). *In silico* analyses (*i.e.* MutationTaster and Human Splicing Finder) predicted a damaging effect with a high probability (1.0). The sequence of this splice acceptor site is highly conserved among selected vertebrates (i.e. human, rhesus, mouse, dog, *Xenopus tropicalis* and zebrafish) and is not present in any of the ~64,928 alleles in the Exome Aggregation Consortium (ExAC) Browser (Cambridge, MA, URL: http://exac.broadinstitute.org, 01/2016). The parents of the patient do not carry the exchange, confirming a *de novo* mutation. The investigation was approved by the Ethics committee of the Ruhr-University Bochum and adhered to the Declaration of Helsinki protocols. The parents of the patient gave informed consent to all analyses and to the publication of results and photographs.

3. *WDR45* gene mutations in neurodegeneration with brain iron accumulation (NBIA), Rett (-like) syndrome and additional phenotypes – appraisal of the current state of knowledge

3.1. BPAN: the first X-linked NBIA type

Mutations in the *WDR45* gene on the X chromosome were first described as causative for a new NBIA subtype in the years 2012 and 2013 via exome sequencing in two groups of patients with a very distinctive phenotype called “static encephalopathy of childhood with neurodegeneration in adulthood” (SENDA) [8,9]. The affected individuals universally showed an early-onset global developmental delay that was static until adolescence/early adulthood when a secondary neurological decline was noted including parkinsonism, dystonia and dementia. All patients in one of the original studies were female, giving rise to the assumption that *WDR45* mutations may be lethal in males [9]. In the second study, however, both males and females were described with equal clinical presentations, and somatic mosaicism in males was suggested as the most likely explanation for this phenomenon [8]. More recent reports indicate that even germline mutations in males may be viable but associated with a more severe phenotype [6,10].

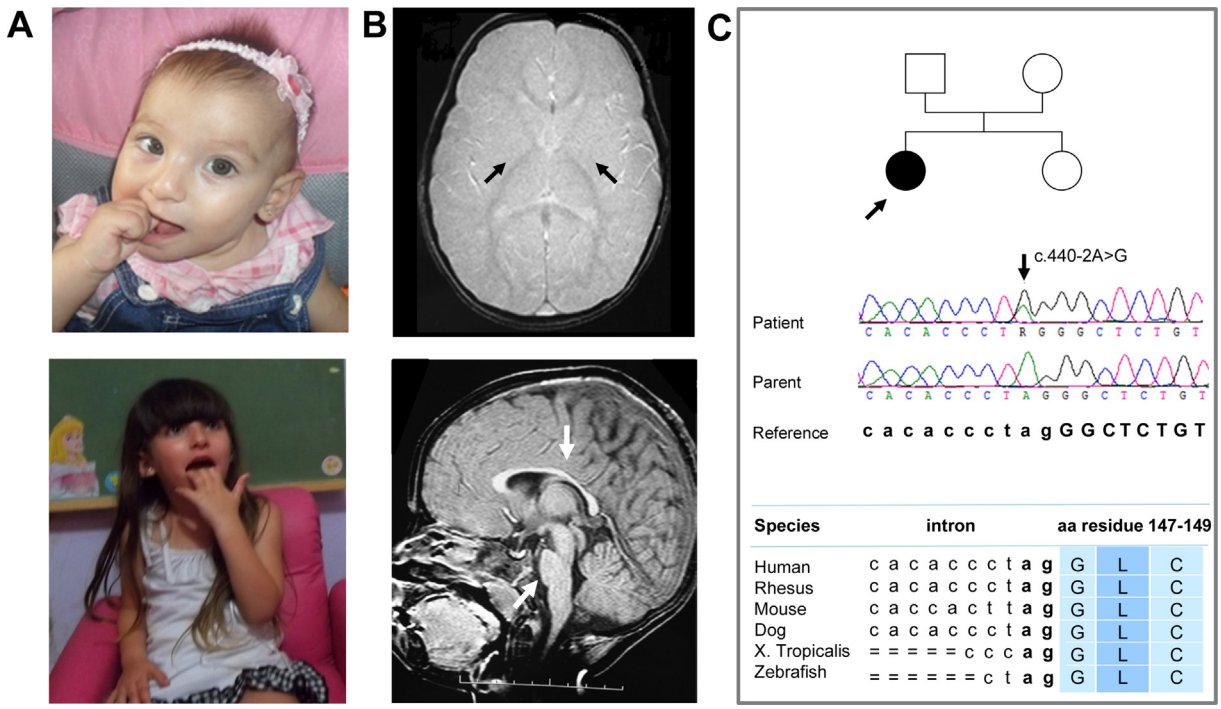

Fig. 1. Panel A: The patient pictured at eight months and 3.8 years of age. Panel B: Cranial MRI images obtained at the age of three years. Upper picture: gradient-echo T2 start-weighted image showing the normal aspect of the *substantia nigra* and *globus pallidus* as well as no evidence of iron deposits (arrows); lower picture: T1-weighted sagital view of the encephalus, revealing a thin *corpus callosum* and hypoplasia of the pons (arrows). Panel C: Pedigree, genomic sequence of the patient compared to a parent sequence, and amino acid alignments (human, rhesus, mouse, dog, *Xenopus tropicalis* and zebrafish), showing high conservation of the mutated base across different species.

Please cite this article in press as: S. Hoffjan, et al., *WDR45* mutations in Rett (-like) syndrome and developmental delay: Case report and an appraisal of the literature, Molecular and Cellular Probes (2016), http://dx.doi.org/10.1016/j.mcp.2016.01.003