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

Sabine Hoffjan [a, b, *], Aysegül Ibisler [a, b], Anne Tschentscher [a], Gabriele Dekomien [a, b], Carla Bidinost [c], Alberto L. Rosa [c]

[a] Department of Human Genetics, Ruhr-University Bochum, Germany
[b] Center for Rare Diseases Ruhr (CeSER), Bochum, Germany
[c] Sanatorio Allende and Fundación Allende, Córdoba, Argentina

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.

* Corresponding author. Department of Human Genetics, Ruhr-University Bochum, Germany.
E-mail address: sabine.hoffjan@rub.de (S. Hoffjan).

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].

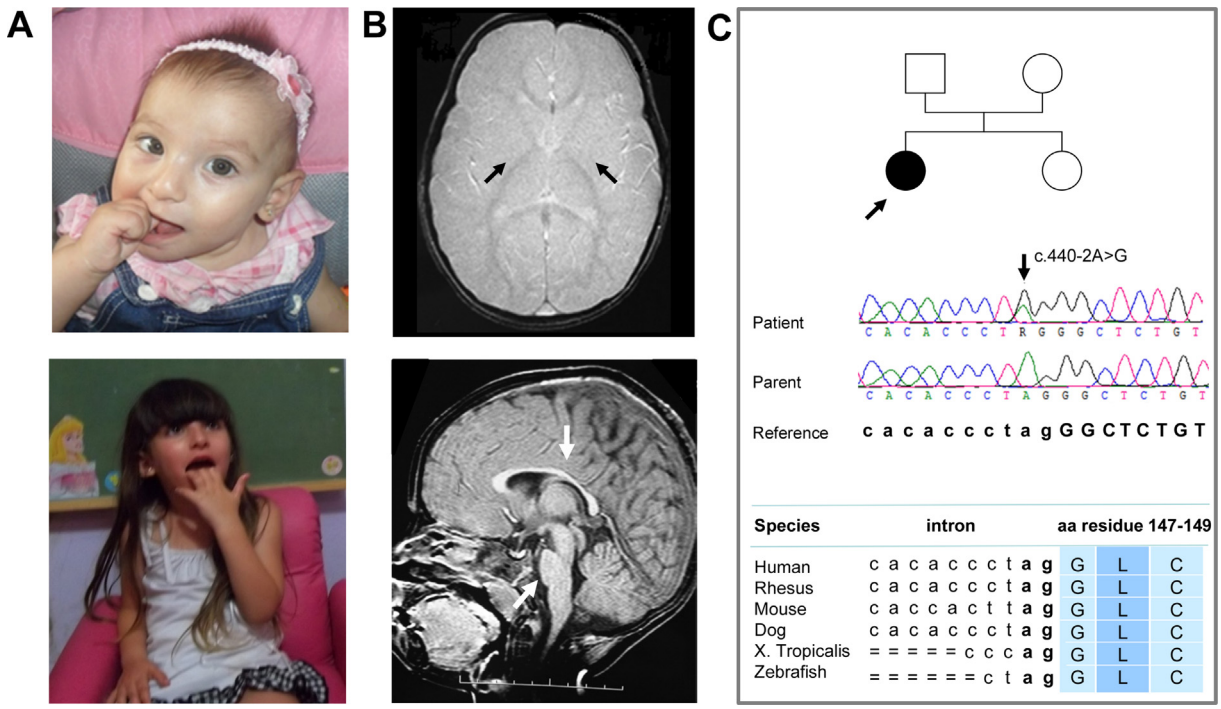

Fig. 1. Panel A: The patient pictured at eight months and 3.8 years of age. Panel B: Cranial MRI images obtained at the age of three years. Upper picture: gradient-echo T2 start-weighted image showing the normal aspect of the *substantia nigra* and *globus pallidus* as well as no evidence of iron deposits (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

The *WDR45* gene is located at Xp11.23 and comprises twelve exons, of which the first two are non-coding (Fig. 2). It encodes a member of the WD40 repeat protein family that displays a β-propeller structure, facilitating protein–protein interactions [8]. Therefore, the X-linked NBIA was named "beta-propeller protein-associated neurodegeneration", BPAN [8]. WDR45 was shown to play a major role in autophagy, suggesting that disturbed intracellular degradation of cytoplasmic materials might be an important pathogenic mechanism for this neurodegenerative disorder [9]. Consistently, autophagic activity was shown to be reduced in lymphoblastoid cell lines from affected individuals, even though not totally impaired [9].

In a thorough evaluation of 23 BPAN patients (20 females and 3 males), Hayflick et al. [3] reviewed the phenotypic spectrum associated with *WDR45* mutations. They showed a rather uniform clinical expression, with global developmental delay in childhood and a secondary neurological deterioration, including dystonia, parkinsonism and/or dementia in early adulthood. Some additional patients with a similar phenotype were subsequently reported [11–17]. Typical MRI signs for BPAN include iron deposition in the substantia nigra and globus pallidus with a 'halo' of T1 hyperintense signal in the substantia nigra [3]. Van Goethem et al. [18] also reported calcification of the globus pallidus in a BPAN patient and, from a review of the literature, suggested that this finding may be a common but non-specific sign of NBIAs. Recent reports have shown that susceptibility-weighted imaging (SWI) MRI may be the most sensitive method to detect iron deposition already in the early stages of clinical disease [19]. Currently, there are no clear biomarkers for BPAN, making clinical diagnosis difficult in early infancy. However, in a patient identified in childhood, a persistent elevation of neuron specific enolase (NSE) in serum and cerebrospinal fluid was reported, which might indicate neuronal damage from infancy [19]. Analyses in additional patients are necessary to confirm NSE involvement in BPAN. Despite the overall uniform clinical picture, it was suggested early that this restricted BPAN phenotype might broaden with future investigations [3]. In the last two years, a total of 12 child patients carrying a *WDR45* mutation have been identified, most of them being before the typical secondary decline (summarized in Table 1). The originally suspected diagnoses in these paediatric patients varied considerably, ranging from Rett (-like) syndrome to epileptic phenotypes and (mild) intellectual disability.

3.2. Rett (-like) syndrome

A substantial number of female patients, who were eventually found to carry pathogenic *WDR45* mutations and thus received the diagnosis of BPAN, had had a former diagnosis of Rett-like syndrome or displayed Rett-like symptoms [3]. Overlapping clinical features between the early stages of BPAN and Rett or Rett-like syndrome include developmental delay, stereotypical hand movements, seizures, sleep disorder and spasticity. Therefore, an analysis of *WDR45* mutations was suggested for patients with features of Rett or Rett-like syndrome who do not carry mutations in known Rett genes (*i.e.*, *MECP2* and potentially *CDKL5* and *FOXG1*), even without the typical iron accumulation in the brain that may not be observable at an early stage [3]. Indeed, a few recent cases, including the present one, provide support for this hypothesis.

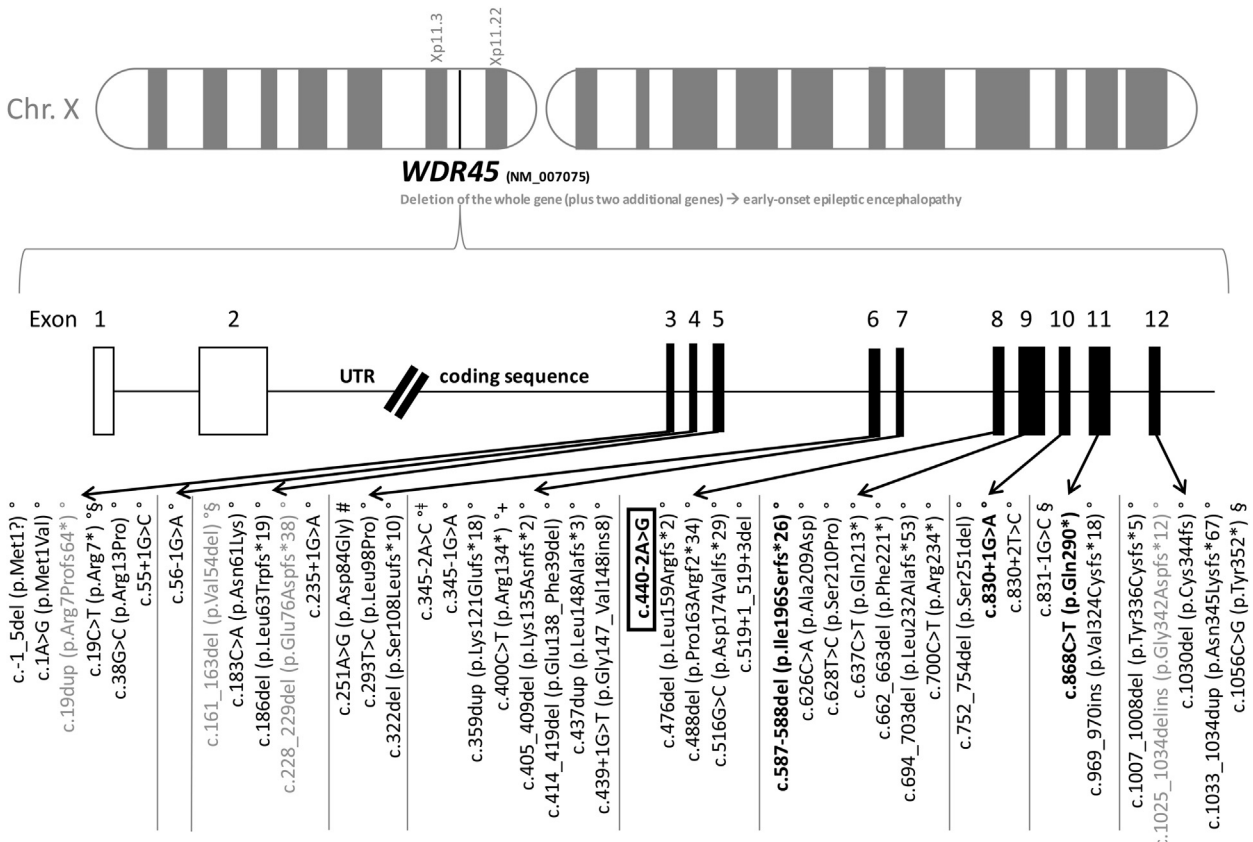

Fig. 2. Localization and structure of the *WDR45* gene with the mutations described for different phenotypes in the literature as well as the present study. bold: Rett (-like) syndrome; °: NBIA (SENDA subtype); §: moderate to severe intellectual disability; #: mild cognitive delay; +: epileptic spasms; ‡: originally described as c.342-2 A > C; blue: male patients; box: novel mutation described in the present study.

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

Table 1
Pediatric patients carrying *WDR45* mutations (modified from Ref. [19]).

Pediatric patient with *WDR45* mutation	Originally suspected diagnosis	*WDR45* mutation	Mutation type	Inheritance	Age at mutation detection	Sex	Age at MRI iron deposition	Additional MRI findings	Microcephaly	Epilepsy	Facial dysmorphism
Present study	Rett-like syndrome	c.440-2 A > G	Splicing	*de novo*	5y	f	n.a.	Thin corpus callosum, atrophy of pons	+	+	(+)
Ohba et al. [4]	Rett syndrome	c.830+1 G > A	Splicing	*de novo*	14y	f	11y	–	–	+	–
Okamoto et al. [20]	Rett syndrome	c.868 C > T, p.Q290*	Nonsense	*de novo*	6y	f	6y	Delayed myelination, enlarged lateral ventricles	+	+	+
Khalifa et al. [21]	Rett(-like) syndrome	c.587-588del[a]	Frameshift	*de novo*	11y	f	11y	Thin corpus callosum, hypomyelination	+	–	(–)
Uchino et al. [24]	Severe developmental delay, stereotypic hand movements	c.1056 C > G, p.Y352*	Nonsense	*de novo*	9y	f	9y	–	–	+	n.a.
Hamdan et al. [25]	Severe ID	c.19 C > T, p.R7*	Nonsense	*de novo*	4y	f	n.a.	–	–	+	–
Rathore et al. [12]	Severe ID, dystonia	c.345-2 A > C[b]	Splicing	*de novo*	15y	f	13y	Cerebellar atrophy, hypomyelinantion	n.a.	+	n.a.
Takano et al. [19]	Severe developmental delay	c.831-1 G > C	Splicing	*de novo*	3y	f	3y	Thin corpus callosum, delayed myelination	+	–	+
Zarate et al. [10]	ID	c.161_163delTGG	In-frame deletion	inherited[c]	14y	f	14	–	n.a.	n.a.	–
Long et al. [5]	Mild cognitive delay	c.251 A > G, p.D84G	Missense	*de novo*[d]	17y	f	17y	–	–	–	–
Abidi et al. [6]	Early-onset epileptic encephalopathy	19.9 kb microdeletion including *WDR45*	Complete deletion	*de novo*	5y	m	5y	Global brain atrophy	–	+	n.a.
Xixis et al. [22]	Epileptic spasms	c.400 C > T, p.R134*	Nonsense	*de novo*	6y	f	n.a.	–	n.a.	+	n.a.

ID: intellectual disability; y: years; ms: months; f: female, m: male; n.a.: not available.
[a] Patient additionally carries three mutations in the *POLR3A* gene.
[b] Originally described as as c.342-2 A > C.
[c] 20-year-old brother carrying the same mutation is more severely affected; mother is mosaic for the mutation.
[d] Mother does not carry the mutation, father is unavailable for testing.

Ohba et al. [4] reported a 14-year-old Japanese girl fulfilling the clinical criteria for classical Rett syndrome, but without a pathogenic mutation in *MECP2*, in whom exome sequencing revealed a *de novo* splice mutation in *WDR45*. Sequential brain MRIs showed that iron deposition in the globus pallidus and substantia nigra was detectable at 11 years of age. Another 6-year-old Japanese girl was presented shortly thereafter; she also had initially been diagnosed with Rett syndrome, and, via exome sequencing, was found to carry a *de novo* nonsense mutation in *WDR45*, confirming a diagnosis of BPAN [20]. Brain MRIs in this little girl were normal at the age of four years, but already showed hypointense signals in the globus pallidus and substantia nigra, presumably indicating iron accumulation, at six years of age. The Argentinian patient with the novel *WDR45* splice mutation presented in the present report was five years old at the time of evaluation and, at this point, iron deposition had not been noted in brain MRIs. However, the MRI techniques used differed between the various reports, and it was recently suggested that susceptibility-weighted imaging (SWI) MRI might be the most sensitive method for the detection of iron deposition in the early stage of disease [19]. In another case report, an 11-year-old Egyptian female patient was presented with severe intellectual disability and Rett-like features, including stereotypic hand movements; she showed both hypomyelination and progressive iron accumulation in brain MRIs [21]. Via exome sequencing, this patient was found to carry likely pathogenic mutations in both the *WDR45* and *POLR3A* genes, making differential diagnosis between X-linked NBIA and a subtype of leukodystrophy difficult [21]. The clinical symptoms of this patient also indicate the possible relevance and role of *WDR45* mutations in patients with Rett (-like) features.

Taken together, the overall frequency of *WDR45* mutations in Rett (-like) syndrome appears to be rather low currently and larger studies are required to confirm this assumption. Still, current reports, including the present one, clearly suggest that *WDR45* should be included in the list of genes that need to be considered when dealing with Rett-like phenotypes, for example in panel analyses (see below). Thorough clinical follow-up of the patients studied to date is required in order to evaluate whether all of them will suffer from a secondary neurological decline in adolescence or early adulthood, as it is characteristic for SENDA/BPAN, or whether the clinical course may also differ from this sequence of events.

Patients and their families may benefit from an early diagnosis in relation to two main aspects: first, an accurate assessment of the recurrence risk (which is assumed to be very low in most cases) is very helpful for family planning issues, and second, physicians can look out for early symptoms of parkinsonism, and initiate prompt and appropriate medication [3]. Through early molecular genetic analysis of *WDR45*, the diagnosis of BPAN is actually possible before signs of iron accumulation, a typical diagnostic hallmark of NBIA disorders. Longitudinal follow-up of additional patients with early diagnosis, preferably with standardized MRI techniques, is needed to gain better knowledge and understanding of the time course of brain iron accumulation in BPAN.

3.3. Intellectual disability

While all patients described so far have shown moderate to severe global developmental delay, regardless of whether they had

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

been clinically diagnosed with SENDA or Rett (-like) syndrome, a recent case report suggests that *WDR45* mutations may also be found in patients with non-specific and even mild cognitive delay [5]. The female patient described in this report mainly showed difficulties with expressive and receptive language, requiring speech therapy, but attended her "age-appropriate school grade" [5]. She underwent the first brain MRI at 17 years of age and showed signs of iron accumulation, then prompting molecular genetic analysis of *WDR45*, which revealed a *de novo* heterozygous missense mutation. Therefore, the authors recommended *WDR45* testing to be considered even in cases of mild cognitive or language delay, if MRI scans indicate possible iron involvement [5]. However, there are presently no data as to whether *WDR45* mutations occur in mildly delayed children, in whom iron accumulation is not detectable by MRI. Future studies using next generation sequencing will hopefully be able to underpin such investigations.

3.4. Early-onset epileptic encephalopathy and epileptic spasms

On the severe end of the phenotypic spectrum, the first male patient carrying a 19.9 kb microdeletion on Xp11.23 including *WDR45* has been described; this patient presented with an early-onset epileptic encephalopathy [6]. This boy had a very severe phenotype, with absence of motor or speech development and cortical blindness. Iron accumulation in the brain was detected at five years of age. Since no evidence for mosaicism (in lymphoblasts) was found in this patient, the authors concluded that the severe disease course may be the result of a germline mutation [6]. On the other hand, the microdeletion included two additional genes of currently unknown significance in relation to brain development, such that involvement of these two genes, as part of a contiguous gene syndrome, cannot be excluded at the moment. Another female patient carrying a heterozygous nonsense mutation in *WDR45* was recently described; she presented with early-onset, focal seizures and epileptic spasms, accompanied by developmental delay [22]. Therefore, the role of *WDR45* deletions as well as point mutations for early-onset epileptic phenotypes warrants detailed investigation.

4. Conclusion and future perspectives

The increasing use of next generation sequencing methods now allows analyses of a group of genes (so-called panel analysis), the whole exome or genome of patients at reduced costs. For heterogeneous diseases, such as NBIA, Rett-like syndrome or intellectual disability, these approaches provide substantial advances compared with classical Sanger sequencing of one (or a few) candidate genes, although interpretation of the results as well as ethical questions remain challenges [23]. From what is currently known about *WDR45* mutations, this gene should be included in panel analyses not only for NBIA, but also for Rett (-like) syndrome, intellectual disability and potentially early-onset epileptic phenotypes. At this stage, no clear genotype–phenotype correlation is obvious. In contrast to original assumptions, recent reports suggest that males with germline mutations are viable but may show a more severe phenotype than heterozygous females [6,10]. Nonetheless, only five males with *WDR45* mutations have been described to date, limiting conclusions regarding the phenotypic spectrum in hemizygotes. Although all other reported BPAN patients have been sporadic cases and mutations presumably occurred *de novo*, a recent report presented a sibling pair carrying an in-frame deletion of *WDR45*, where the affected male was considerably more severely affected than his sister, and the mother was found to be mosaic for the genetic alteration [10]. The authors concluded that inherited *WDR45* mutations are probably very rare, but still possible. Larger exome sequencing studies for NBIA as well as various degrees of intellectual disability will certainly reveal further insights into the clinical spectrum associated with *WDR45* mutations, both in mild and severe cases, in the near future. Additionally, this approach might identify additional familial cases and help to better characterize the phenotype in males. Furthermore, long-term follow-up of patients detected at an early stage is mandatory, in order to delineate the time course of iron deposition and potential neurological decline and, thus, to get a more complete picture of the phenotypical spectrum of *WDR45* mutations.

Acknowledgements

We thank A. Surur and M. Albarenque for help with MRI imaging. ALR is Principal Investigator from the Argentina National Research Council (CONICET). Anne Tschentscher was supported by a dissertation grant of the "Heinrich und Alma Vogelsang Stiftung". The authors do not have any conflicts of interest.

References

[1] S.J. Hayflick, Unraveling the Hallervorden-Spatz syndrome: pantothenate kinase-associated neurodegeneration is the name, Curr. Opin. Pediatr. 15 (2003) 572–577.
[2] P. Hogarth, Neurodegeneration with brain iron accumulation: diagnosis and management, J. Mov. Disord. 1 (2015) 1–13, http://dx.doi.org/10.14802/jmd.14034.
[3] S.J. Hayflick, M.C. Kruer, A. Gregory, T.B. Haack, M.A. Kurian, H.H. Houlden, et al., β -Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation, Brain 136 (2013) 1708–1717, http://dx.doi.org/10.1093/brain/awt095.
[4] C. Ohba, S. Nabatame, Y. Iijima, K. Nishiyama, Y. Tsurusaki, M. Nakashima, et al., De novo WDR45 mutation in a patient showing clinically Rett syndrome with childhood iron deposition in brain, J. Hum. Genet. 59 (2014) 292–295, http://dx.doi.org/10.1038/jhg.2014.18.
[5] M. Long, N. Abdeen, M.T. Geraghty, P. Hogarth, S. Hayflick, S. Venkateswaran, Novel WDR45 mutation and pathognomonic BPAN imaging in a young female with mild cognitive delay, Pediatrics 136 (2015) e714–717, http://dx.doi.org/10.1542/peds.2015-0750.
[6] A. Abidi, C. Mignon-Ravix, P. Cacciagli, N. Girard, M. Milh, L. Villard, Early-onset epileptic encephalopathy as the initial clinical presentation of WDR45 deletion in a male patient, Eur. J. Hum. Genet. (2015), http://dx.doi.org/10.1038/ejhg.2015.159. Epub ahead of print.
[7] M. Erali, C.T. Wittwer, High resolution melting analysis for gene scanning, Methods 50 (2010) 250–261.
[8] T.B. Haack, P. Hogarth, M.C. Kruer, A. Gregory, T. Wieland, T. Schwarzmayr, et al., Exome sequencing reveals de novo WDR45 mutations causing a phenotypically distinct, X-linked dominant form of NBIA, Am. J. Hum. Genet. 91 (2012) 1144–1149, http://dx.doi.org/10.1016/j.ajhg.2012.10.019.
[9] H. Saitsu, T. Nishimura, K. Muramatsu, H. Kodera, S. Kumada, K. Sugai, et al., De novo mutations in the autophagy gene WDR45 cause static encephalopathy of childhood with neurodegeneration in adulthood, Nat. Genet. 45 (2013) 445–449, http://dx.doi.org/10.1038/ng.2562.
[10] Y.A. Zarate, J.R. Jones, M.A. Jones, F. Millan, J. Juusola, A. Vertino-Bell, et al., Lessons from a pair of siblings with BPAN, Eur. J. Hum. Genet. (2015), http://dx.doi.org/10.1038/ejhg.2015.242. Epub ahead of print.
[11] W.M. Verhoeven, J.I. Egger, D.A. Koolen, H. Yntema, S. Olgiati, G.J. Breedveld, et al., Beta-propeller protein-associated neurodegeneration (BPAN), a rare form of NBIA: novel mutations and neuropsychiatric phenotype in three adult patients, Park. Relat. Disord. 20 (2014) 332–336, http://dx.doi.org/10.1016/j.parkreldis.2013.11.019.
[12] G.S. Rathore, C.P. Schaaf, A.J. Stocco, Novel mutation of the WDR45 gene causing beta-propeller protein-associated neurodegeneration, Mov. Disord. 29 (2014) 574–575, http://dx.doi.org/10.1002/mds.25868.
[13] Y. Ichinose, M. Miwa, A. Onohara, K. Obi, K. Shindo, H. Saitsu, et al., Characteristic MRI findings in beta-propeller protein-associated neurodegeneration (BPAN), Neurol. Clin. Pract. 4 (2014) 175–177.
[14] T. Ozawa, R. Koide, Y. Nakata, H. Saitsu, N. Matsumoto, K. Takahashi, et al., A novel WDR45 mutation in a patient with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), Am. J. Med. Genet. A 164A (2014) 2388–2390, http://dx.doi.org/10.1002/ajmg.a.36635.
[15] A. Tschentscher, G. Dekomien, S. Ross, K. Cremer, G.M. Kukuk, J.T. Epplen, et al., Analysis of the C19orf12 and WDR45 genes in patients with neurodegeneration with brain iron accumulation, J. Neurol. Sci. 349 (2015) 105–109, http://dx.doi.org/10.1016/j.jns.2014.12.036.
[16] K. Nishioka, G. Oyama, H. Yoshino, Y. Li, T. Matsushima, C. Takeuchi, et al., High frequency of beta-propeller protein-associated neurodegeneration (BPAN) among patients with intellectual disability and young-onset

parkinsonism, Neurobiol. Aging 36 (2015) 2004, http://dx.doi.org/10.1016/j.neurobiolaging e9-2004.e15.
[17] S.W. Ryu, J.S. Kim, S.H. Lee, Beta-Propeller-Protein-Associated Neurodegeneration: A Case of Mutation in WDR45, J. Clin. Neurol. 11 (2015) 289–291, http://dx.doi.org/10.3988/jcn.2015.
[18] G. Van Goethem, J.H. Livingston, D. Warren, A.J. Oojageer, G.I. Rice, Y.J. Crow, Basal ganglia calcification in a patient with beta-propeller protein-associated neurodegeneration, Pediatr. Neurol. 51 (2014) 843–845, http://dx.doi.org/10.1016/j.pediatrneurol.2014.08.017.
[19] K. Takano, N. Shiba, K. Wakui, T. Yamaguchi, N. Aida, Y. Inaba, et al., Elevation of neuron specific enolase and brain iron deposition on susceptibility-weighted imaging as diagnostic clues for beta-propeller protein-associated neurodegeneration in early childhood: additional case report and review of the literature, Am. J. Med. Genet. A (2015), http://dx.doi.org/10.1002/ajmg.a.37432. Epub ahead of print.
[20] N. Okamoto, T. Ikeda, T. Hasegawa, Y. Yamamoto, K. Kawato, T. Komoto, et al., Early manifestations of BPAN in a pediatric patient, Am. J. Med. Genet. A 164A (2014) 3095–3099, http://dx.doi.org/10.1002/ajmg.a.36779.
[21] M. Khalifa, L. Naffaa, Exome sequencing reveals a novel WDR45 frameshift mutation and inherited POLR3A heterozygous variants in a female with a complex phenotype and mixed brain MRI findings, Eur. J. Med. Genet. 58 (2015) 381–386, http://dx.doi.org/10.1016/j.ejmg.2015.05.009.
[22] K.I. Xixis, M.A. Mikati, Epileptic spasms: a previously unreported manifestation of WDR45 gene mutation, Epileptic Disord. (2015). Epub ahead of print.
[23] V. Precone, V. Del Monaco, M.V. Esposito, F.D. De Palma, A. Ruocco, F. Salvatore, et al., Cracking the code of human diseases using next-generation sequencing: applications, challenges, and perspectives, Biomed. Res. Int. (2015) 161648. Epub 2015 Nov 19.
[24] S. Uchino, H. Saitsu, S. Kumada, S. Nakata, N. Matsumoto, Stereotypic hand movements in ß-propeller protein-associated neurodegeneration: first video report, Mov. Disord. Clin. Pract. 2 (2015) 190–191.
[25] F.F. Hamdan, M. Srour, J.M. Capo-Chichi, H. Daoud, C. Nassif, L. Patry, et al., De novo mutations in moderate or severe intellectual disability, PLoS Genet. 10 (2014) e1004772, http://dx.doi.org/10.1371/journal.pgen.1004772.

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