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ORIGINAL COMMUNICATION

Boucher–Neuhäuser syndrome: cerebellar degeneration, chorioretinal dystrophy and hypogonadotropic hypogonadism: two novel cases and a review of 40 cases from the literature

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Abstract The combination of progressive cerebellar degeneration, hypogonadotropic hypogonadism and chorioretinal dystrophy defines the rare Boucher–Neuhäuser syndrome (BNS), which has recently been linked to autosomal-recessive mutations in the *PNPLA6* gene in four index patients. Here we present two novel unrelated patients with BNS, where we identified four recessive *PNPLA6* mutations (3 of them novel) as the genetic cause, using a targeted high-throughput approach. This finding provides the first replication from independent families that BNS is caused by *PNPLA6* and, moreover, highlights *PNPLA6* as the major gene leading to BNS. Given the fact that the major gene causing BNS has thus now been identified, we summarize the spectrum of clinical presentations and phenotype evolution of BNS based on a systematic in-depth review of the literature of previously published cases ($n = 40$). Both the two cases presented here and our review of the literature propose that the clinical presentation of BNS can be variable regarding both the age (ranging from 1 to 40 years) and the clinical symptoms at onset (cerebellar ataxia in 38 %; vision loss in 36 %; delayed puberty in 26 %). A substantial fraction of BNS cases may present with relatively selective atrophy of the superior and dorsal parts of the cerebellar vermis along with atrophy of the cerebellar hemispheres on MRI, while brainstem or cortical changes on MRI seem to be present only in small fractions. Also in the literature, no other major genetic causes of BNS other than *PNPLA6* mutations were identified.

Keywords Ataxia · Recessive ataxia · Spastic ataxia · Early onset ataxia · Motor neuron disease · Hereditary spastic paraplegia · Genetics · Retina · Chorioretinal dystrophy · Phospholipids

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Introduction

Degenerative cerebellar ataxia is frequently found in combination with additional non-cerebellar deficits, giving rise to distinct syndromes. For example, it can occur in association with hypogonadotropic hypogonadism, as described in 1908 by Holmes [1] (Gordon Holmes syndrome). Similarly, cerebellar ataxia can be accompanied by retinal changes as, e.g., in spinocerebellar ataxia (SCA) type 7. However, the combined presence of deficits within

all three domains—cerebellum, gonadic endocrinology and retina—is rarely found in the same patient. It was Boucher and Gibberd [2] who first reported the combination of slowly progressive ataxia, hypogonadotropic hypogonadism and chorioretinal degeneration in single families. Later, this syndrome was recognized as a specific disease entity known as Boucher–Neuhäuser syndrome (BNS) (OMIM 215470) [1, 3, 4], named after the first authors of the first case descriptions. Very recently, recessive mutations in the *PNPLA6* gene were reported in four families with the clinical phenotype of BNS, but also in one patient with Gordon Holmes syndrome and one with hereditary spastic paraparesis [5], suggesting that *PNPLA6* mutations cause BNS not as an isolated syndrome, but as a disease cluster on a continuous spectrum of neurodegenerative disorders (for an overview see [6]). Here we provide a detailed phenotype description of two novel index patients presenting with variable cerebellar ataxia, chorioretinal dystrophy and hypogonadotropic hypogonadism associated with recessive mutations in the *PNPLA6* gene. Moreover, given the thereby now well-established link between BNS and *PNPLA6* mutations, we review all published BNS cases focusing on the distribution, frequency and onset of both clinical (neurological, ophthalmological and endocrinological) findings and diagnostic testing including imaging, genetics and laboratory work-up.

Case descriptions

Index patient #1

The patient was referred to us at age 22 years with cerebellar ataxia and hypogonadotropic hypogonadism. At this time visual acuity was reportedly normal and a diagnosis of Gordon Holmes syndrome was established. Testosterone substitution was started. Four years after the initial visit this patient was re-evaluated with newly recognized loss of vision, chorioretinal dystrophy and progressive ataxia of gait.

First symptoms occurred in early childhood before age four years and included gait imbalance and frequent falls. Since then, gait slowly deteriorated. Blurred vision and "jumping eyes" were first noted around age 16 years but subjectively improved until age 25 when he complained of reduced vision again. Speech became progressively slurred. The family history including one brother and two stepsiblings was unremarkable (see Fig. 1a for pedigree).

The patient was of tall stature (186 cm) and weighed 65 kg, resulting in a body mass index of 18.6 kg/m^2. On clinical examination cerebellar loss of function was reflected both in ataxia of stance, gait and arm/leg movements, moderately dysarthric speech and ocular motor signs. This included downbeat nystagmus, horizontal gaze-evoked nystagmus, rebound nystagmus and saccadic smooth pursuit. Visual suppression of the vestibulo-ocular reflex (VOR) was severely impaired. At the same time, no clinical signs of peripheral audio-vestibular dysfunction (normal head-impulse test, no head-shaking nystagmus) or peripheral neuropathy could be found. On clinical examination mild-to-moderate spasticity in the legs and increased ankle jerks bilaterally were noted, while plantar responses were flexor.

Motor-evoked potentials showed delayed propagation along the corticospinal tracts to both legs and the left arm. MR-imaging obtained at age 27 years showed severe atrophy of the cranial and dorsal vermis (Fig. 2a). Cerebellar hemispheres and the pons were moderately atrophic. In addition, new focal T2- and flair-hyperintensities were noted within the splenium corporis callosus and in the paramedian pons along the pyramidal tracts (Fig. 2b) and an empty sella syndrome was reported.

Ophthalmologic examination at age 27 years revealed slightly reduced visual acuity (Snellen acuity: right eye 0.6, left eye 0.8) and paracentral scotoma in both eyes. Macular atrophy and atrophic changes in the retinal mid periphery in both eyes were found (Fig. 3), while anterior segment examination was normal. Full-field electroretinogram recorded according to ISCEV standard demonstrated reduced and delayed scotopic and photopic responses.

Laboratory work-up showed normal creatine kinase and calcium levels and no evidence for hypersegmented neutrophils (as reported earlier for BNS patients [7–9]). Muscle biopsy was normal without signs of mitochondrial myopathy. Neuropsychological testing revealed reduced attention and cognitive flexibility and mild psychomotor slowing.

Testosterone levels before substitution (05/2008) were below 0.5 pmol/l (normal range 9.4–34.6 pmol/l), LH (02/2013) below 0.1 IE/l (normal range 1.7–8.6) and FSH (02/2013) 0.8 IE/l (normal range 1.5–12.4).

Index patient #2

This 42-year-old patient (see Fig. 1a for pedigree) noticed a delayed puberty at age 13 years, with endocrinological work-up leading to the diagnosis of hypogonadotropic hypogonadism. He reported being a bit clumsy and worse in athletics since school age, yet slowly progressive disturbance of gait, fine motor skills and speech started at age 32 years. At age 36 years, he noticed reduced vision in darkness. Visual acuity was normal (i.e., >1.0) in both eyes under daylight illumination. Fundus examination revealed chorioretinal degeneration with central retinal atrophy and pigment clumps.

Neurological examinations starting at age 36 years confirmed a cerebellar ocular motor disorder (broken-up

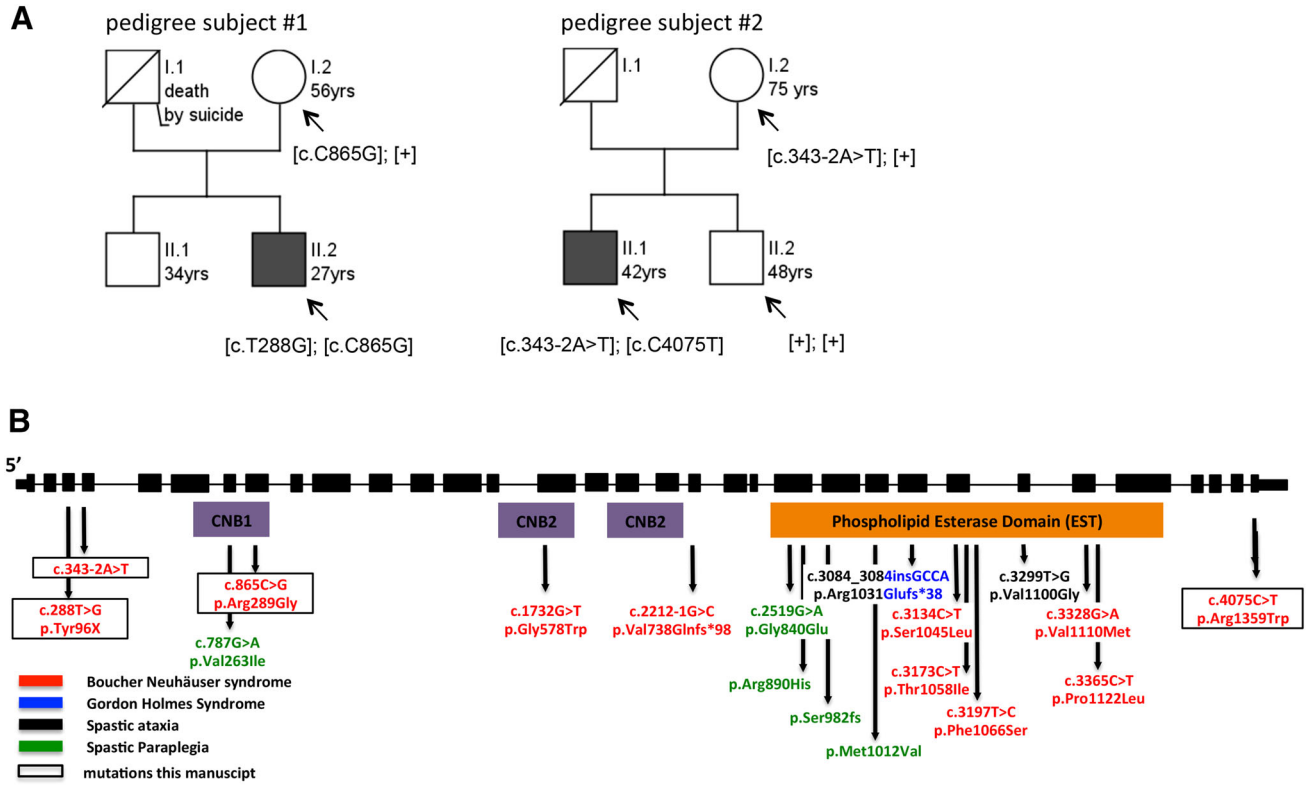

Fig. 1 Genetic investigations in the two index patients. **a** Pedigrees of the two index families and segregation of the *PNPLA6* variants. In both families, the affected subjects were simplex cases without affected parents and without consanguinity. Each of the two mothers carried only one *PNPLA6* variant, suggesting that the respective second *PNPLA6* variant identified in each of the two index patients is not on the same allele. *Arrows* subjects available for genetic testing of segregation of the respective PNPLA6 variants. **b** Schematic of the exon–intron arrangement of PNPLA6 (NCBI reference NM_001166111.1), with positions of the mutations reported here and previously (updated version of the schematic presented in [5]). Exons are indicated as *black boxes*. CNB1/2 and the phospholipid esterase functional domains are indicated by *purple* and *orange boxes*, respectively. The mutations are indicated and *color* coded by the phenotype observed

smooth pursuit, gaze-evoked horizontal nystagmus), cerebellar dysarthria, and a cerebellar trunk and limb ataxia [Scale for the Assessment and Rating of Ataxia (SARA) score: 9/40]. There were no clinical or electrophysiological signs of upper motor neuron damage. Vibration sense tested at the medial malleolus was mildly and symmetrically reduced (4/8), corresponding to the nerve conduction findings of a mild axonal-demyelinating sensory-motor peripheral neuropathy. Brain MRI revealed marked cerebellar atrophy and an empty sella, yet no T2-hyperintensities. Neuropsychological testing demonstrated reduced attention and information speed processing, and reduced short-term and working memory. Also in this subject, we did not find evidence for hypersegmented neutrophils.

Genetic investigation by targeted re-sequencing by a HaloPlex gene panel

DNA of both subjects was investigated by a high coverage (>94 % mean coverage) HaloPlex gene panel kit (Agilent, Santa Clara, CA, USA), which included 120 known ataxia genes (for details, see Supplement 1). Reads were mapped against the hg19 standard reference genome to detect SNPs, SNV, short deletions and insertions (SAMtools, IGV). We then filtered for non-synonymous homozygous or compound heterozygous truncating variants in any of the 120 ataxia genes (frame shift, insertions, deletions, and stop mutations) with low frequency in public databases (minor allele frequency in dbSNP137, NHLBI ESP6500 and the 1000 Genomes project (Annovar) <0.5 %). This filtering identified two recessive variants in both subjects only in the *PNPLA6* gene, but not on any other of the 120 ataxia genes. Subject #1 carried a stop-gain (c.T288G; p.Y96X) and a missense (c.C865G; p.R289G) *PNPLA6* mutation, subject #2 carried a splicing (c.343-2A>T) and a missense mutation (c.C4075T; p.R1359W) in PNPLA6 (see Fig. 1b). All four mutations are either absent (3 of 4) or extremely rare (1 of 4) in large-scale control databases (see Table 1). Two of the mutations were missense mutations, predicted to be damaging by at least two in silico

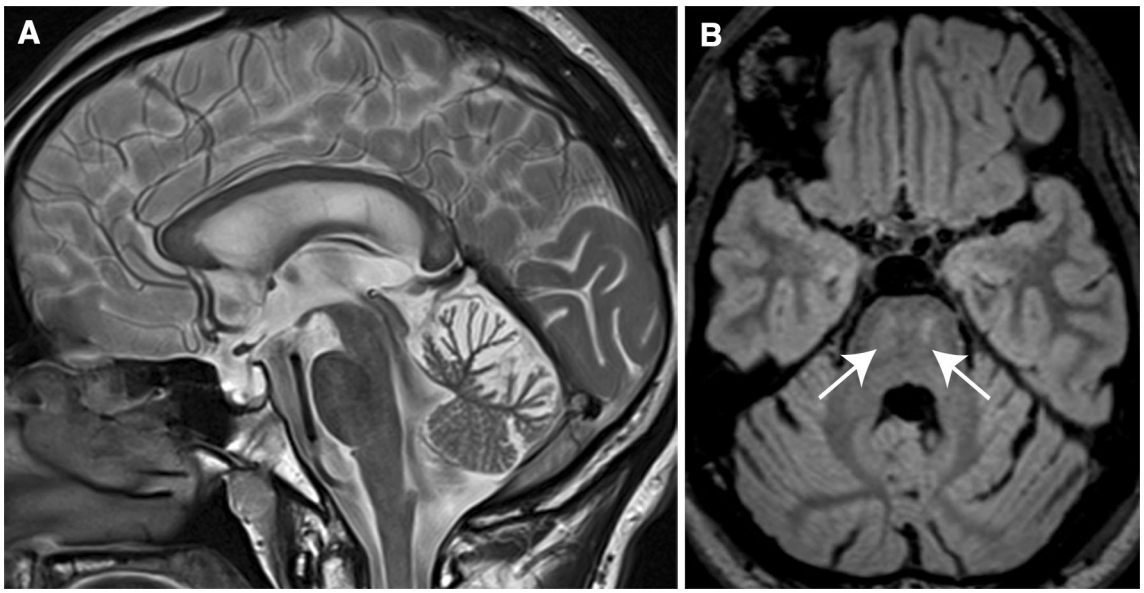

Fig. 2 Structural brain imaging of index case #1: on sagittal T2-weighted MR-imaging (**a**) severe atrophy of the cranial and dorsal lobules (I–VII) of the cerebellar vermis can be seen, whereas the caudal vermal lobuli (VIII–X) are relatively intact. On axial fluid-attenuated inversion recovery (FLAIR) images (**b**) and on T2-weighted sequences (not shown) focal hyperintensities along the pyramidal tracts (referred to by the *white arrows*) at the level of the paramedian pons can be depicted

prediction programs; the other two mutations lead to truncating effects (see Table 1). Three of the four mutations are novel. Testing of all relatives available (the two fathers have already died; the sibling from index patient #1 was not available for genetic testing; see Fig. 1a) showed that both mothers carried *one* of the respective heterozygous *PNPLA6* variants identified in the respective index patient (mother index #1: c.C865G; mother index #2: c.343-2A>T), suggesting that the respective second *PNPLA6* variant identified in each of the two index patients is not on the same allele (Fig. 1a). Moreover, they show that the healthy sibling from family index #2 did not carry any of the *PNPLA6* variants, thus adding further support for their pathogenicity.

Review of the literature

We performed a MEDLINE search using the search string "(boucher neuhauser syndrome) OR (ataxia AND hypogonadotropic hypogonadism AND retina*)". Identified publications were screened for cases that fulfilled the criteria for BNS, i.e., that reported on patients presenting with (spino) cerebellar ataxia, hypogonadotropic hypogonadism and (chorio-) retinal abnormalities. If information about one or several of the core clinical findings in BNS was missing or was unclear, cases were not included. In addition, selected papers were screened for further references reporting on BNS cases. We identified 21 publications reporting a total of 40 patients that met our inclusion criteria. Key findings of the cases identified in the literature and of our own two index cases (i.e., of a total of 42 cases) are summarized below and in Table 2. For a more detailed description of all cases, see online supplement 2.

Gender amongst the 42 cases (including both the 40 cases from the literature and our own two cases) was equally distributed (19 females, 23 males) and consanguinity was present in 13 of 28 cases if specified. In the majority of those cases the parents of the affected patients were second cousins (see Table 2 for details). Genetic testing was performed in 19 cases. An autosomal-recessive mutation in the *PNPLA6* gene was reported in nine cases from four families with the phenotype of BNS [5] and in the two index cases reported here. In a single case a 5.5 kb mitochondrial DNA (mtDNA) single deletion and mitochondrial respiratory chain complex I deficiency was identified [10]. In the remaining seven cases screening for various spinocerebellar ataxias (SCA), dentatorubro-pallidoluysian atrophy (DRPLA), Friedreich ataxia and mtDNA mutations was negative.

Neurological findings included cerebellar ataxia (being present in all cases by definition), dysarthria (29/31 cases reported), pyramidal tract signs (confirmed in 13/31 patients tested), peripheral neuropathy (confirmed in 6/26 patients assessed) and cognitive dysfunction (confirmed in 15/27 patients assessed, including mild cognitive impairment (MCI) in six cases (all from [5]), impaired intelligence in seven cases and reduced attention/cognitive flexibility in two cases). Ocular motor abnormalities were reported in 29/32 patients assessed. Most frequently horizontal gaze-evoked nystagmus (22/32), saccadic smooth

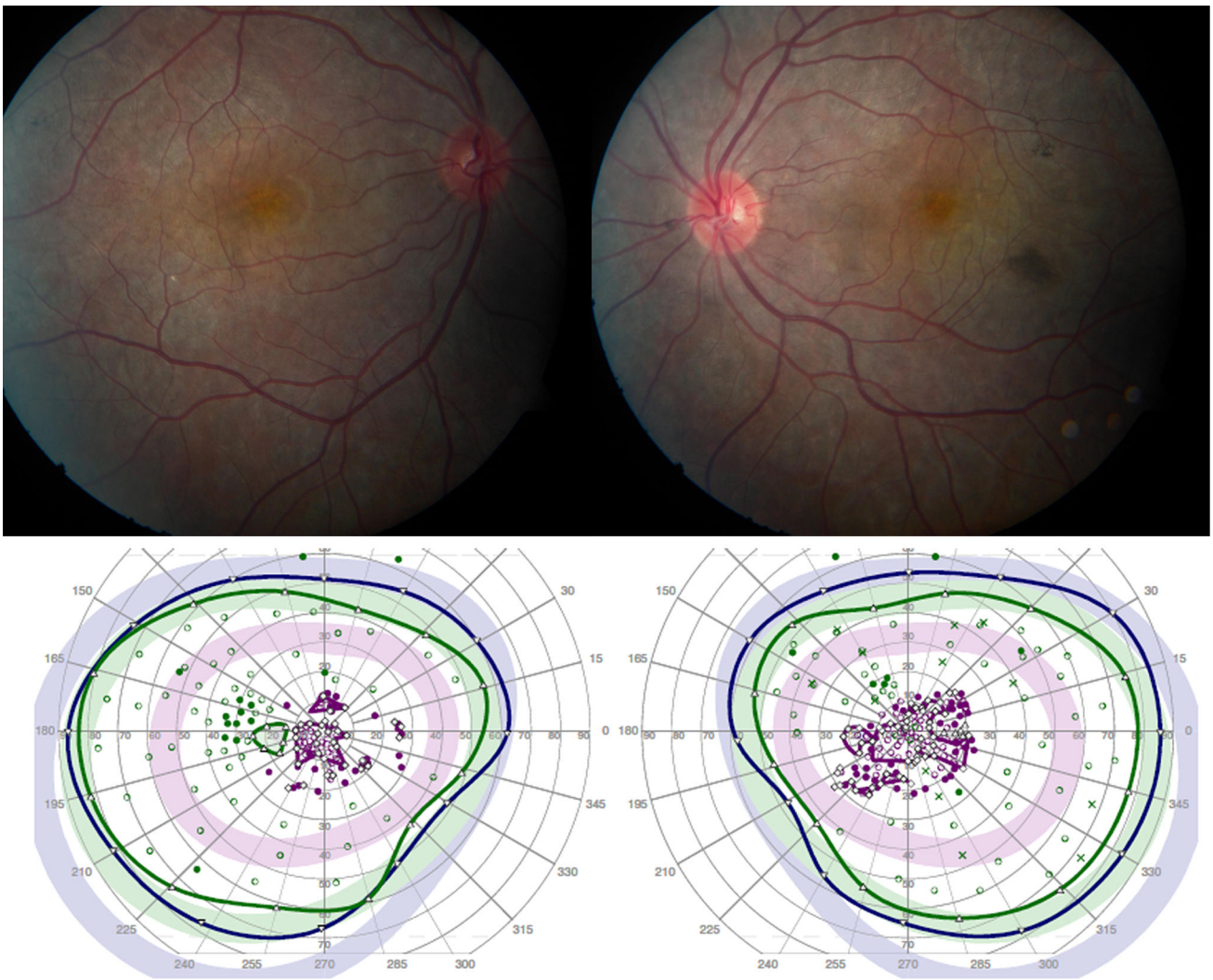

Fig. 3 Ophthalmological findings of index case #1: *color* fundus photography of the right and left eye illustrating retinal atrophy. Visual field examination (*bottom*) shows paracentral scotoma but normal peripheral field response

pursuit eye movements (SPEM; 14/32), spontaneous vertical nystagmus (7/32; direction of fast phase specified in two cases only, reporting downbeat) and "nystagmus" without any further specification (6/32) were described.

Ophthalmological findings included chorioretinal degeneration, being reported in all but one case, in which BNS was genetically confirmed [5]. Visual acuity ranged from normal to bilateral blindness (see Table 2). Visual field defects were present in 13/22 patients tested. Color vision was impaired in 6/11 patients evaluated. Abnormal retinal function was documented by electroretinogram (ERG) in 15/16 cases.

Most often, ataxia or vision loss was the first symptom (in 38 and 36 %, respectively), while delayed puberty was noted less frequently (26 %) (Table 2). Age of onset varied: the first symptoms occurred between age 1 and 40 years (mean = 14.0, 1 SD = 10.5 years), ataxia between age 4 and 40 years (mean = 18.8, 1 SD = 11.2 years) and visual disturbances between age 1 and 48 years (mean = 19.1, 1 SD = 14.3 years).

Brain imaging identified "cerebellar atrophy" in 34/35 cases with more detailed descriptions of the pattern of cerebellar atrophy available only for some of the reported patients. This included atrophy of the cerebellar hemispheres ($n = 10$) and/or atrophy of the cerebellar vermis ($n = 13$). More pronounced atrophy of the superior and dorsal vermal lobules (I to VII) with caudal lobules (VIII, IX and X) being relatively spared was observed in 7/13 cases with reported vermal atrophy. Brainstem atrophy, brainstem T2-hyperintensities and cerebral atrophy were noted infrequently (see Table 2 for details).

All patients presented with hormonal changes of hypogonadotropic hypogonadism (usually low testosterone, FSH and LH values reported) or amenorrhea (primary in

Table 1 PNPLA6 mutations identified in this study

Region	Exon	Chr. position	Nucleic acid change	AA change	Variant type	Status	variant status	Mutation taster ljb2	SIFT ljb2	Polyphen2 hdiv ljb2	esp6500 count	1,000 g count
Exonic	Ex4	chr19:7601105	c.T288G	p.Y96X	Stop gain	Hetero	New	1	1	–	–	–
Exonic	Ex9	chr19:7605851	c.C865G	p.R289G	Missense	Hetero	New	0.947	0.03	0.088	–	–
Splicing	Ex5	chr19:7601333	c.343-2A>T	–	–	Hetero	Known	–	–	–	0.0001	–
Exonic	Ex34	chr19:7626395	c.C4075T	p.R1359W	Missense	Hetero	New	0.2675	0	0.999	0.0002	–

AA, amino acid change, Mutation Taster score between 0 and 1; the higher it is, the higher is the probability of pathogenicity. SIFT, Sorting Tolerant From Intolerant. SIFT scores <0.05 represents damaging effect. PolyPhen2; range: 0–1, higher scores indicate a higher likelihood of pathogenicity. Interpretation: benign (0–0.452), possibly damaging (0.453–0.956), probably damaging (0.957–1). All positions refer to transcript NM_001166111. ESP6500, minor allele frequency (MAF) in NHLBI ESP6500, 1,000 g, count in the 1000 genome project

17/18 cases reported). Eleven out of 42 patients had a short stature. Laboratory abnormalities included hypersegmented neutrophils ($n = 7$) and hypercalciuric hypocalcaemia (in two siblings [11]). Results from lumbar puncture were available in two cases only (being reportedly normal). Muscle biopsy, reported in five patients, did not reveal any abnormalities.

Discussion

Using a novel targeted re-sequencing high-throughput approach, we identified four recessive *PNPLA6* mutations (3 of them being novel) as the cause of the disease in two previously unreported BNS index cases. This finding provides the first replication from independent families that BNS is indeed caused by *PNPLA6* [5] and, in addition, that BNS can also present as a "spastic BNS" (pyramidal tract damage in index patient #1). The latter finding adds support to the previous notion that PNPLA6 mutations do not cause BNS as an isolated syndrome, but as a disease cluster on a continuous spectrum of neurodegenerative disorders extending from pure ataxia or hereditary spastic paraplegia to severe multisystemic syndromes such as BNS additionally complicated by spasticity (for an overview see [6]).

Moreover, our finding highlights *PNPLA6* as the major gene leading to BNS: the first series identified *PNPLA6* mutations in four out of six BNS families [5], and we observed *PNPLA6* mutations in two out of two BNS families. These findings suggest that *PNPLA6*, which encodes neuropathy target esterase (NTE), a lysophospholipase that maintains intracellular phospholipid homeostasis by converting lysophosphatidylcholine (LPC) to glycerophosphocholine [12], should be primarily screened in subjects with BNS. Moreover, they lead to the hypothesis that a substantial fraction of the genetically still undefined BNS cases from the literature as reviewed here will carry *PNPLA6* mutations. Our findings demonstrate for the first time that even mutations leading to the "full-blown" BNS phenotype are not restricted to the phospholipid esterase (EST) or cyclic nucleotide binding-homology (CNB) domains of the gene, but can be found across the whole gene (Fig. 1b). Thus, screening of *PNPLA6* in still undefined BNS patients will require sequencing the full gene, rather than just the main established functional domains.

Clinically, BNS can be distinguished from the Gordon Holmes syndrome [13] and the Woodhouse Sakati syndrome [14] by the presence of chorioretinal dystrophy and absent/mild cognitive dysfunction. For the differential diagnosis of BNS, mitochondrial disorders must be considered as they may present with cerebellar ataxia and progressive retinal degeneration [15] or with cerebellar ataxia and hypogonadotropic hypogonadism [16, 17].

Table 2 Prevalence of key findings in BNS

	Present	Absent	Not reported
Epidemiological findings			
Consanguinity	13/42 (31 %)	15/42 (36 %)	14/42 (33 %)
First cousins	2/13 (15 %)		
Second cousins	8/13 (62 %)		
Not specified	3/13 (23 %)		
Genetic defects[a]	12/42 (29 %)	7/42 (17 %)	23/42 (55 %)
First complaints[b]			
Cerebellar ataxia	16/42 (38 %)		
Progressive visual loss	15/42 (36 %)		
Delayed puberty	11/42 (26 %)		
Neurological findings			
Ocular motor abnormalities	29/42 (69 %)	3/42 (7 %)	10/42 (24 %)
Horizontal gaze-evoked nystagmus	22/42 (52 %)		
Vertical nystagmus[c]	7/42 (17 %)		
Saccadic smooth pursuit	14/42 (33 %)		
Impaired saccades	3/42 (7 %)		
"Nystagmus"	6/42 (14 %)		
Dysarthria	29/42 (69 %)	2/42 (5 %)	11/42 (26 %)
Pyramidal tract signs[d]	13/42 (31 %)	18/42 (43 %)	11/42 (26 %)
Peripheral neuropathy[e]	6/42 (14 %)	20/42 (48 %)	16/42 (38 %)
Cognitive dysfunction	15/42 (36 %)	12/42 (29 %)	15/42 (36 %)
Ophthalmological findings			
Visual loss[f]	26/42 (62 %)	4/42 (10 %)	12/42 (29 %)
Visual acuity $\geq$0.5 on better eye	7/23 (30 %)		
Visual acuity $\geq$0.1 and <0.5 on better eye	11/23 (48 %)		
Visual acuity <0.1 on better eye	5/23 (22 %)		
Chorioretinal dystrophy[g]	41/42 (98 %)	1/42 (2 %)	0/42 (0 %)
Brain imaging[h]	35/42 (83 %)	0/42 (0 %)	7/42 (17 %)
Cerebellum			
Any kind of cerebellar atrophy	34/35 (97 %)		
Atrophy of cerebellar hemispheres	10/35 (29 %)		
Atrophy of cerebellar vermis	13/35 (37 %)		
Brainstem			
Brainstem atrophy	5/35 (14 %)		
Brainstem T2-hyperintensities	2/35 (6 %)		
Cerebrum			
Cerebral atrophy	2/35 (6 %)		
Cerebral T2-hyperintensities	5/35 (14 %)		

[a] In addition to our two index cases, one report found nine cases with heterozygote mutations in the PNPLA6 gene [5] and one report found a 5.5 kb mtDNA single deletion in one case [10]. Negative testing included SCA 1 ($n = 6$), 2 ($n = 6$), 3 ($n = 5$), 6 ($n = 3$), 7 ($n = 2$), 8 ($n = 2$), 12 ($n = 1$, 17 $n = 1$), DRPLA ($n = 2$), mtDNA ($n = 4$), FRDA ($n = 3$)

[b] In one case, first complaints developed at the same time in two domains (delayed puberty and progressive visual loss, reported by Synofzik et al. [5]). In one case first complaints were not reported, total number of events is, therefore, $n = 42$

[c] In two cases the fast phase of vertical nystagmus was specified as downbeat nystagmus

[d] This includes spastic muscle tone ($n = 5$), increased deep tendon reflexes (DTR) ($n = 5$) and extensor plantar response ($n = 6$). Note that more than one complaint was found in part of the affected patients

[e] For a diagnosis of PNP clinical findings as reduced/absent DTRs and/or sensory deficits had to be confirmed either by abnormal ENMG ($n = 2$ with axonal PNP, $n = 1$ with demyelinating PNP, $n = 1$ with mixed axonal-demyelinating PNP) or pathological nerve biopsy ($n = 2$ with axonal degeneration). A normal ENMG exam was reported in 11 cases. In eight cases (all from [5]) only reduced or absent patellar tendon reflex and Achilles tendon reflex were reported, but no information was available regarding sensory loss, ENMG or nerve biopsy. Therefore, these cases were rate das having insufficient information to confirm/dismiss a diagnosis of PNP

[f] Visual loss was defined as corrected visual acuity of less than 1.0 on both eyes. Only patients included with specific visual acuity values or rating as finger counting, hand movements, light perception or blindness ($n = 23$)

[g] Different morphological descriptions, including (chorio-) retinal dystrophy/atrophy/degeneration, maculopathy, macular atrophy, chorio-retinopathy, (atrophic) pigmentary retinopathy, RPE (and choriocapillary) atrophy, peripapillary atrophy, dystrophic retinal pigment epithelium

[h] From 35 cases with imaging, 30 received an MRI and 5 a CT

On the level of single families, a possible autosomal-recessive trait of inheritance (several affected siblings, no genetic testing [2, 7, 18], has been proposed in the past—often in association with parental consanguinity (e.g., [7, 18]). With recent advances in genetic testing in BNS, resulting in the identification of *PNPLA6* as the major target gene and an autosomal-recessive pattern, this originally clinically defined entity is becoming part of a larger spectrum of neurodegenerative disorders including Gordon Holmes syndrome, hereditary spastic paraparesis, and spastic ataxia [5].

Both the cases presented here and the reviewed cases in the literature suggest that the phenotype can be variable regarding the age and the symptoms at disease onset. Albeit BNS is rare, this finding prompts both pediatric and adult caregivers to look for additional key features of BNS if one of the core symptoms is present, especially if the family history for neurological or ophthalmological disorders is positive or consanguinity is the case. Early detection of the syndrome may accelerate hormonal substitution, the prescription of visual aids, balance and speech therapy, and adequate genetic and psychosocial counseling.

As shown by our review, visual loss is severe in about 20 % of the patients. Amongst neurological findings dysarthria accompanies cerebellar ataxia in almost all cases and a substantial fraction of BNS patients presents with pyramidal tract findings, underlining the spinocerebellar character of this disease and the often "spastic BNS" presentation [5, 7]. Ocular motor abnormalities can be observed in almost all cases, with deficient cerebellar gaze holding, saccadic smooth pursuit and vertical (most likely downbeating) nystagmus constituting the core diagnostic findings. Moderate cognitive impairment (see, e.g., cases from [7, 18]) and peripheral polyneuropathy may be present in substantial fractions as well. Pes cavus [2, 4, 19] was described by several authors and movement disorders such as focal (craniocervical) dystonia and chorea may develop in BNS [20]. Hypersegmented neutrophils are an inconstant finding in BNS, and so far none of the genetically confirmed cases showed these hematological changes. Thus, it does not seem to serve as a reliable blood biomarker for underlying *PNPLA6* disease.

As suggested by the reviewed cases and our index patient #1, a significant proportion of BNS cases may present with relatively selective atrophy of the superior and dorsal parts of the vermis along with atrophy of the cerebellar hemispheres, while brainstem or cortical changes seem to be present only in small fractions. However, this pattern is likely not specific for BNS, as it may be observed also in patients with degenerative cerebellar ataxia without chorioretinal disease or hypogonadism. It will be of interest whether the pontine T2-hyperintensities observed in index patient #1 can be identified in future PNPLA6-confirmed BNS subjects as well. In the literature, infratentorial T2-hyperintensities were noted only in a single case (which awaits genetic confirmation) [21], but might have been overlooked in previous cases. Although such hyperintensities are certainly not specific to BNS/PNPLA6-disease, they are not common features in other hereditary ataxias. Moreover, they might provide a link to the pathophysiology of PNPLA6-caused BNS, which is increasingly shown to be related to disorders in phospholipid metabolism [5, 12, 22].

To summarize, albeit defined clinically by the combination of (spino)cerebellar ataxia, chorioretinal degeneration and hypogonadotropic hypogonadism, the Boucher–Neuhäuser syndrome may vary considerably in disease onset, clinical presentation and progression. Thus, we recommend a thorough assessment for ophthalmological, neurological and endocrinological changes in patients presenting with one of the key features. With *PNPLA6* likely causing the large majority of BNS cases, future identification of the underlying gene defect will be facilitated. Moreover, future research clarifying the relationship of BNS with other ataxia syndromes likely will be accelerated and detailed phenotype characterization and phenotype–genotype correlation will be possible.

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Ethical standard Due to its nature, this study was not subject to review by an ethics committee.

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