

Familial 15q11.2 Microdeletions are not Fully Penetrant in Two Cases with Hereditary Spastic Paraplegia and Dysmorphic Features

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Abstract

Hereditary Spastic Paraplegias (HSP) are heterogenic neurodegenerative disorders with progressive spasticity of the lower limbs as a prominent feature. Spastic paraplegia type 6 (SPG6) is an autosomal dominant form of the disorder caused by point mutations in the *NIPA1* gene on chromosome 15q11.2. The microdeletions within the region 15q11.2 spanning the four genes *TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1* were previously reported in several different syndromes, including mental retardation, and/or developmental delay with hypotonia. Furthermore, these genes were associated with several congenital abnormalities, including autism, developmental delay, motor, and language disturbances, behavioural problems, and Idiopathic General Epilepsies (IGE), suggesting the existence of a new microdeletion syndrome. Our index cases, in whom the microdeletion 15q11.2 was detected, suffer from spastic paraplegia, but neither cognitive impairment nor behavioural problems were observed in them and other tested relatives. We considered several interpretations of the 15q11.2 microdeletion's phenotypic significance, including polymorphism, the pleiotropic effect of the microdeletion, and the influence of other modifiers. Specifying the exact range of the microdeletion 15q11.2 in patients with diverse clinical presentation is essential. Though the clinical implications of the microdeletion 15q11.2 remain unclear, our study contributes by extending the phenotypic variability of the subjects carrying this microrearrangement.

Keywords: 15q11.2 Microdeletion; Hereditary spastic paraplegia; Reduced penetrance; MLPA

Introduction

The 15q11-q13 region is associated with two genomic imprinting disorders: the Prader-Willi (PWS [MIM 176270]) and Angelman (AS [MIM 105830]) syndromes. The region is flanked by segmental duplications located between breakpoints 1 (BP1), 2 (BP2), and 3 (BP3), mediating the generation of microdeletions and microduplications. The region between BP1 and BP2 spans four highly conserved genes that are not imprinted: *TUBGCP5* (MIM 052903), *NIPA1* (MIM 144599), *NIPA2* (MIM 030922), and *CYFIP1* (MIM 014608) [1,2]. *NIPA1*, *NIPA2*, and *CYFIP1* are widely expressed in the central nervous system, and expression of the *TUBGCP5* is more specific to the subthalamic nuclei. The *NIPA1* gene encodes a magnesium transporter that is involved in the early formation of endosomes in a variety of neuronal and epithelial cells [3,4]. The *NIPA2* gene codes for a membrane transport protein that plays a role in magnesium metabolism [5]. The *CYFIP1* product interacts with a fragile X mental retardation protein, and the Rho GTPase, Rac1, is involved in regulating axonal and dendritic outgrowth, and the development and maintenance of neuronal structures [6]. *TUBGCP5* encodes gamma-tubulin complex associated protein 5, which is essential for microtubule nucleation at the centrosome [7]. The *NIPA1* gene, named for "non-imprinted in Prader-Willi/Angelman", was reported to be involved in spastic paraplegia in 1995 by Fink et al. [8] and different single nucleotide changes (missense mutation) in this gene are associated with autosomal-dominant spastic paraplegia type 6 – SPG6 [3,9,10].

The deletion of the proximal long arm of chromosome 15 embracing *TUBGCP5*, *NIPA1*, *NIPA2* and *CYFIP1* is well recognised in Prader-Willi syndrome, a complex multisystem disorder that is characterised by neonatal hypotonia, hyperphagia, short stature,

obesity, hypogonadism and behavioural and learning disturbances [11]. Type I deletions involve a larger region between BP1 and BP3, whereas type II deletions cover BP2-BP3 [12].

A deletion between BP1 and BP2 is thought to have implications particularly in psychological problems, compulsive behaviour, and lower intellectual ability in type I Prader-Willi patients [13,14]. Murthy et al. [15] detected a deletion of the 15q11.2 region in a child with neurological disorder, developmental delay, and speech impairment. Doornbos et al. [16] and Lippe et al. [17] observed the same mutation in 9 and 7 patients, respectively. These patients shared several clinical features, including delayed motor and speech development, learning difficulties, and behavioural disturbances. By linking this particular phenotype with the deletion between the BP1 and BP2 regions, Doornbos et al. [16] suggested the existence of a new microdeletion syndrome in 15q11.2. However, the clinical significance of this deletion has been debated because in almost all cases, the mutation was inherited from a normal or mildly affected parent.

In this study, we present two families with the microdeletion at 15q11.2 detected by MLPA (multiplex ligation-dependent probes

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amplification), found within the group of 143 patients suspected of spastic paraplegia investigated towards SPG6 mutations. Microdeletion carriers present with a different clinical picture than had been reported thus far as being associated with this aberration.

Materials and Methods

Patients

The initial group of patients screened for SPG6 rearrangements came from our previous study [18] and consisted of 143 probands with SPG in whom the microrearrangements in SPG3 and SPG4 were excluded. Six individuals with the 15q11.2 microdeletion from 2 families - 2 probands and 4 family members, pedigrees 1 and 2 (Figures 1A and B) were examined with the diagnostic criteria for HSP (Hereditary Spastic Paraplegia) according to Fink [19]. In the probands and their relatives with the 15q11.2 deletion, neurological, neuropsychological and ophthalmological examinations were performed. Moreover, in the probands, Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG) in the cerebral, cervical, and thoracic spines were carried out. In clinical evaluation of all patients suspected of HSP, the following scales were used: the Spastic Paraplegia Rating Scale (SPRS) [20], the scale for assessment rating of ataxia - 5th version (SARA) [21], the Inventory of Non-Ataxia symptoms - 6th version (INAS) [22], and the Mini-mental State Examination (MMSE) [23]. Functional impairment was assessed according to classification used by Dürr et al. [24] Wechsler Adult Intelligence Scale - Revised (WAIS-R) evaluation was performed for two probands to assess intellectual impairment/psychomotor retardation [25].

MLPA analysis and sequencing

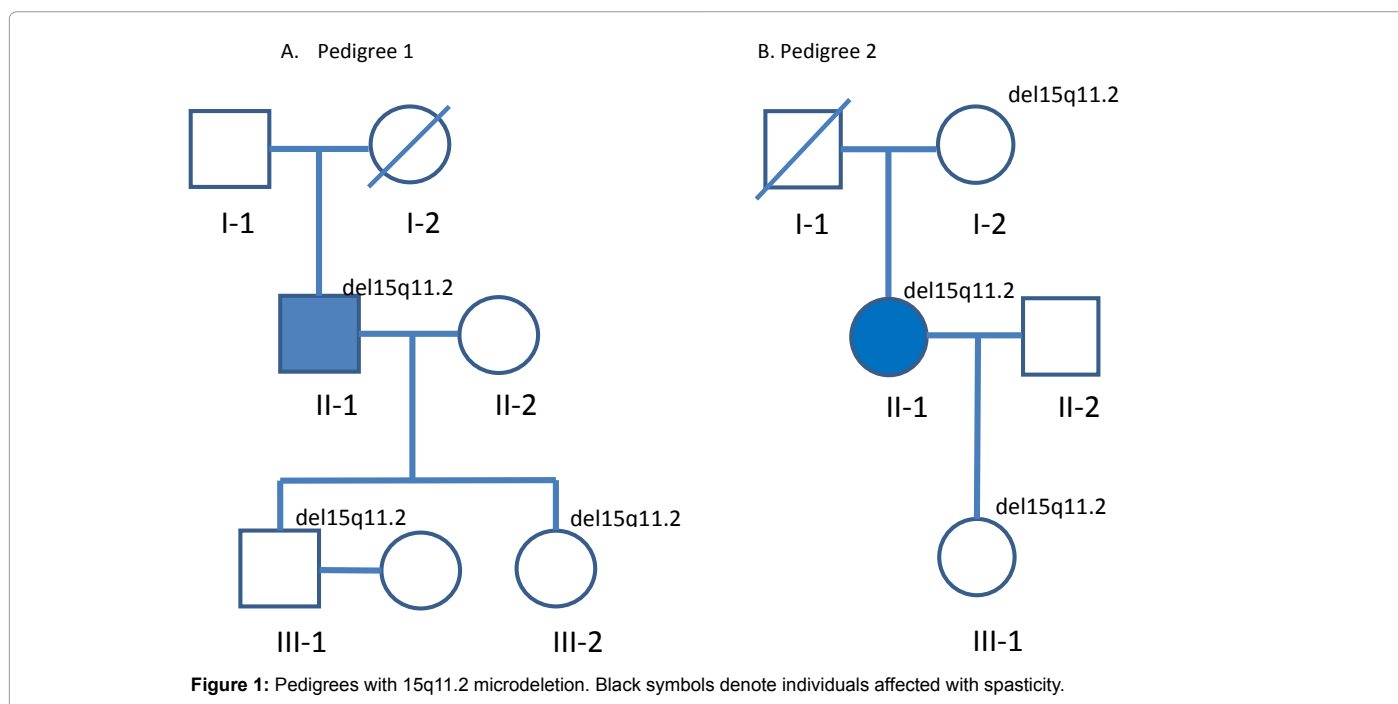
Informed consent was obtained from each participant before blood sampling. Genomic DNA was extracted from peripheral blood leukocytes by applying the standard phenol-chloroform technique or automatic isolation with MagnaPure (Roche). In patients with the 15q11.2 microdeletion, the most frequent microrearrangements

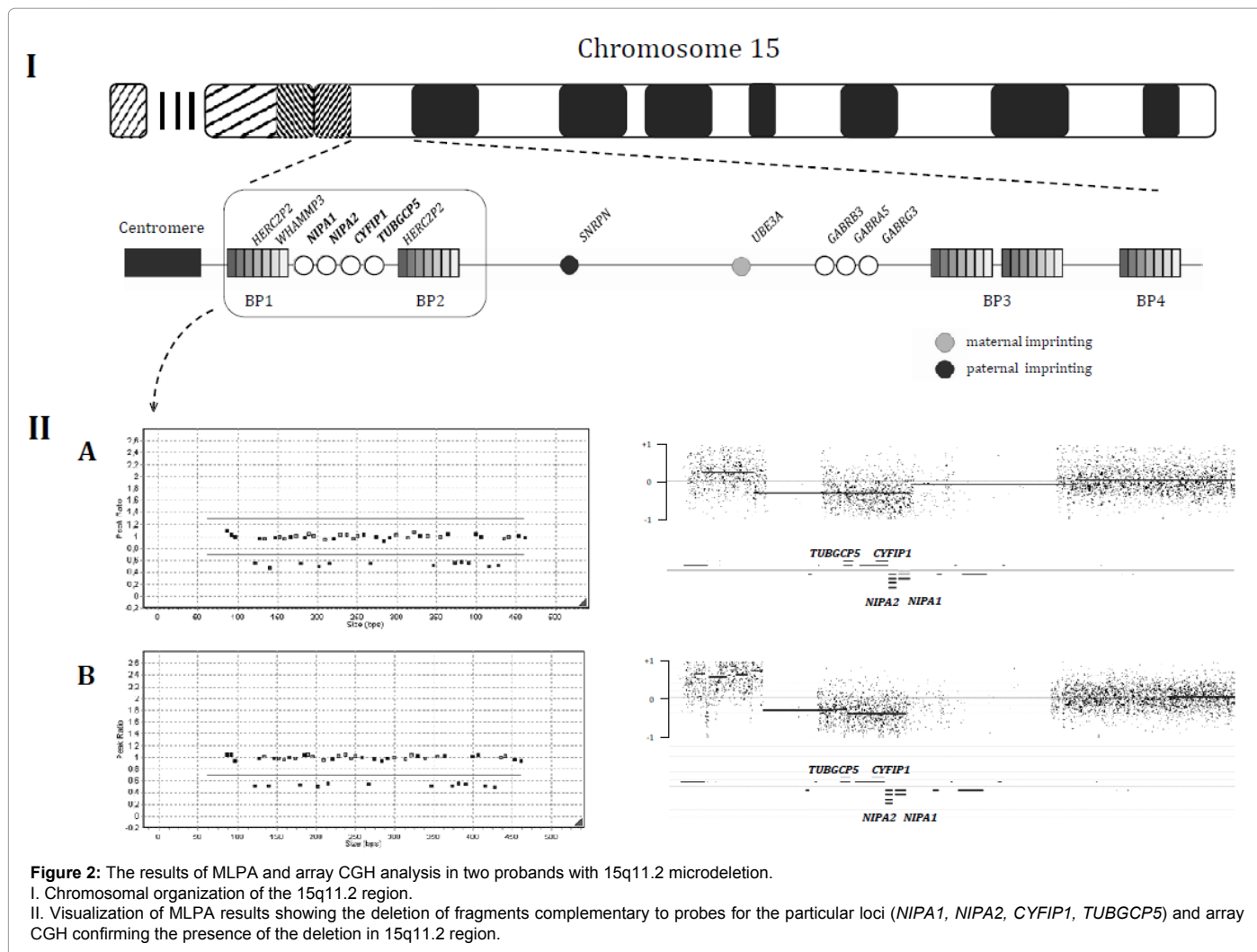
(deletion/duplication) in the *SPAST* (SPG4) and *ATL1* (SPG3) genes were excluded earlier by the MLPA Kit P-165B1 (MRC Holland), as was the *SPG11* gene.

The MLPA P-211B2 HSP probe-mix containing the probes for the regions flanking the *SPAST* (SPG4) gene, as well as the region surrounding the *NIPA1* (SPG6) gene, was used. Three probes for *NIPA2*, two probes for the *NIPA1* and *TUBGCP5* genes, and 1 for the *CYFIP1* gene allowed identification of the microdeletions in 2 probands. The MLPA P-211B2 HSP probe-mix also contains probes for the *SNRPN*, *MKRN3*, and *GOLGA6* genes, and the *HERC2P2* and *WHAMMP3* pseudogenes. The Gene Marker v.1.90 software (SoftGenetics LLC) was used for the dosage ratio analysis (using standard parameters, with dosage ratio boundaries of <0.75 and >1.25 for deletion and duplication, respectively). The analysis indicated a heterozygotic deletion of fragments complementary to all probes for *TUBGCP5*, *CYFIP1*, *NIPA2*, *NIPA1* genes and *HERC2P2*, *WHAMMP3* pseudogenes. Moreover, in both probands, Sanger sequencing of the *NIPA1* (SPG6) as well as the other HSP genes: *SPAST* (SPG4), *ATL1* (SPG3), and *REEP1* (SPG31) excluded the presence of point mutations.

Array CGH

To determine the range of identified mutations, array-based comparative genomic hybridisation was performed using a 385K chromosome 15 tiling array (NimbleGen). Procedures during DNA labelling, hybridisation, and microarray processing were carried out according to the manufacturer's instructions. The arrays were scanned on a 5-micron resolution Agilent Technologies instrument. Data were processed using Feature Extraction (Agilent Technologies). Log₂-ratio values of the probe signal intensities (Cy3/Cy5) were calculated and plotted versus the genomic position using NimbleScan and SignalMap softwares. Genomic positions of the duplications were specified according to Human Mar.2006 (NCBI36/hg18) assembly [http://genome.ucsc.edu].





Results

Pedigree 1 (Figure 1A)

The first proband (II-1) is a 56-year-old man with a progressive gait disturbance, which appeared at around 40 years of age and gradually progressed. He was born after an uncomplicated pregnancy and delivery. No dysmorphic features were presented. Psychomotor development proceeded normally. He had no learning difficulties and no behavioural or cognitive problems, and he attended a regular school. Neurological examination showed signs of spasticity (paraparesis) in the lower limbs (Table 1). Neuropsychological evaluation revealed no significant deviations in particular cognitive functions. The patient complained of sleep disturbances only. His parents are non-consanguineous and he has no siblings. The family history was negative for congenital malformations, dysmorphic features, and neurological and behavioural disturbances.

His family members include a 31-year-old son (III-1) and a 26-year-old daughter (III-2). Their milestones and speech development were normal. They had neither learning difficulties nor behavioural disturbances, and they attended regular school. They have no apparent dysmorphic features. Neurological examination showed only brisk tendon reflexes in both. Otherwise, no signs of spasticity, such as

Babinski reflex, were present. The clinical presentation of the patients is summarised in Tables 1 and 2. The proband's father (I-1) DNA sample was unavailable for genetic evaluation.

Pedigree 2 (Figure 1B)

The second proband (II-1) is a 45-year-old woman with gait disturbances that appeared at approximately 41 years of age and progressed slowly. No pregnancy or delivery complications were reported in her history. Her parents are non-consanguineous. Her psychomotor development was normal, without any learning difficulties at school. No behavioural problems or cognitive impairment were reported. The neuropsychological assessment showed mild impairment of short-term memory and execution of visual-spatial tasks with preservation of other intellectual abilities. She was brought up in a foster family. However, in childhood, the abnormal gait pattern was observed, but it was not diagnosed or treated.

When the patient was 13 years old, she had a head injury complicated with a post-traumatic hematoma in the left parietal region that required surgical intervention. Physicians observed outgoing right-handed hemiparesis and a transient deficit in the precise movements of the right upper limb. She had a Gothic palate, crowded teeth, and a absent buds on the upper lateral incisors that required orthodontic

Pedigree number	Gender	Age at examination (years)	Onset of symptoms (years)	SPRS	SARA	INAS	Hyperreflexia UL/LL	Babinski sign	Clonus	Decreased vibration sense	Bladder disturbances	Degree of disability	MMSE	Other signs
PED1/II-1 proband	M	56	40	24/52	3	18	+/+	+	+	+	+	4	27/30	Fasciculations mm. UL/LL ¹
PED1/III-1	M	31	-	0/52	0	0	-/+	-	-	-	-	0	28/30	
PED1/III-2	F	26	-	0/52	0	0	+/+	-	-	-	-	0	29/30	
PED2/II-1 proband	F	45	41	18/52	4	11	+/+	+	+	-	+	2	29/30	Gothic palate, crowded teeth, lack of upper lateral incisor buds
PED2/II-2	F	65	-	2/52	0	0	-/+ patellar reflexes	-	-	-	-	0	28/30	Gothic palate, crowded teeth, lack of upper lateral incisor buds
PED2/III-1	F	23	-	1/52	0	0	+/+	-	-	-	-	0	30/30	Gothic palate, crowded teeth, lack of upper lateral incisor buds

Legends: SPRS – Spastic Paraplegia Rating Scale, UL – upper limbs, LL – lower limbs, MMSE – mini mental scale examination; mm. – muscles, + present, - absent. Degrees of disability: 0 – asymptomatic; 1 – no functional impairment, but signs at examination; 2 – mild gait stiffness, walking unlimited, limited running still possible; 3 – moderate gait stiffness, limited walking without aid, running impossible; 4 – moderate or severe gait stiffness, walking only with aid; 5 – wheelchair bound ¹ – deltoid muscles and quadriceps muscles of thigh. 1 and 2 – probands, 1a, 1b, 2a, 2b – affected family

Table 1: Clinical presentation of patients with the 15q11.2 microdeletion.

Patient/gender	Cerebral MRI	Cervical spine MRI	Thoracic spine MRI	SEP	VEP	BAEP	EMG and NCS	Ophthal. exam.	Neuropsych. exam
1/M	Moderate cerebral cortex and cerebellum atrophy	Normal imagine	Slight flattening of spine	Conduction disturbances in long ascending sensory tracts with conduction block in the R posterior sensory tract. Diminished peripheral amplitude of Posterior Tibial nerve; normal conduction velocity in peripheral sensory fibres;	L-N Right P100 delayed	Bilateral N	Sensory-motor polyneuropathy of axonal type	N	Slight impairment of executive functions
2/F	Cortico-subcortical scar in the left parietal region	Normal imagine	Slight flattening of spine	N	Bilateral N	Bilateral N	Neuropathy of right common peroneal nerve	N	Slight impairment of executive functions

Table 2: Imaging, electrophysiological, ophthalmological and neuropsychological results of the probands.

Legends: R – Right side, L – Left side, N – Normal, SEP – somatosensory evoked potentials, VEP – visual evoked potentials, BAEP – brainstem auditory Evoked potentials, EMG – electromyography, NCS – nerve conduction studies, Ophthal. exam. – ophthalmological examination, Neuropsych. exam – Neuropsychological examination.

treatment. Neurological examination revealed signs of spasticity in the lower limbs.

Her family members include a 65-year-old mother (I-2) who had no learning difficulties and no behavioural or cognitive disturbances. Physical examination showed a Gothic palate, crowded teeth, and a lack of upper lateral incisors. Neurological examination showed brisk reflexes in the lower limbs.

The 23-year-old proband's daughter (III-1) was of normal intelligence. She had a Gothic palate, crowded teeth, and an absent bud on the left upper lateral incisor that was treated orthodontically with an implant. Neurological examination showed brisk reflexes in the lower limbs.

The phenotype of the 2 probands from 2 different families corresponds to the pure form of HSP. The common feature among the other 4 family members (Pedigree 1: III-1, III-2; Pedigree 2: I-2, III-1), carriers of the microdeletion, are brisk tendon reflexes. However, we decided to consider all of them as unaffected with HSP but as requiring further observation. In both unrelated families, in the affected persons

and their family members, the analysis revealed a heterozygotic deletion of the *TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1* genes. The identified deletion was additionally evaluated by array Comparative Genomic Hybridisation (aCGH). The analysis in the two probands confirmed heterozygotic deletion of the four above-mentioned genes; however, detection of the exact range of the deletion was impossible because the specific oligonucleotide probes were not available on the array. We were only able to approximate the right chromosomal breakpoint, located above the *NIPA1* gene. According to our tentative assessment, the approximate size of the deletion is 330-340 Kbp.

Discussion

The microdeletions within the region 15q11 were observed in several different syndromes, including paternal deletions of the imprinted region 15q11.2-q13 in Prader-Willi syndrome. These deletions manifested as severe neonatal hypotonia, learning disabilities, behavioural problems, and short stature [11]. In other cases of the 15q11 microdeletion reported thus far, the following clinical signs were observed: mental retardation and/or developmental delay with hypotonia, congenital abnormalities, autism, developmental delay,

motor and language disturbances, behavioural problems [15-17,27,28] and Idiopathic General Epilepsies (IGE) [29]. Dysmorphic features were reported infrequently.

Other genetic changes associated with this chromosomal region, such as point mutations in the *NIPA1* gene, were described in patients with pure spastic paraplegia in different populations [4,9,10,30,31]. A complicated form of SPG6, with additional symptoms such as polyneuropathy or epilepsy, was described in only a few families [32,33]. The deletion of the entire *NIPA1* gene has been reported in a single family with spastic paraplegia and dementia so far. However, in the same family, a deletion of exon 17 in the *SPAST* gene was found [34].

Our probands with the 15q11.2 microdeletion of the genes *TUBGCP5*, *CYFIP1*, *NIPA2*, and *NIPA1*, suffer from spastic paraplegia. The deletions not exceeding BP2 were of paternal origin in the first family and of maternal origin in the second one. Neither cognitive impairment nor behavioural problems frequently described in previous studies were observed in the probands and other family members, who are carriers of the microdeletion. Although we excluded point mutations in the *NIPA1* gene and in the most frequent HSP types (SPG3, SPG4, SPG31), we consider the possibility that the signs of spastic paraplegia may be due to a mutation in other genes linked to SPG. Nevertheless, it may be assumed that the spasticity is due to the *NIPA1* deletion, although haploinsufficiency of *NIPA1*, which was often observed in Prader-Willi/Angelman syndrome, was not recognised as the cause of the SPG phenotype [3]. Worthy of note is that these probands, and the remaining carriers of the microdeletion described here, do not reveal the neuropsychological and behavioural problems described in other patients with the 15q11.2 microdeletion. The history of the second proband (pedigree 2, II-1, (Figure 1B) is not entirely clear, and the onset of SPG was reported to be at age 45; however, as a child, she had an abnormal gait pattern, and at age 13, she had a serious head injury with transient hemiparesis. Even if the other causative mutation is found, it seems that microdeletion 15q11 does not give rise to neuropsychiatric and cognitive disturbances in our patients.

In this report, we review that the microdeletion of 15q11 was detected in different syndromes, including neuropsychiatric syndromes with autism, schizophrenia or behavioural and learning problems, neurological syndromes with idiopathic generalised epilepsy or spastic paraplegia, as in the cases described here. Taking into account that the genes located in this region are functionally related to the nervous system, one can make an assumption that the deletion may be a cause of the spectrum of different psychiatric and neurological disorders.

In view of such a diversified clinical picture described by different authors, we propose the following explanations:

- the pleiotropic effect of the deletion, involving CNS;
- the possible coexistence of other factors modifying the phenotype; and
- the possibility that in the patients described by other authors, the behavioural problems and/or developmental delay prevail at a young age, while spasticity develops later.

On the other hand, the frequency of this microdeletion varied in the different groups studied: 0.41% in patients with behavioural and developmental dysfunctions [28], 0.57% in mentally retarded patients [16] and 1% in patients with IGE [29]. The frequency of this microdeletion in our study was 1.4% among 143 probands from families with spastic paraplegia who were screened for the 15q11.2 microdeletion. Presumably, the described microdeletion may represent a polymorphism without any clinical significance, as the same deletion was also found in 0.2% of unaffected controls [29]. The differences between centres 1, 2, 5, 6 and the large de Kovel's control group described in Table 3 are significant ($p < 0.05$). The affected subjects may have other conditions of yet unidentified aetiology, and support of this hypothesis is provided by the observed coexistence of the 15q11 microdeletion and the exon 17 deletion of the *SPG4* gene in 4 members of the family with spastic paraplegia. Moreover, one individual with microdeletion 15q11.2, but free of the *SPG4* mutation, remained asymptomatic at the age of 57 [37]. Table 3 presents the summary of the results of the frequency of the 15q11.2 microdeletion in patients with different phenotypes and controls.

We cannot exclude a possibility that the range of the microdeletion in the 15q11.2 region plays a key role in the phenotype characterised by neurobehavioral disturbances. Recent study by Yoon et al aimed at modelling the genetic risk for schizophrenia, showed that the haploinsufficiency of *CYFIP1* cause the abnormalities in forming of adherent junctions and polarity in the iPSC-derived neural progenitors, carrying the 15q11.2 microdeletion [38].

Considering studies establishing the range of the microdeletion beyond BP2, the location of the gene/genes connected to behavioural disturbances in this particular region may be expected but we did not find any behavioural and psychiatric evidences in our patients. Without a more detailed analysis, the existence of the novel microdeletion syndrome proposed by Doornbos et al. [16] seems to lack sufficient evidence. Nevertheless, in all patients with a microdeletion in 15q11, establishing the precise size and boundaries of the deletion will be essential. Our study contributes by extending the phenotype variability of the subjects carrying microdeletion 15q11.2, but the clinical significance of these microrearrangements remains unclear and needs further studies.

Center No.	Clinical features	Prevalence in patients [%]	Prevalence in controls	Ref.
1	Mental retardation and/or multiple congenital abnormalities (MR/MCA)	9/1576 [0.57%]	-	Doornbos et al. ¹⁶
2	Mental retardation (MR)	1/64 [1.5%]	-	Hirschfeldova et al. ²⁵
3	Subjects referred for microarray analysis (behaviour/neurological problems or developmental delay)	69/17 000 [0.41%]	-	Burnside et al. ²⁸
4	Schizophrenia or bipolar disorder and idiopathic epilepsy	0/315	1/191 [0.5%]	Stewart et al. ³⁶
5	Idiopathic general epilepsies (IGE)	12/1234 [1%]	6/3022 [0.2%]	De Kovel et al. ²⁹
6	Childhood absence epilepsy (CAE)	3/198 [1.5%]	0/400	Jiang et al. ³⁷
7	Amyotrophic lateral sclerosis	15/4434 [0.34%]	15/14618 [0.1%]	Blauw et al. ³⁸
8	Spastic paraplegias (SPG)	2/143 [1.4%]	-	Present study

Table 3: The prevalence of 15q11.2 microdeletion in different groups of patients.

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