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LETTER TO THE EDITOR

De novo SPAST mutations may cause a complex SPG4 phenotype

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Sir,

Spastic paraplegia type 4 (SPG4) is caused by mutations in the *SPAST* gene, and is the most common form of autosomal dominantly inherited pure hereditary spastic paraplegia (HSP) worldwide (Hazan *et al.*, 1999; Salinas *et al.*, 2008; Finsterer *et al.*, 2012; Dong *et al.*, 2018; Koh *et al.*, 2018; Parodi *et al.*, 2018). Age of onset and severity of SPG4 are known to be highly variable. In a recent issue of *Brain*, Parodi *et al.* (2018) described an impressive series of 842 patients with SPG4. They found that the mutation type and the patient's sex modified the age of onset and disease severity. We have carefully read their paper, with specific interest in the variable phenotype of SPG4 and the mode of inheritance. The authors reported that most of the patients had a positive family history; only 5.7% of all cases occurred sporadically, similar to all large (population) studies on SPG4. Parodi *et al.* (2018) did not explicitly mention whether the sporadic cases in their cohort were due to *de novo SPAST* mutations. In general, the identification of sporadic patients with SPG4 is attributed to common mechanisms like incomplete penetrance, somatic mosaicism, non-paternity, and inadequate clinical assessment of the parents. Altogether, true *de novo* occurrence of *SPAST* mutations, i.e. where both parents of the patient are proven not to have the mutation in lymphocytes, appears rare and has—to our knowledge—never been studied separately.

Confronted with the unanticipated complex phenotypes of the first young children that we recently diagnosed with *de novo SPAST* mutations (see below) and the lack of knowledge on the topic, we thoroughly reviewed the literature using Pubmed, searching for papers using the terms 'SPG4', 'SPAST', 'spastin', and 'hereditary spastic paraplegia'. Reference lists were screened for additional papers. All papers were then searched for the description of cases with sporadic HSP in the abstract and the results and discussion

sections, assuming that cases with *de novo* mutations would be identified by this strategy. Additionally, every paper was also screened by an electronic search for the word 'novo' in the pdf file of the paper. We found that, since the discovery of the *SPAST* gene (Hazan *et al.*, 1999), a large number of papers has been published on the clinical and molecular features of SPG4, including many case reports (not all included in the reference list) but also numerous large studies on selected cohorts of hundreds of patients with familial and isolated forms of HSP from all different parts of the world (Fonknechten *et al.*, 2000; Crippa *et al.*, 2006; Depienne *et al.*, 2006; Magariello *et al.*, 2006, 2010; Salinas *et al.*, 2008; Shoukier *et al.*, 2009; De Bot *et al.*, 2010; Finsterer *et al.*, 2012; Elert-Dobkowska *et al.*, 2015; Park *et al.*, 2015; Balicza *et al.*, 2016; Chrestian *et al.*, 2016; Mészárosová *et al.*, 2016; Burguez *et al.*, 2017; Dong *et al.*, 2018; Koh *et al.*, 2018; Parodi *et al.*, 2018). From the literature, we were able to identify only 14 patients who were reported to have true *de novo SPAST* mutations (Table 1) (Crippa *et al.*, 2006; Blair *et al.*, 2007; Depienne *et al.*, 2007; Battini *et al.*, 2011; Aulitzky *et al.*, 2014; Elert-Dobkowska *et al.*, 2015; Mészárosová *et al.*, 2016; Polymeris *et al.*, 2016; Burguez *et al.*, 2017; Gillespie *et al.*, 2018). Interestingly, all of these patients suffered from pure HSP. Six of 14 patients were identified in studies that had pure HSP as an inclusion criterion, which may partly explain the absence of divergent phenotypes in the literature. Disease onset was (far) below 10 years in nine patients (Patients 2, 5, 8–12 and 14) and after 25 years in four patients (Patients 1, 3, 7 and 13). Of note, Patient 6 was an asymptomatic mother with a somatic mosaicism for a *SPAST* mutation and three children affected with SPG4.

After this literature study, we searched the exome database of the Department of Human Genetics of the Radboud University Medical Centre for other patients in whom *de novo* mutations in the *SPAST* gene had been identified. In all cases mutation analysis of both parents had been performed and found to be negative. Referring clinicians were asked to contribute to this study by sharing

Table 1 Patients with *de novo SPAST* mutations reported in the literature

Patient	Paper	Case	Mutation (cDNA)	Protein change	Parents tested negative	Remark
1	Crippa, 2006	HSP4, II:2	c.1216 A>G	p.Ile406Val	Yes	This male (disease onset 30 years, mild HSP) had two daughters with early onset HSP (both at 2 years). The daughters, but not the father carried the proposed modifier variant c.131C>T (p.Ser44Leu) in addition to c.1216 A>G .
2	Blair, 2007	II-3	c.1537G>A	p.Gly471Asp	Yes	Family with pure HSP. Female, onset in infancy, long follow-up; wheelchair dependency from age 48 years; has daughter and son with pure HSP too, both still able to walk at ages 26 and 24, respectively.
3	Depienne, 2007	I	c.1684C>T	p.Arg562X	Not applicable	Family with pure HSP. Somatic mosaicism in the grandfather led to spastic diplegia from 55 onwards; his daughter had disease onset at 18, his grandson at 5.
4	Battini, 2011	8	c.1238C>T	p.Ser413Leu	Yes	Age at onset 3 years. Pure HSP (= inclusion criterion).
5	Battini, 2011	9	c.1360G>A	p.Glu454Lys	Yes	Age at onset 2 years. Pure HSP (= inclusion criterion).
6	Aulitzky, 2014	I.2	c.1837G>C	p.Asp613His	Not applicable	Asymptomatic mother of three affected children (age not given); low grade somatic mosaicism for the variant was shown in blood cells.
7	Elert, 2015	S38	c.1246–4T>C and 1246–2delA	p.Val416fs	Yes	Age at onset 28, pure HSP.
8	Mészárosová, 2016	29	c.1303C>A	p.Pro435Thr	Yes	Childhood onset. Pure HSP (= inclusion criterion).
9	Mészárosová, 2016	33	c.1413+6T>C	Exon 11 skipped	Yes	Childhood onset. Pure HSP (= inclusion criterion from study).
10	Polymeris, 2016	9	c.1636G>A	p.Gly546Arg	Yes	Female, age at onset 1.5. Pure HSP (= inclusion criterion).
11	Polymeris, 2016	15	c.1496G>A	p.Arg499His	Yes	Male, age at onset 1.5. Pure HSP (= inclusion criterion).
12	Burguez, 2017	HSP18	c.1273G>C	p.Ala425Pro	Yes	Father (age 28) with pure HSP (including mild dysarthria and mild intellectual disability); has three sons with pure HSP; age at onset in father and three sons first year of life.
13	Gillespie, 2018	I	c.1496G>A	p.Arg499His	Yes	Female, age at onset <2 years, spastic paraplegia with intellectual decline in first decade of life (follow-up until 13 years).
14	Gillespie, 2018	2	c.1496G>A	p.Arg499His	Yes	Female, age at onset at the end of the first year of life, spastic diplegia with mild global developmental delay (follow-up until 5 years).

Table 2 Clinical and molecular characteristics of 13 Dutch patients with SPG4 caused by *de novo* SPAST mutations

ID	Sex, age[a]	AAO (AAMD)[b,c], y	Mutation and protein change	Presenting symptoms and signs, and disease course
1	F,26	6 (18)	c.1496G>A p.Arg499His[d,e]	Mildly delayed gross motor development; first medical evaluation at 6 y (spastic diplegia). Childhood onset, classic pure HSP with hardly any progression.
2[i]	F,22	<2 (19)	c.1496G>A p.Arg499His[d]	Delayed gross motor development and spastic diplegia. Best motor achievement was walking with support (2 y), but she never reached normal sitting balance without support; initial cognitive functions and functions of upper extremities appeared normal. Starting in childhood: gradual loss of motor and cognitive functions, leading to wheelchair dependency (8 y), gastrostomy from age 15, gradual loss of speech from age 12 on, and use of eye-tracking system for communication (19 y): at last visit: only producing sounds, a few words and severe drooling. Epilepsy: three generalized seizures with spontaneous recovery (17 y). Prominent signs: tetraplegia, no head control, with generalized pain, and lack of energy/fatigue.
3	F,21	<2 (14)	c.1775T>A p.Ile592Lys[d]	Delayed gross motor development and spastic diplegia. Best motor achievement was walking with aids (3 y). Wheel-chair bound at 7–8 y, but otherwise developed normally.
4[i]	F,17	1 mo (13)	c.1496G>A p.Arg499His[d]	Motor abnormalities in the first year (hypotonia, changing to hypertonia in first year). Developed very slowly: learned to sit with support (4 y) and to stand with support, but lost this at 6 y and then became completely wheelchair bound. Arm functions were relatively spared during childhood, but then deteriorated until all functions were lost (11 y). Intellectual disability. Oral motor and speech: able to speak short sentences but lost this at 5–6 y; current communication with eye-tracking system, can only produce a few sounds; gastrostomy from the age of 9 y; severe drooling. Epilepsy: febrile seizure at ages 1 and 3 y. Prominent signs: tetraplegia, with generalized pain, lack of energy/fatigue, scoliosis and a severe head drop. Urinary and faecal incontinence.
5[i]	M,15	1 mo (2)	c.1496G>A p.Arg499His[d]	Motor abnormalities (hypertonia) from first weeks of age. Learned to walk, max 10 m, with aids (3 y). Severe generalized and mixed spastic-dystonic movement disorder, treated with oral medication, local botulin toxin injections, intrathecal baclofen (from 6 y), and selective dorsal rhizotomy (at 10 y). Dystonia was remarkably severe. Arms were equally affected as legs. IQ could not be tested because of motor impairment. Was able to speak short sentences but has lost this; actual communication with eye-tracking system; fully dependent on gastrostomy. Severe scoliosis. Urinary incontinence.
6[i]	M,13	<2 (2)	c.1496G>A p.Arg499His[d]	Delayed gross motor development and spastic diplegia. Learned to stand with support (1 y) but never stood or walked independently; walked with aids until 6 y, then became wheelchair-bound with head support. Intelligence appeared normal during infancy and early childhood but then an early 'ceiling effect' appeared to occur from the age of 6 y. Speech was normal until 4 y, thereafter gradually became slower and dysarthric. Prominent symptom: lack of energy/fatigue.
7[i]	M,12	<2 (11)	c.1326A>T p.Glu442Asp[f,g]	First year relatively unremarkable; standing with support (14 mo), walking with support (18 mo). However, never stood or walked independently; walked with aids until 4 y, then rapidly became spastic diplegic and dependent on a wheelchair with head support (7 y). Learned to write (7 y) but hand function deteriorated, still some hand function at age 10 y. Initial IQ was average, but gradual deterioration occurred (last IQ 69 at age 8 y). Speech slowly deteriorated from 7 y, but is still able to speak at age 10; however, much slower. Epilepsy: febrile seizure at age 2 and two generalized seizures at age 9, treated with levetiracetam. Urinary and faecal incontinence (9 y), and starting dysphagia (10 y). Prominent signs: lack of energy/fatigue.
8	F,12	2.5 (5)	c.1226C>T p.Ala409Val[f,h]	Mildly delayed gross motor development, with unsupported sitting at 12 mo and independent walking at 21 mo. Spastic diplegia diagnosed at age 2.5 y. Uses wheelchair for long distances, otherwise favourable development. IQ (based on school performance) above average.
9[i]	F,11	<2 (3)	c.1496G>A p.Arg499His[d]	At 1 y 9 mo first visit to paediatrician because of not walking independently and saying nothing else than 'mam' and 'dad'. Spastic paraplegia was diagnosed. Did not develop from that moment, and motor performance, speech and swallowing progressively worsened from the third year of life. She was fitted with a gastostomy (3 y) and became wheelchair-bound (6 y).
10	F,10	<2 (3)	c.1169T>G p.Met390Arg[f]	CHD (surgery at age 8 mo). Complaints regarding gross motor development and stiff legs were initially attributed to CHD; first referral to paediatric neurology for evaluation at 2 y 6 mo. Spastic diplegia. Learned to walk independently at 3, but prefers rollator. Uses a wheelchair for long distances, otherwise normal development.
11	F,6	<2 (2)	c.1072G>T p.Val358Phe[f]	Delayed gross motor development and spastic diplegia: sitting <12 mo, 15 mo standing. Learned to walk with support (3 y). Otherwise normal development. Underwent selective dorsal rhizotomy at age 5. Walks with rollator.
12[i]	M,5	<2 (2)	c.1360G>A p.Glu454Lys[d,e]	Difficult to classify developmental disorder. At 2 y: sits but cannot sit from supine; does not roll over, does not stand, does not speak. Arms with some dystonic posturing; axial hypotonia; legs severely involved (appear spastic, but with atypical posturing, remarkable floppiness with rapid increase of muscle tone when manipulating; increased tendon reflexes but without clonus; bilateral striatal toes or spontaneous Babinski signs). At 2.5 y: can stand but not walk. At 5 y: face normal, arms only mildly affected; legs show spastic diplegia with inability to walk (uses a wheelchair from an early age). Floppiness and extrapyramidal features have largely disappeared. Speech development is still almost absent (says only some single words), despite impression of normal IQ, and despite nearly normal oral motor functions.
13	M,2	<2 (2)	c.1483G>C p.Ala495Pro[f]	Delayed gross motor development and spastic diplegia: unable to sit at 12 mo, stiffness of the legs. Spastic paraplegia. Still unable to walk with aids at 2 y 4 mo; arms are only mildly affected. Intelligence appears fully normal. Speaks single words at 2 y, 4 mo.

[a]Age at 31 December 2018, in years unless otherwise stated.
[b]The parents of most young patients only gradually became aware of the fact that the gross motor development of their children progressed too slowly, and their legs were stiff; therefore, it was impossible to determine the exact age at which symptoms occurred. For that reason, we decided to denote 'in the first 2 y of life' here, in all these cases; only when the history was evidently different, and an age at onset could be given more precisely, we indicated this.
[c]Whole exome sequencing led to the molecular diagnosis in all patients, except Patients 1, 3, 8 and 9, in whom targeted *SPAST* mutation analysis was performed.
[d]Known *SPAST* mutations: c.1496G>A (Park *et al.*, 2015); c.1775T>A (Parodi *et al.*, 2018); c.1360G>A (Fogli *et al.*, 2009).
[e]The proposed modifier c.131C>T (p.Ser44Leu) (Svenson *et al.*, 2004) was only found in the *SPAST* gene in Patients 1 and 12.
[f]Novel mutations: c.1326A>T; c.1226C>T; c.1169T>G; c.1072G>T; and c.1483G>C.
[g]The same codon is affected by a known mutation, 1324G>A, Glu442Lys (Ribai *et al.*, 2008; Parodi *et al.*, 2018).
[h]Alternatively, c.1226C>T may also lead to p.Ala409_Tyr415del.
[i]Complex HSP.
AAO = age at onset; AAMD = age at molecular diagnosis; CHD = congenital hip dysplasia; mo = months; y = years.

clinical, neuroimaging and molecular data of their patients, after having obtained informed consent of the patient and/or the parents, in order to get a first impression of the clinical significance of the *de novo* occurrence of *SPAST* mutations. Doing so, we identified 13 patients (Table 2) and found that six patients (Patients 1, 3, 8, 10, 11 and 13) had pure HSP (note, Patient 13 may be too young for final phenotyping). Contrasting this classic phenotype in six patients, however, the other seven patients showed an exceptional phenotype. Patients 2, 4–7, 9 and 12 suffered from a complex, generalized and progressive motor disorder with onset in the first or second year of life. Additionally, they almost invariably also suffered from severe, progressive loss of cognitive functions, loss of spoken language, and severe dysphagia requiring tube feeding. Three of these patients also had seizures. MRI studies in these 13 Dutch patients had been performed at different ages, on different machines, and following different protocols; irrespective of these disadvantages we could conclude that cerebral imaging generally did not show any abnormalities, neither in the patients with pure HSP nor in the more severely affected children.

Most of the *SPAST* mutations that occurred *de novo* in the patients identified in the literature study (Table 1) and our cohort (Table 2) are also present in families with multiple generations with pure HSP. The common c.1496G>A mutation was even found in nine of the 27 (33%) patients identified with a *de novo SPAST* mutation; remarkably, five of the seven Dutch patients with the complex SPG4 phenotype harboured this mutation. In addition to a *de novo* mutation, the proposed modifier c.131C>T (p.Ser44Leu) (Svenson *et al.*, 2004) was found in the *SPAST* gene in 2 of the 13 Dutch patients, one with a pure HSP phenotype (Patient 1) and one with a complex phenotype (Patient 12). The low number of cases and the relative high occurrence of c.131C>T in controls (between 1–2% in Europe; Database ExAC, Lek *et al.*, 2016) does not allow for any conclusions.

We have no explanation for the fact that some *SPAST* mutations can lead to pure HSP as well as to the highly complex phenotype presented here. The *SPAST* mutations that may be associated with complex SPG4 when occurring *de novo* never seem to cause such a severe phenotype in individuals from large, multi-generation SPG4 families. This observation pleads against the presence of a simple, independent explanation in addition to the *de novo* occurrence of the *SPAST* mutation, such as a genetic or environmental modifier, for the existence of the complex SPG4 phenotype.

Based on all available data, only a minority of patients with *de novo SPAST* mutations appear to suffer from the complex SPG4 phenotype. The high number of patients (22/27, 81%) with a *de novo SPAST* mutation and an extremely early onset of disease, in our series (13/13) as well as the literature (9/14), however, may point to a relationship between age of onset and the *de novo* occurrence of the mutation. Of note, this observation may also simply reflect the greater need to study parental carriership (and thus the chance to find a *de novo* mutation) in paediatric practices compared to adult neurogenetic services.

With regard to the apparent (extreme) rarity of the complex SPG4 phenotype, it seems reasonable to assume that the true incidence may be higher since many paediatric cases with such a severe phenotype may never have had *SPAST* mutation analyses and thus may have been missed in the era before next generation sequencing techniques became available. This possibility might be illustrated by the fact that we identified most Dutch patients in a relatively short period. Recognition and acceptance of the complex SPG4 phenotype at the far end of the clinical spectrum of SPG4 are the first steps towards an appropriate diagnosis. Future studies will hopefully contribute to the further delineation of the complex phenotype, and the understanding of its underlying molecular mechanisms.

In conclusion, we recognized a complex SPG4 phenotype with an infantile onset, complex, generalized, and progressive motor disorder and severe cognitive decline and loss of spoken language. This phenotype has never been reported in SPG4 families, and it appears to us that only *de novo SPAST* mutations can cause such a complex phenotype. Our clinical, observational study does not allow us to explain the remarkable findings. Nevertheless, we gladly add our data to the recent work of Parodi *et al.* (2018), and are willing to open a scientific discussion on what we think is a new clinical SPG4 phenotype.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Competing interests

The authors report no competing interests.

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