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# Spinocerebellar ataxia 48 presenting with ataxia associated with cognitive, psychiatric, and extrapyramidal features: A report of two Italian families

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ABSTRACT

*Introduction:* Spinocerebellar ataxia 48 has recently been described as an adult onset ataxia associated with a cerebellar cognitive affective syndrome, caused by a heterozygous mutation in the *STUB1* gene.

*Methods:* We characterized the clinical and neuroimaging phenotype of eight patients from two autosomal dominant ataxia multigenerational Italian families, in whom we conducted whole exome sequencing, targeted multigene sequencing, and Sanger sequencing studies.

*Results:* We describe a complex syndrome characterized by ataxia and cognitive-psychiatric disorder in all cases, variably associated with chorea, parkinsonism, dystonia, urinary symptoms, and epilepsy. MRI showed a significant cerebellar atrophy, coupled to a T2-weighted hyperintensity affecting the dentate nuclei and extending to the middle cerebellar peduncles, whereas FDG-PET studies revealed glucose hypometabolism in cerebellum, striatum, and cerebral cortex.

We identified two different novel *STUB1* mutations segregating in the two families. One of the two mutations, p.(Gly33Ser), occurs in the TRP domain, whereas p.(Pro228Ser) is located in the ubiquitin ligase region.

*Discussion:* We emphasize the similarity of the described clinical picture with that of SCAR16, an autosomal recessive ataxia caused by biallelic mutations in the same gene, and of spinocerebellar ataxia type 17, which is considered the main Huntington's disease-like syndrome. The pathogenesis of the disease and the relationship between SCA48 and SCAR16 remain to be clarified.

## 1. Introduction

The Spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominant neurodegenerative diseases characterized by progressive gait and stance ataxia, often associated with dysmetria and dysarthria. In some forms, ataxia is the only phenotypic finding, whereas other SCAs present additional neurological symptoms and signs, including pyramidal and extrapyramidal features, peripheral neuropathy, cognitive decline, and seizures. The prevalence of SCAs is estimated to be 1.5–4.0 $\times 10^{-5}$ population [1].

More than 40 genetic subtypes of SCAs have been identified and they are numbered in the order of gene identification. There are three major genetic categories of SCAs: 1) expanded CAG repeat ataxias; 2) non-coding zone repeat ataxias; and 3) ataxias caused by conventional mutations [2].

Recently, a new form (SCA48) has been described in a Spanish kindred presenting with an autosomal dominant cerebellar cognitive affective syndrome associated with a heterozygous mutation in the *STUB1* gene [3]. Previously, biallelic mutations in *STUB1* had been associated in about thirty families with SCAR16, an autosomal recessive form of spinocerebellar ataxia, characterized by an early onset and additional features such as spasticity, peripheral neuropathy, myoclonus, epilepsy, cognitive impairment [4], and occasionally hypogonadism [5], mimicking Gordon Holmes syndrome.

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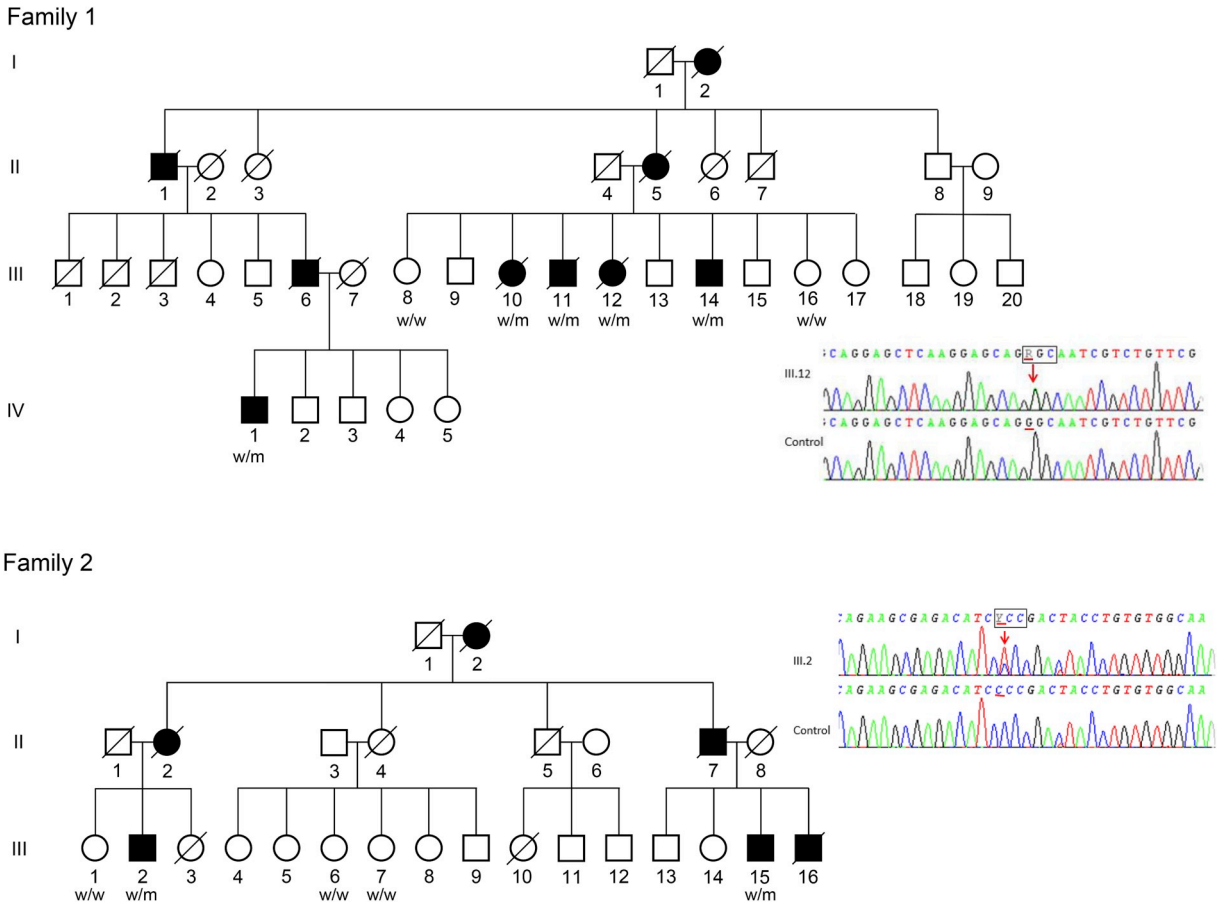


**Fig. 1.** Pedigrees of Family 1 and Family 2. Empty symbols indicate unaffected individuals and filled symbols affected individuals. Square are men and circles are women; slashed symbols indicated deceased individuals; "m" and "w" depict the presence of causative and wild-type alleles, respectively. Electropherograms of the *STUB1* region flanking the c. 97G > A variant (p.G33S) (Family 1; upper panel) and the c.682C > T (p.P228S) (Family 2; lower panel) mutations (underlined nucleotide and arrowhead). The mutant residue is boxed in the patients (numbers correspond to family tree) compared to normal controls.

Herein, we describe two Italian SCA48 families harboring novel heterozygous mutations in *STUB1*.

## 2. Patients and methods

This study investigated two kindreds with autosomal dominant ataxia originating from Southern Italy. Family 1 included nine patients in four generations and Family 2 six patients in three generations (Fig. 1).

Phenotyping by clinical evaluation, neuroimaging, neuropsychological and neurophysiological studies was performed in the affected subjects at the Neurology Unit of the Federico II University in Naples, Italy. Patients provided written consent to the study. Whilst detailed medical records were collected in all affected individuals, six of the nine patients in Family 1 and two of the six affected subjects in Family 2 were personally examined (Table 1).

Total genomic DNA was purified from peripheral blood lymphocytes of seven examined patients and five unaffected family members. Prior to this study, in each family at least one affected individual had undergone genetic testing for expanded pathological repeats associated with SCAs (SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA17, and DRPLA) and pathological expansion in the *HTT, C9orf72,* and *JPH3* genes. The proband in Family 1 (1.III-14) underwent whole exome sequencing using a SureSelect (Agilent, Santa Clara, CA) All Exon v6 exome capture kit and performed on the Illumina sequencing platform, using a reported bioinformatics pipeline [6]. In addition, two patients (1.III-12 and 2.III-02) underwent targeted multigene sequencing to investigate the coding exons and flanking intronic regions of 285 genes linked to inherited ataxia, alone or associated with spastic paraplegia [7]. To analyse the data obtained from our study, we used a routine bioinformatics pipeline [6] that adopts the Ingenuity Variant analysis suite (Qiagen, https://apps.ingenuity.com). To assign pathogenicity, we set up a precise Alissa (Agilent) pipeline using the following criteria: a sequence quality score greater than 30, a read depth greater than 30, and rare occurrence in publicly available polymorphic datasets (with a minor allele frequency < 0.01% for autosomal dominant genes) with less than one occurrence in homozygosity in gnomADv2.1 (http://gnomad.broadinstitute.org/; macarthurlab.org/2018/10/17/gnomad-v2-1). As reported previously [6], we determined predictably or probably deleterious scores using an *in silico* pipeline employing a set of eight prediction software packages. These included the following: SIFT (https://sift.bii.a-star.edu.sg/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org/), LRT (http://www.genetics.wustl.edu/jflab/lrt_query.html), GERP++ (https://varsome.com/), Mutation Assessor (https://varsome.com/), UMD-Predictor (http://umd-predictor.eu/), and CADD phred (https://cadd.gs.washington.edu/). Upon validation of the results, we tested segregation of the identified variants in *STUB1* by capillary Sanger sequencing in five patients (III-10, III-11, III-12, III-14, IV-1) and two unaffected relatives (III-8, III-16) in Family 1 and in two patients (III-2 and III-15) and three unaffected members (III-1, III-6, III-7) of Family 2.

## 3. Results

Mean age at onset ± SD was 39.9 ± 11.1 years in the eight

**Table 1**
Clinical features of SCA48 patients.

| | Family 1 | | | | | | Family 2 | |
|---|---|---|---|---|---|---|---|---|
| | 1.II-5 | 1.III-10 | 1.III-11 | 1. III-12 | 1.III-14 | 1.IV-1 | 2.III-2 | 2-III-15 |
| **Sex, age at examination, yrs** | F (60) | F (59) | M (44) | F (41) | M (61) | M (54) | M (60) | M (39) |
| **Signs/symptoms at onset (age, yrs)** | ataxia, tremor (50) | GTC (12), ataxia (40) | GTC (5), ataxia (22) | ataxia (28) | psychiatric disorders (45), GTC, ataxia (49) | dysarthria, ataxia, dizziness (44) | ataxia (55) | ataxia (35) |
| **Ataxia** | + + + | + + + | + + + | + + + | + + | + + | + + + | + + + |
| **Dysarthria** | + | + + | + | + | + + | + + | + + | + + |
| **Tremor** | | | | + | + | | | + |
| **Parkinsonism** | + | + | + | + | + + | | | |
| **Chorea** | + + | + | + | + + | | | + + | |
| **Increased Tendon Reflexes** | | + | + | + + | + | + + | | + |
| **Psychiatric disorders** | + + + | + + | + | + | + + | + + | + | + + |
| **Cognitive dysfunction** | + | + + | + + | + + | + + | + | + + | + |
| **Other features** | UTS | GTC UTS DYSP | GTC UTS DYST | DYST | GTC DYSP DYST | UTS DYSP HL | DYSP | DYSP HL |
| **Cerebellar atrophy at MRI (age at exam, yrs)** | | + + + (59) | + + + (44) | + + (42) | + + + (58) | + + (54) | + + + (55) | + + + (39) |
| **Age at death, yrs** | 70 | 65 | 52 | 60 | | | | |

Severity of features is scored from + (mild) to + + + (marked). GTC: generalized tonic-clonic seizures; UTS: urinary tract symptoms. DYSP: dysphagia; DYST: dystonia; HL: hearing loss.

personally observed patients (excluding seizures onset), whereas age at death was 63.9 ± 12.5 in the eleven deceased patients from the two families.

*Clinical features*. Family 1. The main clinical features of the six personally observed patients are summarized in Table 1. The age of onset of ataxia, which was the first symptom in three cases, varied from 22 to 50 years. One patient presented with depression and two with generalized epilepsy and later developed gait ataxia. Ataxia was present in all, parkinsonism (5/6 patients) and mild choreic movements (4/6) were common features. Tendon reflexes were increased in five patients. Over the years, all patients developed multi-domain cognitive impairment, with decline in memory performances and executive functions. Psychiatric symptoms were present in all patients. In particular, severe depression, including suicidal attempts, was the most common feature. Anxiety, insomnia, and irritability were also frequent.

A depressive disorder was also reported in some of the unaffected relatives (III-8, III-16, III-17), who did not manifest motor nor cognitive symptoms.

Family 2. Table lists the clinical features of the two examined patients. The first symptom was ataxia in both cases, with onset varying from 35 to 55 years. Case III-2 also presented multi-domain cognitive impairment, and several movement disorders, such as tongue tremor, diffuse choreic dyskinesias, and blepharospasm. Psychiatric symptoms, such as apathy and anxiety, were also present. Patient III-15 presented with ataxia in early adulthood, mild postural tremor, mild hearing loss (reported also in his father), progressive cognitive impairment, and anxiety disorder. Two additional cases had died prior to this study but upon reviewing their medical records they were considered as affected by ataxia and parkinsonism with onset in the sixth decade.

*Neuroimaging*. A brain MRI scan was performed in seven patients. In all patients a moderate to marked cerebellar atrophy was present, affecting both the vermis and the cerebellar hemispheres, with a prominent involvement of postero-lateral lobules. In three cases, revision of the MRI images demonstrated a bilateral hyperintensity affecting the dentate nuclei, extending to the medial portion of the middle cerebellar peduncles (Fig. 2). In addition, FDG-PET, performed in cases 1.III-14, 2.III-2, and 2.III-15, revealed a marked cerebellar glucose hypometabolism involving both the cerebellar cortex and the vermis and a less severe striatal and cortical hypometabolism (Fig. 3). These findings were observed in all the three patients and appeared slightly more severe in 2.III-2. Reduced cortical metabolism involved mainly the frontal cortex in 2.III-2, and was more widespread in the other two patients. DaTSCAN, performed in two patients, detected a slight decrease in tracer uptake in the right striatum of patient 1.III-14 and in the left putamen of 2.III-2 (Fig. 3).

*Neuropsychological studies*. Neuropsychological evaluation documented multi-domain cognitive impairment, with decline in memory performances and executive functions in the tested patients (1.III-10, 1.III-14, 1.IV-1, 2.III-2).

*Neurophysiological studies*. Nerve conduction studies and electromyography, performed in three patients (1.III-14, 1.IV-1, 2.III-2) did not reveal any abnormalities. Electroencephalograms, available in 1.III-11, 1.III-14 and 2.III-15, showed generalized background slowing with mild epileptiform abnormalities in the last patient.

*Genetic analysis*. The heterozygous c.97G > A variant (p.G33S) in *STUB1* segregated in affected individuals from Family 1, as well as c.682C > T (p.P228S) recurred only in patients from Family 2 (Fig. 1). Both mutations were novel, affected residues conserved throughout evolution, and the variants were absent in public available databases, including ExAC (http://exac.broadinstitute.org) and gnomAD (https://gnomad.broadinstitute.org/). The mutations were deemed predictably deleterious upon combined assessment of eight *in silico* tools.

## 4. Discussion

Here we describe two Italian families carrying novel heterozygous mutations of *STUB1*, responsible for SCA48. The phenotype in these kindreds appeared more complex than observed in the previously described Spanish family where a cerebellar cognitive affective syndrome with onset in late adult life was associated with ataxia [3]. The clinical picture we here report included a heterogeneous age at onset of ataxia (range 22–55 years), associated with psychiatric (8/8 cases) and cognitive (8/8) features, various combination of movement disorders such as chorea (5/8), parkinsonism (5/8), and dystonia (3/8), in addition to sphincter disturbances (4/8) and epilepsy (3/8). Parkinsonism and chorea were mild and did not require treatment in our patients. Interestingly, our SCA48 patients presented features also described in SCAR16, where, beside ataxia, also mental impairment, movement disorders (chorea, dystonia, tremor), myoclonus, and seizures have been reported. At large, the clinical picture we observed also mimicked SCA17, a dominantly inherited ataxia with expansion of the CAG/CAA trinucleotide repeats in the TATA-binding protein (TBP). SCA17 is associated with cognitive and psychiatric abnormalities, extrapyramidal features, and seizures. SCA17 was indeed the initial clinical diagnosis in patients 1.III-14 and 2.III-2, before receiving a negative diagnostic DNA test. Of note, we observed later age at onset (39.9 ± 11.1 yrs vs

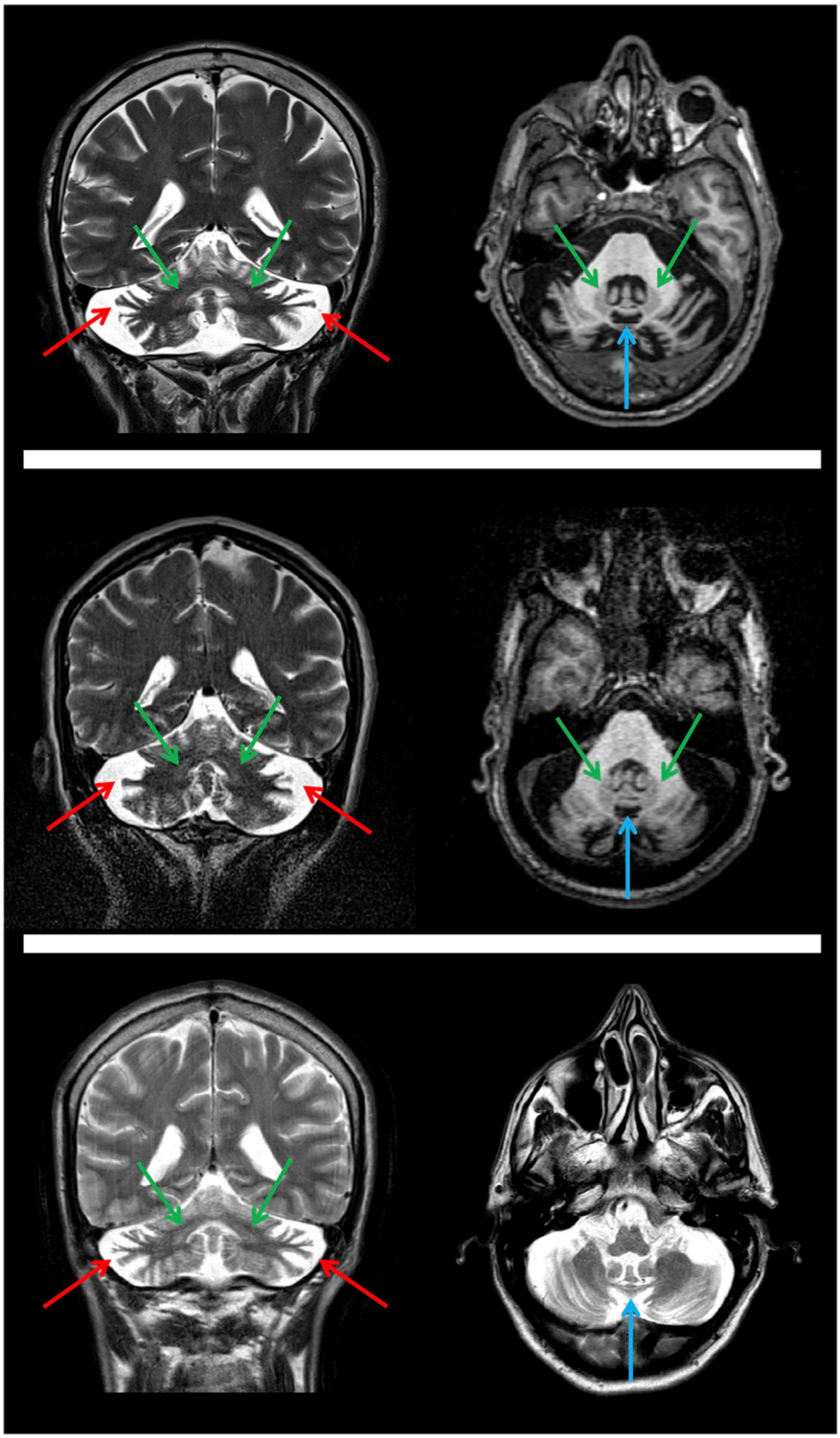

**Fig. 2.** Selected coronal and axial T2-weighted slices, along with axial T1-weighted images, showing typical MRI findings in three SCA48 patients (TOP-BOTTOM: 1.III-14, 1.IV-1, 2.III-2). In all cases, a significant atrophy of both vermis (blue arrows) and cerebellar hemispheres, more pronounced at the level of the posterior and lateral cerebellar areas (i.e. Lobule VI, Crus I, Crus II and Lobule VIII, red arrows), was present. Furthermore, hyperintensity of both dentate nuclei was found, extending to medial portion of the middle cerebellar peduncles (green arrows).

31.4 ± 9.6) and at death (64.3 ± 13.1 vs 51.7 ± 7.6) in SCA48 patients when compared with our SCA17 families [8]. Further studies are necessary to show if also SCA48, like SCA17, might be considered a Huntington's Disease (HD)-like disorder.

In our study, MRI showed cerebellar atrophy in all the patients, whereas FDG-PET studies revealed a pattern of glucose hypometabolism including not only the cerebellum but also, to a lesser extent, the striatum and the cerebral cortex. The pre-synaptic dopaminergic system in two patients was only minimally affected. With the limitation of a relatively small number of cases, the above neuroimaging pattern resembles, at least in part, that found in SCA17 [9–11]. Furthermore, in the three patients undergoing a thorough and comprehensive MRI examination, we also found a characteristic T2-weighted hyperintense signal extending from the dentate nuclei, bilaterally, to the middle

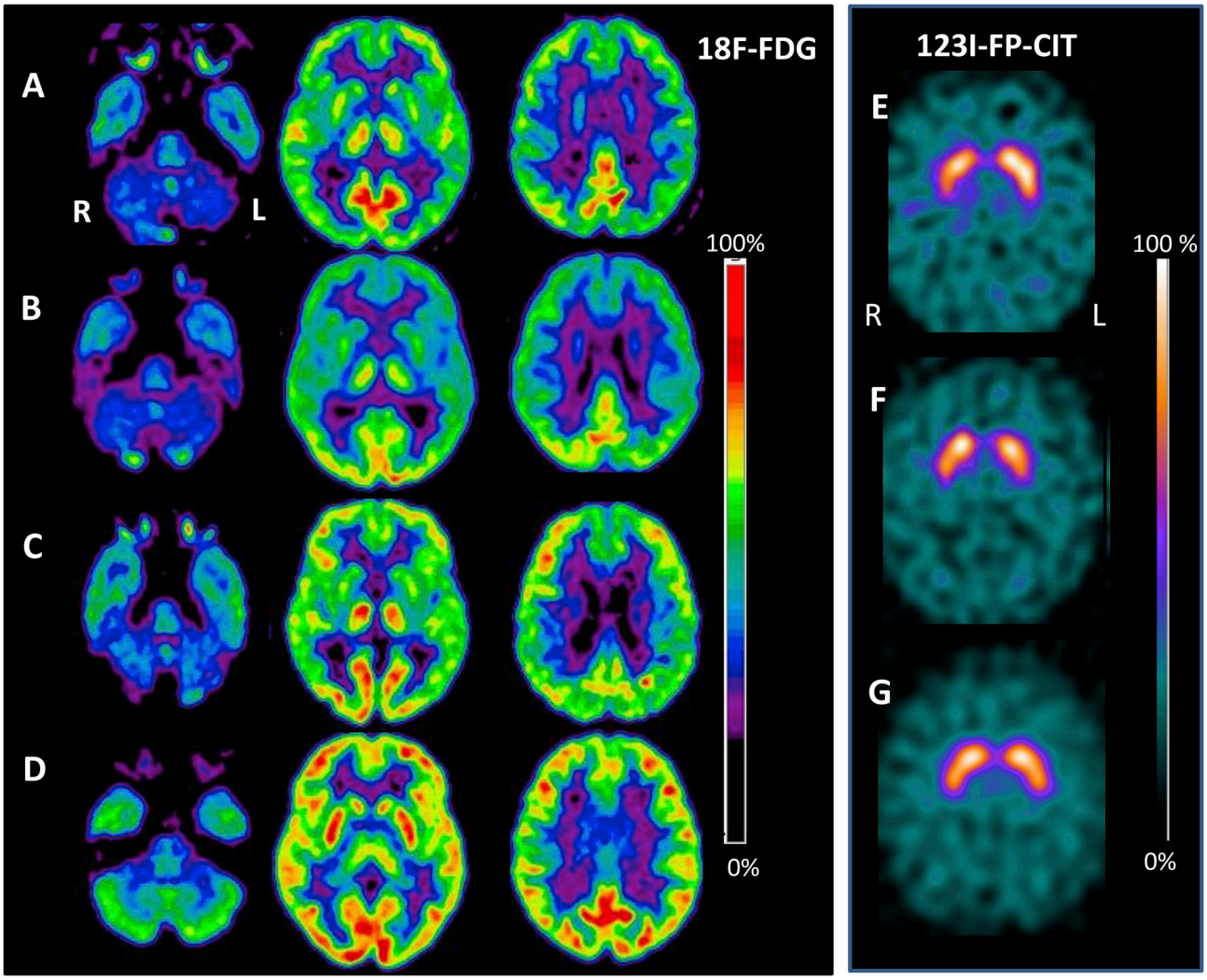


**Fig. 3.** Positron emission tomography (PET) transaxial images at three different sections show [18F]FDG uptake in 1.III.14 (A), 2.III-2 (B), 2.III.15 (C) and in a control (D). Compared to control, all the patients showed a similar metabolic pattern characterized by severe cerebellar hypometabolism and moderate striatal-cortical hypometabolism, more marked in 2.III-2 (B). The cortical hypometabolism was diffuse and, in 2.III-2 (B), more marked in the dorsolateral prefrontal cortex and in the anterior cingulate. SPECT transaxial images at the level of the striatum in 1.III.14 (E), 2.III-2 (F), and in another control (G) show very mild decrease of striatal 123I-FP-CIT uptake in both patients within the lower normal ranges of controls or just below (about 25% reduction) in the right putamen in 1.III.14 (E). The colour scales represent the lower (blue) and the higher (red) cerebral radioactive 18FDG and the lower (blue) and the higher (white) cerebral radioactive 123I-FP -CIT concentration values (%). R = right; L = left.

cerebellar peduncles. Although its evidence is limited to a small number of cases, this MRI finding could represent a useful imaging biomarker of the disease.

*STUB1* encodes CHIP (Carboxy terminus Hsp70 Interacting Protein), a ubiquitin ligase/cochaperone with a role in ubiquitination as a co-chaperone with heat shock proteins, and as an E3 ligase [12,13]. CHIP comprises an N-terminal tetratricopeptide repeat (TPR) domain required for binding to HSP70 and HSP90 chaperones, a linker region, and a C-terminal U-box domain important for recruitment of E2 ubiquitin-conjugating enzyme. CHIP is believed to participate in protein quality control by targeting a broad range of chaperone protein substrates for degradation. Why mutations in *STUB1* lead to the complex phenotype observed in SCAR16 and SCA48 remains to be clarified but it is possible that the pathogenetic mechanism implies dysfunction of autophagy pathway. CHIP regulates autophagy flux via its function in targeting phosphorylated transcription factor EB (TFEB) for degradation or controlling regulation of mitochondrial biogenesis via reduction in the master gene PGC1alpha, or both [14,15]. Also, a *Stub1*$^{-/-}$ mouse [16] shows findings suggestive of impaired autophagy. In our SCA48 families, p.(Gly33Ser) occurs in the TRP domain, whereas p.(Pro228Ser) is located in the ubiquitin ligase region, similar to the Spanish SCA48 kindred, but also to at least twelve SCAR16 families (Supplementary Figs. 1 and 2). Whilst we cannot exclude that the new mutations affect the ability of CHIP to dimerize *in vitro* as observed for a subset of variants in SCAR16 [17], we noted that both protein regions are critical for adequate functioning of CHIP in the endoplasmic reticulum protein quality control and for mediating its interactions with chaperones [18], all necessary steps in the homeostasis of the autophagy–lysosome pathway.

It remains an open question why *STUB1*-related ataxias can act through different pattern of transmission. It is noteworthy that carrier parents in SCAR16 families are healthy in spite of a partially inactive gene product. It seems unlikely that type and location of mutation influence the final phenotype. Missense, frameshift or nonsense mutations occur in SCAR16, and they are located not only in the U-box domain and adjacent regions, but also in the TPR domains [19] (recapitulated in Supplementary Fig. 2). On the other hand, coexistence of autosomal recessive and dominant inheritance has been observed in families harboring mutations in other genes (i.e., *KIF1A, SPG7*) suggesting that zygosity is no longer a barrier to defining a molecular diagnosis in

inherited ataxias. Similar observations can be proposed in other forms of neurodegeneration associated with dysregulated autophagy–lysosome pathway [20]. We are tempted to speculate that some CHIP mutations might alter protein-protein interactions and lead to the formation of dysfunctional complexes or rapid degradation with consequences for the associated cellular processes. However, the hypothesis of a dominant negative effect does not fully explain why SCA48 mutations, like SCAR16, occur in the U-box domain and, therefore, alternative possibilities should be considered.

To summarize, we described in two families a complex adult-onset neurological disorder where ataxia, cognitive impairment, psychiatric disorders, and chorea are part of the clinical picture. Expanding the imaging and phenotypic spectrum of the *STUB1* related disorders, we showed that monoallelic gene mutations cause a widespread degeneration pattern, with involvement of the cerebral cortex, the basal ganglia, and the cerebellum. The pathogenetic mechanisms of the disease and its relationship with SCAR16 should be still explored.

## Disclosures

Sirio Cocozza received fees for speaking from Sanofi Genzyme and Shire

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.001.

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