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Short communication

The movement disorder spectrum of SCA21 (ATX-TMEM240): 3 novel families and systematic review of the literature

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ABSTRACT

Spinocerebellar ataxia type 21 (SCA21/ATX-TMEM240) was recently found to be caused by mutations in *TMEM240*, with still limited knowledge on the phenotypic spectrum and disease course. Here we present five subjects from three novel SCA21 families from different parts of the world (including a novel c.196G > A, p.G66R *TMEM240* variant from Colombia), demonstrating that, in addition to cerebellar ataxia, not only hypokinetic features (hypomimia, bradykinesia), but also hyperkinetic movement disorders (poly-mini-myoclonus, proximal myoclonus) are a recurrent part of the phenotypic spectrum of SCA21. Presenting first prospective longitudinal data, our results provide examples of two different disease trajectories: while it was inherently progressive in adult-onset cases, a dramatically improving trajectory was observed in an infantile-onset case. A systematic review of all previously reported SCA21 patients (n = 42) demonstrates that SCA21 is a relatively early-onset SCA (median onset age 18 years; range 1–61 years) with frequent non-cerebellar involvement, including hyporeflexia (69%), bradykinesia (65%), slow saccades (38%) and pyramidal signs (17%). Our results characterize SCA21 as a multisystem disorder with substantial extra-cerebellar involvement, including a wide spectrum of hypo- as well as hyperkinetic movement disorders as well as damage to the midbrain, corticospinal tract and peripheral nerves. However, in contrast to the current perspective on SCA21 disease, cognitive impairment is not an *obligatory* feature of the disease. The disease course is inherently progressive in adult-onset subjects, but might also be characterized by improvement in infantile-onset cases. These findings have important consequences of the work-up and counseling of SCA21/ATX-TMEM240 patients.

1. Introduction

While the genetic cause of spinocerebellar ataxia type 21 (SCA21/ATX-TMEM240) has recently been identified, knowledge on its phenotypic spectrum and disease course is still limited [1–3]. Clinically, SCA21 is considered a slowly progressive cerebellar ataxia with variable degrees of cognitive impairment and parkinsonism, yet longitudinal data and in-depth phenotyping are largely missing. Genetically, a recurrent mutation in *TMEM240* has been identified in five families with SCA21 [1–3], while all other *TMEM240* variants were unique.

Here, we report five subjects from three new families with SCA21 (including a novel *TMEM240* variant), combined with a systematic review of all 42 published cases, demonstrating a broad movement disorder spectrum in SCA21, which includes - as shown here - also hyperkinetic movement disorders. Exemplary prospective data on SCA21 indicate not only a late-onset progressive disease cluster, but also an infantile-onset improving disease course.

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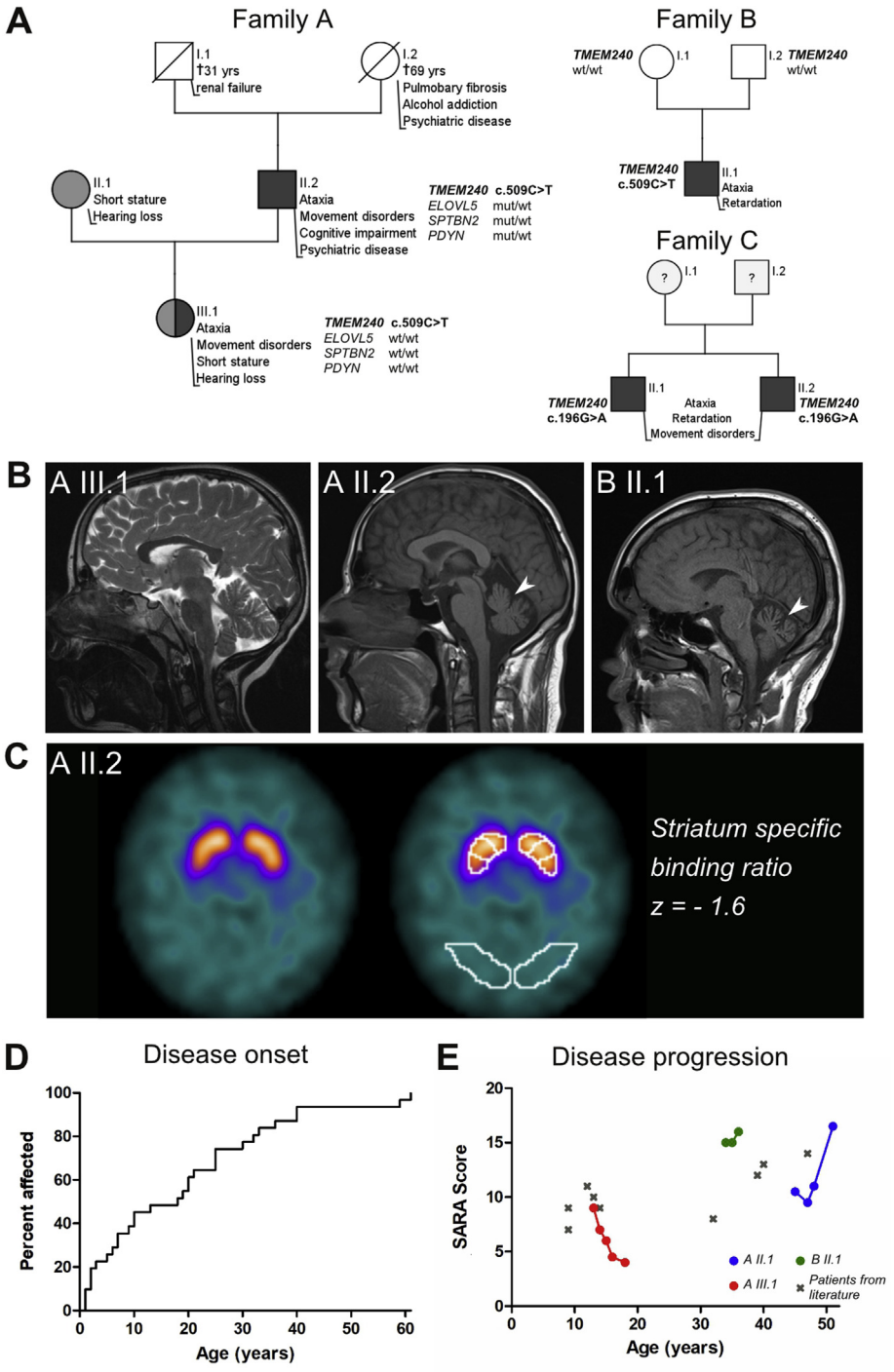

Fig. 1. A) Pedigree of three families with SCA21. The *TMEM240* variant segregated with disease in family A and family C, and occurred *de novo* in family B. Short stature and hearing loss were present as a second phenotype in family A. Note that II.2 was also carrier of rare variants in three additional SCA genes, which were, however, not found in the likewise affected daughter (subject III.1). **B) Structural MRI of SCA21 patients.** Mild cerebellar atrophy was present in adult patients II.2 of family A and II.1 of family B (arrowheads). MRI was normal in children up to at least 10 years of age, as illustrated by patient III.1 of family A (MRI: mid-sagittal plane; left. T2; middle and right: T1 sequence). **C) Dopamine transporter imaging.** ^{123}I-FP-CIT SPECT in subject A II2. showed a normally configured striatum, but low-normal binding values for all subparts of the striatum (white demarcation lines) (age-corrected). **D)** Cumulative distribution of disease onset across 31 SCA21 patients where disease onset data were available. Disease onset was before age 18 in more than 50%, and before age 40 in more than 90% of cases. **E)** Distribution of cross-sectional (crosses) and longitudinal (dots with lines) SARA scores. Two separate clusters suggest an early improving and a late deteriorating phenotype. Connecting lines indicate prospective longitudinal data, all from subjects of the current study.

2. Methods

In-depth phenotyping (clinics, MRI, and PET, where available) and genetic work-up was performed in 5 subjects from 3 families with *TMEM240* variants recruited from three ataxia centers (Tübingen, Germany and Nijmegen and Maastricht, Netherlands). All patients or guardians expressed their consent according to the regulations of the Institutional Review Board at each study site. The analysis was complemented by a systematic literature review to delineate the phenotypic and genetic spectrum of SCA21. Primary research articles were searched in PubMed using the terms “SCA21” or “TMEM240” until June 2018.

3. Results

3.1. Clinical phenotypic spectrum

In family A (German), the 51-year-old index patient (subject II.2, family A; pedigree: Fig. 1A; subject details: Table 1) developed progressive ataxia starting at age 40 years. Prospective longitudinal assessment by the Scale for the Assessment and Rating of Ataxia (SARA) revealed a score of 9.5 points at age 45 years, increasing to 16.5 points at age 51 years (average progression 1.2 points/year). He also showed hypomimia and bradykinesia, distal minimyoclonus of the fingers, proximal intermittent myoclonus of the forearm, slow horizontal saccades, and saccadic intrusions. He had progressive mild cognitive

Table 1
Clinical and genetic characteristics of SCA21 subjects from the 3 novel families identified here. IQ = Intelligence quotient; MOCA = Montreal cognitive assessment; MRI = Magnetic resonance imaging; n.a. = not applicable; n.d. = not determined; SARA = Scale for the assessment and rating of ataxia.

Family	A		B	C	
Patient	II.2	III.1	II.1	II.1	II.2
Origin	German	German	Dutch	Colombian	Colombian
Sex	m	f	m	m	m
Age at last examination (years)	51	18	36	8	3
Age of onset (years)	40	2	32	7	3
SARA at last examination	16.5	4	16	n.d.	n.d.
Gait ataxia	+	–	+	+	+
Limb ataxia	+	+	+	+	+
Oculomotor abnormality	Saccadic pursuit, slow saccades, saccadic intrusions	Saccadic pursuit, saccadic intrusions	Hypermetric saccades	Gaze-evoked nystagmus	Gaze-evoked nystagmus
Rigidity	–	–	–	+	–
Bradykinesia	Bradykinesia, hypomimia	–	–	Hypomimia	Bradykinesia, hypomimia
Resting tremor	–	–	–	–	–
Postural tremor	+	–	–	+	+
Hyperkinetic movement disorders	Mini-myoclonus, mild myoclonus of arms/legs	Mini-myoclonus, mild myoclonus of arms/legs	Action tremor	–	myoclonus
Others	–	Short stature, hearing aids (like mother)	Amblyopia of right eye	Cataract	–
Motor delay	–	+ (mild)	+ (mild)	+	+
Mental retardation	–	- (IQ 93)	+ (special needs education)	+ (IQ 71 age 9, IQ 50 age 15)	+ (special school for retardation)
Later cognitive decline	+ MOCA 21/30	n.a.	–	n.a.	n.a.
Cognitive profile	Deficits in attention, memory, verbal fluency, and abstract thought	n.a.	n.d.	n.d.	Deficits in visuospatial memory
Behavioral abnormalities	Obsessive-compulsive, depression, suicide attempt	n.a.	n.a.	Aggressiveness, panic attacks, substance abuse	irritation and swearing
Cerebellar atrophy on MRI	+	–	+	–	–
Electrophysiology	SEPs delayed, normal ENG and EEG	Slow sNCVs, normal SEPs and EEG	–	–	Normal SEPs and EEG
TMEM240 mutation	c.509C > T p.P170L	c.509C > T p.P170L	c.509C > T p.P170L	c.196G > A p.G66R	c.196G > A p.G66R

impairment (Mini Mental State Examination age 48 years: 26/30, Montreal Cognitive Assessment age 51: 21/30 points), with impairments of attention, memory, verbal fluency and abstract thought, but normal orientation and visuospatial skills. His psychiatric history included a longstanding obsessive-compulsive personality disorder, triggering recurrent episodes of depression that required treatment upon changes of demand or setting at work since age 36 years, with psychotic symptoms and a suicide attempt at age 38.

His 18-year-old daughter (subject III.1, family A, Fig. 1A) exhibited chronic ataxia starting with mild motor developmental delay at age 2 years. In addition, she also revealed distal minimyoclonus of the fingers, proximal intermittent myoclonus of the forearm and saccadic intrusions. She showed no signs of cognitive or behavioral impairment (IQ 93, regular school). Prospective longitudinal SARA assessments demonstrated that cerebellar ataxia was non-progressive, and in fact improved from 9 points at age 12 years to 4 points at age 18 years (average improvement 0.8 points/year), demonstrating only mild residual ataxia (SARA cut-off for clinical diagnosis of ataxia: ≥ 3 points). Apart from ataxia and movement disorders, she also showed short stature (152 cm, < 3rd percentile) and severe hearing loss. Both were also observed in her mother (subject II.1, family A, Fig. 1A), but not in her father, indicating syndromic hearing loss as a second, maternally inherited disease. This is in line with a recent study showing that about 5% patients with a genetic disorder in fact have *multiple* genetic diagnoses [4].

In family B (Dutch) the 34-year-old male index patient presented with progressive cerebellar ataxia (SARA 15 points at age 34 years, 16 points at age 36 years; average progression 0.5/year), starting at age 32 years, with concomitant action tremor, but no bradykinesia. He had a history of mild motor delay and mental retardation, which required special needs education and permanent cognitive and social support, but he has no behavioral abnormalities, lives on his own, and pursues two jobs for people with intellectual disabilities.

Family C comprised of two adopted brothers of Colombian origin, in whom progressive cerebellar ataxia was first noted at ages 3 and 7 years, respectively. Postural tremor and hypomimia were present in both brothers, rigidity in II.1, and bradykinesia and intermittent myoclonus in II.2. Both subjects required special needs education because of motor delay and mental retardation, and antipsychotic treatment for behavioral abnormalities (aggression, panic attacks and substance use in II.1, irritation and swearing in II.2). Early-onset cataract was present in II.1.

3.2. Brain imaging

While MRI was unremarkable until at least age 10 years (family A, C), there was moderate cerebellar atrophy, especially of the superior vermis, in subjects above age 30 years (family A, B) (Fig. 1B). No other significant signal alterations (e.g. indicating iron overload) or atrophy patterns were observed. A 123I-2b-carbometoxy-3b-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane dopamine transporter scan (123I-FP-CIT-SPECT) in patient II.2 of family A showed borderline reduced binding values (z-score = −1.6, with age correction) for all subparts of the striatum (Fig. 1C).

3.3. Genetics

In families A and B, whole exome sequencing (WES) revealed the known pathogenic c.509 C > T (p.Pro170Leu) *TMEM240* mutation (ENST378733.4) [1]. This mutation segregated with disease in family A, and occurred *de novo* in family B (pedigrees: Fig. 1A). Subject II.2 from family A carried three additional rare missense variants in established SCA genes (ELOVL5 (SCA38), SPTBN2 (SCA5) and PDYN (SCA23), details: supplement 1), none of them segregating with disease (Fig. 1A). In family C, WES revealed a previously undescribed c.196G > A (p.G66R) variant in *TMEM240*, segregating with disease in both affected brothers. As they were adopted, segregation analysis was not possible. The G66R variant is (i) absent in ExAc and gnomAD, (ii) affects a highly evolutionary conserved amino acid (GERP score: 3.46; PhastCons score: 1; CADD score: 18) in the extracellular loop of TMEM240, and (iii) is predicted to be pathogenic by PolyPhen (HumVar score 0.933), SIFT (score: 0), Mutation Taster (p-value: 1), and AlignGVGD (class C65).

4. Systematic review of the literature

In addition to the five individuals reported here, we identified 42 affected individuals from ten families, published in five articles (see supplement 2 for a detailed clinico-genetic characterization of all subjects) [1–3,5,6]. The recurrent c.509C > T (p.Pro170Leu) mutation was found in 5/10 families [1,2], whereas all other 5 *TMEM240* variants reported so far (c.489C > T (p.Y163*), c.346C > T (p.R116C), c.239C > T (p.T80M), c.511C > T (p.R171W) and c.445G > A (p.E149K)) were unique [1]. In three of the 10 families, a *de novo* occurrence of the respective *TMEM240* variant was shown (the recurrent c.509C > T mutation in two families; the unique c.346C > T variant in one family) [1,2]. While the recurrent c.509C > T mutation has previously been found in France, Japan and China, all other variants were detected previously only in French families.

As defining features of SCA21, ataxia of gait (93%) and limb ataxia (86%) were present in the vast majority of individuals (Table 2). Like in our patients, not only cerebellar oculomotor disturbances (saccadic pursuit, gaze-evoked nystagmus) were observed (67%), but also brainstem oculomotor disturbances such as slow saccades (38%). Movement disorders other than ataxia are also common, most prominently bradykinesia (14/21 subjects; 65%). The present case series is the first to associate SCA21 with hyperkinetic movement disorders. Across all 47 patients, mental retardation has been described in 14/18, and cognitive impairment in 15/17 individuals. If combined, the estimated prevalence of mental retardation or at least mild cognitive decline was 83%. Cognitive deficits were predominantly characterized by deficits in attention, memory and executive functions. Other recurrent features included hyporeflexia (69%) and pyramidal signs (17%).

The median age of onset of SCA21 was 18 years, albeit with a considerable range between 1 and 61 years (Fig. 1D). Disease onset was

Table 2
Phenotypic spectrum of SCA21 disease. This table summarizes the systematic review and prevalence estimates of phenotypic features of SCA21 subjects, listing all features reported as absent or present in at least 20 of 47 patients. The denominator gives the number of subjects where the respective information was available. 95% CI were calculated with the adjusted Wald method. * The denominator of the ratio of behavioral/psychiatric abnormalities should be interpreted with caution, as it likely presents an inflated rate due to reporting bias in the literature. Most reports do not provide any information on this feature if it is absent, thus leading to an exaggerated rate of positive subjects where this information is available.

Clinical feature	Present	Prevalence	95% CI Estimate
Gait ataxia	25/26	93%	80–100%
Limb ataxia	23/26	86%	70–97%
Cerebellar eye movement disorder	15/22	67%	47–84%
Non-cerebellar eye movement disorder	8/22	38%	20–57%
Bradykinesia	14/21	65%	45–83%
Rigidity	6/22	29%	13–48%
Resting tremor	9/26	36%	16–54%
Postural tremor	14/25	56%	37–73%
Hyporeflexia	17/24	69%	51–85%
Pyramidal signs	4/27	17%	5–33%
Mental retardation or cognitive impairment	24/28	83%	68–95%
Behavioral/psychiatric abnormalities	12/(14*)	86%	59–97%

before 18 years in more than 50%, and before 40 years of age in more than 90% of cases. A qualitative description of disease progression in SCA21 suggested a very slow or no disease progression over a time period of 3 years [5], but no quantitative longitudinal data on disease progression have been reported so far. Cross-sectional SARA scores at single time points were available in 9 subjects (excluding 1 subject with cerebral ischemia and hemorrhage [3]) from the literature. Together with the longitudinal ratings presented above, SARA scores were divided in two clusters (Fig. 1E). One cluster indicates a group of children with mild to moderate ataxia (SARA ≤ 11), which might be improving with age, as exemplified by subject III.1 from family A. The second cluster indicates a group of adults above 30 years of age, which seem to be deteriorating with age, as exemplified by subject II.2 from family A and subject II.1 from family B.

5. Discussion

Our analysis of 5 novel plus 42 published subjects delineates and extends the phenotypic spectrum of SCA21. We not only confirm hypokinetic movement disorders as a recurrent feature, but also reveal that hyperkinetic movement disorders are part of the SCA21 phenotype, particularly limb myoclonus. The normal DAT scan shows that bradykinesia does not result from obvious nigrostriatal degeneration, yielding such SCA21 subjects similar to the growing number of SWEDD patients, i.e. subjects with parkinsonism but a scan without evidence of a dopaminergic deficit (SWEDD) [7]. This may explain why previous SCA21 studies have noted a lack of response of any parkinsonian symptom to levodopa [5].

The high frequency of hypo- and hyperkinetic movement disorders, in addition to cerebellar ataxia, highlights SCA21 as a multisystemic neurodegenerative disease extending well beyond cerebellar dysfunction. This concept is supported by the substantial prevalence of extracerebellar oculomotor disturbances. For example, slow horizontal saccades reflect damage to the paramedian pontine reticular formation in the midbrain [8]. The recurrent finding of hyporeflexia and pyramidal signs moreover demonstrates damage of the peripheral nerves and corticospinal tract, respectively, in SCA21. While some cognitive dysfunction might be attributable to cerebellar dysfunction (in particular executive and affective dysfunction as part of a Cerebellar Cognitive Affective Syndrome (CCAS) [9], e.g. related to vermal cerebellar atrophy), the profound memory dysfunction and the frequent mental retardation also point to a cortical dysfunction. At the same time, however, our findings as well as the systematic review indicate that cognitive impairment can be very mild or even completely absent, i.e. that it is not an *obligatory* feature of SCA21. This finding revises the current notion of SCA21 and has important implications for clinical recognition and in particular also for counseling of future SCA21 patients. More detailed studies focusing in depth on cognitive and behavioral functioning in a larger series of SCA21 patients will be of high interest.

Further important information for patient counseling is provided by our disease progression data, which are – albeit very preliminary – the first quantitative longitudinal data available for SCA21. We exemplarily show that infantile-onset SCA21 can follow a markedly *improving* course, towards only mild residual ataxia at age 18 years. Such early-life improvements in genetic ataxia have also been observed in children with other non-repeat expansion SCAs, e.g. *ITPR1*-ataxia/SCA29 [10]. This early-life improvement contrasts with the disease trajectory of late-life deterioration in SCA 21, as exemplified by our prospective longitudinal data from late-onset SCA21 patients. More comprehensive, adequately powered natural history studies are required to disentangle whether these trajectories represent different disease courses *between individuals* (e.g. with infantile-onset subjects improving, but late adult-onset cases deteriorating), or two different phases even *within individuals* (with early-life disease improvement and late-life disease deterioration). Early-life ataxia improvement might reflect a true improvement of the underlying disease per se, or it might reflect the natural development of a child where motor coordination skills improve during childhood until adolescence (which runs protracted in the SCA21 child III.1) [11], possibly outweighing the natural course of the underlying disease.

Our genetic findings highlight the c.509C > T *TMEM240* mutation as a recurrent hot-spot mutation, not only in Chinese and French patients [1,2], but also in German and Dutch patients. It can occur both *de novo* (family B) and in an autosomal-dominant fashion (family A). The novel c.196G > A variant adds to the still limited list of five reported *TMEM240* variants, all of them representing unique (i.e. private) mutations [1]. In the absence of functional assays (as the functional role of this transmembrane protein is still unknown), evidence for pathogenicity of *TMEM240* variants against the background of manifold variants of unknown significance (VUS) currently completely relies on in silico predictions and segregation analyses. As the c.196G > A *TMEM240* variant was (i) well compatible with the SCA21 phenotype (early-onset ataxia with mental retardation), (ii) highly conserved (GERP, PhastCons, CADD) and predicted to be pathogenic (PolyPhen, SIFT, Mutation Taster, AlignGVGD), (iii) absent in large control databases (gnomAD, ExAc) and (iv) segregated with disease in both affected subjects, we consider this variant to be likely pathogenic.

Nevertheless, this variant as well as other missense variants in SCA genes will require thorough functional work-up to ultimately proof pathogenicity. This has recently been shown for missense variants in *ITPR1* (SCA29), where manifold *ITPR1* variants identified in ataxia patients do not seem to have any pathogenic relevance for the phenotype, although all of them are ultra-rare and well-conserved [10]. This notion is emphasized by our genetic findings in patient II.2 in family A, who carried not only the *TMEM240* variant, but also ultra-rare variants in the other SCA genes *ELOVL5*, *SPTBN2* and *PDYN, none of them segregating with disease.* This finding highlights how missense variants in SCA genes can easily prompt misdiagnoses without proper segregation analysis and/or functional work-up [10].

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Appendix A. Supplementary data

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