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Published online: February 22, 2018Phenotypic Variability in Autosomal Dominant  
Familial Alzheimer Disease due to the S170F  
Mutation of Presenilin-1Hannes O. Tiedt<sup>a</sup> Beate Benjamin<sup>a</sup> Michael Niedeggen<sup>b</sup> Andreas Lueschow<sup>a</sup><sup>a</sup>Department of Neurology, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin (CBF), and<sup>b</sup>Department of Psychology, Freie Universität Berlin, Berlin, Germany

## Keywords

Alzheimer disease · Early-onset Alzheimer disease · Familial Alzheimer disease · Presenilin-1 · PSEN1 protein, human · Cerebellar ataxia · Hereditary diseases · Neurodegenerative disease · Neuropsychology

## Abstract

**Background:** In rare cases, patients with Alzheimer disease (AD) present at an early age and with a family history suggestive of an autosomal dominant mode of inheritance. Mutations of the presenilin-1 (*PSEN1*) gene are the most common causes of dementia in these patients. Early-onset and particularly familial AD patients frequently present with variable non-amnestic cognitive symptoms such as visual, language or behavioural changes as well as non-cognitive, e.g. motor, symptoms. **Objective:** To investigate the phenotypic variability in carriers of the *PSEN1* S170F mutation. **Methods:** We report a family with 4 patients carrying the S170F mutation of whom 2 underwent detailed clinical examinations. We discuss our current findings in the context of previously reported S170F cases. **Results:** The clinical phenotype was consistent regarding initial memory impairment and early onset in the late twenties found in all S170F patients. There were frequent non-amnestic cognitive changes and, at early

stages of the disease, indications of a more pronounced disturbance of visuospatial abilities as compared to face and object recognition. Non-cognitive symptoms most often included myoclonus and cerebellar ataxia. A review of the available case reports indicates some phenotypic variability associated with the S170F mutation including different constellations of symptoms such as parkinsonism and delusions. **Conclusion:** The variable clinical findings associated with the S170F mutation highlight the relevance of atypical phenotypes in the context of research and under a clinical perspective. CSF sampling and detection of A $\beta$  species may be essential to indicate AD pathology in unclear cases presenting with cognitive and motor symptoms at a younger age.

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## Introduction

A very small proportion of Alzheimer disease (AD) patients presents with an early onset of dementia (before 65 years of age) and a suggestive familial pattern with several other affected first-degree relatives in 2 or more generations indicating an autosomal dominant mode of inheritance [1, 2]. Three causative genes for such early-onset familial Alzheimer dementia (EOFAD) have been

identified: presenilin-1 (*PSEN1*) on chromosome 14 and its homologue presenilin-2 (*PSEN2*) on chromosome 1 as well as amyloid- $\beta$  ( $A\beta$ ) precursor protein (*APP*) on chromosome 21 [1]. So far, the Alzheimer Disease & Frontotemporal Dementia Mutation Database [3] (<http://www.molgen.vib-ua.be/ADMutations>) comprises 286 mutations of *PSEN1*, *PSEN2*, and *APP* in 635 affected individuals or families. Most frequent are mutations of *PSEN1*<sup>1</sup> ( $n = 219$ , 76.6%) as compared to *APP* ( $n = 51$ , 17.8%), and *PSEN2* ( $n = 16$ , 5.6%) [4–6]. *PSEN1* codes for the transmembrane protein presenilin-1 which assembles with cofactors nicastrin, Aph-1 and Pen-2 to form the 4 subunits of the  $\gamma$ -secretase complex [7, 8]. Pathogenic mutations of *PSEN1* have been found to alter the cleavage of *APP* by the  $\gamma$ -secretase complex [9], increasing the production of  $A\beta$  fragments associated with the deposition of amyloid plaques, most notably  $A\beta_{42}$  but also other  $A\beta$  isoforms [10, 11]. These findings have been interpreted in support of the amyloid cascade hypothesis stating that accumulation of  $A\beta$  is the primary event in AD pathophysiology which eventually leads to tau-mediated neurodegeneration and cognitive decline [12].

Investigations in asymptomatic *PSEN1* mutation carriers have demonstrated that first changes of cerebrospinal fluid (CSF) biomarkers and positron emission tomography using Pittsburgh compound B tracer indicate deposition of  $A\beta$  already decades before the expected onset of symptoms [13]. Given the failure of several drug trials in clinically affected AD patients, this has emphasized the question “when, where, and how” [14] first pathophysiological changes in AD occur and may be therapeutically targeted [15]. In this context, observations in familial AD cases are generally considered as informative for the generation and adaptation of hypotheses about AD pathophysiology and possible treatment strategies [16, 17].

However, some significant differences apart from age at onset have also raised the question to what extent one can infer from familial to sporadic, late-onset AD [18, 19]. For instance, familial and sporadic AD share the neuropathological hallmarks of AD pathology such as deposition of amyloid plaques and accumulation of neurofibrillary tangles [17], but the pathological results in EOFAD are more variable and frequently include findings such as cotton wool plaques, Lewy bodies, Pick bodies, and pronounced inflammation [20–22]. Likewise, the clinical phenotype of *PSEN1* mutation carriers is characterized

by widespread deficits involving multiple cognitive domains [23–25], resembling cognitive changes observed in sporadic AD [26], but atypical findings such as early non-amnesic cognitive, behavioural or motor symptoms are observed more frequently [27–34]. There is, however, considerable intra- and interfamilial variability regarding e.g. the occurrence of such atypical symptoms, age at onset, and the course of disease [35–38]. To account for this diversity of clinical findings genotype-phenotype correlations can be investigated in larger populations of EOFAD patients [25, 32, 39] or single patients in comparison to previous descriptions of a given mutation [37, 38]. The latter is however complicated due to a bias towards the publication of novel mutations whereas the informative value of detailed clinical observations in known mutations is underestimated [3, 27–29]. Beyond a research-oriented perspective, this is also clinically relevant: familial AD may be overall rare, it is nevertheless underdiagnosed in relation to its assumed prevalence [40], and this may be attributed to its heterogeneous and atypical clinical presentation.

Against this background, the aim of this article is to report a family with overall 4 individuals in 3 generations affected by EOFAD due to the S170F<sup>2</sup> mutation of *PSEN1* as determined by genetic testing in 2 patients. Observations in patients harbouring this mutation have been described – with considerable differences across reports – in consecutive publications since 2005 [41–45]. The most consistent findings associated with this mutation are a very early onset of dementia in the late twenties and cerebellar ataxia as a prominent non-cognitive symptom whereas the degree of variability of genotype-phenotype correlations in S170F carriers remains unclear. We will discuss the clinical and neuropsychological information obtained in our detailed examinations of 2 affected family members in the context of these previous reports.

## Methods

Two patients consulted the outpatient memory clinic at the Department of Neurology of the Charité – Universitätsmedizin. Before, both had been seeking genetic counselling where a genetic neurodegenerative disorder had been suspected and genetic testing was performed. Simultaneously, both patients were referred to our department for the required clinical investigations. Here, they underwent detailed examinations in the hospital or as

<sup>1</sup> The frequency of mutations per gene is taken from the Alzheimer Disease & Frontotemporal Dementia Mutation Database (as of September 2017).

<sup>2</sup> We use the 1-letter code for mutations throughout the article for consistency.

outpatients including neuropsychological testing at various points in time as well as magnetic resonance imaging (MRI), electroencephalography (EEG), and CSF sampling. All diagnostic procedures were performed after the patients had given their informed consent and in accordance with current diagnostic guidelines, and the study was conducted in accordance with the declaration of Helsinki. To maintain anonymity of patients and relatives, we do not include a pedigree and limit the report to information relevant to the description of the clinical presentation and course of disease.

## Results

### *Family History*

Both the index patient (III.1) and his sister (III.2) had a family history of early-onset dementia in their mother and maternal grandmother. The mother of both patients (II.1) had developed progressive memory loss approximately in her late twenties and died from pneumonia by the age of 32 after becoming mute and bedridden in an advanced stage of dementia. A medical record then had noted severe cognitive dysfunction, dysarthria, ataxia, dystonic hand movements, and reduced facial expressions. EEG was abnormal showing generalized cerebral dysfunction without further specification in the report. A computed tomography scan showed massive general cortical atrophy. The maternal grandmother (I.1) of both patients died by the age of 36 after cognitive decline over few years; further information was not available. Taken together, the family history was highly suggestive of autosomal-dominant inheritance with apparently 4 affected individuals including first-degree relatives in 3 generations [2].

Genetic testing at the Institute for Medical Genetics of the Charité – Universitätsmedizin Berlin was initially done for spinocerebellar ataxia type 17 (*SCA17*) due to ataxia and dementia being the leading symptoms in the index patient (III.1), yielding a negative result. Thereupon, sequencing of *PSEN1* revealed the S170F mutation, which was later confirmed in his sister (III.2). The pathogenic nature of the S170F mutation has been established before in several familial as well as sporadic cases [41–45].

### *Clinical Findings*

In the following, the signs and symptoms noted in both of our patients as well as the results of neuropsychological examinations are summarized, the testing procedures employed are given in parentheses. An overview about the tests and results can be taken from Table 1.

### Individual III.1

The index patient III.1 was 31 years old at the time of the first clinical examination. Signs of short-term memory loss, problems of coordination and unsteady gait had become apparent during the past 3 years, eventually leading to genetic counselling and referral to our clinic. He was disoriented in time, and neurological examination showed limb ataxia, dysmetria and intention tremor, dysdiadochokinesia, insecure stance and gait, saccadic pursuit, slight dysarthria, and spontaneous limb myoclonus. A neuropsychological examination showed reduced verbal memory (delayed recall of 1/10 words), impaired attention and task switching (Trail-Making Test, TMT A/B). In addition, results of verbal and visuospatial working memory tests (forward and backward digit span task, block-tapping test) were below normal. Verbal fluency was also reduced in the phonemic (K words) and semantic (animals) task. The performance in face and object recognition tasks (Benton Facial Recognition Test; Boston Naming Test) was within normal. The result of the Clock-Drawing Test (CDT) was also within normal (2 points, cut-off  $\geq 3$ ), despite obvious difficulties while completing the task. The Mini-Mental State Examination (MMSE) score was 23/30 (cut-off 26/30).

In 2 follow-up evaluations 6 and 15 months later at the age of 32 years, the patient was no longer able to follow some test instructions (e.g., TMT) so that the obvious further decline of some cognitive functions could not be substantiated. The available tests showed deterioration of visuoconstruction (CDT: 4 points; Fig. 1), verbal fluency, impaired executive functioning (executive interview EXIT-25) [46] and visuospatial abilities (computer-based assessment of visual functions) [47] such as mental rotation and estimating the positioning of objects. The latter must be taken as rather qualitative information because the computer-based assessment of visual functions was not completed due to problems comprehending the more complex test instructions.

Due to the rapid cognitive decline and progressive gait disturbance, the patient was referred to a nursing home at the age of 32. At 34, the patient was bedridden, tubed, and frequent epileptic seizures were reported, but no further follow-up information was available.

### Individual III.2

Individual III.2 was referred to our clinic at the age of 28 after the diagnosis of EOFAD had been established in her older half-brother. The patient complained of progressive memory loss and “clumsiness” over the last year. She was disoriented in time and had an insecure stance

**Table 1.** Neuropsychological examinations

Tests	Subject III.1	Subject III.2
1 Orientation MMSE (cut-off $\leq 26/30$ )	22	21
2 Visual perception Clock-Drawing Test (cut-off $\geq 3$ )	4	4
ROCF copy		16 (PR <1)
ROCF immediate recall		not able to complete
ROCF delayed recall		not able to complete
CERAD figure: immediate copy	9 (PR <2)	
CERAD figure: recall	1 (PR <1)	
CAV object recognition	not able to complete	PR >25
CAV visuospatial abilities	not able to complete	PR <10
Benton facial recognition test (short form)	22 (normal)	
Benton facial recognition test (long form)	45 (normal)	
3 Attention TMT A	145 s (PR <1)	105 s (PR <1)
TMT B	aborted >300 s	aborted >300 s
SKT attention	16 (PR <2)	16 (PR <2)
TAP alertness (no warning cue)		555 ms (PR <1)
TAP alertness (with warning cue)		363 ms (PR <4) with 29 anticipations
4 Memory Forward digit span task	4 (PR 4)	6 (PR <28)
Backward digit span task	3 (PR 5)	3 (PR <5)
SKT memory	8 (PR <15)	7 (PR <15)
VLMT immediate recall		14 (PR <5)
VLMT recall after interference		0 (PR <5)
VLMT delayed free recall		0 (PR <5)
VLMT recognition		4 (PR <5)
CERAD word list learning	7 (PR <1)	10 (PR <5)
CERAD word list recall	0 (PR <1)	0 (PR <1)
CERAD word list recognition	75% correct (PR <1)	80% correct (PR <1)
5 Executive function and language EXIT-25 (cut-off >10)	17	13
Verbal fluency, semantic	6 (PR <2)	<14 (PR <10)
Verbal fluency, phonemic	2 (PR <2)	<7 (PR <10)
Boston Naming Test	54 (PR 31)	

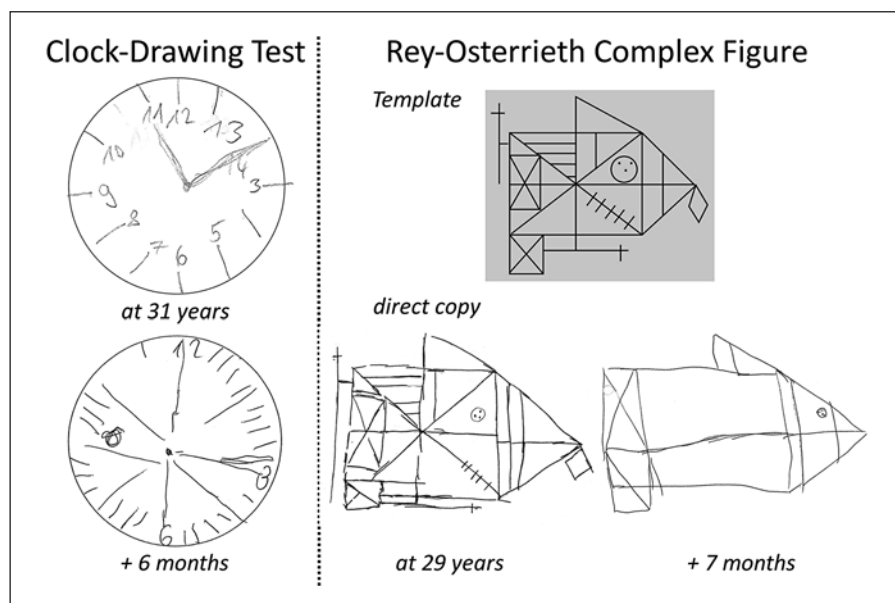
If tests were performed repeatedly, results of the latest examinations are shown. Due to the cognitive impairment of both patients, some tests could not be repeated or performed at all; therefore, the applied tests vary in both individuals. If applicable, a cut-off value for the respective test is given in parentheses; otherwise, all results are given with respect to the percentile rank (PR) of the control groups. PR >25 = unaffected, PR >10 to <25 = minor deficits, PR <10 = major deficits. The given numbers are points or scores unless noted otherwise. CAV, computer-based assessment of visual functions; CERAD, Consortium to Establish a Registry of Alzheimer's disease (battery of neuropsychological tests); EXIT-25, executive interview; MMSE, Minimal Mental Status Examination; ROCF, Rey-Osterrieth Complex Figure; SKT, Syndrom-Kurz-Test (Syndrome Short Test); TAP, Test of Attentional Performance; TMT, Trail-Making Test; VLMT, Verbal Learning and Memory Test.

and gait as well as limb ataxia, bilateral pyramidal signs, mild dysarthria, and ideomotor apraxia. A first neuropsychological assessment showed impaired verbal (Verbal Learning and Memory Test) and non-verbal memory

(Rey-Osterrieth Complex Figure Test) whereas working memory was intact (forward/backward digit span task). Tests of attention (TAP alertness), cognitive speed processing and task-switching (TMT A/B), executive func-



**Fig. 1.** Deterioration of visuoconstruction. The results of the CDT (left, patient III.1) and the Rey-Osterrieth Complex Figure Test (right, patient III.2) indicate a rapid deterioration of visuoconstructive abilities over the course of 6 and 7 months, respectively. The instruction for the CDT was to draw a clock showing a time of 11.10 h. The right part of the figure shows the direct copy of the Rey-Osterrieth Complex Figure Test, a delayed recall of the figure was not possible. Some lines of the original pencil drawings were too faint for scanning and thus were traced, but not altered.



tioning (EXIT-25) [46], and visuoconstruction (CDT) yielded abnormal results. A subsequent neuropsychological assessment 7 months later illustrated further decline in working memory tasks (digit span task) and visuoconstructive functions (Table 1; Fig. 1). Some of the tests previously conducted could not be performed again due to deficits in comprehension of test instructions. Visuospatial abilities such as mental rotation or angle estimation (computer-based assessment of visual functions) had also deteriorated. Of note, object recognition remained intact. Verbal fluency (semantic and phonemic) was markedly reduced; the MMSE score was 21/30. Due to rapid progression of dementia and motor symptoms, the patient was living in a nursing home at the time of the last follow-up at the age of 30 years.

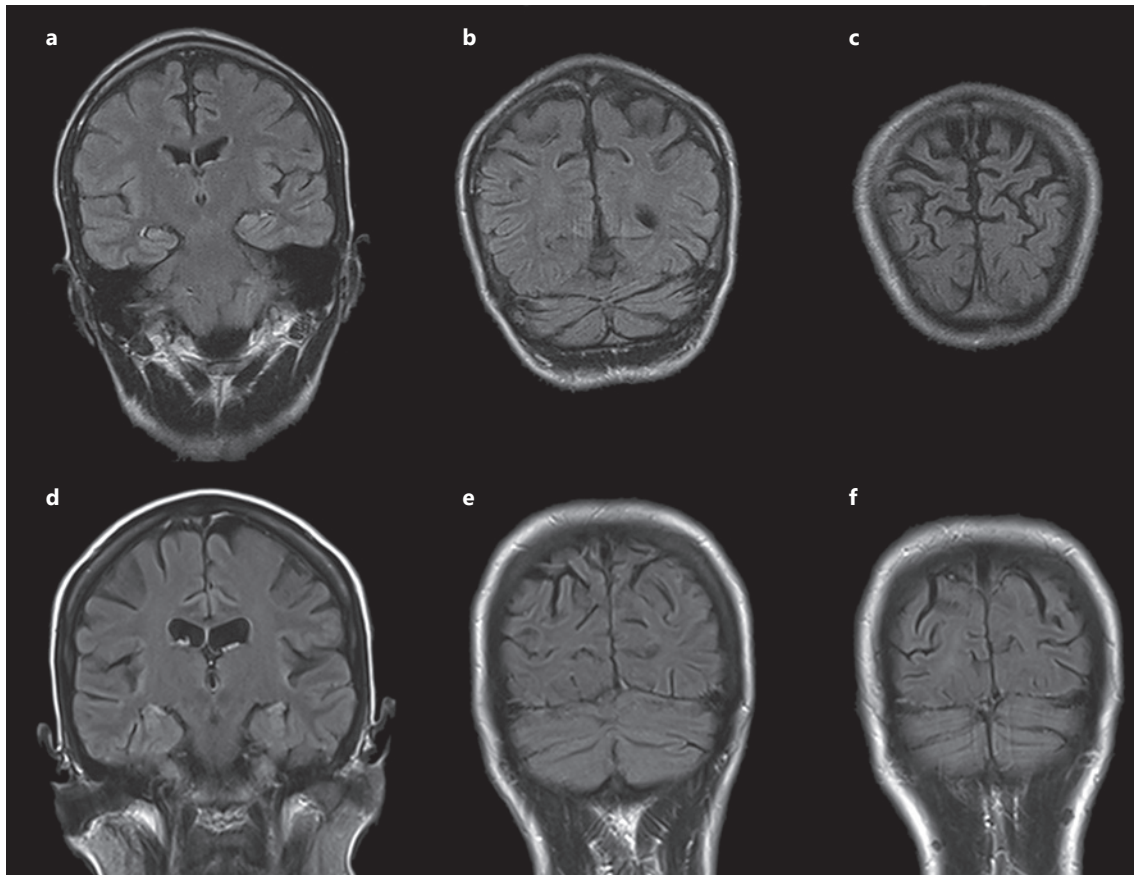
#### Diagnostic Procedures

Clinical examination included MRI of the brain, EEG and blood/CSF sampling yielding altogether similar results in both patients. MRI revealed cortical atrophy accentuated in the parietal lobes as well as deepened and widened cerebellar sulci (Fig. 2). EEG showed diffuse slowing of background activity within theta frequency (5–6 Hz) with intermittent delta waves over bilateral frontal electrodes (III.1), extending to parietal and temporal areas (III.2). Additionally, the EEG of III.2 showed generalized spikes whereas epileptiform activity was not observed in III.1. CSF samples showed normal routine parameters and no oligoclonal bands;  $A\beta_{42}$  was reduced

(III.1: 444 pg/mL, III.2: 521 pg/mL; normal value >600), and levels of total tau protein were markedly increased (in both patients >1,200 pg/mL; normal value <225).

#### Discussion

We report a German family with 4 individuals affected by early-onset dementia and presenting with similar phenotypes. The *PSEN1* S170F mutation was detected by DNA sequencing in 2 patients. This mutation results in an amino acid change from serine (TCT) to phenylalanine (TTT) at codon 170 on exon 6 of the *PSEN1* gene encoding the transmembrane domain III of presenilin-1, where many pathogenic mutations are found to cluster [28]. The pathogenic nature of the S170F mutation has been established before in several reported familial as well as sporadic cases: it was first demonstrated in a North American family with 3 affected family members in 2 generations [44], another family from Austria with 5 cases spanning 3 generations [45] as well as single sporadic cases from Great Britain and Poland with de novo mutations [41, 42] and 1 patient in Italy with an incomplete family history [43]. Altogether, data from 15 patients (9 women) with more detailed clinical information in 10 are currently available; a comparative summary of findings associated with the S170F mutation can be found in Table 2.



**Fig. 2.** Neuroradiological findings. Fluid-attenuated inverse recovery (FLAIR) MRI of family members III.1 at 31 years (**a–c**) and III.2 at 28 years (**d–f**); coronal planes (with oblique “temporal angulation” in the upper row). Whereas there is no marked mesiotemporal atrophy, both examinations show cortical atrophy in bilateral parietal lobes as well as cerebellar atrophy.

#### *Pathogenicity of the PSEN1 S170F Mutation*

The S170F mutation is among the highly pathogenic *PSEN1* mutations with a very early onset as well as rapid and severe course of disease in our cases as well as across publications. First symptoms are typically observed in the late twenties (mean age at onset  $29.1 \pm 2.3$  years, range 26–34 years). The time from symptom onset until a state of dependency was less than 5 years (mean  $3.7 \pm 1.1$  years), and 10 of the reported patients had died before or passed away during observation at a mean age of  $35.4 \pm 3.2$  years (range 32–43 years), the mean disease duration from symptom onset until death being  $7.2 \pm 4.2$  years. The majority of *PSEN1* mutations is associated with a greater range [27], especially when investigations involve larger populations of mutation carriers [35, 48], and in some cases pedigree-specific age at onset [37]. Carriers of the S170F mutation were also affected earlier than pa-

tients included in larger investigations of autosomal-dominant AD in general (mean age at onset 46.2 years [39]) and *PSEN1* mutations in particular (mean age at onset of 43 years in 3 separate studies [31, 33, 34]). This difference is smaller when comparing the S170F cases with other *PSEN1* mutations also located before codon 200 (mean age at onset 37.3 years [32]), indicating an interaction between the location of a given mutation and its neurotoxicity. The S170F mutation, like most pathogenic *PSEN1* mutations, is located at one of the transmembrane domains of presenilin-1, and in silico modelling suggests that it alters interaction between proteins within the  $\gamma$ -secretase complex [41]. However, the aggressiveness of a given mutation is better reflected by the increase in  $A\beta_{42}$  levels and the  $A\beta_{42}/A\beta_{40}$  ratio [10, 49], which are inversely correlated with the age at onset in familial AD [50]. With respect to the S170F mutation, in vitro investiga-

**Table 2.** Clinical findings in the published S170F cases

	Snider et al. [44], 2005	Golan et al. [41], 2007	Piccini et al. [43], 2007	Langheinrich et al. [42], 2011	Ehling et al. [45], 2013	Tiedt et al. (this study)
Country	USA	Poland	Italy	UK	Austria	Germany
Affected individuals (generations)	3 (2)	1 (de novo)	1 (incomplete family history)	1 (de novo)	5 (3)	4 (3)
Age at onset (age at death or last follow-up), years	II.1: 27 (†37) III.1: 27 (†35) III.3: 26 (†43) <sup>1</sup>	29 (+2 years) <sup>1</sup>	28 (†35) <sup>1</sup>	34 (+2 years)	I.2: unknown († around 30s) II.2: 30 (†34) III.3: 33 (†37) III.5: 28 (†33) III.6: 31 (+5 years)	I.1: around 20s (†36) II.1: around 30 (†32) III.1: 28 (+6 years) III.2: 29 (+5 years)
Clinical signs and symptoms	Ataxia, insecure gait, myoclonus, dysarthria, hyperreflexia, pyramidal signs, seizures	Depression, myoclonus, parkinsonism, delusions, non-fluent speech, apraxia, seizures	Ataxia, delusions, limb jerks, myoclonus, intentional tremor	Ataxia, dysdiadochokinesis, myoclonus, dysarthria, hyperreflexia, seizures	Ataxia, apraxia, dysarthria, depression, pyramidal signs	Ataxia, gait unsteadiness, myoclonus, pyramidal signs, seizures
Brain Imaging (MRI, CT)	n.a.	MRI: symmetric cortical and subcortical brain atrophy	MRI: cortical atrophy in the parietal and temporal lobes	MRI: generalized cerebral and cerebellar atrophy, increased signal from both hippocampi and amygdalae	MRI: parietal/global cortical atrophy (3/3), FLAIR hyperintensities in bilateral mesial temporal lobe (1/3)	MRI: cortical atrophy of the parietal lobes (2/2) CT: generalized brain atrophy (1)
SPECT/PET	n.a.	Hypoperfusion in parietal, temporal, and occipital regions	Temporoparietal and frontobasal hypometabolism	n.a.	Bilateral temporal (1/2) and parietal (2/2) hypometabolism	n.a.
EEG	n.a.	“Disorganized basic rhythm, disengaged theta and delta waves, mainly generalized”	Bilateral parietal slowing (5/s theta waves)	Bilateral temporal slowing, sharp waves and spikes	“Low pseudoperiodic sequences” (1)	abnormal theta/delta rhythm (2/2); intercurrent spikes and sharp waves (1/2)
CSF	n.a.	“vCJD excluded,” details n.a.	Normal protein 14-3-3 levels Tau/Aβ n.a.	Normal protein 14-3-3 levels Tau/Aβ n.a.	h-tau↑ (1/2) p-tau↑ (2/2) Aβ↓ (2/2)	h-tau↑ (2/2) Aβ↓ (2/2)
Neuropathology	AD pathology (3/3), α-synuclein pathology (1/3)	n.a.	AD pathology including cerebellum, no α-synuclein pathology	AD pathology, no α-synuclein pathology (frontal lobe biopsy)	AD pathology including cerebellum, no α-synuclein pathology (1)	n.a.

Most examinations were only available in a limited number of cases, and findings were heterogeneous, therefore the proportion of a given result with respect to the overall number of available examinations is indicated in parentheses. If only “late twenties” or “early thirties” could be specified as age at onset or death, estimated values are indicated by “around.” For 5 patients, the last follow-up status relative to disease onset is reported. Memory loss was present in all cases and is therefore not noted under clinical signs and symptoms. Standard CSF parameters (cell count, protein, glucose, and lactate) were reported as normal when available. Aβ refers to Aβ<sub>42</sub>. n.a., not available. <sup>1</sup> In these patients, the apolipoprotein ε allele was reported (E3/E3 in all cases).

tions have consistently demonstrated that it results in a marked, approximately threefold increase in Aβ<sub>42</sub> production [43, 51, 52] and, with variations across publications due to methodological differences, an elevated Aβ<sub>42</sub>/Aβ<sub>40</sub> ratio as well [51]. It should be noted that these results were obtained from in vitro investigations or animal studies so that it remains to be determined how they relate to the measurement of Aβ CSF levels in patients.

As for *PSEN1* mutations in general it remains undetermined whether other genetic or environmental factors might contribute to the high neurotoxicity of the S170F mutation. The apolipoprotein E allele, for instance, was analysed in 3 patients, who were homozygous for the “neutral” type (E3/E3). Furthermore, Ehling et al. [45]

reported 3 patients where the S170F mutation co-segregated with a variant of the cathepsin D gene. The relevance of this finding remains unclear, considering that all patients inherited the cathepsin D variant from their (unaffected) father.

#### *Phenotypic Variability of the PSEN1 S170F Mutation*

Atypical phenotypes of *PSEN1* mutations are typically characterized by cognitive symptoms beyond episodic memory impairment typically characterizing the onset of sporadic AD as well as frequent non-cognitive (e.g., motor) symptoms. This greater variability of clinical findings might be associated with stronger white matter involvement and more widespread cortical atrophy in *PSEN1*

mutations [53]. Moreover, it has recently been proposed that, aside from altered processing of A $\beta$  species being the common denominator of familial AD [10], various other  $\gamma$ -secretase substrates may also contribute to atypical phenotypes associated with *PSEN1* mutations [31]. In the following we will review clinical findings associated with the S170F mutation in the context of phenotypic variability alongside possible clinicopathological correlations and findings yielded by standard diagnostic procedures in these patients.

#### Non-Amnestic Cognitive Symptoms

All observed S170F patients had initial memory symptoms with frequent and variable non-amnestic cognitive symptoms. Due to different neuropsychological testing procedures performed at onset or later stages of disease, however, phenotypic variability is difficult to determine in this regard. Cognitive dysfunction beyond memory loss included impaired verbal fluency, attention, and apraxia. Furthermore, visuoconstruction and visuospatial abilities were affected in contrast (at onset) to relatively intact object and face recognition. Both face and object perceptions have been associated with the mainly temporal “ventral stream” whereas other visuospatial abilities (e.g., mental rotation) involve the parietal “dorsal stream” [for reviews on this model in the context of neurodegeneration, see 54, 55]. Altogether, the presence of noticeable non-amnestic cognitive impairment associated with the S170F mutation corresponds to the literature suggesting frequent atypical findings in *PSEN1* mutations [27–29, 34, 56]. There is, however, some disagreement about its exact prevalence in different publications based on either reviews and meta-analyses of published cases or data from the Dominantly Inherited Alzheimer Disease Network (DIAN) study including a larger population of patients. There are several possible explanations for these differences, such as a variable time of observation and thus more or less information about initial versus late stages of disease. Furthermore, atypical clinical findings might be overestimated in case reports in addition to possible measurement and ascertainment bias [32]. In a recent investigation the prevalence of aphasia (57.9 vs. 23.0%), visual agnosia (55.1 vs. 5.6%), and behavioural changes (61.7 vs. 31.7%) was indeed significantly higher in DIAN patients than in published case reports [32]. Moreover, Ryan et al. [31] reported atypical cognitive findings in addition to amnesia in 16% of *PSEN1* mutations based on a large case series. Although non-amnestic presentations are more frequent in familial than sporadic AD cases, a comparison of cognitive profiles does not dis-

tinguish both groups [25, 57]. Generally, non-amnestic cognitive symptoms at disease onset are more common in younger AD patients [58, 59].

#### Non-Cognitive Symptoms

The most frequently observed non-cognitive symptoms in the S170F cases were motor abnormalities including cerebellar ataxia, pyramidal signs, myoclonus, and seizures. Most often (in 73% of all cases) a combination of cerebellar signs, including insecure gait with limb and trunk ataxia as well as intention tremor, dysmetria, dysdiadochokinesia, poor coordination, and saccadic pursuit, was noted. Nevertheless, there were also single patients presenting with purely amnestic [44] or predominantly neuropsychiatric and parkinsonian features [41]. Similarly, seizures occurred in several patients in late stages of the disease, but (along with myoclonus) were absent in the Austrian family reported by Ehling et al. [45]. Apparently, an ataxic variant is the most frequent, but not specific clinical phenotype of the S170F mutation. There is not enough available evidence to suspect another clinical subtype associated with the S170F mutation (e.g., ataxia and myoclonus vs. parkinsonism and delusions) as for instance 4 possible clinical presentations of the M146L mutation [36].

When comparing the most frequent non-cognitive symptoms to their prevalence in larger groups of EOFAD patients, the results again vary between the DIAN observational study and the literature with respect to myoclonus (9.3 vs. 19.4%), seizures (2.8 vs. 20.3%), and ataxia (15 vs. 3.1%). Worth noting, the prevalence of cerebellar ataxia was much higher in *PSEN1* mutations located before codon 200, in younger patients and those with severer symptoms [32]. In this context, the presence of distinctive cerebellar signs in the majority of S170F patients corresponds to other *PSEN1* precodon 200 mutations with a very early onset and a marked “cerebellar” phenotype as for instance the P117A [60], N135S [61], M139V [62], T147P [63], H163P [64], L166P [65], and S169L mutations [66]. In the case series reported by Ryan et al. [31], myoclonus was present in 47%, seizures in 24%, and pyramidal signs in 25% of *PSEN1* mutation carriers. The occurrence of myoclonus increased the risk of later seizures. As to cerebellar ataxia, this was only noted in 4% of all *PSEN1* patients.

#### Clinicopathological Correlations

To what extent are these clinical symptoms correlated with neuropathological findings? First, the available neuropathological examinations in 6 patients (including 1



frontal lobe biopsy) describe characteristic AD pathology with amyloid plaques and neurofibrillary tangles. In addition, Lewy bodies were found in 1 case [44] but absent in another 3 patients where neuropathological examinations included staining for Lewy bodies using monoclonal antibodies against  $\alpha$ -synuclein [42, 43, 45]. A clinical phenotype resembling Lewy body dementia with parkinsonism and delusional symptoms was observed in altogether 2 patients [41, 44]. It should be noted that  $\alpha$ -synuclein pathology is, alongside other atypical findings and with considerable variability, described relatively often in familial AD cases [21, 67]. Consistent with frequent cerebellar symptoms, abundant amyloid deposits in the cerebellum and loss of Purkinje cells was described in 2 patients [43, 45]. However, in contrast to its relatively rare clinical manifestations, cerebellar pathology is consistently described in both sporadic [68–72] and familial AD cases [35, 67, 73–75]. Cerebellar damage is thought to characterize a late event in the sequence of amyloid deposition in distinct brain regions [76]. Considering the high pathogenicity of the S170F mutation this may resemble a “quick motion” picture of AD pathology.

#### Diagnostic Procedures

The diagnostic procedures conducted in the patients yielded several results indicating AD pathology that helped to establish the diagnosis in the end. Before genetic testing, a variety of suspected differential diagnoses were investigated in the reported S170F cases including Wilson’s disease, prion disease (CJD/vCJD), hereditary spinocerebellar ataxia and infectious or auto-immune encephalitis. The latter was suspected in 2 S170F due to T2-weighted and fluid-attenuated inverse recovery (FLAIR) hyperintensities of the medial temporal lobes. Similar MRI findings including white matter abnormalities associated with T2-weighted/FLAIR hyperintensities have been observed previously in several other *PSEN1* mutations [77–79] and might reflect cerebral amyloid angiopathy, which, however, was found to be severest in post-codon 200 *PSEN1* mutations [80]. Furthermore, structural imaging (MRI was available in overall 8 cases) most consistently showed cortical atrophy accentuated in parietal areas alongside generalized and temporal atrophy, paralleled by hypoperfusion or -metabolism in these areas using functional imaging techniques (in 4 patients). This pattern of cortical atrophy may correspond to the more pronounced deterioration of cognitive abilities associated with the dorsal visual stream in several S170F patients. A similar correlation of the topography of cortical atrophy and neuropsychological profile was suggested

in early-onset AD patients in contrast to late-onset AD patients where mesiotemporal and hippocampal atrophy were the most consistent findings [81]. A pattern of temporoparietal cortical atrophy was also linked to the behavioural and dysexecutive variant of sporadic AD [82].

CSF biomarkers (available in 4 patients) included reduced  $A\beta_{42}$  and increased t-tau and p-tau protein, reminiscent of sporadic AD [83]. This is in line with recent investigations of larger populations suggesting that changes of CSF biomarkers are comparable in familial and sporadic AD [13, 34, 84]. Similarly, EEG alterations including general or regional slowing over temporal and parietal areas and epileptiform activity in particular in several of the S170F cases are frequently observed in both sporadic and familial AD with epileptic seizures [85, 86].

#### Conclusions

In conclusion, the findings in our patients and in previously published cases suggest that very early onset in the late twenties and initial memory impairment are consistently found in S170F patients whereas non-amnesic cognitive and non-cognitive symptoms were common but also variable. A combination of widespread cognitive impairment with myoclonus and/or cerebellar ataxia was most frequently observed. As there was considerable interindividual phenotypic variability, the question of another subtype with symptoms resembling Lewy body dementia remains unresolved. Furthermore, the observation of visuospatial impairment with less affected face and object recognition at initial stages in the sense of a dissociation between cognition related to the ventral and dorsal stream needs confirmation in further investigations. Finally, the findings in S170F patients highlight the relevance of obtaining detailed clinical phenotypes, since determining genotype-phenotype associations is mostly limited by scarce or heterogeneous information available from previous case reports. Moreover, variable and atypical clinical presentation of *PSEN1* mutations also represents a special diagnostic challenge [40], and the examination of CSF  $A\beta$  species may be particularly important to indicate the underlying AD pathology.

#### Disclosure Statement

No conflict of interest concerning the research related to the manuscript is to report.

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