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LETTER TO THE EDITOR

Reply: A distinct clinical phenotype in a German kindred with motor neuron disease carrying a *CHCHD10* mutation

Sylvie Bannwarth,[1,2] Samira Ait-El-Mkadem,[1,2] Annabelle Chaussenot,[1,2] Emmanuelle C. Genin,[1] Sandra Lacas-Gervais,[3] Konstantina Fragaki,[1,2] Laetitia Berg-Alonso,[1] Yusuke Kageyama,[4] Valérie Serre,[5] David Moore,[6] Annie Verschueren,[7] Cécile Rouzier,[1,2] Isabelle Le Ber,[8,9] Gaëlle Augé,[1,2] Charlotte Cochaud,[2] Françoise Lespinasse,[1] Karine N'Guyen,[10] Anne de Septenville,[8] Alexis Brice,[8] Patrick Yu-Wai-Man,[6,11] Hiromi Sesaki,[4] Jean Pouget[7] and Véronique Paquis-Flucklinger[1,2]

1 IRCAN, UMR CNRS 7284/INSERM U1081/UNS, School of Medicine, Nice Sophia-Antipolis University, France
2 Department of Medical Genetics, National Centre for Mitochondrial Diseases, Nice Teaching Hospital, France
3 Joint Centre for Applied Electron Microscopy, Nice Sophia-Antipolis University, France
4 Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
5 UMR7592 CNRS, Jacques Monod Institute, Paris Diderot University, France
6 Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, International Centre for Life, Newcastle University, Newcastle upon Tyne NE1 3BZ, UK
7 Department of Neurology, Timone Hospital, Marseille Teaching Hospital, France
8 Sorbonne Université, UPMC Univ Paris 06, UM75, Inserm U1127, Cnrs UMR7225, Institut du Cerveau et de la Moelle épinière (ICM), F-75013 Paris, France
9 National Reference Centre on Rare Dementias, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
10 Department of Medical Genetics, Timone Hospital, Marseille Teaching Hospital, France
11 Newcastle Eye Centre, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, UK

Correspondence to: Prof. Véronique Paquis-Flucklinger,
IRCAN UMR CNRS 7284 / INSERM U1081 / UNS
School of Medicine, 28 av de Valombrose
06107 Nice cedex 2, France
E-mail: paquis@hermes.unice.fr

Sir,

In a relatively short period of time, an increasing body of evidence has accumulated confirming the primary role of mitochondrial dysfunction in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) clinical spectrum through the involvement of *CHCHD10* both in familial and sporadic cases (Bannwarth *et al.*, 2014; Chaussenot *et al.*, 2014; Johnson *et al.*, 2014; Müller *et al.*, 2014; Ronchi *et al.*, 2015). In a new Letter to the Editor submitted to *Brain*, Kurzwelly *et al.* (2015) report another large German family with a history of autosomal dominant pure ALS. Affected individuals harboured the c.44G > T (p.Arg15Leu) heterozygous mutation in *CHCHD10*, which has been previously identified in five of six families with pure ALS associated with mutations in this gene (two from Germany and three from the USA) (Johnson *et al.*, 2014; Müller *et al.*, 2014). The main characteristics of patients reported with *CHCHD10* mutations and FTD-ALS clinical spectrum have been summarized in Table 1. The additional German family reported by Kurzwelly *et al.* highlights several important clinical points that are of diagnostic significance. First, all patients exhibited upper limb onset, spasticity and bulbar signs rather late in the disease course, similar to the affected patients from the two other reported German families carrying the p.Arg15Leu mutation (Müller *et al.*, 2014). In our original paper in *Brain*, which first established a pathological link

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Table 1 Review of studies reporting *CHCHD10* mutations

	Bannwarth *et al.*, 2014	Chaussenot *et al.*, 2014	Müller *et al.*, 2014	Johnson *et al.*, 2014	Ajroud-Driss *et al.*, 2015	Ronchi *et al.*, 2015	Kurzwelly *et al.*, 2015
Patients with *CHCHD10* mutations (*n*)	8	3	5	6	10	3	4
Families (*n*)	1	3	3	3	1	3	1
FTD	7/8 (87.5%)	3/3 (100%)	–	–	–	–	–
MND onset/predominance	6/8 (75%) Pseudobulbar	3/3 (100%) Pseudobulbar	5/5 (100%) Upper limbs (4/5)	6/6 (100%) ?	–	3/3 (100%) Upper limbs (1/3)	4/4 (100%) Upper limbs
Cerebellar signs	Ataxia 5/8 (62.5%)	–	–	–	–	–	Oculomotor signs 1/4 (25%)
Parkinsonism	–	1/3 (33.3%)	–	–	–	–	–
Other symptoms	Ptosis, myopathy, deafness	Deafness	–	–	Myopathy, short stature	–	–
Age at onset (average)	49-65y (55.5)	59-67 y (61.6)	35-73 y (46.7)	? (?)	First decade (?)	25-75 y (53)	41-73 y (59.5)
Mean disease duration (min-max)	>10 y (1-27 y)	? (4-8 y)	10.7 y (6-17 y)	? (?)	>30 y (?)	? (2-8 y)	6.3 y (2-15 y)
Muscle biopsy (patients, *n*)	RRF, COX-(8/8)	ND	ND	ND	RRF, lipid accumulation	RRF, COX-(1/3)	ND
Penetrance	Complete	Insufficient information	Incomplete	?	Complete	NA	Complete
Mutations (families, *n*)	p.Ser59Leu (1/1)	p.Ser59Leu (1/3) p.Pro34Ser (2/3)	p.Arg15Leu (2/3) p.Gly66Val (1/3)	p.Arg15Leu (3/3)	p.Arg15Ser / p.Gly58Arg in *cis* (1/1)	p.Pro80Leu (2/3) p.Pro34Ser (1/3)	p.Arg15Leu (1/1)
Frequency of patients with *CHCHD10* mutations in the studied disease cohorts	NA	3/115 FTD-ALS patients (2.6%)	3/128 patients with familial ALS (2.3%)	3/85 patients with familial ALS (3,5%)	NA	3/224 patients with sporadic ALS (1.3%)	NA

MND = motor neuron disease; ? = unknown; ND = not done; NA = not applicable; RRF = ragged-red fibres.

between *CHCHD10* mutations and FTD-ALS, we performed in-depth phenotyping of an extensive French family that was found to carry the p.Ser59Leu mutation (Bannwarth *et al.*, 2014). We subsequently identified *CHCHD10* mutations in three other unrelated probands presenting with FTD and ALS phenotypes (Chaussenot *et al.*, 2014). Interestingly, in all four of these independent families, the clinical presentation was characterized by early and predominant bulbar symptoms, in marked contrast to the German family reported by Kurzwelly *et al.* (2015) in their letter. Despite a lack of detailed clinical information on the three families reported by Johnson *et al.* (2014), Kurzwelly *et al.* (2015) suggested that the three German families share a common disease phenotype with predominant upper limb manifestations. However, this clinical presentation is not specific to the p.Arg15Leu mutation because Ronchi *et al.* (2015) described an Italian patient, carrying the p.Pro80Leu mutation, who developed a flail-arm syndrome with sparing of both the bulbar and lower limb muscles.

Second, patients from the French family that we described initially presented with a complex phenotype including motor neuron disease and cognitive decline but eventually, five of eight patients (nearly two-thirds) also developed cerebellar ataxia. This observation suggested that it might be useful to screen for *CHCHD10* mutations in cases with familial ataxia. However, ataxia has not been reported in all the five series of non-French patients carrying *CHCHD10* mutations that have been published subsequently. In the family described by Kurzwelly *et al.* (2015), one patient out of four exhibited cerebellar oculomoteur dysfunction but no other clinical signs of ataxia. With the caveat that large ataxia cohorts will need to be screened, the currently available data suggest that cerebellar ataxia is probably infrequent in disorders associated with *CHCHD10* mutations.

The last point that we would like to make relates to the issue of incomplete penetrance raised by Müller *et al.* (2014) in their two German ALS families carrying the p.Arg15Leu mutation. In contrast, the family reported by Kurzwelly *et al.* was consistent with complete phenotypic penetrance given the absence of unaffected individuals transmitting the disease. In our French family carrying the Ser59Leu mutation, Individual II.3 was labelled as being asymptomatic due to the lack of detailed information at the time (Bannwarth *et al.*, 2014). We have since obtained additional information regarding this *CHCHD10* mutational female carrier who died after having developed a neurological illness, therefore suggesting complete penetrance in this French family as well. It can be difficult to ascertain true disease status in late-onset neurodegenerative disorders and it should, therefore, be noted that the age of unaffected individuals, who are still alive or who have died, were not specifically mentioned by Müller *et al.* (2014) in their two German ALS families.

In conclusion, it is becoming increasingly apparent that *CHCHD10* mutations can present with a spectrum of clinical manifestations that can also vary in their chronological development. It shows that it is difficult for the time being to identify clinical criteria that can direct research towards *CHCHD10* rather than to other genes associated with FTD and ALS clinical presentations. The p.Arg15Leu mutation seems to predominate in familial pure ALS and further studies will be necessary to clarify the intriguing hypothesis that this could be due to a mutational founder effect. Although functional analyses are still lacking that explain how *CHCHD10* mutations eventually promote the emergence of motor neuron disorder, this new case report by Kurzwelly *et al.* (2015) further strenghtens the mechanistic link between primary mitochondrial dysfunction and ALS.

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