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CASE REPORT

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A heterozygous mutation in the *CCDC88C* gene likely causes early-onset pure hereditary spastic paraplegia: a case report

Ashraf Yahia^{1,2,3†}, Zhefan Stephen Chen^{4†}, Ammar E. Ahmed⁵, Sara Emad⁶, Rawaa Adil⁶, Rayan Abubaker⁷, Shaimaa Omer M. A. Taha⁸, Mustafa A. Salih⁹, Liena Elsayed^{1*}, Ho Yin Edwin Chan^{4,10} and Giovanni Stevanin^{3,11}

Abstract

Background: *CCDC88C* is a ubiquitously expressed protein with multiple functions, including roles in cell polarity and the development of dendrites in the nervous system. Bi-allelic mutations in the *CCDC88C* gene cause autosomal recessive congenital hydrocephalus (OMIM #236600). Studies recently linked heterozygous mutations in *CCDC88C* to the development of the late-onset spinocerebellar ataxia type 40 (OMIM #616053).

Case presentation: A 48-year-old Sudanese female presented with pure early onset hereditary spastic paraplegia. Exome sequencing, in-silico analysis, and Sanger sequencing identified the heterozygous NM_001080414.4:c.1993G > A (p.E665K) variant in *CCDC88C* as a potential cause of her illness. To explore the pathogenicity of the NM_001080414.4:c.1993G > A (p.E665K) variant, we expressed it in human embryonic kidney 293 cells and assessed its effects on apoptosis. In our experiment, NM_001080414.4:c.1993G > A (p.E665K) induced JNK hyper-phosphorylation and enhanced apoptosis. In contrast to previous reports, our patient developed neurological symptoms in early childhood and showed neither features of cerebellar ataxia, extrapyramidal signs, nor evidence of intellectual involvement.

Conclusion: We, herein, highlighted the possibility of extending the phenotype associated with variants in *CCDC88C* to include early-onset pure hereditary spastic paraplegia.

Keywords: Spinocerebellar ataxia type 40, Hereditary spastic paraplegia, *CCDC88C*, Sudan

Background

Hereditary spastic paraplegia and hereditary ataxia are distinct entities that share common clinical features and pathological mechanisms [1, 2]. Bi-allelic mutations in the *CCDC88C* gene are known to cause autosomal recessive non-syndromic congenital hydrocephalus (OMIM #236600) [3]. Furthermore, two reports recently linked heterozygous mutations in *CCDC88C* to the development of the autosomal dominant spinocerebellar ataxia type 40

(SCA40; OMIM # 616053) [4, 5]. In the first report, the variant NM_001080414.4:c.1391G > A (p.R464H) caused a phenotype of ataxia, dysarthria, and pyramidal features, brisk reflexes in one patient and spastic lower limbs in a second patient, in a family from Hong Kong [4]. In the second report, the variant NM_001080414.4:c.127G > A (p.D43N) caused a phenotype of ataxia with parkinsonian features and dementia in a Polish family [5]. The age at onset in the patients from both families, when provided, was above 30 years [4, 5]. The severity of the ataxia ranged from severe in the Chinese family to relatively mild in the Polish family. However, unlike in the Chinese patients, the

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phenotype in the Polish family involved extrapyramidal features [4, 5].

We, herein, report for the first time a case of pure childhood-onset hereditary spastic paraplegia caused by the heterozygous variant NM_001080414:c.1993G > A (p.E665K) in the *CCDC88C* gene.

Case presentation

A 48-year-old Sudanese lady, coded as F83–581, presented with an abnormal gait as a manifestation of pure hereditary spastic paraplegia. Her condition started in early childhood with tip-toeing that progressed gradually in severity. At the age of 30 years, she could walk only using two sticks. She did not complain of any additional symptoms apart from occasional muscle cramps. Her parents were distantly related and had no family history of similar conditions. She was not on treatment. On examination, her lower limbs were spastic with severe weakness (power grade 3). There were bilateral deformities in the feet (pes equinovarus on the right and hammertoe on the left) and up-going plantar responses. Her upper limbs were normal except for mild spasticity and hyperreflexia on the right side. The patient (F83–581) had neither signs of cerebellar involvement nor evidence of sensory deficit. She was cooperative, oriented, and had no evidence of intellectual alteration. She could barely walk supported by two sticks, and her gait was spastic. Nerve conduction studies were normal. Brain magnetic resonance imaging (MRI) showed periventricular leukomalacia with scattered ischemic foci in the white matter, cerebellum, and right side of the pons. The isthmus of the corpus callosum was thin, but it could be a normal variant. We noted neither cerebral, brain stem, nor cerebellar atrophy, nor acute ischemic changes on the brain MRI (Fig. 1).

We extracted DNA from the patient and four of her family members and investigated the patient and one of

her healthy siblings, coded F83–582, using whole-exome sequencing [6]. Whole-exome sequencing of the patient revealed a heterozygous variant, NM_001080414:c.1993G > A (p.E665K) (rs956104232), in the *CCDC88C* gene that results in substituting Glutamate at position 665 of the protein for Lysine. Sift [7], Polyphen2 HDIV [8], Mutation Taster [9], Provean [10] and M-cap [11] embedded in VarAFT software [12] predicted this substitution as pathogenic with prediction scores of 0.002, 0.982, 1, –3.21 and 0.069, respectively. Glutamate at position 665 of *CCDC88C* is highly conserved during evolution. The CADD score of 25 was also in favor of a pathogenic role of this change. We did not detect other convincing variants that could explain the phenotype in our patient. The variant NM_001080414:c.1993G > A (p.E665K) was reported once in the gnomAD v2.1.1 database in an individual of African ancestry and had a global allele frequency of 0.0000032 [13]. Using Sanger sequencing, we validated that the variant NM_001080414:c.1993G > A (p.E665K) was heterozygous in the patient and absent in her healthy family members (Fig. 2-I).

To validate the pathogenicity of the NM_001080414:c.1993G > A (p.E665K) variant, we expressed the *CCDC88C* cDNA in human embryonic kidney (HEK) 293 cells and assessed its effect on c-Jun N-terminal kinase (JNK) / caspase-3 signaling pathway according to the presence or absence of the variant. Overexpressing *CCDC88C*^{E665K} mutant protein caused a significant increase of JNK hyperphosphorylation and caspase-3 cleavage compared to the wild type protein, a pattern also seen when overexpressing the known *SCA40* pathogenic proteins *CCDC88C*^{D43N} and *CCDC88C*^{R464H} (Fig. 2-III and supplementary data [6]). NM_001080414:c.1993G > A (p.E665K) was likely a de novo variant, though we did not have DNA samples from the parents. It had a low frequency in gnomAD database, predicted as pathogenic by multiple computational tools, and its pathogenicity was

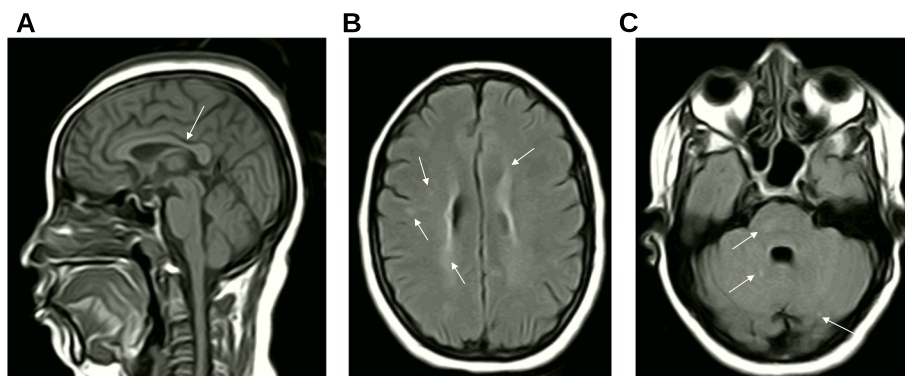
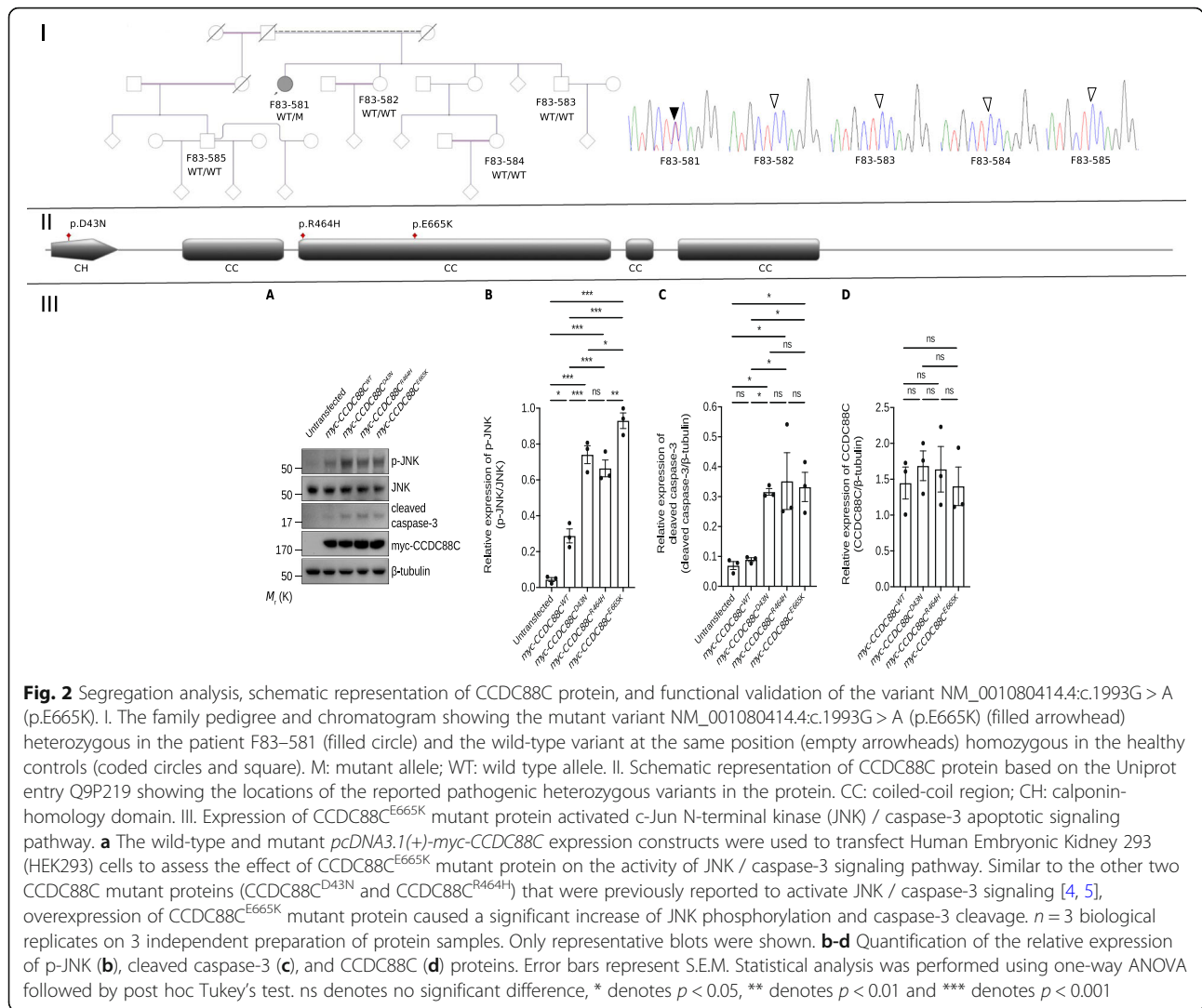


Fig. 1 Brain MRI of the patient F83–581. **a** Sagittal T1 section showing thinning in the isthmus of the corpus callosum (arrow). **b** and **c** Axial T1 section showing periventricular white matter changes and scattered hyperintensities in the white matter, cerebellum, and right side of the pons (arrows). The cerebrum, brain stem, and cerebellum were not atrophied



corroborated by functional studies, thus, fulfilling the criteria of likely pathogenic variants according to the American college of medical genetics and genomics guidelines for interpreting sequence variants published in 2015 [14]. We have submitted the variant to the Clinvar database (accession VCV000978819.2).

Discussion and conclusion

CCDC88C is a cytoplasmic protein ubiquitously expressed in mammals and has a variety of functions [15]. Up-to-date, mutations in CCDC88C are linked to monogenic neurological phenotypes by one of two mechanisms depending on the mutant allele, activation of hetero-trimeric G-proteins [16] and activation of JNK cascade [4].

Bi-allelic loss of function mutations in CCDC88C cause autosomal recessive congenital hydrocephalus (OMIM #236600) by disrupting the morphogenesis of

the nervous system [3, 16]. On the other hand, gain-of-function mutations in CCDC88C cause SCA40 through mechanisms that induce JNK hyper-phosphorylation and prompt apoptosis [4].

In this report, we showed that a mutation in the CCDC88C gene induces JNK hyper-phosphorylation and the resulting activation of apoptosis in early-onset pure hereditary spastic paraplegia. Recently the borders between hereditary ataxia and hereditary spastic paraplegia have been questioned [2]. SCA40 is an emerging clinical entity identified up-to-date in only two families worldwide (Table 1), the first family was from China and the second family was from Poland [4, 5]. Cerebellar features were present in both families, though with different degrees of severity. Extrapyramidal features and dementia dominated the phenotype in the Polish family. Pyramidal involvement, hyperreflexia in one patient and spasticity in a second patient, was only evident in examining the Chinese family's patients. The pathogenic mutation in the Polish family,

Table 1 Summary of the reported clinical phenotypes of the patients with pathogenic mutations in the *CCDC88C* gene

Patient	II:4	II:5	IV-2	IV-1	IV-3	III-3	F83-581
Reference	(Tsoi et al., 2014) [4]		(Leńska-Mieciek et al., 2019) [5]				This report
Origin	China		Poland				Sudan
Gender	Female	Male	Male	Female	Male	Female	Female
Age	65 years	62 years	59 years	63 years	53 years	84 years	48 years
Age at onset	43 years	42 years	49 years	45 years	33 years	–	Early childhood
Presentation	Ataxic gait and dysarthria	Ataxic gait and dysarthria	Rest and action upper limbs tremors	Rest and action right upper limb tremors	Rest and action upper limbs tremors	Rest and action upper limbs and head tremors	Abnormal gait (spastic)
Signs on examination							
Cerebellar ataxia	Yes	Yes	Yes	Yes	Yes	–	No
Hyper-reflexia	Yes	Yes	Yes	–	–	–	Yes
Spasticity	–	Yes	–	–	–	–	Yes
Extra-pyramidal features	No	No	Rigidity and bradykinesia	Bradykinesia	Rigidity and bradykinesia	–	No
Others	–	Ophthalmo-plegia	Cognitive impairment	Cognitive impairment	Cognitive impairment	Cognitive impairment	Lower limbs weakness
SARA score	24/40	22/40	10/40	5/40	3/40	–	–
Brain MRI	Ponto-cerebellar atrophy, subcortical T2 hyper-intensities	Moderate ponto-cerebellar atrophy, sub-cortical T2 hyper-intensities	Normal	Normal	Normal	–	Periventricular leukomalacia with scattered ischemic foci
Nerve conduction studies	–	–	–	–	–	–	Normal

NM_001080414.4:c.127G > A (p.D43N), is located in the calponin-homology domain of the *CCDC88C* protein. The mutations reported in our patient and in the Chinese patients, NM_001080414.4:c.1993G > A (p.E665K) and NM_001080414.4:c.1391G > A (p.R464H), respectively, are located in a coiled-coil domain in the protein (Fig. 2-II).

Although we did not have DNA samples from the patient's parents, we assumed NM_001080414.4:c.1993G > A (p.E665K) was a de novo variant because the parents neither manifested the disease throughout their lives nor had a positive family history. However, we could not completely rebut the possibility of incomplete penetrance in the parents. The early age at onset in our patient compared to the two previously reported SCA40 families, adds another layer of complexity and suggests the presence of unknown modifiers. More studies are needed to delineate the phenotypes' spectrum associated with *CCDC88C* mutations and investigate genotype-phenotype correlations.

In conclusion, this report suggests the extension of *CCDC88C*-associated phenotype to include early-onset pure hereditary spastic paraplegia.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12883-021-02113-y>.

Additional file 1.

Abbreviations

SCA40: Spinocerebellar ataxia type 40; OMIM: Online inheritance in man; MRI: Magnetic resonance imaging; JNK: c-Jun N-terminal kinase; HEK: Human Embryonic Kidney

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Authors' contributions

AY, ZSC, LE, HVEC, and GS designed the study. AEA, AY, SOMAT, and MAS evaluated the patient and her investigations. AY, ZSC, SE, RA1, and RA2 collected the samples and relevant data and performed the experiments. AY, ZSC, HVEC, MAS, and GS interpreted the results. LE, AEA, HVEC, and GS supervised the study. AY and ZSC wrote the manuscript. All authors critically revised and approved the final version of the manuscript. All authors agreed to be accountable for all aspects of the work and ensured that questions related to the accuracy and the integrity of all parts of the work were appropriately investigated and resolved.

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Availability of data and materials

Supplementary data for this study are openly available in Figshare repository at <https://doi.org/10.6084/m9.figshare.13020581.v1> [6].

Ethics approval and consent to participate

The study was approved by the ethics committee of the National University, Sudan (approval number NU-RECG200). All procedures in this study were performed following the ethical standards of the institutional research committee at the National University, Sudan, and with the 1975 Helsinki declaration and its later amendments. Informed written consent forms for participation were obtained from all participants.

Consent for publication

Signed informed consent forms were obtained from participants for publication of personal and medical details included in this report.

Competing interests

The authors declare that they have no competing interests.

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