Expanding the global prevalence of spinocerebellar ataxia type 42

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Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders that involve the degeneration of the cerebellum and brainstem.[1] These genetic diseases are characterized by autosomal dominant inheritance with approximately 44 known subtypes. Recently, dominant mutations in the *CACNA1G* gene, encoding the voltage-gated calcium channel $Ca_V3.1$, have been linked to SCA42 in French[2] and Japanese[3,4] families. SCA42 prevalence elsewhere in the world has yet to be documented. Through a combination of whole-exome sequencing (WES) and linkage analysis, we have identified an SCA42 mutation in patients from 3 additional countries, expanding the worldwide prevalence of this disease.

Methods

All study methods were approved by the Institutional Review Board of UCLA. All patients received a comprehensive clinical evaluation for acquired causes of ataxia.[5] All patients provided written informed consent for collection of DNA. Only patients who tested negative for common genetic ataxias (SCA1, SCA2, SCA3, SCA6, SCA7, and Friedreich ataxia) were enrolled.[5] WES was performed for 8 members of 3 families (figure, A and B). Genomic DNA (gDNA) libraries were prepared using the Nextera Rapid Capture Exome kit (Illumina, San Diego, CA). Sequencing for these libraries was performed with 107-bp paired-end reads on a HiSeq 2500 sequencer in the rapid-run mode platform (Illumina, San Diego, CA). The gDNA library for B-III-3 was prepared using the SureSelect Human All Exon V4 Capture kit (Agilent Technologies, Santa Clara, CA), and 101-bp paired-end reads were sequenced on the Illumina HiSeq 4000 platform (Illumina, San Diego, CA). Sequencing data were processed as described.[5] Linkage analysis was conducted with ALLEGRO on 190,569 single nucleotide polymorphisms (SNPs) (average distance between SNPs $\approx$ 0.015 Mb) under a dominant model ($f_0/f_1/f_2 = 0/1/1$) with estimated minor allele frequencies drawn from HapMap3 project[6] Centre d'Etude du Polymorphism Humain - Utah population data, comprised Utah residents with Northern and Western European ancestry.[7] Self-reported ancestry was confirmed via principal component analysis (PCA) of WES variants with a minor allele frequency of >5% and 1000 Genomes Project Phase 3[8] reference data. Segregation analysis for family A was performed by PCR, followed by Sanger sequencing.

Results

Family A was clinically evaluated in Italy, their country of origin, and PCA confirmed European ancestry. Affected members exhibited pure cerebellar ataxia with onset between ages 22 and 58
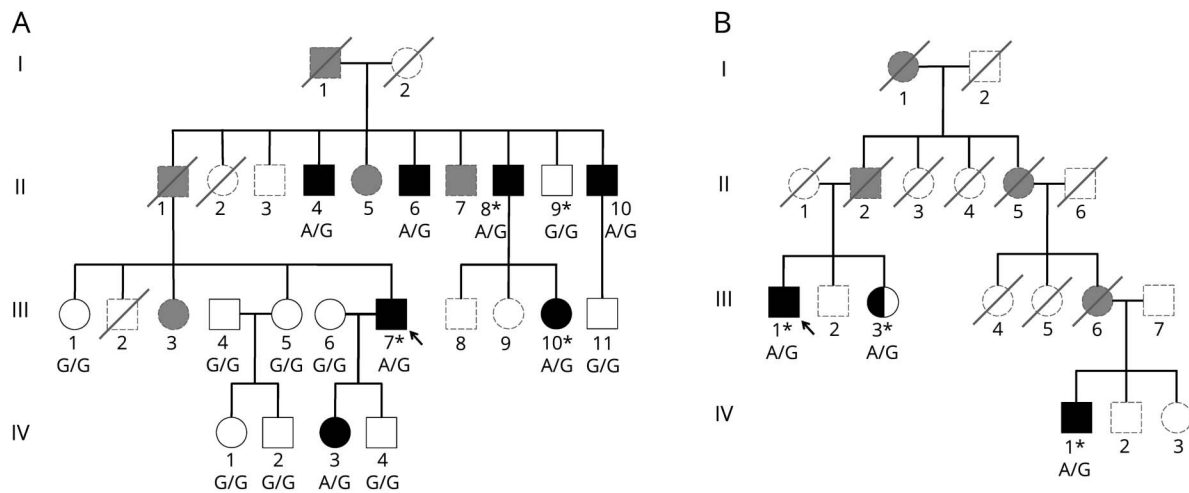
Figure Pedigrees of the SCA42 families identified in this study

(A) Pedigree of family A. (B) Pedigree of family B. Probands are indicated by an arrow. Shaded symbols represent affected individuals. Individuals who had WES are indicated by an asterisk. Genotypes of the c.5144 position in *CACNA1G* are shown under each patient sequenced. G is the reference, and A is the p. R1715H mutation. Individuals who were unavailable for genotyping are represented in gray with dashed lines. Shaded gray individuals were reported as affected. SCA = spinocerebellar ataxia.

years (mean 37.5 years). All affected members initially experienced a subjective sense of leg weakness and imbalance that slowly progressed to gait and limb ataxia with dysarthria. There was no nystagmus, abnormal saccadic pursuit, motor deficits, pyramidal or extrapyramidal signs, abnormal sensation, or cognitive decline noted in any patients. MRI of the brain demonstrated cerebellar atrophy in all patients. WES identified a known pathogenic variant in the *CACNA1G* gene in all 3 affected family members (A-II-8, A-III-10, and A-III-7) tested. All other dominant SCAs were excluded by linkage analysis and/or by the absence of rare missense variation.[5] The *CACNA1G* variant (hg19:chr17:48694921G>A, p.Arg1715His) was previously observed in patients from France and Japan.[2–4] This variant was not present in the ExAC (exac. broadinstitute.org) or gnomAD (gnomad.broadinstitute.org) databases of human variation. The variant segregated with disease and was located within a linkage peak, consistent with being pathogenic.

In a second family with pure cerebellar ataxia, family B of Eastern European ancestry living in the United States, the proband (B-III-1) developed, at age 67 years, a sense of imbalance that slowly progressed to a gait and limb ataxia with dysarthria. His first cousin once removed (B-IV-1) was also affected, with an age at onset of 39 years, initially also involving his balance and speech and slowly progressing to a gait and limb ataxia with dysarthria. MRI of the brain showed cerebellar atrophy. PCA verified European ancestry. The above *CACNA1G* variant was identified in both patients by WES. The proband's sister (B-III-3) also carried the variant but reported herself as asymptomatic and was unavailable for neurologic examination.

Lastly, WES identified the same variant in a man from Yemen, clinically evaluated in Israel, who, at age 25 years, presented

with a sense of imbalance and intermittent jerking movements of his neck that slowly progressed to a tremor with cervical dystonia manifesting as a rightward tilt. His imbalance progressed to a mild gait and lower limb ataxia. The remainder of his neurologic examination was normal. MRI of the brain showed mild cerebellar atrophy, primarily of the vermis. His parents and 6 younger siblings were all reported as asymptomatic; however, none were available for examination or genetic testing. Although the 1000 Genomes Project does not include Yemeni samples, this sample clustered with admixed American samples, indicating primarily European ancestry with small amounts of Asian and African admixture, consistent with expectations for a Middle Eastern population.

We next questioned whether *CACNA1G* variants were common in neurologic disease in the US population, so we reviewed a recent analysis of 3,040 clinical WES cases,[9] comprising 1,082 patients with involvement of the CNS, including cerebellar ataxia, and noted that it did not identify any patients with the p.Arg1715His variant we detected and found only 1 patient with a novel variant in *CACNA1G* deemed pathogenic, suggesting that the mutation of this gene may be rare in the US population. Next, to assess the prevalence of this disease within a specific US ataxia population, we reviewed WES data from 225 sporadic or familial cases seen at our tertiary referral center at UCLA. Aside from family B, we identified no additional cases. Therefore, we estimate the frequency in our ataxia cohort to be 1 of 225 (0.4%) undiagnosed families.

Discussion

In this report, we describe 3 additional SCA42 families originating from Italy, the United States (via Europe), and Yemen,

respectively, expanding the worldwide prevalence of the disorder. In addition, we report a case with the new finding of cervical dystonia, along with tremor, previously reported in another family.[3] Although previously reported in French and Japanese families,[2–4] none of the families in this report had clear evidence of French or Japanese ancestry to the best of our ability to ascertain. Although we find the disorder to be rare in our center's US ataxia population (0.4%, N = 225), we recommend that clinicians broadly consider the possibility of SCA42 in undiagnosed patients with autosomal dominant ataxia, without regard to country of origin.

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This information is current as of April 5, 2018

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In the Clinical/Scientific Note "Expanding the global prevalence of spinocerebellar ataxia type 42" by Ngo et al.,[1] the first and fourth authors' names are missing their middle initials, which should read Kathie J. Ngo and Jason A. Chen, respectively. The publisher regrets the omission. There is also a small typo in the Methods section, which should read, "…with estimated minor allele frequencies drawn from HapMap3 project Centre d'Etude du Polymorphisme Humain—Utah population data." The authors regret the error.

Reference

1. Ngo K, Aker M, Petty LE, et al. Expanding the global prevalence of spinocerebellar ataxia type 42. Neurol Genet 2018;4:e232.