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Letter to the Editor

Screening for spinocerebellar ataxia type 36 (SCA36) in the Greek population

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Dear Editor,

Spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominant (AD) neurodegenerative disorders with cerebellar ataxia as a prominent feature. Spinocerebellar ataxia type 36 (SCA36) is an AD disorder, clinically characterized by late onset cerebellar ataxia usually between 5th and 6th decade of life, dysarthria, sensorineural hearing loss (SNHL), lower motor neuron involvement, and tongue atrophy. A hexanucleotide repeat expansion, namely GGCCTG in intron 1 of the *NOP56* gene, was reported in 2011 as the cause of the disease. This gene encodes for the nucleolar protein 56, a ribonucleoprotein which plays a role in transcription and splicing. Normal size alleles vary from 3 to 14 repeats, alleles of uncertain significance from 15 to 650 repeats and pathogenic alleles have more than 650 repeats [1]. Interestingly there is a study indicating that even short repeat expansions can cause the disease [2]. There has been no clear evidence of anticipation in SCA36 yet, despite the fact that anticipation is common in other repeat expansion diseases [1].

The disease is caused by an RNA gain of function mechanism, in which RNA foci formed in nucleus causing cell toxicity [1]. Even though the distribution of SCA36 is still largely unknown, up to-date literature shows that the frequency of SCA36 appears to vary among different countries while possibly forming clusters of affected families, indicating a possible founder effect. The frequency of SCA36 in non-European populations accounts for 3.6% of SCAs in Western Japan, which is among the highest in the world, followed by 1.5% in Eastern Japan, 0.6% in China and 0.7% in US [1–4]. SCA36 is absent from north European populations (Germany 0.0%, UK 0.0% of SCA patients) except from Poland, where five families were identified [2,5,6]. In the Mediterranean basin the frequency spans from 0.0% Portugal, 1.9% France, 3% Italy to 6.3% Spain-Galicia, all frequencies determined in SCA cohorts, excepting Italy where a purely AD SCA cohort was screened [2,7–9]. Although triplet repeat expansions SCAs have been previously clinically and molecular characterized in Greece by our group, no data exist at present regarding SCA36 [10].

The aim of current study was to investigate the presence of hexanucleotide repeat GGCCTG causing SCA36 in a cohort of Greek ataxia patients.

Our cohort consisted of 98 selected index patients. All cases had ataxia; 6 had additional SNHL; 12 additional lower motor neuron involvement; and 56 had onset in the 5th or 6th decade of life. Ninety two patients came from an ataxia cohort (n = 600), negative for the most common SCAs (SCA1, SCA2, SCA3, SCA6, SCA7), while 6 came from a suspected Kennedy's disease cohort (n = 200), negative for the CAG trinucleotide repeat in Androgen Receptor gene (AR). Twenty six out of 98 patient's pedigrees presented familial inheritance (10 of which had unequivocal AD inheritance), with the rest of them indicating sporadic cases. Mean age was 58 years and mean age of onset was 44 years ranging from 16 to 69 years. Patients were referred to Neurogenetics Unit from all over Greece, gave informed consent for the performance of molecular diagnostic testing and the study was approved by the Eginition hospital ethics committee [10].

DNA was extracted from peripheral blood leucocytes. To determine the number of GGCCTG hexanucleotide repeats we used conventional PCR for the smaller alleles and RP-PCR [9] for the larger ones, using primers that have previously been published [1]. Fragment length analysis was performed in an ABI3500 genetic analyser (Applied Biosystems), followed by *in silico* analysis, using GeneMarker V2.2.0. Positive samples for the SCA36 expansion, kindly offered by Prof. Henry Houlden (Institute of Neurology Queen Square, London), were used in every run as controls.

No pathologic repeat expansions were detected in our cohort. However we identified multiple normal repeats varying from 3 to 9 with 6 as the most common followed by 3 and 4 as the second and the third most common repeats respectively.

Supplementary to our previous work [10], we studied a less common gene causing AD SCA, SCA36. The highest frequencies worldwide have been reported in clusters of affected families in specific

Abbreviations: SCAs, spinocerebellar ataxias; SCA36, spinocerebellar ataxia type 36; AD, autosomal dominant; SNHL, sensorineural hearing loss; AR, androgen receptor gene

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geographical areas (Galicia-Spain, Italy, Han Chinese, East and West Japan) [1–3,9]. In fact, the distribution of triplet repeat expansion SCAs in Greece has been very similar to Italian data [10]. This could be attributed to the fact that Greek people populated large areas of Italy in ancient and Byzantine times and that large parts of Southern and Western Greece were under Venetian rule for centuries. Given that the SCA36 expansion has been identified at 3% of AD SCA patients, the absence of SCA36 in Greece supports the theory of disease clusters and amplifies the possibility of founder effect [7].

In our population the normal range of repeats was slightly narrower than reported in literature. The most common normal repeat in our cohort was 6 instead of 9 reported in most studies so far [2,3,7,9]. A probable limitation of our study is that none of our patients had the full range of clinical symptoms typical for SCA36.

In conclusion in line with SCA3, SCA36 seems to be a rare finding in the Greek population compared to other AD SCAs. SCA36 frequency in Greece appears to be similar to Germany Portugal and UK [2,5,8], reinforcing the findings of an uneven distribution in Europe.

The present study could contribute to the investigation of the genetic heterogeneity of SCAs in the Greek population and, concerning the implications for genetic SCA testing, inform us that testing for SCA36 should only be performed following the exclusion of other more common SCAs in Greek patient cohorts.

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Author contributions

K.D.: carried out the molecular genetic analysis, performed the *in silico* analysis and wrote the manuscript with K.C.

K.C.: established the molecular genetic methodology (fragment analysis, RP-PCR), performed the *in silico* analysis and wrote the manuscript with K.D.

B.M., P.M. and Koutsis G: examined patients clinically and carried out the selection of index patients.

Koutsis G and Karadima G: conceived of the study and participated in its design and coordination and helped to draft the manuscript.

All authors read and approved the final manuscript.

Declaration of interest

The authors report no conflict of interest.

Patient consent

Obtained.

Ethical approval

The present study was approved by the Ethics Committee of Eginition Hospital.

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Katsimpouris D., Kartanou C.*, Breza M., Panas M., Koutsis G.[1], Karadima G.[1]

Neurogenetics Unit, 1st Department of Neurology, University of Athens Medical School, Eginition Hospital, Athens, Greece

E-mail address: ckartano@med.uoa.gr (C. Kartanou).

* Corresponding author at: Neurogenetics Unit, 1st Department of Neurology, Medical School National and Kapodistrian University of Athens, Eginition Hospital, 74 Vas. Sophias Ave., 11528 Athens, Greece.

[1] Equal contribution.