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No pathogenic *GNAL* mutations in 192 sporadic and familial cases of cervical dystonia

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Recently, using a whole exome sequencing approach, mutations in *GNAL* were identified as a novel cause of primary dystonia by one group[1] and subsequently confirmed by another.[2] Mutations in this gene appear to cause autosomal dominant, primary dystonia with a cervical predilection and evidence of incomplete penetrance.[1]

The initial discovery paper by Fuchs et al reported *GNAL* mutations in 6 out of 39 families screened (~15%). However, in the subsequent study by Vemula et al, only 3 *GNAL* mutations were detected in 760 subjects with familial or sporadic primary dystonia (<0.5%). An accurate estimate of the prevalence of GNAL mutations is important as a mutation frequency of ~15% would justify early and widespread genetic testing of *GNAL* in familial dystonia, whereas a frequency of <0.5% would not.

We screened *GNAL* by Sanger sequencing using the DNA samples from 192 probands (136 female and 56 male) with either familial or sporadic cervical dystonia, selected from a library of research samples on the basis of a clinical description of focal or segmental dystonia that included the cervical region. Local ethics committee approval was obtained for the study. A family history, defined as one or more first or second-degree relatives with dystonia, was recorded in 84 cases. Tremor was recorded in 53 cases. All familial cases had been screened for TOR1A, THAP1 and ANO3 mutations and were negative.

Primers were designed to amplify all exons, the exon/intron boundaries and the 5′UTRs of both major isoforms of GNAL (ENST00000334049 and ENST00000423027).

We identified only two novel single nucleotide variations in *GNAL* in three individuals in our case cohort. The first was a missense mutation in exon 2 of the gene (cDNA.1053C>T; P149S in ENST00000334049) that was detected in one individual with onset of cervical dystonia in the 4th decade, with a similarly affected father, suggesting autosomal dominant

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inheritance. However, segregation analysis revealed the variant had in fact been inherited from his unaffected mother and was also present in his unaffected brother (see Fig. 1A), ruling it out as the cause of the dystonia in this family. The second variant, located in the 5′UTR of isoform 2 (cDNA.199C>T in ENST00000423027), was found in two individuals in our cohort exhibiting onset of cervical dystonia in the 6th decade. One individual was a sporadic case whereas the other was part of family with multiple affected members (see Fig. 1B-C). Despite affecting a highly conserved base (PhyloP score = 4.158), the variant failed to segregate with disease in the family, being absent in two affected individuals (see Fig. 1C).

In summary, we did not identify any mutations in *GNAL* that could be a cause of the dystonia in 192 cases drawn from the United Kingdom, including 84 familial cases. Our own data suggest that *GNAL* mutations do not represent a common cause of dystonia — in the U.K. population at least — and that the overall frequency of *GNAL* mutations may be closer to the figure obtained by Vemula et al[2] than the 15% initially reported by Fuchs et al.[1] This study also emphasises the importance of segregation analysis in establishing the pathogenicity or otherwise of novel variants and suggests that other novel genetic causes of dystonia remain to be identified.

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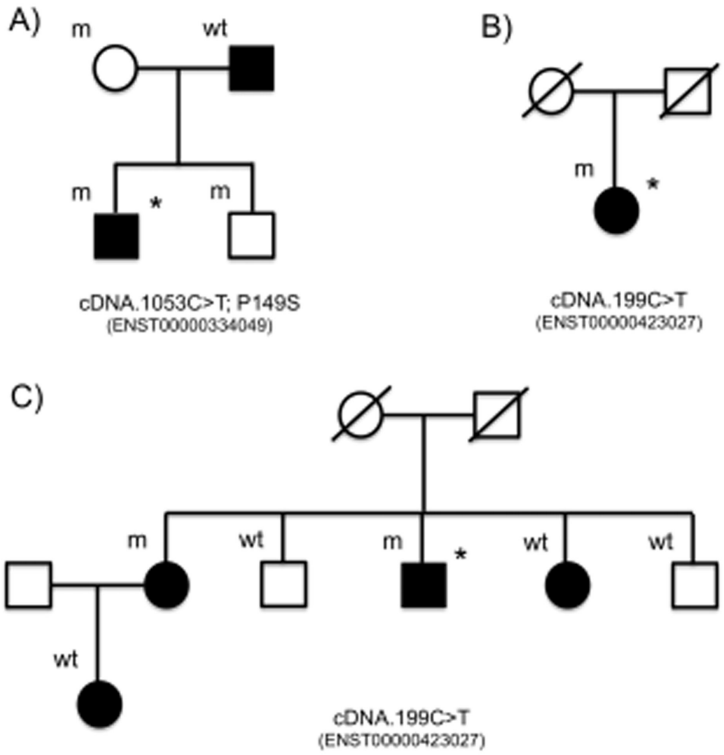

Figure 1. Family trees for individuals with novel variants in GNAL.

Genetic pedigrees for individuals with novel variants in GNAL. Affected family members are marked by shaded symbols. The variant found is indicated under the pedigree with transcript ID. Mutational status is indicated by ‘m’ for heterozygous mutation carriers and ‘wt’ for homozygous wildtype alleles. Index cases included in the initial screening are marked with an asterisk.

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