Rare autosomal dominant mutations in GNAL are associated with primary torsion dystonia

References

Mutations in GNAL cause primary torsion dystonia


Dystonias are clinically and genetically heterogeneous group of movement disorders, characterized by involuntary muscle contractions that cause slow and painful repetitive movements or abnormal postures. Tremors are the only neurological presentation shown by some patients. Dystonia may result from an abnormality in or damage to the basal ganglia or other brain regions that control movement (1). Primary torsion dystonia (PTD) is dystonia in isolation without brain degeneration and without an acquired cause. The phenotypic spectrum associated with PTD is broad ranging, from early onset generalized to adult-onset focal dystonia (2). PTD presents an autosomal dominant pattern of inheritance with reduced penetrance making it difficult to identify the genes involved in its pathogenesis. Only three genes for PTD have previously been identified—TOR1A (DYT1), THAP1 (DYT6) and CIZ1.

Fuchs et al. in their study identify a new causative gene, GNAL, using exome sequencing in individuals from two families affected with PTD (families D1 and P), both of mixed European ancestry (Fig. 2a). With the average coverage of 52× followed by mapping the reads to the human reference genome sequence, around 60,000 variants were called per individual. The variants were further compared with dbSNP and annotated by both SIFT and SeattleSeq Annotation servers. These variants were narrowed down following linkage analysis for family P to four single-nucleotide substitutions and three indels, of which a nonsense mutation in GNAL gene, p.Ser293* was found to cosegregate with dystonia in all the affected members of this family. Similarly, from the 20 missense variants called post-annotation for family D1, all the carriers of PTD shared an extremely rare heterozygous variant encoding a p.Val137Met alteration in the same gene, GNAL. Both these variants were neither found in the 572 control chromosomes nor 3500 European exomes in the National Heart, Lung, and Blood Institute Exome Sequencing Project database.

Fuchs et al. additionally screened 39 PTD affected families of mixed European origin who were negative for mutations in TOR1A and THAP1 and identified six new mutations in the GNAL gene in six of these families. These included a nonsense mutation (encoding p.Arg21*), two frameshift mutations (encoding p.Ser95fs*110 and p.Arg198fs*210), one missense mutation (encoding p.Glu155Lys), one in-frame deletion of three amino acids (p.Pro102_Val104del) and one possible splice site mutation at chromosome 18:11,753,820 (hg19) (c.274-5T>C) (Fig. 2b). These variants were absent in the dbSNP135, 3500 European exomes or the 572 control chromosomes. The average age of dystonia onset in these mutation carriers was 31.3 years and the majority of them had the onset in the neck (82%), which later progressed to other sites. Focal dystonia was observed in only 46% of the carriers at the final exam while cranial and speech involvement were seen in 57% and 44% of the carriers, respectively. Eventual arm involvement was present in only 32% carriers. The GNAL mutation carriers exhibited a distinct phenotype from those of THAP1 mutation as they lacked brachial onset.

Fig. 2. (a) Schematic representation of the genomic locus of GNAL on Chr18. (b) Pictorial depiction of eight novel mutations associated with primary torsion dystonia identified by Fuchs et al. in the GNAL exon–intron structure.
Located on chromosome 18p, GNAL encodes the stimulatory α subunit Go\textsubscript{olf}, a G protein involved in odorant signaling in the olfactory epithelium. This G protein functions as heterotrimer along with β and γ subunits and links the transmembrane domain receptors to downstream effector molecules. Any nonsense or frameshift mutations in the coding region of Go\textsubscript{olf} would result in a loss-of-function phenotype or degradation of the protein by non-sense mediated decay, thereby impairing the signaling pathway. Thus, Fuchs et al. in their study used a cell-based bioluminescence resonance energy transfer (BRET) reporter system to investigate the impact of truncating mutations, which they reported in GNAL. This reporter assay assessed the Go\textsubscript{olf} activity by its ability to interact with the G\(\beta\gamma\) subunit. Following the stimulation of dopamine type 1 receptor (D1R) with dopamine (which binds the heterotrimer Go\textsubscript{olf} and G\(\beta\gamma\)), the Go\textsubscript{olf} subunit dissociates from the heterotrimer and the released G\(\beta\gamma\) subunit interacts with a RLuc8 tagged G-protein coupled receptor kinase (GRK) reporter, to produce a BRET signal that is determined by the change in emission ratio.

On the other hand, inactivating D1R resulted in heterotrimer reassociation due to GTP hydrolysis, which brought the BRET signal back to baseline. Interestingly, individuals harboring the missense mutations, Glu155Lys and Val37Met, showed an intermediate phenotype potentially resulting from impaired association with the G\(\beta\gamma\) subunit.

Previous studies in heterozygous and homozygous Gnal-null mouse models have shown that these mice are hyperactive and do not respond to psycho-stimulant exposure. Also mice overexpressing mutant torsin A in the dopaminergic neurons exhibit alterations in D1R signal transduction system, and share phenotypic features that include dystonia and levodopa-induced dyskinesias (LID). As the amount of striatal Go\textsubscript{olf} is rate limiting in the activation of adenylate cyclase type 5 upon D1R stimulation, it is believed that any imbalance in the striosomal activity compared with the matrix compartment would result in the development of hyperkinetic movement disorder. Also, work by other groups previously has established that Go\textsubscript{olf} is associated with attention deficit hyperactivity disorder and schizophrenia. All this evidence suggests that mutations in GNAL would possibly result in dystonia by impairing the downstream signaling of D1R and/or adenosine A2A receptors (A2ARs), of the indirect pathway leading to the activation of adenylate cyclase type 5.

In summary, Fuchs et al. identified GNAL, a novel causative gene in PTD. The mutations were found to segregate with the disease in eight PTD affected families. A recent study by another group Vemula et al., also report mutations in GNAL in both familial and sporadic primary dystonia, thereby further supporting the role of Go\textsubscript{olf} in adult onset dystonia (3). Although not much is known about the specific action of GNAL mutations, they are believed to impair Go\textsubscript{olf} function resulting in a disease phenotype, which the authors tested using a functional assay. It would be interesting to look at the molecular mechanism by which alteration in Go\textsubscript{olf} levels result in hyperkinetic movement disorders for better understanding of the disorder. Restoring the levels of Go\textsubscript{olf} post dopamine administration could be a possible therapeutic strategy for GNAL related dystonia.