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Review

A mechanistic review on *GNAO1*-associated movement disorder

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ABSTRACT

Mutations in the *GNAO1* gene cause a complex constellation of neurological disorders including epilepsy, developmental delay, and movement disorders. *GNAO1* encodes $G\alpha_o$, the α subunit of G_o, a member of the $G_{i/o}$ family of heterotrimeric G protein signal transducers. G_o is the most abundant membrane protein in the mammalian central nervous system and plays major roles in synaptic neurotransmission and neurodevelopment. *GNAO1* mutations were first reported in early infantile epileptic encephalopathy 17 (EIEE17) but are also associated with a more common syndrome termed neurodevelopmental disorder with involuntary movements (NEDIM). Here we review a mechanistic model in which loss-of-function (LOF) *GNAO1* alleles cause epilepsy and gain-of-function (GOF) alleles are primarily associated with movement disorders. We also develop a signaling framework related to cyclic AMP (cAMP), synaptic vesicle release, and neural development and discuss gene mutations perturbing those mechanisms in a range of genetic movement disorders. Finally, we analyze clinical reports of patients carrying *GNAO1* mutations with respect to their symptom onset and discuss pharmacological/surgical treatments in the context of our mechanistic model.

1. Introduction

Mutations in *GNAO1* were first reported in patients with Ohtahara syndrome and early infantile epileptic encephalopathy 17 (EIEE17, OMIM 615473; Nakamura et al., 2013). More recently, a syndrome of neurodevelopmental disorder with involuntary movements without epileptic seizures (NEDIM, OMIM 617493) has been defined, expanding the phenotypic spectrum of *GNAO1* mutation-associated neurological disorders (Ananth et al., 2016; Zhu et al., 2015). Currently, there have been published reports on 50 patients representing 25 different *GNAO1* mutations (23 missense, 1 in-frame deletion and 1 splicing site mutation, see Fig. 1; Ananth et al., 2016; Arya et al., 2017; Bruun et al., 2018; Danti et al., 2017; Dhamija et al., 2016; Dietel et al., 2016; Epi et al., 2013; Epi and Epi, 2016; Euro et al., 2014; Honey et al., 2018; Farwell et al., 2015; Gawlinski et al., 2016; Gerald, 2017; Helbig et al., 2016; Kulkarni et al., 2016; Law et al., 2015; Marce-Grau et al., 2016; Menke et al., 2016; Nakamura et al., 2013; Saitsu et al., 2016; Sakamoto et al., 2017; Schorling et al., 2017; Talvik et al., 2015; Ueda et al., 2016; Waak et al., 2018; Xiong et al., 2018; Yilmaz et al., 2016).

Although recent reviews on monogenic complex hyperkinetic disorders recognized *GNAO1* mutations as pathogenic (Carecchio and Mencacci, 2017; Mencacci and Carecchio, 2016), our review focuses on a mechanistic analysis illustrating the shared pathways of pathogenic mutations across multiple movement disorder-associated genes. It is important to consider the mechanisms that underlie the *GNAO1*-associated movement disorders to rationalize the clinical heterogeneity resulting from different mutations in *GNAO1*, as well as the implications for therapeutic choices. We (H.F. and R.R.N.) recently demonstrated that *GNAO1* mutations associated with movement disorders result in a gain-of-function (GOF) biochemical behavior related to control of cAMP levels, while epilepsy-associated mutations cause loss-of-function (LOF) behavior (Feng et al., 2017). This is consistent with other single-gene epilepsy and movement disorders, which also share causal genes (Batty et al., 2017; Szczepanik et al., 2015). Focusing on movement disorders, there is a clear functional connection between *GNAO1* and other "movement disorder genes" related to two molecular mechanisms. Both the cAMP pathway (*GNAL*, *GNB1*, *ADCY5*, *PDE10A*) and regulation of synaptic vesicle fusion and neurotransmitter release (*GNB1*, *CACNA1A*, *CACNA1B*, *KCNMA1*, *SYT1*, *SNAP25*, *and PRRT2*) have been implicated. In this review, we attempt to develop models of these systems and explore how they may connect pathophysiology with clinical patterns and therapeutic responses.

2. $G\alpha_o$ (*GNAO1*) mechanisms

GNAO1 encodes the α-subunit of a heterotrimeric guanine

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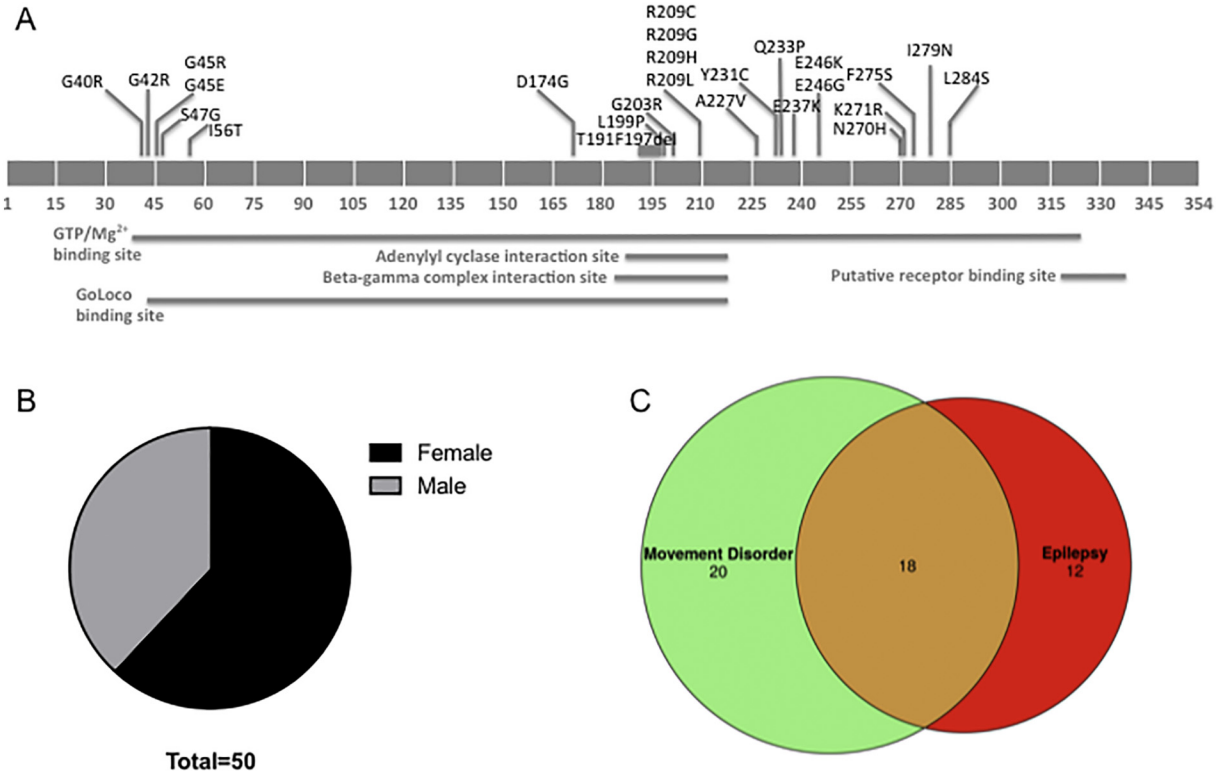

Fig. 1. Summary of reported cases of *GNAO1* encephalopathy.
A. Locations of reported mutations on the $G\alpha_o$ amino acid sequence. The splicing site mutation c.723 + 1G > A is not included here. B. Sex distribution among the 48 patients reported. C. Distribution of movement disorders and/or epilepsy symptoms in *GNAO1* encephalopathy patients (Green = movement disorder only; Red = epilepsy only; Orange = both phenotypes).

nucleotide-binding protein ($G\alpha_o$), which is the most abundant membrane protein in the mammalian central nervous system, constituting approximately 1% of total brain membrane protein. $G\alpha_o$ localizes ubiquitously throughout the brain with relatively high expression in hippocampus, striatum and cerebellum (Worley et al., 1986). It couples to a variety of important G protein coupled receptors (GPCRs) including $GABA_B$, α_2 adrenergic, adenosine A_1 (A_1R), and dopamine D_2 (D_2R) receptors. These play key roles in regulating neurotransmitter release, movement, and neural development.

There are multiple downstream signaling targets of G_o, as well as of the other members of the $G_{i/o}$ family. These include: inhibition of adenylyl cyclases (ACs) which decreases cAMP production, inhibition of N-type ($Ca_v2.2$) and P/Q type calcium channels ($Ca_v2.1$; Colecraft et al., 2001; McDavid and Currie, 2006), and direct inhibition of neurotransmitter vesicle release by the binding of $G\beta\gamma$ released from active G_o to inhibit syntaxin 1A and SNAP25 (Zamponi and Currie, 2013). Both $G\alpha_o$ and $G\beta\gamma$ subunits also bind to G protein-coupled inward rectifying potassium (GIRK) channels to stimulate channel opening (Luscher and Slesinger, 2010). GIRK channels are well-recognized as playing a role in seizure disorders (Mayfield et al., 2015; Signorini et al., 1997; Torrecilla et al., 2002).

Many of these targets of G_o signaling are also implicated in movement disorders. Mutations in *ADCY5* (which encodes adenylyl cyclase type 5) have been reported in patients with dyskinesia and dystonia (Meijer et al., 2017; Mencacci et al., 2015a; Shaw et al., 1993). Mutations in *CACNA1A* (encoding Cav2.1) cause episodic ataxia type 2 (EA2; Sintas et al., 2017; Wan et al., 2011). In the G protein family, mutations in both *GNAL* (Dufke et al., 2014; Kumar et al., 2014; Putzel et al., 2016) and *GNB1* (Lohmann et al., 2017; Steinrucke et al., 2016) are also associated with dystonic syndromes. The former encodes $G\alpha_{olf}$ which mediates dopamine $D_{1/5}$ receptor stimulation of AC and the latter encodes $G\beta_1$ which mediates many actions of $G_{i/o}$.

3. The clinical spectrum of *GNAO1* mutation-associated movement disorders

3.1. *GNAO1* encephalopathy displays a variety of neurological symptoms

To understand the molecular mechanisms underlying *GNAO1* disorders, it is important to consider the substantial clinical heterogeneity which includes both early-onset epileptic encephalopathy (Nakamura et al., 2013) and patients with complex movement disorders with or without epilepsy (Ananth et al., 2016; Kulkarni et al., 2016; Menke et al., 2016; Saitsu et al., 2016; Sakamoto et al., 2017; Zhu et al., 2015). Recently, we reported a biochemical analysis of 15 different *GNAO1* mutant alleles (Feng et al., 2017) which revealed that LOF mutations are associated with epileptic seizures while mutations that result in GOF for inhibition of cAMP as well as mutations that show largely normal function in this assay (p.R209 mutations) are mainly associated with movement disorders (Feng et al., 2017).

The two most common manifestations of patients with *GNAO1* mutations (Table S1 and Fig. S1), regardless of their clinical pattern or biochemical phenotype, are hypotonia (68%) and developmental delay (78%, Table S1). Choreoathetotic movements (44%) and dystonia (32%) are the next most common findings (Table S1). Approximately 28% of patients had intellectual disability.

While many individuals have abnormal EEG or MRI findings (Table S1), less than half of patients with *GNAO1* mutations (50%) showed markedly abnormal EEGs and that was primarily in epilepsy patients with LOF mutations. Approximately 64% of the reported patients showed significant MRI findings and these were distributed across both epilepsy and movement disorder patients (Table S1). This heterogeneity in both clinical pattern and effect on brain structure/function suggests a role for both neurodevelopmental alterations and functional signaling perturbations. The latter seems more prominent in patients with the