Epileptic encephalopathy, movement disorder, and the yin and yang of *GNAO1* function

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GNAO1 encephalopathy comprises a spectrum of neurologic phenotypes that result from de novo heterozygous mutations in *GNAO1*, a gene coding for the subunit of a G protein that is highly expressed in the CNS and is involved in second messenger signaling. De novo heterozygous mutations in the gene were first described in patients with a severe, infantile-onset epileptic encephalopathy known as Ohtahara syndrome.[1] However, patients with a predominant motor disorder, characterized by infantile hypotonia developing into severe chorea and dystonia, have also been identified.[2,3] While it is not unusual for novel neurogenetic disorders to have some degree of phenotypic range, the discrepancy between these 2 phenotypes in patients with *GNAO1* encephalopathy is striking. What may account for this phenotypic variability?

In this issue of *Neurology*®, Feng et al.[4] report that the predominant movement disorder phenotype of *GNAO1* encephalopathy is associated with gain-of-function mutations, while epileptic encephalopathy is associated with loss-of-function mutations. $G\alpha_o$ proteins relay information from neurotransmitter receptors and subsequently activate downstream signaling cascades. The specific functional measure chosen by the authors was the ability of each mutant $G\alpha_o$ protein to inhibit intracellular cyclic AMP (cAMP) production upon binding of an agonist to the α_{2A} adrenergic receptor. The authors studied 15 different de novo mutations from 25 previously reported patients with *GNAO1* encephalopathy. The recurrent p.E246K mutation that accounts for 5 of the 11 patients with movement disorders resulted in a clear gain of function. In contrast, 6 mutations previously identified in patients with early infantile epileptic encephalopathy caused a complete loss of function.

Functional studies for most genes implicated in neurodevelopmental disorders are difficult. This may be due to the complexity of functional assays, as in the case of ion channels such as *SCN1A*, *SCN2A*, *SCN8A*, *KCNQ2*, or *KCNT1*.[5] Alternatively, functional studies to assess altered protein function may not be available because the critical pathways are incompletely understood, as with *STXBP1*,[6] *FOXG1*,[7] or *CDKL5*.[8,9] Given this complexity, the findings of Feng et al.[4] provide an interesting illustration of how genotypes can be correlated with phenotypes in a specific neurogenetic disorder using a relatively simply model system.

There are some limitations in the study by Feng et al.[4] First, the clinical phenotypes in *GNAO1* encephalopathy may not be as distinct as postulated by the authors. In fact, some patients with *GNAO1* encephalopathy experience both movement disorders and epilepsy. In addition, not all patients were followed over time. Therefore, the spectrum of movement disorders in patients who initially present with EIEE may not be fully appreciated. Second, the results by Feng et al.[4] indicate that the biology of *GNAO1* encephalopathy may not be fully captured in their experimental assay. For example, the recurrent p.R209G/H/C mutation that was found in 6 patients with movement disorder was associated with normal $G\alpha_o$ function. This suggests that assessment of cAMP inhibition after α_{2A} adrenergic receptor stimulation may be an imperfect tool to assess the functional consequences of disease-causing *GNAO1* mutations. This limitation, which is fully recognized by the authors, is a call to action to look at the effect of *GNAO1* in other biological pathways.

How does a gain of function result in a severe movement disorder while a loss of function results in severe epileptic encephalopathy? The current study suggests that a comprehensive framework for the role of $G\alpha_o$ function in the setting of neurologic disorders is critical, but still missing. $G\alpha_o$, one of the most abundant proteins in the CNS, which accounts for 1% of brain membrane protein alone, likely mediates signaling of different receptor types in cortical and subcortical structures. One testable hypothesis is that these distinct signaling cascades are susceptible to gain vs loss of functions to different degrees. An alternative hypothesis is that the gain-of-function mutations disrupt $G\alpha_o$ function by a mechanism that is unrelated to cAMP signaling.

With regard to therapeutic approaches, the study by Feng et al.[4] suggests that there are no one-size-fits-all

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precision medicine approaches for *GNAO1* encephalopathy. Future treatment strategies aimed at restoring altered $G\alpha_o$ function will need to take the functional consequences of specific *GNAO1* mutations into account.

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