Phenotype–genotype complexities: opening DOORS

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See Articles page 44

The escalating pace of molecular genetic discoveries in neurological diseases is repeatedly providing surprises that challenge our ability to match phenotype and genotype. With the current transition of whole-exome sequencing from the laboratory to clinical use, the ability to understand and interpret molecular-level data becomes ever more important.[1] The classic view of one gene encoding one protein, with disruption resulting in one disease, is rooted in Archibald Garrod's remarkable insights into inborn errors of metabolism more than 100 years ago. This simplistic view now seems to be in doubt for many genes.

In *The Lancet Neurology*, Philippe Campeau and colleagues[2] show that, in about half of affected people from the 26 families studied, DOORS syndrome is due to a mutation in the gene *TBC1D24*. DOORS, a rare autosomal recessive disorder, gets its name from an acronym of its five main features—deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures.[3,4] Campeau and colleagues' findings[2] draw attention to several important issues.

First, with the widespread availability of whole-exome sequencing technology, novel findings, or discoveries, are now easier to come accross, even in small series or single case studies. Some of these findings might be false positives, but in Campeau and colleagues' report, robust inferences about the genetics of DOORS syndrome can be made because the investigators identified *TBC1D24* mutations in a large proportion of affected individuals in a unique, large international cohort of patients with this rare disorder.

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Second, even rare, distinctive, and multisystem disorders can be genetically heterogeneous. In Campeau and colleagues' study,[2] 18 families had individuals with all five main features of DOORS—in only nine of these families was the *TBC1D24* mutation detected, leaving 17 families (including the eight who had an individual with fewer than five features) with the cause for their DOORS undetermined. Genetic heterogeneity is emerging as the rule in many neurological disorders that seem otherwise clinically homogeneous.

Third, pleiotropy, in which the same or different mutations in a gene can have different clinical manifestations, provides a big challenge to understanding mechanisms and to the use of exome-sequence data in diagnosis and prognosis.[5] Recessive mutations of *TBC1D24* not only affect normal development of nails, bone, and brain in DOORS syndrome, but also cause a large array of other neurological phenotypes. These phenotypes include mild infantile-onset myoclonic epilepsy with normal intellect and neuroimaging,[6] a more severe syndrome with focal epilepsy, cognitive impairment, and cerebro-cerebellar malformations,[7,8] a severe infantile-onset myoclonic epilepsy with dementia, progressive cerebral atrophy and childhood death,[9] and epilepsy in infancy with migrating focal seizures.[10] In these other *TBC1D24*-associated syndromes, the investigators did not detect deafness or bone or nail abnormalities. Epilepsy in infancy with migrating focal seizures is more often due to mutation of the potassium channel gene *KCNT1*,[11] another example of genetic heterogeneity.

The molecular function of TBC1D24 protein has begun to emerge over the past 4 years. Our group[7] and Falace and colleagues,[6] using different in-vitro assays, have shown that overexpression of TBC1D24 protein in primary mouse neurons directly affects neurite length and branching[6,7] as well as axonal arborisation and specification.[7] TBC1D24 interacts with Arf6, one of a Ras-related family of small GTPases,[6] which, among other functions, is involved in the regulation of exocytosis and endocytosis dynamics and neuronal cell polarity,[12] providing an attractive molecular mechanism for the seizures and intellectual disability seen in most

TBC1D24-associated phenotypes, including DOORS. Campeau and colleagues[2] also show that the crucial function of TBC1D24 extends beyond neuronal cells, to chondrocytes and bone. Why only some *TBC1D24* mutations are associated with a chondrocyte and bone phenotype is unknown.

The underlying cellular and molecular mechanism for the growing number of TBC1D24-associated phenotypes is far from clear. Whether the explanation is in the *TBC1D24* mutations themselves, *TBC1D24*-associated proteins and pathways, or precise timing of *TBC1D24* function during development has not been established. The framework for understanding phenotype–genotype correlation is more complicated than was envisaged by Garrod and his early successors. Elucidation of this association will be crucial for deeper understanding in the laboratory and the clinic, and for the development of new treatments. In view of what is known so far about *TBC1D24*-mutation pleiotropy, studies such as that of Campeau and colleagues[2] will provide new opportunities toward achieving this goal.

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