To an increasing extent, the desire to catalog and categorize neurologic disorders based on genotype–phenotype correlations is challenged by frequent departures from the syndromic categorizations that were commonplace in the pregenomic era. This challenge is not limited to the recent striking revelations concerning diseases attributable to noncoding, nonconventional mutations, such as repeat expansions in C9ORF72. There are abundant examples of conventional mutations, identified using nonbiased, whole-exome sequencing, that lead to unanticipated phenotypes in the world of hereditary motor system disorders. The report by Pfeffer et al. further the supports the idea that, as targeted sequencing based on clinical phenotype moves toward nonbiased sequencing, we must be prepared to expect surprises that link genetic abnormalities to unanticipated clinical syndromes.

In this study, the authors identified previously described mutations in the gene responsible for spastic paraplegia type 7 (SPG7) in 2 patients presenting with the predominant finding of cerebellar ataxia, although in follow-up examinations these 2 patients and their affected siblings had evidence of pyramidal tract involvement. In a prospective study, the authors then identified SPG7 mutations in 13 of 70 patients who presented with complaints and findings of ataxia, most of whom had cerebellar atrophy documented by MRI scan. Each of them had at least one known pathogenic mutation, p.Ala510Val, at one allele and the same or other mutations at the other allele. Thus, the high frequency of SPG7 mutations in undiagnosed ataxia is partially from the low frequency polymorphism p.Ala510Val (0.346%) in persons of European descent. All these patients additionally manifested signs of pyramidal involvement such as hypertonia, spasticity, or extensor plantar responses, but the cerebellar involvement initially pointed toward the recognized causes of cerebellar degeneration. The presence of cerebellar involvement occurs in several other kindreds with SPG7, resulting in its classification as a form of complicated spastic paraparesis, but until now cases had not been recruited based on the predominance of cerebellar findings. These authors also recently reported that mutations in the SPG7 gene are a cause of chronic progressive external ophthalmoplegia. Most of these patients also showed ataxia. Thus, a gene originally identified as one responsible for progressive spastic paraparesis can also lead to and present with progressive cerebellar disease or progressive external ophthalmoplegia.

Among the growing list of genetic forms of hereditary spastic paraparesis, evidence of cerebellar involvement is common, although often present in combination with other neurologic findings. Of the 48 other genetically defined subtypes of SPG, 16 (3 autosomal dominant, 13 autosomal recessive) have been associated with cerebellar findings or dysarthria, or both. The converse is also true. Corticospinal tract involvement occurs in many genetic subtypes of hereditary ataxia, including SCA1, SCA3, SCA7, SCA8, SCA17, SCA28, Friedreich ataxia, autosomal recessive spastic ataxia of Charlevoix-Saguenay, and X-linked spastic ataxia with sideroblastic anemia, where spasticity and extensor plantar responses can be very prominent or even the presenting features. Although differences from the expected phenotype can sometimes be attributed to distinct alleles (including loss vs gain of function) or repeat expansion sizes, in other cases the correlation is not so obvious. This argues against the concept that one day there will be easily identifiable cell-specific vulnerabilities that will point to cell-type specific disease pathways.

These findings have several important implications for diagnosis and the future of therapy for these diseases. First, the blurring of the boundaries between different neurologic syndromes attributed to mutations in the same gene indicates the importance of thinking diagnostically about more diverse genetic etiologies for a given syndrome.

Second, this justifies the transition to genetic diagnosis by exome sequencing, rather than by disease-specific genetic panels, and compels consideration of identified variants for a broader set of candidate genes. Diagnosis of neurologic disease will clearly be facilitated, and more exceptions discovered, by this technology.

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Third, these observations have important implications for the understanding of the pathogenesis of neurologic disease, broadening, for example, the list of genetic mechanisms known to give rise to cerebellar and presumably Purkinje cell degeneration. While seeming to be of endless complexity, the application of newer disciplines such as systems biology will inevitably lead to a deeper understanding of selective neuronal vulnerability and to new insights for therapies that focus on disturbances in molecular rather than cellular pathways.

Finally, with the emergence of other technologies, the concern arises that the acuity of neurologic skills and reasoning will suffer as a result of the heavy reliance on genetic testing. The compensation will be increased understanding of disease pathogenesis as the pieces to the puzzle of human disease continue to be filled in.

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REFERENCES