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GENETICS

# Exome sequencing sheds light on hereditary spastic paraplegia

New results published in *Science* describe how whole-exome sequencing, combined with interaction network analysis, can not only elucidate novel genes linked to hereditary spastic paraplegia (HSP), but also provide a framework for validation of further candidate genes linked to this disease.

HSP, also known as corticospinal motor neuron disease, is a genetically heterogeneous neurodegenerative disorder that displays several distinct modes of inheritance. Although 22 HSP disease genes are already known, the genetic basis of HSP cannot be established in most patients.

Novarino and colleagues conducted whole-exome sequencing of 93 individuals from 55 families affected by autosomal recessive HSP from countries throughout the Middle East, where this disorder is particularly prevalent, perhaps owing to increased familial consanguinity. The investigators found 15 novel candidate genes that had not previously been linked to HSP.

"For about half of the newly identified genes, we found two or more families with a mutation," notes group leader Joseph Gleeson, which provided internal validation of these HSP mutations. A further five genes were validated by genotyping an independent cohort of 200 patients with HSP. The remaining genes were partially validated in zebrafish knockdown models, which demonstrated phenotypes reminiscent of HSP.

The investigators also generated an HSP-specific 'interactome' by extracting all known and novel HSP candidate genes and proteins, along with those known to interact directly with them, from the total human gene and protein interaction network. The resulting subnetwork was highly interconnected, supporting the concept that diseases caused by

Courtesy of Evgeny Onutchin, Buryat Studio.

a wide range of individually rare mutations involve disruption of a few key biological processes—in the case of HSP, cellular transport, nucleotide metabolism, synapse formation and axon development.

Moreover, when the authors compared interaction networks of genes affected in HSP to similar networks generated by other disorders, they discovered significant overlap. "Our network analysis suggests that HSP is more highly connected to other neurodegenerative diseases—specifically Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis—than to other neurological diseases such as epilepsy, and non-neurological diseases," says Gleeson, "and this suggests that neurons display particular vulnerabilities across the neurodegenerative spectrum."

Although these results have clear implications for the diagnosis and treatment of HSP, the lasting legacy of this investigation might actually arise from the methodology itself. "We plan to apply the same exome sequencing and network analysis approach to other neurological disorders," says Gleeson. "We hope that this genetic approach to neurological disease will change the way that neurologists practice."

***Alex Chase***

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