Mutational burden analysis of interaction networks in inherited neuropathies

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Abstract

Inherited axonopathies, such as hereditary spastic paraplegias and inherited peripheral neuropathies are clinically and genetically heterogeneous diseases. Together, more than 150 genes have been described to cause axonopathies in a monogenic fashion; yet, there are still between 40-60% of patients without an overt mutation in any of these genes. This argues for the existence of additional disease related alleles and new disease genes. Given the rarity of large families new methods are required to identify such genetic factors. With exomes and genomes more widely available an approach known as mutational burden analysis becomes feasible in these rare disorders. We have performed a pilot mutational burden analysis study on ~400 peripheral neuropathy patients and ~900 controls. All individuals had whole exomes available. Extensive quality controls, including missingness of sequence coverage, ancestry matching, and relationship studies, left us with ~1200 individuals for the final statistical analysis using the C-alpha method. We identified three novel candidate genes that crossed the genome wide significance value for multiple correction. Assuringly, we also re-discovered a number of known Mendelian peripheral neuropathy genes. We are currently evaluating whether these novel genes are connected with known CMT gene networks. After this demonstration project succedeed, a similar study is currently planned for hereditary spastic paraplegia.