

PRIORITIZATION OF RESULTS FROM WHOLE EXOME SEQUENCING IN FAMILIAL INTRACRANIAL ANEURYSM

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Whole exome sequencing (WES) is an innovative approach to identifying rare variants associated with disease; however, reducing the large number of variants to a useful set of candidate genes is challenging. We developed a ranking system utilizing data from a previous genome-wide linkage analysis and various bioinformatics databases to prioritize the results of WES from families having multiple members with intracranial aneurysms.

WES was performed in 35 affected individuals and 10 unaffected individuals across 7 families. All samples were genotyped (Illumina® OmniExpress) and sequenced (Agilent© SureSelect™ 50Mb Human All Exon Kit). Linkage analysis (Illumina 6K) was previously performed using autosomal dominant/recessive modes of inheritance.

Application of quality filters resulted in 91,659 single nucleotide variants (SNVs). Nonsynonymous SNVs within an exon having an allele frequency of <3% were retained. Further filtering was performed based on Mendelian inheritance (autosomal dominant or recessive). A ranking system prioritized retained variants based on the inheritance pattern specific to each family, occurrence in multiple families, relation to pathways and genes of interest, degree of penetrance, presence within a linkage peak, and whether the resultant proteins were predicted to be deleterious. Out of a 9-point score, 292 variants in 190 genes received scores of at least 5. Of these, 14 variants in 10 genes met the majority of prioritization criteria by achieving scores of over 7.

While several WES studies have been successful at identifying genes important to rare diseases, few have examined how to produce a list of candidate genes contributing to a complex disease from WES data. We show that a ranking system that combines WES with bioinformatics resources and linkage data is a powerful approach to prioritize candidate genes for a complex disease like familial intracranial aneurysms. Subsequent studies are required to validate the utility of this approach.

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