

The Weighted-Sum Method: Identifying rare disease-associated mutations

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Abstract

Thinking about deep resequencing: are we able to benefit from this new source of data? Human resequencing studies have shown that genetic heterogeneity is a probable scenario, where multiple rare mutations altogether explains a large part of the individuals affected by a disease. Along this line, the weighted-sum method is designed. It jointly analyse groups of mutations in order to test for groupwise association with disease status. For example, a group of mutations may result from resequencing a gene. We compare the proposed weighted-sum method to alternative methods and show that it is powerful for identifying disease-associated genes, both on simulated and Encode data. Using the weighted-sum method, a resequencing study can identify a disease-associated gene with an overall population attributable risk (PAR) of 2%, even when each individual mutation has much lower PAR, using 1,000 to 7,000 affected and unaffected individuals, depending on the underlying genetic model. This demonstrates that resequencing studies can identify important genetic associations, provided that specialised analysis methods, such as the weighted-sum method, are used.

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