Whole-Exome Sequencing of 2,000 Danish Individuals and the Role of Rare Coding Variants in Type 2 Diabetes

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It has been hypothesized that, in aggregate, rare variants in coding regions of genes explain a substantial fraction of the heritability of common diseases. We sequenced the exomes of 1,000 Danish cases with common forms of type 2 diabetes (including body mass index $> 27.5$ kg/m$^2$ and hypertension) and 1,000 healthy controls to an average depth of $56\times$. Our simulations suggest that our study had the statistical power to detect at least one causal gene (a gene containing causal mutations) if the heritability of these common diseases was explained by rare variants in the coding regions of a limited number of genes. We applied a series of gene-based tests to detect such susceptibility genes. However, no gene showed a significant association with disease risk after we corrected for the number of genes analyzed. Thus, we could reject a model for the genetic architecture of type 2 diabetes where rare nonsynonymous variants clustered in a modest number of genes (fewer than 20) are responsible for the majority of disease risk.

General information
Publication status: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of California, BGI-Shenzhen, Aarhus University, University of Southern Denmark, University of Copenhagen
Pages: 1072–1086
Publication date: 2013
Peer-reviewed: Yes

Publication information
Journal: American Journal of Human Genetics
Volume: 93
Issue number: 6
ISSN (Print): 0002-9297
Ratings:
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 9.58 SJR 7.863 SNIP 3.01
Web of Science (2013): Impact factor 10.987
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Original language: English
DOIs:
10.1016/j.ajhg.2013.11.005
Source: dtu
Source ID: u::9738
Research output: Contribution to journal › Journal article – Annual report year: 2013 › Research › peer-review