Genome Medicine

RESEARCH Open Access

Whole-genome DNA/RNA sequencing identifies truncating mutations in *RBCK1* in a novel Mendelian disease with neuromuscular and cardiac involvement

Kai Wang[1,2*], Cecilia Kim[2], Jonathan Bradfield[2], Yunfei Guo[1], Elina Toskala[2], Frederick G Otieno[2], Cuiping Hou[2], Kelly Thomas[2], Christopher Cardinale[2], Gholson J Lyon[2,3], Ryan Golhar[2] and Hakon Hakonarson[2,4*]

Abstract

Background: Whole-exome sequencing has identified the causes of several Mendelian diseases by analyzing multiple unrelated cases, but it is more challenging to resolve the cause of extremely rare and suspected Mendelian diseases from individual families. We identified a family quartet with two children, both affected with a previously unreported disease, characterized by progressive muscular weakness and cardiomyopathy, with normal intelligence. During the course of the study, we identified one additional unrelated patient with a comparable phenotype.

Methods: We performed whole-genome sequencing (Complete Genomics platform), whole-exome sequencing (Agilent SureSelect exon capture and Illumina Genome Analyzer II platform), SNP genotyping (Illumina HumanHap550 SNP array) and Sanger sequencing on blood samples, as well as RNA-Seq (Illumina HiSeq platform) on transformed lymphoblastoid cell lines.

Results: From whole-genome sequence data, we identified RBCK1, a gene encoding an E3 ubiquitin-protein ligase, as the most likely candidate gene, with two protein-truncating mutations in probands in the first family. However, exome data failed to nominate RBCK1 as a candidate gene, due to poor regional coverage. Sanger sequencing identified a private homozygous splice variant in RBCK1 in the proband in the second family, yet SNP genotyping revealed a 1.2Mb copy-neutral region of homozygosity covering RBCK1. RNA-Seq confirmed aberrant splicing of RBCK1 transcripts, resulting in truncated protein products.

Conclusions: While the exact mechanism by which these mutations cause disease is unknown, our study represents an example of how the combined use of whole-genome DNA and RNA sequencing can identify a disease-predisposing gene for a novel and extremely rare Mendelian disease.

Background

Over 5,500 confirmed Mendelian diseases have been described in the Online Mendelian Inheritance in Man (OMIM) database as of June 2013, but a third of them do not have a known molecular basis. With the rapid development and deployment of next-generation sequencing techniques, this situation is changing rapidly [1,2]. Over the past a few years, exome sequencing has been successfully used to identify candidate predisposing genes for multiple Mendelian diseases, and it is likely that this technique will impact clinical medicine in the relatively near future [3,4]. However, we also note two important points from recently published studies. First, the vast majority of Mendelian sequencing studies used exome sequencing rather than whole-genome sequencing. This is due to several reasons, such as the lower cost of exome sequencing, the assumption that Mendelian diseases are more likely to be caused by mutations at exons than non-coding regions, and the concern that too much

* Correspondence: kaiwang@usc.edu; hakonarson@email.chop.edu
[1]Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, 1501 San Pablo St, Los Angeles, CA 90089, USA
[2]Center for Applied Genomics, Children's Hospital of Philadelphia, 3615 Civic Center Blvd, Philadelphia, PA 19104, USA
Full list of author information is available at the end of the article