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Homozygous loss-of-function mutation causes the lethal disorder mitogenic cardiomyopathy in two siblings

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Introduction: Two siblings from consanguineous parents of Turkish descent presented with isolated dilated cardiomyopathy, leading to early death in infancy. The diagnosis of an extremely rare and lethal disorder, mitogenic cardiomyopathy, was made histologically.
Methods:Genomewide parametric linkage analysis was performed, SNP typing platform was used in a recessive model. Genotyping was done in parents and both the unaffected and affected siblings. Exome sequencing analysis was performed. Data analysis was done using commercial and in-house developed software. Only variants in genes from the linkage regions were retained. All homozygous calls were excluded in the parents and the unaffected sibling, reference calls were excluded in the affected sibling. Only exonic and splicing variants were included, synonymous variants were excluded. Variants occurring with a frequency of <1% in the 1000 genomes project or with an unknown frequency were included.
Results:Linkage analysis identified 8 regions. After variant filtering of the exome sequences, 6 candidate genes were identified in the linkage regions with homozygous mutations in the patient, inherited from both parents, and for which the unaffected sibling is heterozygous or reference. This gene list was manually curated using functional data and genotype-phenotype correlations. We identified a deleterious mutation in the ALMS1 gene as the most likely cause. Results were confirmed by Sanger sequencing. The two affected siblings are homozygous for a frameshift deletion of one basepair in the ALMS1 gene. This is predicted to cause a premature stop at position 5 downstream. The unaffected sister and parents are heterozygotes.
Conclusions: Linkage analysis combined with exome sequencing identified a homozygous deleterious mutation in the ALMS1 gene as the cause of this phenotype. Alström syndrome is characterized by a typically transient dilating cardiomyopathy in infancy, suggesting that mitogenic cardiomyopathy represents the extreme phenotype, resulting in demise before the other clinical symptoms become evident. This observation further illustrates the role of ALMS1 and cell cycle regulation. Reaching a genetic diagnosis in rare disorders remains a challenge. We illustrate that even in a single family with only two affected individuals, the identification of the underlying defect is feasible, using a combination of the sophisticated genetic tools.