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Biallelic Truncating Mutations in ALPK3 Cause Severe Pediatric Cardiomyopathy.

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Abstract: BACKGROUND: Cardiomyopathies are usually inherited and predominantly affect adults, but they can also present in childhood. Although our understanding of the molecular basis of pediatric cardiomyopathy has improved, the underlying mechanism remains elusive in a substantial proportion of cases. OBJECTIVES: This study aimed to identify new genes involved in pediatric cardiomyopathy. METHODS: The authors performed homozygosity mapping and whole-exome sequencing in 2 consanguineous families with idiopathic pediatric cardiomyopathy. Sixty unrelated patients with pediatric cardiomyopathy were subsequently screened for mutations in a candidate gene. First-degree relatives were submitted to cardiac screening and cascade genetic testing. Myocardial samples from 2 patients were processed for histological and immunohistochemical studies. RESULTS: We identified 5 patients from 3 unrelated families with pediatric cardiomyopathy caused by homozygous truncating mutations in ALPK3, a gene encoding a nuclear kinase that plays an essential role in early differentiation of cardiomyocytes. All patients with biallelic mutations presented with severe hypertrophic and/or dilated cardiomyopathy in utero, at birth, or in early childhood. Three patients died from heart failure within the first week of life. Moreover, 2 of 10 (20%) heterozygous family members showed hypertrophic cardiomyopathy with an atypical distribution of hypertrophy. Deficiency of alpha-kinase 3 has previously been associated with features of both hypertrophic and dilated cardiomyopathy in mice. Consistent with studies in knockout mice, we provide microscopic evidence for intercalated disc remodeling. CONCLUSIONS: Biallelic truncating mutations in the newly identified gene ALPK3 give rise to severe, early-onset cardiomyopathy in humans. Our findings highlight the importance of transcription factor pathways in the molecular mechanisms underlying human cardiomyopathies.