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RESEARCH LETTER

# A Pathogenic Variant in *ALPK3* Is Associated With an Autosomal Dominant Adult-onset Hypertrophic Cardiomyopathy

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The alpha kinase 3 (*ALPK3*, [MIM: 617608]) gene has previously been associated with autosomal recessive pediatric-onset cardiomyopathy.[1–5] Affected individuals develop dilated cardiomyopathy in utero or soon after birth, with subsequent progression to hypertrophic cardiomyopathy (HCM). Most affected individuals die within the first year of life. Among their relatives who were heterozygous for the familial variants in *ALPK3*, 3 of 25 had HCM.[1–5] Whether monoallelic variants in *ALPK3* causes familial HCM has not been established, and there has been no report focusing on the phenotype of monoallelic *ALPK3* variant carriers.

Here, we report a nonconsanguineous Thai family with 18 individuals, 7 of whom are affected with adult-onset HCM (Figure [A]). Affected is defined by the presence of HCM features in echocardiogram or cardiac magnetic resonance imaging. The proband (IV-1) was discovered to have HCM at age 42 from screening echocardiogram. His cardiac magnetic resonance imaging showed mixed apical form of HCM, and ECG showed left ventricular hypertrophy with T-wave inversion in multiple inferior and precordial leads (Figure [B] and [C]). The proband's mother (III-7) presented at age 48 with chest pain and her echocardiogram showed mixed apical HCM. She subsequently developed atrial fibrillation and died at age 68 from heart failure. Microscopic examination of postmortem heart tissue showed marked hypertrophy and cardiomyocyte disarray (Figure [D]). Mixed apical HCM was seen in 5 of the 7 affected individuals, 4 of whom also had right ventricular involvement. The range of maximal left ventricular wall thickness in the affected individuals is 15 to 27 mm. Two members were asymptomatic and underwent echocardiograms either because of abnormal ECG (III-10) or as part of a family screening (V-1). These 2 individuals had left ventricular hypertrophy located more on the septal side of the left ventricle. Atrial fibrillation was diagnosed in 2 individuals, and there was no history of sudden death or left ventricular outflow track obstruction in any of the family members.

DNA samples of 18 individuals (Figure [A]) were sent for whole genome sequencing at Beijing Genomics Institute (Guangdong, China). The heterozygous c.2023delC p.(Gln675Serfs*30) variant in *ALPK3* was identified in all 7 affected and 3 unaffected members, producing a 70% penetrance rate. Sanger sequencing confirmed the findings (Figure [E]). The ages at last follow-up of the 3 unaffected (III-2, III-3, and III-12 in Figure [A]) were 55, 53, and 54, respectively. The c.2023delC variant in *ALPK3* is found in the East Asian population with an allele frequency of ≈0.005% in the genome aggregation database (https://gnomad.broadinstitute.org). It is absent from our in-house database of 2166 Thai individuals. This variant was previously reported in biallelic form in an infant with dilated cardiomyopathy, which later progressed to HCM.[2] Investigation for modifier variants related to HCM in all affected individuals based on genes from the HCM—teen and adult (V2.4) panel from PanelApp (https://panelapp.genomicsengland.co.uk/) did not identify any pathogenic variants; however, 15 rare variants of uncertain significance in 11 genes were identified, none of which were found jointly in the affected individuals.

**Key Words:** atrial fibrillation ■ cardiomyopathy, hypertrophic ■ genetics ■ heart failure ■ whole genome sequencing

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## Nonstandard Abbreviation and Acronyms

| | |
|---|---|
| **AF** | atrial fibrillation |

Our cohort is the first HCM family with an autosomal dominant mode of inheritance involving a monoallelic *ALPK3* variant. Except for mixed apical subtype of HCM and right ventricular involvement, findings which were shared by heterozygous *ALPK3* variant carriers in a previous report,[1] no additional phenotype apart from adult-onset HCM was found in our cohort. This contrasts with pediatric biallelic *ALPK3* variant carriers who have congenital abnormalities in addition to cardiomyopathy.[1–5] Previously reported individuals with monoallelic variants were either asymptomatic[5] or had maintained status quo[1] but in our cohort, complications such as heart failure and atrial fibrillation could develop.

Our report indicates that a monoallelic *ALPK3* variant can cause adult-onset HCM with a penetrance of 70%. We suggest for monoallelic loss of function variants in *ALPK3* be considered as disease-causing for adult-onset HCM and for *ALPK3* to be included in adult-onset HCM gene panels.

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was approved by Chulalongkorn University's institutional review committee and the subjects gave informed consent.

## ARTICLE INFORMATION

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### Disclosures

None.

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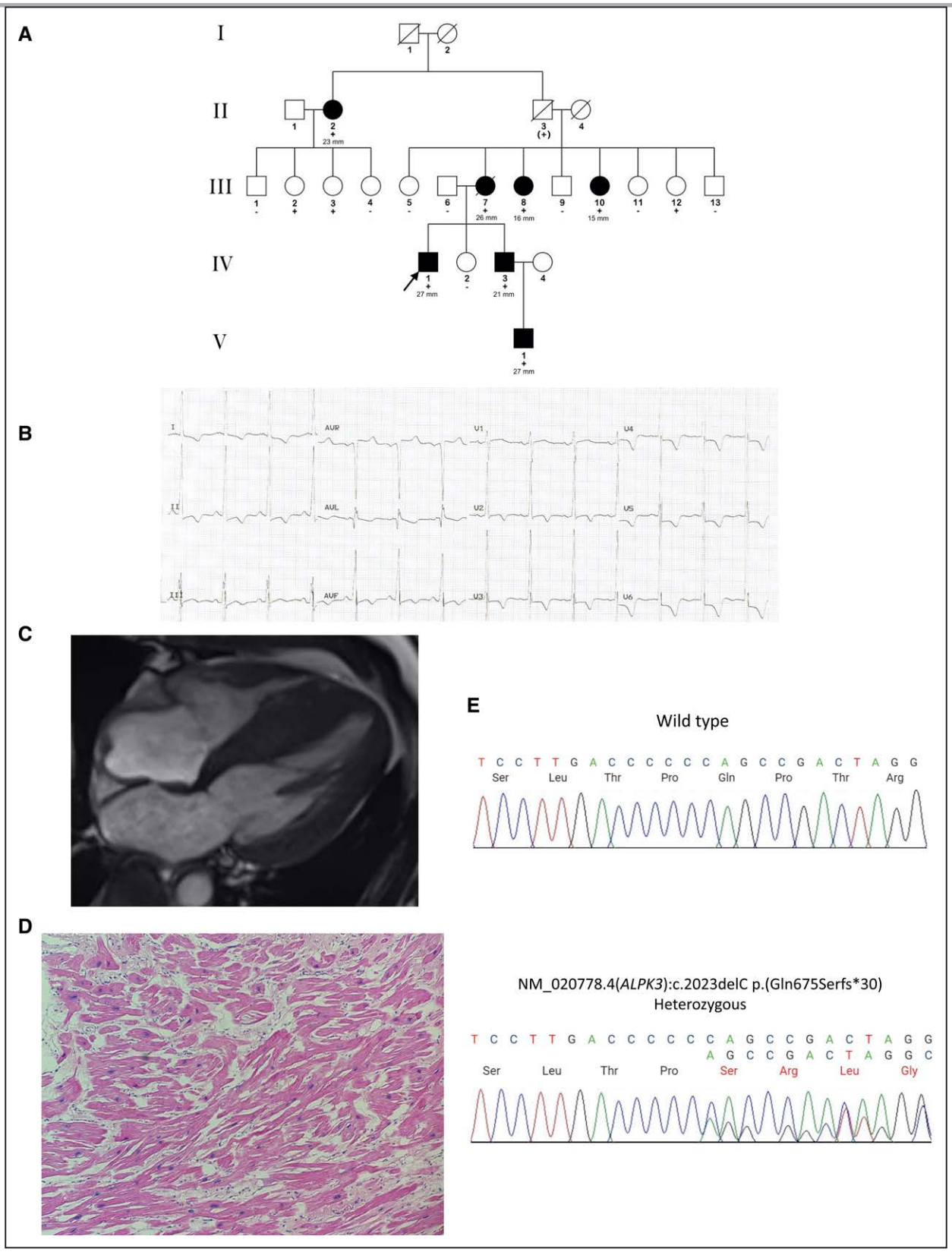


**Figure. Clinical, pathological, and molecular features of the family.**
**A**, Pedigree of the family. Filled symbols indicate individuals affected with hypertrophic cardiomyopathy. Arrow indicates the proband. Presence and absence of the *ALPK3* variant is indicated by the symbols + and −, respectively. (+) denotes an obligate carrier. The maximal left ventricular wall thickness for affected individuals is indicated below their symbols. **B**, ECG of the proband. **C**, Cardiac magnetic resonance imaging of the proband showing biventricular hypertrophy with relative sparing of the basal segment. **D**, Microscopic H&E image taken from the left ventricular septum mid-wall of III-7's heart, showing cardiomyocyte disarray. **E**, Sanger sequencing results for the wild-type genotype and the heterozygous *ALPK3* variant.