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Clinical Research

Genotypes and Phenotypes of Chinese Pediatric Patients With Idiopathic and Heritable Pulmonary Arterial Hypertension—A Single-Center Study

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ABSTRACT

Background: The relationship between clinical outcomes and gene mutations in Chinese pediatric patients with idiopathic and heritable pulmonary arterial hypertension (PAH) is unclear.

Methods: We retrospectively studied the clinical characteristics and outcomes of pediatric patients who visited Beijing Anzhen Hospital from September 2008 to December 2018.

Results: Eighty-two pediatric patients were included. Forty-two gene mutations were identified in 41 patients (50%), including 25 mutations in BMPR2, 5 mutations in ACVRL1, 3 mutations each in ABCA3 and NOTCH3, 2 mutations each in KCNK3 and HTR2B, 1 mutation in ENG, and 1 mutation in EIF2AK4. The mean age at diagnosis of PAH was 86.4 ± 55.1 months. Forty-eight patients (twenty-eight mutation

RÉSUMÉ

Contexte : La relation entre les résultats cliniques et les mutations génétiques chez les enfants chinois atteints d'hypertension artérielle pulmonaire (HTAP) idiopathique et héréditaire n'est pas bien comprise.

Méthodologie : Nous avons examiné rétrospectivement les caractéristiques et les résultats cliniques d'enfants qui ont visité l'hôpital Anzhen de Beijing entre septembre 2008 et décembre 2018.

Résultats : Au total, 82 enfants ont été admis dans l'étude. Quarante-deux mutations génétiques ont été détectées chez 41 patients (50 %), soit 25 mutations de *BMPR2*, 5 mutations de *ACVRL1*, 3 mutations chacun de *ABCA3* et de *NOTCH3*, 2 mutations chacun de *KCNK3* et de *HTR2B*, 1 mutation de *ENG* et 1 mutation de *EIF2AK4*. L'âge moyen au diagnostic de HTAP s'établissait à 86,4 ± 55,1 mois. Quarante-huit

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vessel disease, which can ultimately lead to progressive right heart failure and premature death.[1] Idiopathic pulmonary arterial hypertension (IPAH) is a sporadic form of PAH of unknown etiology,[2] although heritable pulmonary arterial hypertension (HPAH) occurs in familial aggregates. If left untreated, these patients often face rapid disease progression, with a median survival of 2.8 years in adults and 10 months in children.[3,4] Despite recent advances in diagnostic and therapeutic measures, the exact mechanisms underlying IPAH and HPAH remain elusive.

Genetic studies have indicated that mutations of some genes involved in the transforming growth factor β pathway are associated with HPAH, including BMPR2 (bone morphogenetic protein receptor type II), ACVRL1 (activin receptor–like kinase 1), ENG (endoglin), and the SMAD family.[5-8] The development of gene detection technology has helped to identify additional genes associated with IPAH, including KCNK3 (potassium two-pore-domain channel subfamily K member 3), CAV1 (caveolin 1), NOTCH3, bone morphogenetic protein receptor type 1B (BMPR1B), EDN1 (endothelin 1), TBX4 (T-box 4), TRPC6 (transient receptor potential cation channel, subfamily C, member 6), and SERPINE1 (serpin family E member 1).[8,9] Pediatric patients are more prone to be affected by IPAH and HPAH,[10,11] indicating that genetic factors play a larger role in the pathogenesis of pediatric PAH.

In addition to the pathogenic role in PAH, gene mutations have previously been linked to worse clinical outcomes in

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carriers) underwent cardiac catheterization examinations, with acute vasodilator testing performed simultaneously. Results showed that mutation carriers demonstrated a higher pulmonary vascular resistance index ($P = 0.037$). Patients with gene mutations responded poorly to vasodilators ($P = 0.001$). The 1-, 2-, and 3-year survival rates of mutation noncarriers were 95.1%, 87.8%, and 82.5% respectively; while for mutation carriers, the proportions were 86.6% ($P = 0.216$), 63.8% ($P = 0.021$), and 52.2% ($P = 0.010$), respectively. Cardiac index was an independent predictor of death ($P = 0.005$; odds ratio [OR] 2.16, 95% confidence interval [CI] 1.258-3.704), as well as RAP ($P = 0.01$; OR 1.26, 95% CI 1.056-1.503).

Conclusions: In our cohort of Chinese pediatric patients, those with an identified gene mutation demonstrated worse clinical outcomes. Therefore, early gene screening for pediatric patients with idiopathic and heritable PAH is recommended, and more aggressive treatment for mutation carriers may be advisable.

patients (28 porteurs de mutations) ont subi un examen par cathétérisme cardiaque, pendant lequel un test de vasodilatation aiguë était réalisé simultanément. Les résultats révèlent un index de résistance vasculaire pulmonaire plus élevé chez les porteurs de mutation ($p = 0,037$). Les patients porteurs d'une mutation génétique ne répondaient pas bien aux vasodilatateurs ($p = 0,001$). Les taux de survie à 1 an, 2 ans et 3 ans chez les patients non porteurs de mutation s'établissaient respectivement à 95,1 %, 87,8 % et 82,5 %; chez les porteurs de mutation, les taux étaient de 86,6 % ($p = 0,216$), 63,8 % ($p = 0,021$) et 52,2 % ($p = 0,010$), respectivement. L'index cardiaque était un facteur de prédiction indépendant de décès ($p = 0,005$; rapport de cotes [RC] de 2,16; intervalle de confiance [IC] à 95 % : de 1,258 à 3,704), ainsi que de pression auriculaire droite ($p = 0,01$; RC de 1,26; IC à 95 % : de 1,056 à 1,503).

Conclusions : Dans la cohorte d'enfants chinois étudiée, les résultats cliniques étaient moins bons chez les porteurs d'une mutation génétique. Un dépistage génétique précoce est donc recommandé chez les enfants atteints de HTAP idiopathique et héréditaire; un traitement plus énergique pourrait aussi être indiqué chez les porteurs de mutation.

adult patients.[12,13] An international multicenter study revealed that pediatric patients with BMPR2 or ACVRL1 mutations had worse prognoses than mutation noncarriers.[14] However, the sample size of the study was relatively small. Thus, there is a dearth of research addressing the relationship between gene mutations and clinical outcomes of pediatric patients with IPAH.

In the present study, we retrospectively studied the clinical characteristics and outcomes of pediatric patients with IPAH and HPAH. We aimed to assess the prevalence of gene mutations in this group of patients and to assess the relationship between genotypes and clinical phenotypes.

Methods

Selection of patients

Eight-two Chinese pediatric patients with IPAH and HPAH who visited Beijing Anzhen Hospital from September 2008 to December 2018 were included in the study. PAH was defined as a mean pulmonary arterial pressure (MPAP) $\geq$ 25 mm Hg, with a pulmonary artery wedge pressure $\leq$ 15 mm Hg and pulmonary vascular resistance $>$ 3 Wood units, as measured by means of cardiac catheterization.[1] Acute pulmonary vasodilation testing (AVT) was performed with the use of inhaled iloprost during cardiac catheterization, and a positive response was defined according to current guidelines as a decrease in MPAP of at least 10 mm Hg to $<$ 40 mm Hg, with a stable cardiac output.[15] For patients who were unable to undergo cardiac catheterization, diagnosis of PAH was made through echocardiography (peak tricuspid regurgitation velocity $>$ 2.8 m/s), in combination with clinical symptoms and other signs of right heart overload. Clinical, functional, and hemodynamic characteristics of patients were collected at the time of diagnosis and during the follow-up period. Study procedures were approved by the Research Ethics Committee of Beijing Anzhen Hospital. Parents or guardians of all patients provided informed consent in accordance with local ethical guidelines.

Genetic studies

Genomic DNAs were isolated from peripheral venous blood. Exon and exon-intron junction sequences of 28 PAH-associated genes (ABCA3, ABCD4, ACVRL1, ARHGAP31, ATP5A1, BMPR2, BOLA3, CAV1, CPS1, DLL4, DOCK6, EIF2AK4, ENG, EOGT, GDF2, HTR2B, KCNK3, KRT18, KRT8, NFU1, PIEZO2, RBPJ, SARS2, SMAD4, SAMD9, THBS1, and TOPBP1; Supplemental Table S1) were enriched with the use of a GenCap custom enrichment kit (MyGenostics), to capture exons of all candidate genes. The enriched libraries were sequenced on an Illumina Hi Seq 2000 sequencer for paired reads of 100 bp in length.[16] Bioinformatics analysis was applied as described previously.[17] Four algorithms (PolyPhen, SIFT, PANTHER, and Pmut) were applied to determine pathogenicity of nonsynonymous variants. Some of the parents/siblings/families of mutation-positive patients were further tested and verified.

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD. Categoric variables were expressed as percentages. Continuous variables were compared by means of independent-sample t tests, and categoric variables by means of chi-square test. Survival analysis was performed with the use of the Kaplan-Meier method to investigate the time from diagnosis to death. Logistic regression analysis was performed to determine factors associated with an increased risk of death. A P value $\leq$ 0.05 was considered to be statistically significant. All analyses were performed in SPSS version 19.0.

Results

Clinical characteristics

Eighty-two unrelated childhood IPAH or HPAH patients (39 female, 47.6%), were included in this study. The mean age at diagnosis of PAH was 86.4 $\pm$ 55.1 months. Thirty-two patients (39.0%) suffered from markedly decreased right

cardiac function (New York Heart Association [NYHA] functional class III-IV). The median plasma BNP concentration was 369.0 (50.9-906.0) pg/mL (normal range 0-100 pg/mL). In total, 42 mutations were identified in 41 patients. These included 25 mutations in BMPR2 (30.5%), 5 in ACVRL1 (6.1%), 3 each in NOTCH3 and ABCA3 (3.7%), 2 each in KCNK3 and HTR2B (2.4%), 1 in ENG (1.2%), and 1 in EIF2AK4 (1.2%; Supplemental Table S2). Missense mutations were the most common mutation type (n = 34; 81.0%), followed by frameshift mutations (n = 4; 9.5%) and splicing mutations (n = 4; 9.5%). One patient carried a heterozygous mutation of both ACVRL1 and EIF2AK4. All other patients carried a single mutation of PAH-related genes. Because some of the patients' family members did not undergo gene testing for various reasons, the specific proportion of HPAH and IPAH was not clear. Available data (n = 38) showed that de novo mutation was identified in only 1 patient, and all of the other patients (n = 37; 97.4%) were found to have inherited from the previous generation. Patients were divided into 2 groups (mutation, nonmutation) and clinical/blood biochemical indexes were compared (Table 1). Forty-eight patients, 28 of them mutation carriers, underwent cardiac catheterization examinations with AVT performed simultaneously (Table 1). Results showed that mutation carriers had higher pulmonary arterial resistance index than noncarriers ($P = 0.037$). In addition, mutation carriers tended to have higher pulmonary arterial pressure, higher right atrial pressure, and a higher ratio of mean pulmonary arterial pressure to mean aortic pressure, although the differences were not statistically significant. AVT was positive in 10 patients, 9 of whom were mutation noncarriers ($P = 0.001$).

Table 1. Clinical and hemodynamic characteristics of patients at diagnosis

Variables	Carriers	Noncarriers	*P* value
Female, n (%)	19 (46.3%)	20 (48.8%)	0.825
Age at diagnosis, months	94.8 ± 52.0	78.0 ± 57.4	0.169
NYHA FC, I-II/III-IV	24/17	26/15	0.651
BNP, pg/mL	377 (53-885)	345 (47-1157)	0.718
UA, μmol/L	429.0 ± 157.6	400.6 ± 153.3	0.434
PASP, mm Hg	97.9 ± 26.9	86.7 ± 30.5	0.182
PADP, mm Hg	56.6 ± 17.9	48.1 ± 20.7	0.137
MPAP, mm Hg	72.3 ± 20.4	62.5 ± 22.4	0.124
RAP, mm Hg	9.5 ± 3.7	7.6 ± 2.6	0.068*
MPAP/AoMP	0.98 ± 0.33	0.80 ± 0.35	0.090
PVRI, WU·m^2	19.9 ± 10.2	13.8 ± 8.5	0.037*
CI, L/min/m^2	3.6 ± 1.4	3.9 ± 1.4	0.429
SvO_2, %	68.5 ± 10.4	68.6 ± 7.5	0.989
AVT	1/20 (4.8%)	9/9 (50.0%)	0.001*

Values are presented as n (%), mean ± SD, or median (range).

AoMP, Aortic mean pressure; AVT, acute pulmonary vasodilation test; BNP, B-type natriuretic peptide; CI, cardiac index; MPAP, mean pulmonary arterial pressure; NYHA FC, New York Heart Association functional class; PADP, pulmonary arterial diastolic pressure; PASP, pulmonary artery systolic pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; UA, uric acid; WU, Wood units.

* $P \leq 0.05$ or trend.

Targeted drug therapy

Although surgical lung transplantation and interventional palliative shunt are options for some patients,[18,19] drug therapies targeting the nitric oxide, endothelin, and prostacyclin pathway are still the most commonly used therapy approach. Seventy-nine patients (96.3%) received targeted drugs for PAH. The utilization of targeted drugs is listed in Table 2. Three patients did not receive PAH therapy, owing to economic reasons, intolerance of drug side-effects, and mild PAH disease with light symptoms. In patients treated with a single drug, endothelin receptor antagonists were the most commonly used. A total of 58.5% of mutation carriers and 56.1% of mutation noncarriers received combination therapy. No differences were found between mutation carriers and noncarriers regarding treatment regimen.

Patient outcomes

The median follow-up time was 32.0 months (16.0-54.0 months). One patient underwent a double lung transplant at the age of 16 years, after 4 sequential years of therapy. Sixteen mutation carriers (39.0%), including 13 BMPR2 mutation carriers, 2 ACVRL1 mutation carriers, and 1 KCNK3 mutation carrier, as well as 7 noncarriers (17.1%) died during the follow-up period. The median survival time for mutation carriers was 53.0 months (range 3-112 months). No differences were observed in age at diagnosis of PAH or age at death between mutation carriers and noncarriers. The 1-, 2-, and 3-year survival rates of mutation noncarriers were 95.1%, 87.8%, and 82.5%, respectively. Conversely, these survival rates for mutation carriers were 86.6% ($P = 0.216$), 63.8% ($P = 0.021$), and 52.2% ($P = 0.010$), respectively (Fig. 1). The clinical and hemodynamic characteristics between the death and survival groups were further compared (Table 3). Patients who died had higher right atrial pressure and lower cardiac index than survivors. Logistic regression analysis showed that cardiac index was an independent predictor of death ($P = 0.005$; odds ratio [OR] 2.16, 95% confidence interval [CI] 1.258-3.704) as well as right atrial pressure ($P = 0.01$; OR = 1.26, 95% CI 1.056-1.503). However, gene mutation, MPAP, and pulmonary vascular resistance index were not significant independent risk factors for mortality.

Table 2. Targeted drug protocols of patients

Protocols	All (n = 82)	Carriers (n = 41)	Noncarriers (n = 41)
None, n (%)	3 (3.7%)	2 (4.9%)	1 (2.4%)
Monotherapy, n (%)	32 (39.0%)	15 (36.6%)	17 (41.5%)
ERAs	23	13	10
PDE-5is	5	2	3
Prostanoids	2	0	2
CCBs	2	0	2
Combination therapy, n (%)	47 (57.3%)	24 (58.5%)	23 (56.1%)
ERAs + PDE-5is	35	18	17
ERAs + prostanoids	5	4	1
PDE-5is + prostanoids	1	0	1
CCBs + prostanoids	1	0	1
ERAs + PDE-5is + prostanoids	5	2	3

CCBs, calcium channel blockers; ERAs, endothelin receptor antagonists; PDE-5is, phosphodiesterase-5 inhibitors.

Discussion

In this study, we retrospectively analyzed the clinical outcomes of Chinese pediatric patients with IPAH/HPAH and

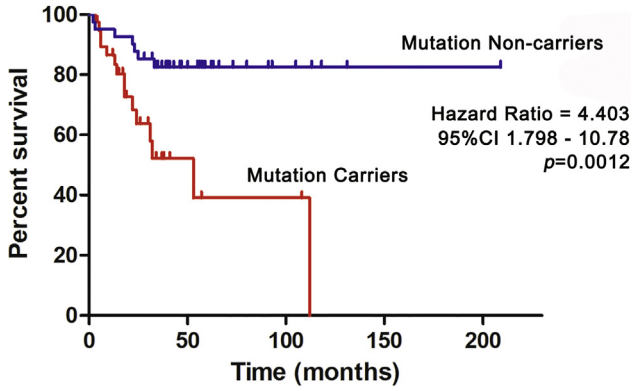

Figure 1. Survival rate of mutation carriers and noncarriers with idiopathic and heritable pulmonary arterial hypertension. The 1-, 2-, and 3-year survival rates of mutation noncarriers versus carriers were 95.1% vs 86.6% ($P = 0.216$), 87.8% vs 63.8% ($P = 0.021$), and 82.5% vs 52.2% ($P = 0.010$).

gene mutations. Previous studies suggested that around 25%-30% of patients diagnosed with IPAH have an underlying genetic cause. In our study, 50% of the patients carried mutations of related genes, which was higher than that reported for European adult and pediatric cohorts,[9,20,21] indicating that genetic factors also play an important role in the mechanism of IPAH in Chinese pediatric patients, even though more genes were included in our screening list.

The first gene proved to be related to PAH, BMPR2, encodes for a transmembrane serine/threonine kinase receptor of the bone morphogenetic protein pathway, which is involved in the regulation of growth and apoptosis of pulmonary smooth muscle cells and pulmonary endothelial cells.[22] Hundreds of BMPR2 mutations have been identified in nearly 70% of HPAH patients and up to 40% of IPAH cases.[12,23] In our study, a BMPR2 mutation was the most common gene mutation, accounting for 30.5% of all patients.

Table 3. Characteristics of dead and surviving patients

Variables	Deaths/LT (n = 24)	Survivors (n = 58)	*P* value
Female, n (%)	8 (33.3%)	31 (53.4%)	0.097
Age at diagnosis, months	94.9 ± 48.4	82.9 ± 57.4	0.375
NYHA FC			0.752
I-II, n (%)		36 (62.1%)	
III-IV, n (%)		22 (37.9%)	
Gene mutation, n (%)	16 (66.7%)	25 (43.1%)	0.052*
BNP, pg/mL	508 (53-1151)	318 (47-869)	0.497
PASP, mm Hg	95.8 ± 13.7	92.4 ± 32.3	0.729
PADP, mm Hg	56.1 ± 12.0	52.0 ± 21.3	0.536
MPAP, mm Hg	70.8 ± 11.6	67.3 ± 24.1	0.640
RAP, mm Hg	11.5 ± 3.8	7.8 ± 2.8	0.001*
PVRI, WU·m^2	22.3 ± 11.1	15.9 ± 9.2	0.060*
CI, L/min/m^2	3.0 ± 1.2	3.9 ± 1.3	0.040*
AVT, n (%)	1/11 (8.3%)	9/27 (25.0%)	0.218
SvO_2, %	65.0 ± 11.9	69.7 ± 8.1	0.145
PAH-targeted drugs, n (%)			0.578
Monotherapy	10 (41.7%)	22 (37.9%)	
Combination therapy	12 (50.0%)	35 (60.3%)	

AVT, acute pulmonary vasodilation test; BNP, B-type natriuretic peptide; CI, cardiac index; LT, lung transplantation; MPAP, mean pulmonary arterial pressure; NYHA FC, New York Heart Association functional class; PADP, pulmonary arterial diastolic pressure; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; WU, Wood units.

*$P \leq 0.05$ or trend.

Mutations of the ACVRL1 or ENG gene result in PAH associated with hereditary hemorrhagic telangiectasia (HHT).[13] Among our 6 patients with ACVRL1 or ENG mutations, only 1 patient had symptoms of skin telangiectasias and recurrent epistaxis, and none of the 5 other patients met the diagnostic criteria for HHT. Because clinical manifestations of HHT develop with increasing age, the majority of ACVRL1 and ENG mutation carriers might not presented with clinical evidence of HHT during childhood.[13] The role of ACVRL1 and ENG mutations in the pathogenesis of PAH requires further exploration, because a large portion of patients who develop severe pulmonary hypertension PAH present with prior clinical manifestations of HHT. Furthermore, 2 ACVRL1 mutation carriers died during the follow-up period, indicating its role in rapid disease progression.

The KCNK3 gene encodes for an outward K^+ channel, and is a member of 2-pore-domain K^+ channels.[24] KCNK3 inhibition participates extensively in the whole spectrum of PAH pathomechanism, from vasoconstriction and vascular cell proliferation to PAH-associated chronic inflammation.[25] NOTCH3 is a transmembrane receptor protein that participates in the modulation of cell proliferation, differentiation, apoptosis, and migration.[26] Mutations in the ABCA3 gene have been reported to result in fatal surfactant deficiency in term newborn infants and chronic interstitial lung disease in older children.[27,28] Compared with studies of BMPR2 and ALK1, studies on the relationships of KCNK3, NOTCH3, and ABCA3 and PAH are relatively few. Therefore, the relationships between these gene mutations and clinical phenotypes need further verification.

Previous studies have suggested that gene mutations are associated with adverse outcomes in patients with IPAH. Sztrymf et al. found that mutation carriers present PAH more than 10 years earlier than noncarriers, with more compromised hemodynamic status and worse prognosis.[12] Similar results were also obtained from studies of pediatric patients with IPAH and HPAH.[14,29] In our study, no obvious age difference was found between mutation carriers and noncarriers. This is likely because our patients were generally younger, and the sample size was relatively small. Mutation carriers presented worse hemodynamic status at diagnosis, and responded poorly to AVT. There were no significant differences between the 2 groups in World Health Organization functional class or blood biochemical indexes. Many of our patients did not come to our center until obvious symptoms of right heart failure occurred, because the clinical symptoms were atypical. Therefore, the baseline blood biochemical indexes and heart function classification may not be enough to assess the whole progression of the disease.

Targeted drugs have benefited patients with pulmonary hypertension.[30,31] Targeted drugs were approved in China starting in the 2000s, with bosentan and iloprost in 2006, ambrisentan in 2011, treprostinil in 2014, and macitentan in 2018. Endothelin receptor antagonists were the most commonly used targeted drugs in our patients, followed by phosphodiesterase inhibitors. Bosentan plus tadalafil was the most commonly used drug combination. The choice of

combination therapy was made according to the severity of disease and the economic condition of the patients. Patients with NYHA functional class III-IV were more likely to be prescribed combination therapy. With the increase of drugs available and health insurance coverage, an increasing number of patients have been prescribed combination therapy. The application of intravenous treprostinil was limited by the price as well as the side-effects of subcutaneous catheterization, and is mainly used in patients with heart function III-IV. In our study, patients with gene mutations responded poorly to AVT, and despite similar baseline clinical characteristics and treatment protocols, mutation carriers had poorer outcomes than noncarriers, suggesting a diminished response to therapy for mutation carriers.

Our results indicate that Chinese pediatric patients with PAH-related gene mutations present with worse prognosis than noncarriers, and the survival rate difference between the 2 groups expanded with the duration of follow-up. The 3-year survival rate of patients with mutations was only 52.2%, which was significantly lower than that of noncarriers (82.5%). In this study, high right atrial pressure and low cardiac index were risk factors of death, which suggests that right ventricular function is the most critical factor influencing the prognosis. Gene mutations were not an independent risk factor of death, despite the striking trend, which is likely due to the relatively small sample size.

Bias may exist because this was a retrospective study from a single center. The sample size of our study is relatively small, and measurement of hemodynamic variables by means of heart catheterization was not acquired for all patients. Furthermore, most deaths occurred at home or in local hospitals, making them difficult to determine and to further analyze the exact causes. Larger sample size, multicenter data, and long-term longitudinal follow-up are needed to better depict the relation between genotypes and phenotypes in patients with IPAH/HPAH.

Conclusions

In conclusion, the survival rates of patients with IPAH and HPAH have improved in China in the modern treatment era. However, in our cohort of Chinese pediatric patients, those with PAH-related gene mutations had a worse prognosis. Early gene screening for pediatric patients with IPAH or HPAH is recommended, and more aggressive treatments for mutation carriers may be advisable.

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Disclosures

The authors have no conicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.07.628.