



Commentary

A novel RIT1 mutation causes deterioration of Noonan syndrome-associated cardiac hypertrophy

Jingjing Cai^{a,b,c,d}, Hongliang Li^{a,b,c,*}^a Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan 430060, China^b Institute of Model Animal of Wuhan University, Wuhan 430072, China^c Basic Medical School, Wuhan University, Wuhan 430071, China^d Department of Cardiology, The Third Xiangya Hospital, Central South University, Changsha 410013, China

Introduction

Noonan syndrome (NS) is an autosomal dominant inherited condition characterized by unusual facial features, short stature, congenital heart disease, bleeding problems, metabolic and endocrine abnormalities, and other problems [1]. An estimated 1 in 1000–2500 live births are affected by various forms of the disease [2]. Multiple genotype-phenotype analyses have revealed numerous gene mutations (*PTPN11*, *SOS1*, *RAF1*, *KRAS*, *BRAF*, *NRAS*, *MAP2K1*, *RIT1*, *SOS2*, *LZTR1*, and *A2ML1*) that result in NS, typically involving hyperactivation of the RAS-MAPK pathway and leading to various developmental disorders. Accumulating knowledge of the genetic etiology and pathophysiology of NS could facilitate individualized disease management and development of specialized pharmacogenetic therapies.

The Ras-MAPK pathway is one of the most well characterized and most complicated pathways involved in physiological processes. The pathway is initiated by binding of extracellular ligands to transmembrane receptors. This allows a small G protein (RAS) to activate the MAPK (e.g., MAP3K, MAP2K, ERK) signaling cascade, which regulates transcription factors and subsequent gene alterations [3]. This signaling pathway transduces signals from the extracellular milieu to the nucleus, where expression of genes important for numerous biological processes, such as cell proliferation and differentiation, metabolic profile alterations, and cell survival can be regulated. When a gene in the pathway is mutated, normal signal transduction is disrupted, which can result in tumors, cardiac abnormalities and metabolic disorders [2,4].

In this article of *EBioMedicine*, Shingo Takahara and colleagues described a novel mutation (A57G) of the *RIT1* gene that disrupts the RAS-MAPK signal transduction pathway and causes NS and its associated hypertrophic cardiomyopathy (HCM) [10]. This group successfully generated a gain-of-function *RIT1* mutant (*RIT1*^{A57G/+}) in a mouse model, that partly recapitulates the phenotypes of NS. Notably, this mutant strain is prone to adrenaline-stimulated cardiac hypertrophy, partly via AKT-mediated signaling. This finding suggests a new mechanism

underlying the pathology of NS patients with an *RIT1* mutation and suggests new options for the treatment of NS-related cardiac hypertrophy.

Up to 85% of NS patients have congenital heart diseases, among which 20% suffer from HCM [1]. The presentation of cardiac hypertrophy can be mild or severe and can be apparent early in life, with more than half of those affected identified by 6 months of age [1,5]. Moreover, 15% of children with NS have severely increased ventricular wall thicknesses, while others have moderate or mild ventricular wall hypertrophy. Due to a more significant left ventricular outflow tract obstruction, congestive heart failure and cardiac mortality are more predominant in young children under 6 months of age than in children with other forms of HCM or NS patients without HCM [6]. Some gene mutations have been reported to increase the risk of HCM in NS patients. *RAF1* gene mutations are commonly diagnosed in patients with HCM (61%). Among the subset of patients with *RAF1* mutations and multiple NS-related lentigenes, approximately 100% have comorbid HCM. Additionally, HCM is more prevalent in patients with *RIT1* (36%), *KRAS* (20%), *BRAF* (23%), *SHOC2* (29.7%), and *SOS2* (28.5%) gene mutations than in those with *PTPN1* (8.5%) mutations [6]. In 2013, Aoki Niihori's group first identified that gain-of-function mutations in *RIT1* cause NS and show a similar biological effect to mutations in other RASopathy-related genes [7]. Currently, 14 amino acid substitutions have been reported as NS-associated *RIT1* alterations, including p.K23 N, p.G31R, p.S35T, p.A57G, p.A77T, p.E81G, p.F82 L/S/V, p.T83P, p.Y89H, p.M90I, and p.G95A [8]. In addition to HCM, investigators have discovered that gain-of-function mutations in *RIT1* also closely interact with other cardiac defects, such as pulmonary valve stenosis, atrial septal defects, ventricular septal defects, patent ductus arteriosus, aortic/mitral valve abnormalities, and left main coronary artery atresia [6,9].

Shingo Takahara Hallan and colleagues' research has provided important evidence that the A57G mutation in *RIT1* causes cardiac hypertrophy, fibrosis and other NS-associated features via an AKT-related mechanism. Although the detailed mechanism remains unknown, this study provides a new perspective for treatment of NS-associated HCM. The mouse strain developed in this study could be a useful tool for studies of the mechanism of NS in patients with an *RIT1* mutation and to facilitate the development of pharmacogenetic therapies.

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* Corresponding author at: Department of Cardiology, Renmin Hospital of Wuhan University, Luojia Mount Wuchang, Wuhan 430072, China
E-mail address: lihl@whu.edu.cn (H. Li).

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Authors' contribution

Jingjing Cai and Hongliang Li wrote the manuscript. Hongliang Li conceived the idea and revised the text.

Conflict of interests

The authors have nothing to disclose.

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