Circulation: Heart Failure

IMAGES AND CASE REPORTS IN HEART FAILURE

BAG3 Genetic Cardiomyopathy May Overlap Fulminant Myocarditis Clinical Findings

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We present a clinical report on severe cardiomyopathy caused by a rare variant of the *BAG3* gene among individuals with European ancestry that debuted as acute heart failure (HF) with clinical features of acute myocarditis but coinciding with suspicious familial history.

The first case occurred in 2004. A 15-year-old girl (IV.4) was admitted for dyspnea, preceded by 15 days of abdominal pain and vomiting, that rapidly progressed to cardiogenic shock. ECG demonstrated sinus tachycardia, low voltages and flattened T-waves in limb leads, late R-wave transition, J-point elevation in anterior leads, and isodiphasic T-waves in lateral leads (Figure S1, 1); and in the echocardiography severe biventricular dysfunction and left ventricle (LV) dilatation was observed. She required a biventricular assist device and emergent heart transplantation. Diagnostic suspicion was fulminant myocarditis as the cardiac biopsy showed myocardial neutrophilic infiltration (borderline diagnosis of myocarditis according to Dallas criteria; Figure [A and B]). The explanted heart depicted fibrin-hemorrhagic pericarditis, thickened LV wall, and biventricular dilatation.

In 2005, her mother's cousin (III.1) was admitted at the age of 38 due to a 45-day onset of progressive HF preceded by fever and myalgias. Echocardiography depicted severe LV impairment and dilatation. He was transplanted 2 days later in an Interagency Registry for Mechanically Assisted Circulatory Support 2 situation. Clinical course suggested myocarditis, but no inflammation was observed in the explanted heart.

Nine years later, in 2016, the sister of the index case (IV.5) was admitted due to cardiogenic shock at 17 years old after a 15-day course of rhinorrhea and dry coughing. ECG demonstrated sinus tachycardia and nonspecific repolarization abnormalities resembling those of her sister (Figure S1, 2). Echocardiography showed dilated LV and severe biventricular systolic dysfunction. A biventricular assist device assist device was implanted (Interagency Registry for Mechanically Assisted Circulatory Support 2), and she underwent heart transplantation 12 days later. Cardiac biopsy did not demonstrate inflammatory infiltrates but diffuse distortion of myocardial fibers with interfibrillary edema (Figure [C through G]).

The third case in the same family raised the suspicion of a familial disease and genetic testing (next-generation sequencing panel including 50 genes associated with inherited cardiomyopathies) was performed revealing a *BAG3* p.Gln88* pathogenic variant (American College of Medical Genetics and Genomics classification[1]), causing premature truncation of the protein. The index case (IV.4), her mother (III.4), grandmother (II.3), and her mother's uncle and cousin (II.1 and III.1) carried the same rare pathogenic variant (Figure [H]). To our knowledge, this report is the first clinical description in literature of individuals carrying this variant. The 2 sisters (IV.4 and IV.5) also had a novel rare variant -p.(Pro52Arg)- in *BAG3*, absent in their mother, and classified as a variant of uncertain significance.[1] This variant is absent in large

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Nonstandard Abbreviations and Acronyms

HF	heart failure
LV	left ventricle

international population databases[2] and is predicted to be deleterious by in silico data.

Clinical evaluation of the proband's mother (III.4) at 45 years old demonstrated dilated cardiomyopathy with isolated LV involvement. Since she was at New York Heart Association functional class II and had left bundle branch block on ECG (Figure S1, 3), cardiac resynchronization therapy device was implanted. Proband's grandmother (II.3) and great-uncle (II.1) had no dilated cardiomyopathy at the age of 67 and 76, respectively, although her grandmother's ECG showed nonspecific negative T-waves in lateral leads (Figure S1, 4) along with moderate septal hypertrophy on echocardiography.

Of note, we have found the same *BAG3* p.Gln88* rare variant in an unrelated patient from our cohort of

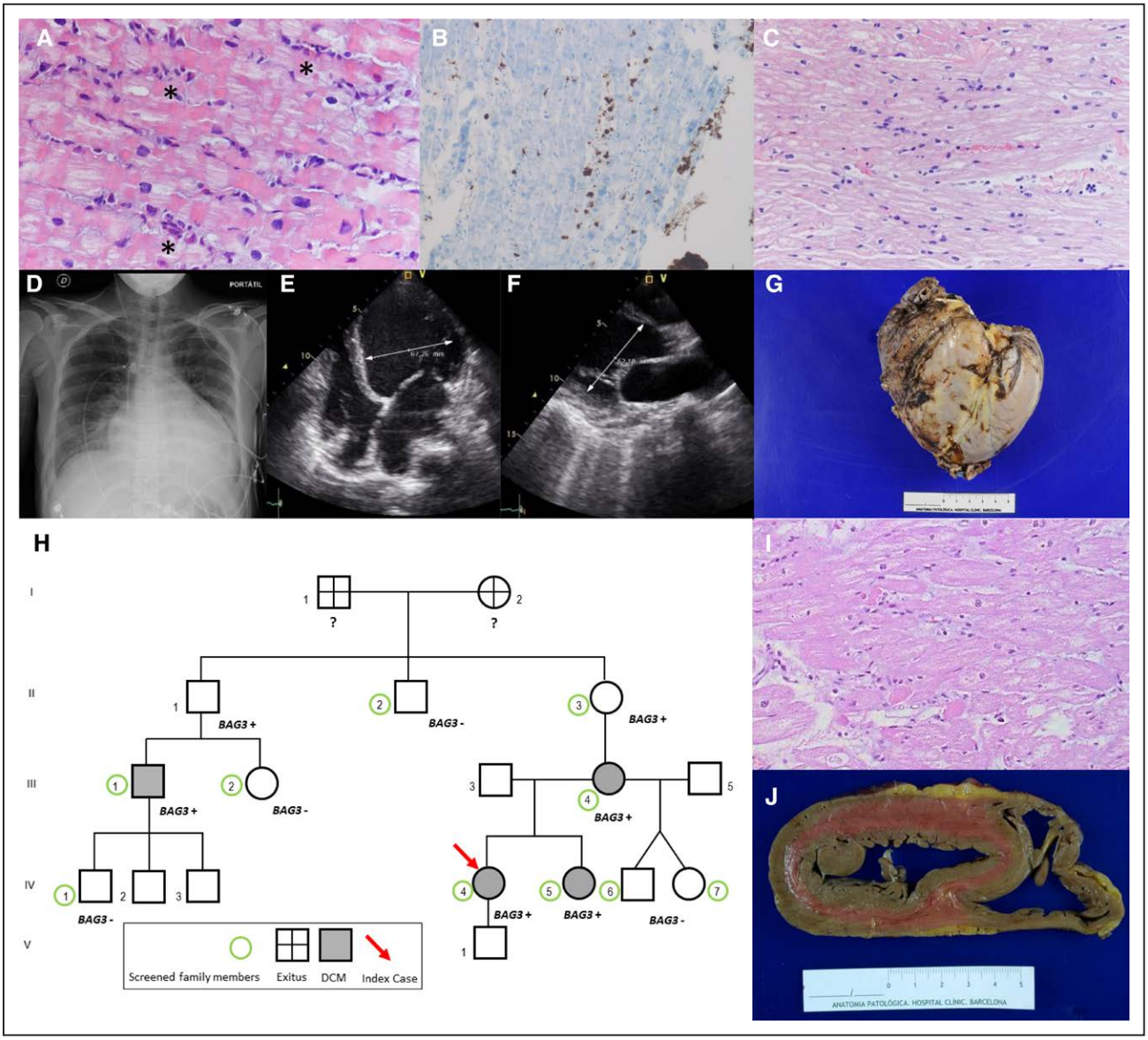

Figure. Family tree of the related cases and iconography of the radiologic, echocardiographic, and histopathologic findings. **A** and **B** correspond to case IV.4. **A** depicts hematoxylin-eosin staining of the cardiac biopsy specimen which shows foci of neutrophilic perivascular infiltration (marked with black asterisks) and occasional eosinophils but no myocyte degeneration. **B** shows CD15 immunohistochemical staining for neutrophils in brown. **C** through **G** correspond to case IV.5. **C** depicts vacuolated cardiomyocytes, diffuse distortion of myocardial fibers, and interfibrillary edema but no inflammation infiltrates nor necrosis in the cardiac biopsy tissue. Thoracic x-ray (**D**) and echocardiography (**E** and **F**) at admission show dilated left ventricle (LV) and pulmonary congestion. Biventricular dilatation of the explanted heart is shown in **G**. **H** depicts cosegregation of the *BAG3* p.88* pathogenic mutation in the related individuals. **I** and **J** describe the findings in the unrelated patient with the same *BAG3* mutation. Histopathology of the explanted heart depicted mild lymphocytic infiltration and focal myocyte necrosis (**I**) in a thickened and dilated LV (**J**). DCM indicates dilated cardiomyopathy.

transplanted patients. Reviewing medical history, the story repeated. At 30 years old, he had a 10-day course of fever and progressive dyspnea presumed to be severe pneumonia. Echocardiography showed dilated and severely impaired LV. He was supported with intraaortic balloon pump and left ventricle assist device due to cardiogenic shock and underwent emergent heart transplantation subsequently. The diagnostic suspicion was acute myocarditis based on lymphocytic infiltration and focal myocyte necrosis in the explanted heart (Figure [I and J]). No other cases in this family have been found to date. Genotyping was performed in the course of a protocol investigating the genetic background of myocarditis.

No patient was positive for IgM titers of cardiotropic viruses. Polymerase chain reaction viral analysis on the heart has been retrospectively performed, following current recommendations,[3] in all transplanted patients except in case III.1 (no sample remained). A low viral load of parvovirus B19 was found in the index case and the unrelated patient. The absence of other cardiotropic viruses and the low viral load suggest that its presence lacks etiopathogenic relevance, as the role of parvovirus B19 in endomyocardial biopsies still remains unclear.[4] Patient characteristics at diagnosis or at the time of family screening are presented in the Table.

More than 100 genes have been reported associated with inherited dilated cardiomyopathy; 33 of these genes carry sufficient evidence to be classified as definitive disease-causing genes, including *BAG3*.[5] In the largest cohort of *BAG3* carriers described so far (n=129), 15.5% of them developed severe HF defined as the composite outcome of heart transplantation, left ventricle assist device or death due to HF.[6] Our work describes other interesting findings. Severe cardiomyopathy with acute HF onset appeared at very young ages, specifically in 2 individuals (15 and 17 years old). Early onset in these patients may be partially explained by compound heterozygous rare variants in *BAG3*. In addition, 4 out of 7 individuals carrying the same *BAG3* p.Gln88* mutation (one of them unrelated) were transplanted due to cardiogenic shock (57%) suggesting an aggressive disease course. Our findings regarding this specific variant do not replicate male-associated aggressive course previously reported.[4] Of note, acute and severe presentation of this genetic cardiomyopathy in our patients associates clinical features (viral infection-like symptoms and acute onset) and pathological findings (myocardial inflammatory infiltrates and distortion of myocardial fibers) that

Table. Patient Characteristics at the Time of Diagnosis or Family Screening

Case	Mutations	Age	Viral symptoms	HF symptoms	Echocardiography/CMR	Suspected myocarditis[3]/Dallas criteria/ cardiac viral PCR	Biomarkers	VAD or HTx
Index case (IV.4)	*BAG3* p.Gln88*, p.(Pro52Arg)	15	Gastrointestinal (also attributable to low cardiac output)	HF rapidly progressing to CS (15 d)	Severe LV dilatation and impairment. Moderated RV dilatation with severe RV impairment.	Yes/Yes, borderline/Parvovirus B19: 92 copies per mL	↑ CRP (×4), ↑ CK and TnI (×1.2)	IABP, BiVAD, and HTx
Sister (IV.5)	*BAG3* p.Gln88*, p.(Pro52Arg)	17	Respiratory (rhinorrhea and cough)	HF rapidly progressing to CS (15 d)	Dilated and impaired LV (LVEF 15%, LVEDd 66 mm). Nondilated but severe hypokinetic RV.	Yes/No, but diffuse distortion of myocardial fibers with interfibrillary edema/Negative	Normal values of CRP, TnI and CK	BiVAD and HTx
Mother (III.4)	*BAG3* p.Gln88*	45	No	NYHA functional class II	Dilated and impaired LV (LVEDd 67 mm). CMR: Indexed LVED 185 mL/m^2, LVEF 21%. Normal RV. No edema nor LGE.	No/ – / –	Normal values of TnI and CK	No
Grandmother (II.3)	*BAG3* p.Gln88*	67	No	No	Hypertensive cardiomyopathy (septal thickness 14 mm) with nondilated LV and normal LVEF.	No/ – / –	–	No
Great-uncle (II.1)	*BAG3* p.Gln88*	76	No	No	Normal echocardiography.	No/ – / –	–	No
Cousin (III.1)	*BAG3* p.Gln88*	38	Unspecific (fever and myalgias)	HF progressing to CS (45 d)	LV severely impaired and dilated and RV dysfunction.	Yes/No/ –	↑↑ CRP (×10), normal CK and TnI	IABP, BiVAD, and HTx
UR	*BAG3* p.Gln88*	30	Fever	HF progressing to CS (10 d)	LVEF 29%, LVEDd 57 mm. RV with mild dilatation and hypokinesia. CMR without edema nor LGE.	Yes/Yes/Parvovirus B19: 9 copies per ml	↑ CRP (×4), normal CK and TnI	IABP, LVAD, and HTx

Description of the clinical, genetic, biochemical, and imaging characteristics of patients with acute presentation (IV.4, IV.5, III.1, and UR) at the time of disease onset or at the time of family screening in other related individuals. BiVAD indicates biventricular assist device; CK, creatine kinase; CMR, cardiac magnetic resonance; CRP, C-reactive protein; CS, cardiogenic shock; HF, heart failure; HTx, heart transplantation; IABP, intraaortic balloon pump; LGE, late gadolinium enhancement; LV, left ventricle; LVAD, left ventricle assist device; LVEDd, left ventricle end-diastolic diameter; LVEDv, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; PCR, polymerase chain reaction; RV, right ventricle; TnI, troponin I; UR, unrelated patient; and VAD, ventricular assist device.

may overlap with myocarditis typical findings, albeit other mechanisms may be present.

Further research and characterization of myocardial infiltrates and immune activation (including immunohistochemical study of the heart and serum cardiac autoantibodies), as well as the presence of viral genome in the myocardium and peripheral blood,[3] will help clarify the contribution of immune-mediated mechanisms to fulminant presentations of genetic cardiomyopathies. Furthermore, assessment of disease progression according to site-specific mutations in future cohorts may aid prognosis stratification.

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Disclosures

None.

Supplemental Material

Figure S1

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