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Hypertrophic Cardiomyopathy in RASopathies:

Diagnosis, Clinical Characteristics, Prognostic Implications, and Management

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INTRODUCTION

RASopathies are a group of developmental multisystemic disorders caused by germline mutations in genes encoding signal transducers and regulatory proteins functionally linked to the RAS/mitogen-activated protein kinase (MAPK) pathway. Collectively, these disorders have an estimated prevalence of 1 in 1000 to 1 in 2500[1] among live births.

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DISCLOSURE

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According to a large clinical registry,[2] RASopathies may represent the underlying diagnosis in ~18% of childhood hypertrophic cardiomyopathy (HCM), particularly among infants younger than 1 year, where they account for ~42% of the cases.

The disorders constituting the RASopathies include Noonan syndrome (NS), NS with multiple lentigines (NSML, previously known as LEOPARD syndrome), cardiofaciocutaneous syndrome (CFCS), Mazzanti syndrome (also known as NS-like disorder with loose anagen hair), Costello syndrome (CS), type 1 neurofibromatosis, and Legius syndrome which are well recognized and clinically characterized[3]; however, other clinically related conditions are emerging.[4]

Although each RASopathy exhibits a unique clinical phenotype, these syndromes share many overlapping characteristics, including growth retardation, craniofacial features, cryptorchidism, cognitive deficits, renal malformations, bleeding disorders, variable predisposition to certain cancers, and congenital heart disease (CHD).[5–8] Diagnosis of a RASopathy could be suggested by clinical clues ("red flags"),[9] which could raise the suspicion of an underlying malformation syndrome and direct the clinician toward a specific genetic test (Table 1).

It should be noted that the extent of clinical variability characterizing each RASopathy is strictly related to the extent of molecular variability and heterogeneity of these disorders. For example, NS, which is the most common disorder among the RASopathies. This disease is caused by mutations in more than 10 genes (ie, *PTPN11*, *SOS1*, *SOS2*, *NRAS*, *KRAS*, *MRAS*, *RRAS2*, *RIT1*, *LZTR1*, *RAF1*, *MAP2K1*), which are preferentially associated with certain features, including proper growth and cognition (*SOS1*, *SOS2*), high prevalence of pulmonary stenosis (PS) (*PTPN11*), or HCM (eg, *RAF1*, *MRAS*, and *RIT1*).[4,10–15] On the contrary, other RASopathies are relatively homogeneous, being caused by a narrow spectrum of mutations in single genes, as in the case of CS and Mazzanti syndrome, which are caused by a bunch of mutations in *HRAS* and *SHOC2*, respectively.[3]

HYPERTROPHIC CARDIOMYOPATHY IN RASopathies

After CHD, HCM is the second most common cardiovascular abnormality observed in RASopathies,[2,16–22] with worse clinical outcomes when associated with early onset presentation.

Compared with sarcomeric forms (S-HCM), HCM in RASopathies (R-HCM) shows increased prevalence and severity of left ventricular outflow tract obstruction (LVOTO)[17,19,20,23] and higher rates of hospitalizations for heart failure or need for septal myectomy during childhood.[23] R-HCM presents earlier in infancy, with a mean age at diagnosis of 6 months, whereas S-HCM mostly presents during adolescence.[24] Congestive heart failure (CHF) is significantly more common in R-HCM (24% vs 9%)[25] and accounts for a substantial early mortality. Patients affected by RASopathies are more likely to require heart failure hospitalizations or cardiovascular interventions,[23] mainly septal myectomies and pulmonary valvuloplasties.[26–28]

In 5% to 10% of the cases, R-HCM is associated to a severe clinical presentation, particularly for infants with signs of heart failure, with a 70% one-year mortality. With the exception of these cases, clinical status tends to improve over time, and progression of left ventricular hypertrophy (LVH), described in S-HCM, seems uncommon in R-HCM.[23,29] On the contrary, left ventricular reverse remodeling with regression of myocardial wall thickness z-scores over time on serial echocardiography has been reported in many clinical studies.[23,26,28]

LVOTO is common among patients with RASopathies, and its prevalence may be due to the contribution of other cardiovascular abnormalities such as displacement of papillary muscles, anomalous insertion of mitral chordae, or fibrous tissue causing midventricular obstruction.[7,30,31] Mitral valve disease has been considered a marker of complexity in patients with HCM and may carry a negative prognosis, being associated with reintervention and mortality.[32] In particular, compared with age- and sex-matched healthy controls, the length of the anterior leaflet of mitral valve is significantly increased in patients with R-HCM[30]; moreover, anterior displacement of the papillary muscles may cause distortion of the subvalvular apparatus.

Biventricular hypertrophy may represent a useful clinical clue (“red flag”) for the suspicion of R-HCM,[33] and its presence may indicate the co-occurrence of right ventricular outflow tract obstruction. The prevalence of PS ranges between ~25% and 70% in this subgroup of patients: The pulmonary valve is often dysplastic and shows signs of commissural fusion.[27,34] In particular, PS is severe in ~30% of the cases and moderate in ~10%. Patients with mild PS are unlikely to require intervention, and their natural history is similar to that of patients without PS.[28,35] In contrast, patients with moderate-to-severe PS often require percutaneous balloon valvuloplasty, but due to valvular dysplasia, the outcomes may be unfavorable, with high rates of reintervention.[26,36]

Beyond PS, which is observed in up to 65% of the patients, other CHDs commonly occur among patients with RASopathies: “Secundum atrial septal defect” (ASD) has been observed in ~8% to 30% of the cases,[11,26–28,31,37–39] as well as ventricular septal defect (VSD) (~5%–10%)[19,26,27,31,40] and atrioventricular canal defect (AVCD) (up to 15% of the cases). The association with AVCD is of pivotal importance: Mitral valve abnormalities (such as double orifice and parachute mitral valves) have a significant association with AVCD. Moreover, cranial displacement of the aortic valve anulus relative to the ventricular apex, which determines the so-called “gooseneck” deformity, may contribute to LVOTO.[39,41,42] Complete AVCD is uncommon in RASopathies, and morphologic data are insufficient to define whether a specific AVC subtype, according to the Rastelli classification, is more prevalent.

Left-sided obstructive lesions are rare in RASopathies, although aortic stenosis, coarctation of the aorta, and isolated MV stenosis have been reported in the setting of NS.[43–45]

Coronary artery abnormalities are a relevant finding in RASopathies and may contribute to cause myocardial ischemia and worsen the imbalance between myocardial oxygen supply and demand. According to a registry,[31] aneurysms in coronary arteries have been identified

in ~15% of the cases, invariably involving left coronary artery but independently from a specific pathogenic variant.[46] Long-term outcomes of coronary dilatation are not completely understood: As coronary artery aneurysms have been associated to athero-thrombosis, the role of antiplatelet drugs in primary prevention of myocardial infarction is debated, and no specific recommendation can be made.[47]

Although HCM, AVCD, and PS have been considered classic cardiovascular defects in the setting of RASopathies, recent data coming from a multicenter retrospective study seem to report a high prevalence of primary mitral regurgitation (24%, 4%) and aortic insufficiency (25%) or structural abnormalities of the ascending aorta, including kinking and aortic root dilatation.[31]

The summary of cardiovascular manifestations, involved genes, and their relative prevalence among RASopathies is shown in Table 2. The proposed algorithm for the diagnosis and management of R-HCM is shown in Fig. 1.

Hypertrophic Cardiomyopathy in Noonan Syndrome with Multiple Lentigines

HCM is present in ~85% of the patients affected by NSML, among the highest rate among RASopathies. LVOTO may be associated to NSML in up to 40% of the cases, and biventricular hypertrophy is reported in nearly half of the patients. HCM is often diagnosed in early infancy, and the clinical phenotype almost invariably manifests before the appearance of the lentigines.[19] Interestingly, patients with severe biventricular involvement often show high mortality rates, compared with mild asymptomatic cases, who have relatively benign clinical outcomes and frequent regression of LVH.[27,48] Electrocardiographic abnormalities and progressive conduction abnormalities often coexist with HCM: In particular, a superiorly oriented QRS axis even in the absence of biventricular involvement, pseudo-infarction q waves, and prolonged corrected QT interval have been observed among NSML patients.[19] A possible limitation in the existing study outcomes among patients with NSML is that, in some studies, diagnosis is based on clinical criteria without genotype corroboration. Of note, differentiating NSML from NS can be challenging, particularly in infants, for whom the prevalence of cutaneous manifestations is incomplete, and lentigines are not present.[24] NSML is caused by a narrow spectrum of dominantly acting mutations in *PTPN11*. Many clinically relevant genotype-phenotype correlations should be considered: Patients harboring missense RASopathy variants in *BRAF*, *LZTR1*, *RAF1*, and *RIT1* show an increased prevalence of LVH compared with carriers of *PTPN11* pathogenic variants. In addition, some authors have reported worse HF and arrhythmic outcomes in a subgroup of patients harboring the missense Gln510Glu allele (*PTPN11*, exon 13).[16] Interestingly, the molecular spectrum of NSML-causing *PTPN11* mutations does not overlap the pattern of mutations observed in NS, and the biochemical behavior of these two classes of mutations is completely different, with the former impairing the catalytic activity of SHP2, the protein encoded by *PTPN11*, and the latter promoting enhanced activation of the phosphatase[49–51]

Hypertrophic Cardiomyopathy in Costello Syndrome

Among patients diagnosed with CS, approximately 65% fulfills diagnostic criteria for HCM: In this subgroup, the coexistence with CHD is reported in ~40% of the cases, and 60% may have LVOTO. Most patients seem to show subaortic septal thickening, although other patterns, such as biventricular or concentric hypertrophy, have been reported.[52] The natural history of HCM in CS is variable, with a documented rate of progression in ~40% of the cases. Of note, a significant number of patients with severe HCM underwent septal myectomy (25%). Regression of LVH has been reported in 10% of the patients, although data reported do not allow the establishment of genotype-phenotype correlations.[18,24,52,53] The comparison between the two commonest alleles for the *HRAS* gene (pG12S and pG13 C) with a pathogenic role in CS has shown no significant difference in the prevalence of HCM.[54] Severe cardiomyopathy, associated with pleural and pericardial effusion as well as lung abnormalities has been observed in carriers of G12 C and G12D alleles.[55] Atrial tachyarrhythmias are seen in more than 50% of the patients affected by CS, particularly non-reentrant atrial tachycardia and multifocal or ectopic atrial tachycardia.[56] The natural history of atrial arrhythmias is usually benign in CS, with spontaneous regression within the first year of life and responsiveness to medical therapy, whereas ventricular arrhythmias are rare. Later-onset atrial fibrillation and atrial flutter have been reported, but their prognostic significance is unknown.[57]

Hypertrophic Cardiomyopathy in Cardiofaciocutaneous Syndrome

CFCS is caused by dominantly acting mutations in *BRAF*, *MAP2K1*, and *MAP2K2*. Nearly 75% of children with CFC have cardiovascular involvement, mainly PS, which can be diagnosed in 45% of the cases. HCM can be identified in ~40% of patients during infancy,[6] with a variable phenotype, sometimes rapidly progressive and resulting in heart transplantation or death and, in other cases, with a mild phenotypic expression.[6] Of note, the prevalence of HCM is not significantly different among patients who carry *BRAF* pathogenic variant mutation compared with carriers of MEK1 or MEK2 alleles.[58,59] The most common coexisting forms of CHD are ASD (8%–18%) and VSD (11%–22%).[60,61] Although uncommon in CFCS, arrhythmias can include ventricular preexcitation, atrioventricular block, or supraventricular tachycardia.[59]

Hypertrophic Cardiomyopathy in Noonan Syndrome and Clinically Related Disorders

Among RASopathies, HCM seems less common in NS, with a reported prevalence of ~20% among affected individuals. Interestingly patients with Mazzanti syndrome and harboring a recurrent missense substitution in *SHOC2* seem to have a slightly higher prevalence of HCM (25%).[62] Three independent studies reported that germline variants in *CBL* underlie a clinical syndrome with many overlapping features with NS, although HCM seems not to be associated to this condition.[63–65] Among children with NS and HCM, asymmetrical septal hypertrophy is the most common presentation (75.6%), whereas apical involvement is rare.[66] A 12-lead electrocardiogram can show extreme right heart deviation (“north west axis”), reflecting biventricular involvement.[33] Genotype characterization can offer useful diagnostic clues in the management of NS-associated HCM. In particular, among patients

harboring *PTPN11* variants, the prevalence of HCM is low, whereas individuals affected by NS with causal variants in *RAF1* and *RIT1* are more likely to develop HCM.[24]

PATHOPHYSIOLOGY OF HYPERTROPHIC CARDIOMYOPATHY IN RASopathies

Different signaling pathways seem to be involved in the molecular pathogenesis of HCM in RASopathies. Almost 50% of the cases of NS are caused by missense gain-of-function mutations in *PTPN11*, which typically cluster around the phosphotyrosine phosphatase domains of SHP2, causing constitutive activation of the protein.[67] Interestingly, HCM is underrepresented in patients harboring missense changes in *PTPN11* or *SOS1*, whereas it is overrepresented is *RAF1*-mutated NS, where it seems to be allele-specific.[14,68] A distinct class of variants in *PTPN11* was associated to NSML, which carries a higher lifetime risk of HCM.[49] While NS-causing variants may promote upregulation of RAS/MAPK cascade, alleles involved in NSML should be considered as dominant negative mutants promoting enhanced signal flow through the PI3K-AKT-mTOR pathway. In a murine model of NS bearing the p.L613 V mutation in the *Raf1* gene, increased RAS/MAPK signaling was observed both in fibroblasts and in neonatal cardiomyocytes. Consistent with that observation, treatment with an MEK inhibitor seemed to induce positive reverse remodeling in $Raf1^{L613V}$ mice.[69] Treatment with trametinib, an MEK inhibitor, has been associated to reversal of LVH and LVOTO in two cases of *RIT1*-mutated NS within 4 months after initiation of the therapy. Remodeling was associated with a favorable clinical response and a catch-up in somatic growth, which may be attributable to recovery from severe HF.[70] In contrast, a mouse model of NSML bearing the p.Y279 C mutation in the *Ptpn11* gene showed impaired ligand-evoked ERK phosphorylation and increased signal flow through the PI3K-AKT-mTOR pathway. Treatment with rapamycin, an mTOR inhibitor, rescued the cardiac phenotype in $Ptpn11^{Y279C}$ mice.[71] In the last years, everolimus was used to prevent CHF in patients with severe HCM, but regression of LVH was not documented.[48]

PROGNOSTIC IMPLICATIONS OF HYPERTROPHIC CARDIOMYOPATHY IN RASopathies

The diagnosis of HCM significantly affects the outcome in patients affected by NS: Long-term studies have demonstrated that severity of cardiovascular involvement is associated with a lower survival rate, with higher risk of death in patients younger than 2 years and adolescents. Specific risk factors for early mortality include evidence of HF during the first 6 months of life, low cardiac output, significant diastolic disfunction, and several cardiac interventions.[7,25]

Taken together, the outcomes of children affected by R-HCM seem to reflect a distinct disease course compared with carriers of sarcomere pathogenic variants: Patients with R-HCM can be severely affected during the perinatal and infancy periods, are more likely to require septal myectomy or pulmonary balloon valvuloplasty, and lack the typical progression of LVH during adolescence and young age.[23,28]

Histopathologic studies have demonstrated that patients with R-HCM had a similar amount of quantified fibrosis compared with nonsyndromic familial HCM caused by sarcomere protein mutations. Of note, fibrotic changes are already present in an early phase of disease, in contrast to S-HCM, in which myocardial disarray and fibrosis develop over time.[23]

Apical aneurysms have been described in R-HCM, nonetheless their overall prevalence and clinical significance have not been assessed yet.[72]

HCM is the main cause of sudden cardiac death (SCD) among adolescents and young adults.[73] Among patients with R-HCM, sustained ventricular tachycardia (VT) is frequent and related to the risk of SCD.[74–76] Although the overall risk of SCD appears lower than that in HCM caused by sarcomere mutations, disease-specific risk factors are currently an area of debate.[23,28] A previous history of VT or cardiac arrest, unexplained syncope, non-sustained VT, or massive LVH has been associated with higher risk of SCD and may require Implantable cardioverter defibrillator implantation.[73] However, the weight of isolated risk factors, irrespective of their magnitude (ie, massive LVH), is not clear, and the risk could be higher when many risk factors coexist in the same patient. Interestingly, other conventional risk factors such as age, family history of SCD, and left atrial z score should be evaluated carefully in children, whereas LVOT gradient seems not associated to SCD.[77] Recently, two scores have been validated for risk stratification in pediatric patients.[77,78]

MANAGEMENT AND FUTURE PERSPECTIVES

Medical therapy remains the first-line option in patients with R-HCM. Nonvasodilating beta blockers should be titrated to the maximum tolerated dose in patients, and diuretic dose should be accurately set to reduce congestive status and HF symptoms, while avoiding hypovolemia, which could increase LVOTO. When beta blockers are ineffective or not tolerated, nonvasodilating calcium channel blockers could be administered in children older than 6 months. Of note, there are several reports of severe bradycardia and HF worsening in infants with LVOT gradients greater than 100 mm Hg, suggesting that verapamil could be harmful in this clinical setting.[79,80]

In patients who remain symptomatic despite beta-blockers, disopyramide could be a therapeutic option to reduce obstruction. Recently, mavacamten has shown to improve functional status in S-HCM, nevertheless further studies are needed to assess its role in nonsarcomeric variants. Surgical myectomy may be considered in patients who remain symptomatic for significant LVOTO despite maximal medical therapy and should be performed in specialized centers with high-volume experience.[81,82] Orthotopic heart transplantation (OHT) is rarely performed in patients with NS,[83] although it should be considered in patients with severe HF symptoms with evidence of refractoriness to medical therapy, intractable ventricular arrhythmias, cardiogenic shock requiring inotropes, and in case of severe diastolic dysfunction.[84,85] Early multiorgan damage should not be considered a contraindication for heart transplantation, but careful evaluation of absolute contraindication is required, to exclude the risk of futility in case of moderate or severe end organ dysfunction.[86] According to the Pediatric Cardiomyopathy Registry,[87,88] cumulative waitlist mortality was significantly high in infants affected by HCM, suggesting a malignant

course of disease and the presence of comorbidities in critically ill infants. Poorer outcomes were observed in patients listed for priority in status 1 or younger than 1 year than in older children and patients listed in status 2.[89] Therefore, OHT should be considered as early as possible and before clinical deterioration in patients with R-HCM.

Proof of concept that inhibition of the RAS/MAPK cascade could induce regression of LVH and cardiac remodeling in patients affected by RASopathies has been achieved by clinical evaluation of trametinib, an MEK inhibitor, in two patients with RIT1-induced NS, with significant regression of LVH within 4 months after initiation of treatment.[70] On the contrary, among children with NSML with germline loss-of-function variation in *PTPN11*, the overactivation in PI3K-AKT-mTOR pathway was partially reversed with the use of rapamycin.[48,71] The design of therapeutic trials is challenging in patients with RASopathies because of the rarity of disease, patient variability in disease progression and regression, and the heterogeneity of molecular mechanisms.[90] Possible future treatment candidates may include farnesil transferase inhibitors, pan-RAF inhibitors, SHP2 inhibitors, and, because copper is required for catalytic activity of MEK kinases, chelation with ammonium tetrathiomolybdate.

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KEY POINTS

- RASopathies are developmental multisystemic disorders caused by germline mutation in genes linked to the RAS/mitogen-activated protein kinase pathway.
- Hypertrophic cardiomyopathy is the second most common cardiovascular manifestation in RASopathies and exhibits unique features such as the coexistence of congenital heart disease and early-onset congestive heart failure and accounts for significant mortality rates.
- Diagnosis of a RASopathy could be suggested by clinical clues (“red flags”), which could raise the suspicion of an underlying malformation syndrome and direct the clinician toward a specific genetic test.

CLINICS CARE POINTS

- RASopathy should be suspected in infants (<1 year) with new-onset HCM and clinical red flags.
- Patients affected by RASopathies are more likely to require HF hospitalizations or cardiovascular interventions.
- In 5% to 10% of the cases, R-HCM is associated to a severe clinical presentation, particularly for infants with signs of heart failure.
- The prevalence of pulmonary stenosis (PS) ranges between ~25% and 70% in this subgroup of patients.
- Other CHDs commonly occur among patients with RASopathies: “secundum atrial septal defect”, as well as ventricular septal defect, atrioventricular canal defect (AVCD), mitral valve abnormalities, coronary arteries abnormalities, and left-sided obstructive lesions.
- In selected cases, rapamycin or MEK1 inhibitors may promote regression of left ventricular hypertrophy and should be considered as a therapeutic option.

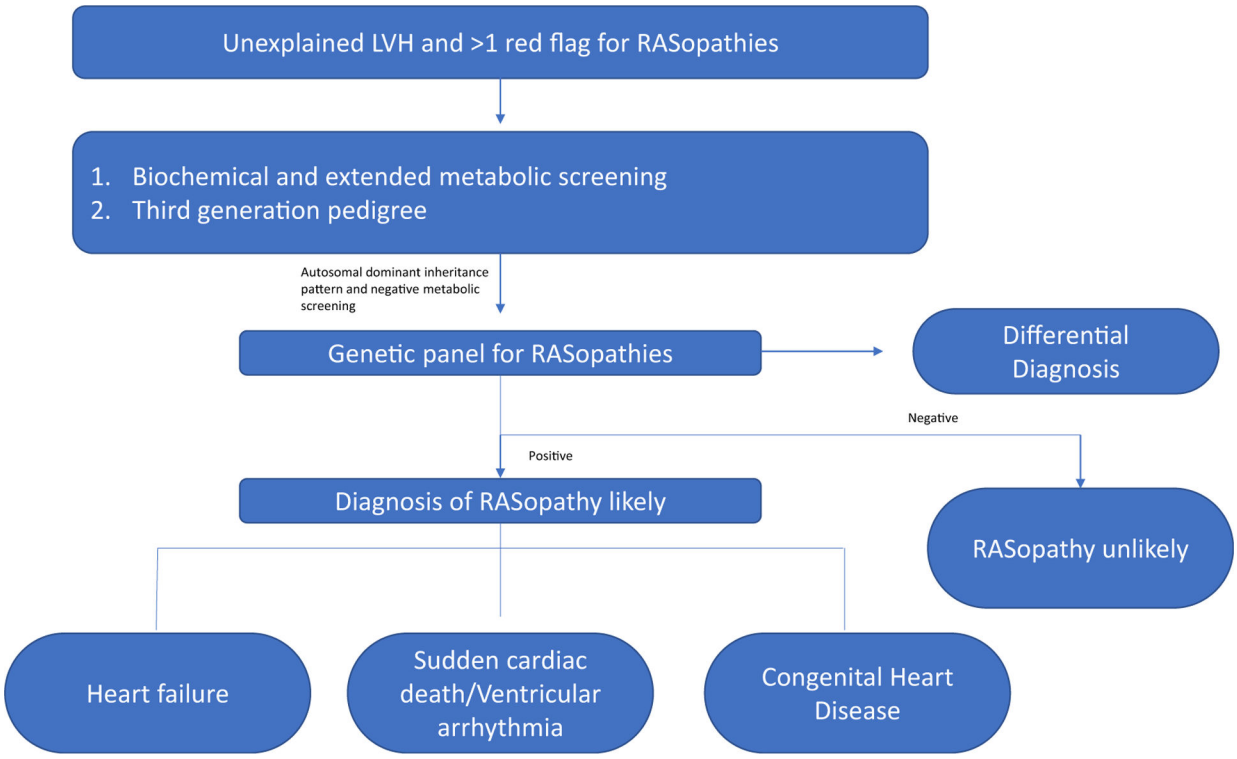

Fig. 1.

Proposed algorithm for the diagnosis and management of RASopathy-associated HCM (R-HCM).

Table 1

Clinical red flags for RASopathies

Facial features	NS: broad forehead, down slanting palpebral fissures, hypertelorism, low set ears, pterygium colli, epicanthal folds, short and depressed nasal root CS: hypertelorism, down slanting palpebral fissures. Facial features are coarser. Feeding and suction difficulties are more prevalent. CFCS: macrocephaly, bitemporal narrowing, coarse facial features, small curly friable hair with sparse eyebrows with hyperkeratosis (ulerythema ophryogenes), broad nasal base, wide labial philtrum. Coarser than NS
Cardiovascular	Pulmonary valve stenosis, hypertrophic cardiomyopathy, mitral valve dysplasia, atrial septal defect, ventricular septal defect, atrioventricular septal defect, aortic coarctation, coronary arteries abnormalities
Electrocardiography	Extreme right-axis deviation (north west axis), left or right bundle branch block (NSML), prolonged QT (NSML), repolarization abnormalities, multifocal atrial tachyarrhythmia (CS)
Musculoskeletal	Short stature, hypotonia (CFCS), Pes planus (CFCS), scoliosis, pectus deformity, hip dysplasia, osteopenia/osteoporosis
Dermatologic	Cafè-au-lait spots, papillomas (CS), palmar keratoderma, acanthosis nigricans, keratosis pilaris (CFC), ulerythema ophryogenes (CFC), lentigines (NSML), multiple pigmented nevi
Genitourinary	Cryptorchidism, transitional cell carcinoma of the urinary bladder (CS)
Hematopoietic	Easy bruising, von Willebrand disease, coagulation defects, thrombocytopenia, NS/myeloproliferative disease (leukocytosis with monocytosis, thrombocytopenia, and hepatosplenomegaly)
Gastrointestinal	Failure to thrive, gastroesophageal reflux, intestinal malrotation, pyloric stenosis
Sensorineural	Hearing loss, laryngomalacia, cataract, strabismus
Neurologic	Seizures, infantile spasms, hydrocephalus, Chiari I malformation, intellectual disability
Endocrine	Growth hormone deficiency, hypoglycemia, delayed puberal spurt, short stature
Oncology	Juvenile myelomonocytic leukemia, lymphedema

Abbreviations: CFCS, cardiofaciocutaneous syndrome; CS, Costello syndrome; HCM, hypertrophic cardiomyopathy; NS, Noonan syndrome.

Table 2

Clinical manifestations, mutated genes, and classical heart defects with their relative prevalence among RASopathies and relative prevalence of hypertrophic cardiomyopathy

Gene	Clinical Features	HCM
Noonan syndrome		
PTPN11	PVS (65%), atrioventricular septal defects (18%), ASD (10%), VSD (9%), PDA (6%), mitral valve abnormalities (2.5%), Tetralogy of Fallot (<1%), aortic coarctation (<1%)	HCM (20%)
SOS1	PVS (70%), ASD (14.5%), mitral valve abnormalities (4%)	HCM (18%)
RAF1	PVS (21%), ASD (20%), mitral valve abnormalities (13%), Tetralogy of Fallot (2.8%), aortic coarctation (1.8%)	HCM (65%)
RIT1	PVS (74%), ASD (30%), PDA (7%), mitral valve abnormalities (13%), biventricular obstruction (<1%)	HCM (36%)
SHOC2	PVS (32%), ASD (32%), mitral valve abnormalities (27%), VSD (13%)	HCM (30%)
NRAS	PVS (14%)	HCM (39%)
CBL	PVS (50%), ASD (10%), mitral valve abnormalities (10%)	HCM (10%)
Noonan syndrome with multiple lentigines		
PTPN11	Biventricular hypertrophy (46%), LVOTO (40%), ventricular tachycardia, conduction abnormalities, mitral valve abnormalities (42%), PVS (21%), ASD (6%), atrioventricular septal defects, coronary artery abnormalities	HCM (85%)
RAF1	Mitral valve abnormalities (100%), PVS (40%), high risk of SCD	HCM (100%)
BRAF	-	HCM (60%–85%)
Costello syndrome		
HRAS	Atrial tachycardia (56%), PVS	HCM (65%)
Cardiofaciocutaneous syndrome		
BRAF1	PVS (45%), ASD (30%), VSD (8%). Tetralogy of Fallot (7%)	HCM (40%)
MAP2K1-MAP2K2	PVS (65%–100%), septal defects (15%)	HCM (40%)
KRAS	PVS (40%), mitral valve abnormalities (26%), ASD (20%), VSD (13%)	HCM (20%)

Abbreviations: ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; PDA, patent ductus arteriosus; PVS, pulmonary valve stenosis; VSD, ventricular septal defect.