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COMMENT

RASopathies and sigmoid-shaped ventricular septum morphology: evidence of a previously unappreciated cardiac phenotype

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We read with great interest the article by Kauffman et al.[1] entitled "Genotype-phenotype association by echocardiography offers incremental value in patients with Noonan syndrome with multiple lentigines." The occurrence of clear-cut correlations between specific cardiac features and involved genes/variants has been established, with hypertrophic cardiomyopathy (HCM) as the most common complication in patients with Noonan syndrome (NS) due to pathogenic *RAF1* variants,[2,3] Costello syndrome (CS),[4] and Noonan syndrome with multiple lentigines (NSML, previously known as LEOPARD syndrome),[5] while pulmonic stenosis (PS) is the most recurrent cardiac abnormality in patients with NS associated with *PTPN11* mutations.[6,7] In subjects with cardio-facio-cutaneous syndrome (CFCS), HCM is also frequently detected, with a similar prevalence of PS.[8]

In their report,[1] the authors investigated the morphology of the ventricular septum determined by echocardiography in 17 patients with NSML and 67 patients with NS. In this retrospective single-center study, the authors observed the occurrence of a sigmoid septum and/or ventricular septal bulge (VSB) in >70% of NSML patients. In contrast, biconvex septa were more common in NS patients (>90%, with <5% of patients showing a sigmoid septum). Biconvex septal morphology was documented in 85% of NS patients with HCM. Of note, the presence of VSB was not always associated with HCM in NSML. In their study, each cardiac phenotype showed association with specific genotypes, and the clearest genotype–cardiac phenotype correlation occurred in patients carrying variants affecting specific exons of *PTPN11*. The authors speculated that genotype-phenotype associations between echocardiographic septal morphologies and pathogenic variants could have important clinical implications, as they may offer incremental diagnostic value for early differentiation between NSML and NS patients. Furthermore, they concluded that establishing genotype-phenotype associations may have important treatment implications on potential pharmacological strategies.

In the context of these observations, we discuss recently published echocardiographic findings collected in our cohort of patients, including 116 cases with molecularly confirmed RASopathy, followed in our center.[9] In our series, a sigmoid-shaped ventricular septum morphology was detected in 11 cases (9%). In 5 of these patients, a concomitant congenital heart disease (CHD) was identified, whereas no cardiac defect was found in the other 6 patients.[9] As shown in Table 1, 4 of these patients (36%) had a diagnosis of NS (*PTPN11, SOS1*, and *KRAS*), 3 subjects (27%) were diagnosed with CFCS (*BRAF*), 2 individuals (18%) had a molecularly confirmed diagnosis of CS (*HRAS*), and single individuals were diagnosed with Mazzanti syndrome (also known as NS with loose anagen hair, NS-LAH) (*SHOC2*) and NSML (*PTPN11*). These data support the idea that the sigmoid-shaped septum occurs in different RASopathies and is associated with pathogenic variants involving multiple genes.

According to the guidelines of the European Society of Cardiology,[10] none of the patients with sigmoid-shaped septum identified in our series satisfied the criteria for diagnosis of HCM, despite the localized hypertrophy of the ventricular septum. Notably, the evidence of an isolated thickening limited to the basal/mid septal segments occurring in absence of any obvious outflow tract obstruction (Figs. 1 and 2) is in line with the findings by Kauffman et al.[1]

It is not clear how sigmoid-shaped septum morphology has to be considered in terms of functional and morphological cardiac implications. Whether this feature represents a non-progressive anomaly not predisposing to HCM development vs an early stage of disease in patients at risk for HCM requires to be addressed with dedicated observational studies.

In conclusion, we underline the importance of routinely cardiac monitoring in patients affected by RASopathies without significant heart involvement, with particular attention to the ventricular septum morphology. Although the clinical significance of the sigmoid-shaped septum morphology remains to be fully understood, its presence in various RASopathies and its association with pathogenic variants affecting multiple genes document the relevant role of the RAS/MAPK signaling pathway in myocardial hypertrophy and remodeling.

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Table 1. Patients with sigmoid-shaped ventricular septum morphology and correlation with genetic mutations.

Pt	Syndrome	Gene	Mutation	CHD
1	CS	*HRAS*	c.350A > G, p.Lys117Arg	No
2	CS	*HRAS*	c.37G > A;p.Gly13Cys	No
3	CFC	*BRAF*	c.770A > G; p.Gln257Arg	No
4	CFC	*BRAF*	c.1408A > C;p.Thr470Pro	PS
5	CFC	*BRAF*	c.1574T > C;p.Leu525Pro	No
6	NS	*PTPN11*	c.179G > C, p.Gly60Ala	PVDy
7	NS	*SOS1*	c.2197A > T;p.Ile733Phe	No
8	NS	*KRAS*	c.40G > A;p.Val14Ile	No
9	NS	*KRAS*	c.466T > C;p.Phe156Leu	PS+PVDy
10	NSML	*PTPN11*	c.836A > G;p.Tyr279Cys	MVD
11	NS-LAH	*SHOC2*	c.4A > G;p.Ser2Gly	ASD

CFCS cardio-facio-cutaneous syndrome, *CS* Costello syndrome, *NS* Noonan syndrome, *NSML* Noonan syndrome with multiple lentigines, *NS-LAH* Noonan syndrome with loose anagen hair, *PS* pulmonary stenosis, *PVDy* pulmonary valve dysplasia, *MVD* mitral valve disease, *ASD* atrial septal defect.

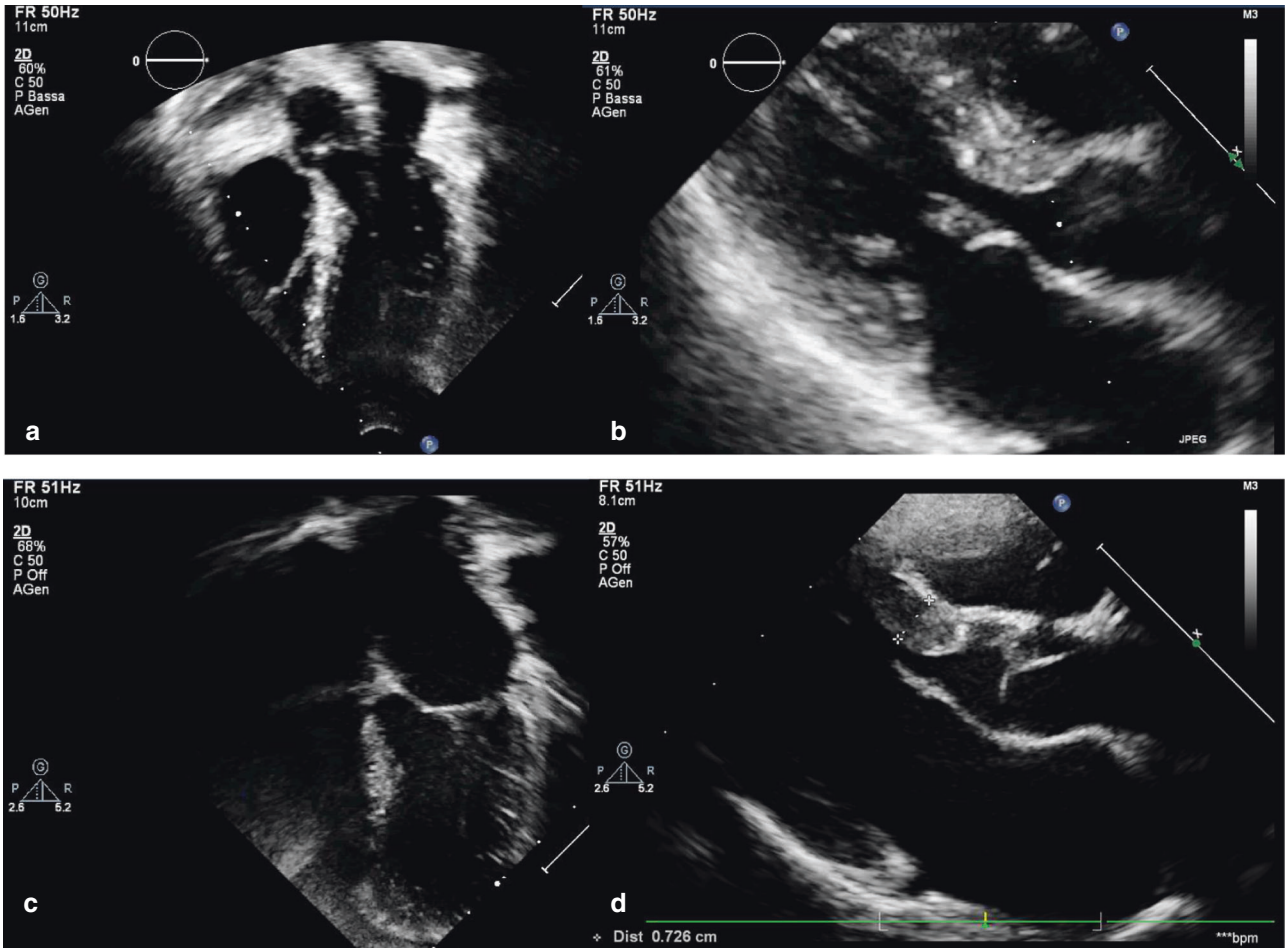

Fig. 1 Sigmoid-shaped ventricular septum in patients with Noonan syndrome. The figure shows two examples of sigmoid-shaped ventricular septum morphology with isolated and localized thickening of its basal/mid septal segments, in echocardiographic apical 4-chamber (**a**, **c**) and parasternal long-axis (**b**, **d**) views in two Noonan syndrome patients (*PTPN11* in top frames, and *KRAS* in bottom frames). In both patients, a sigmoid septum and a ventricular septal bulge are shown to occur without hypertrophy of the rest of the ventricular septum.

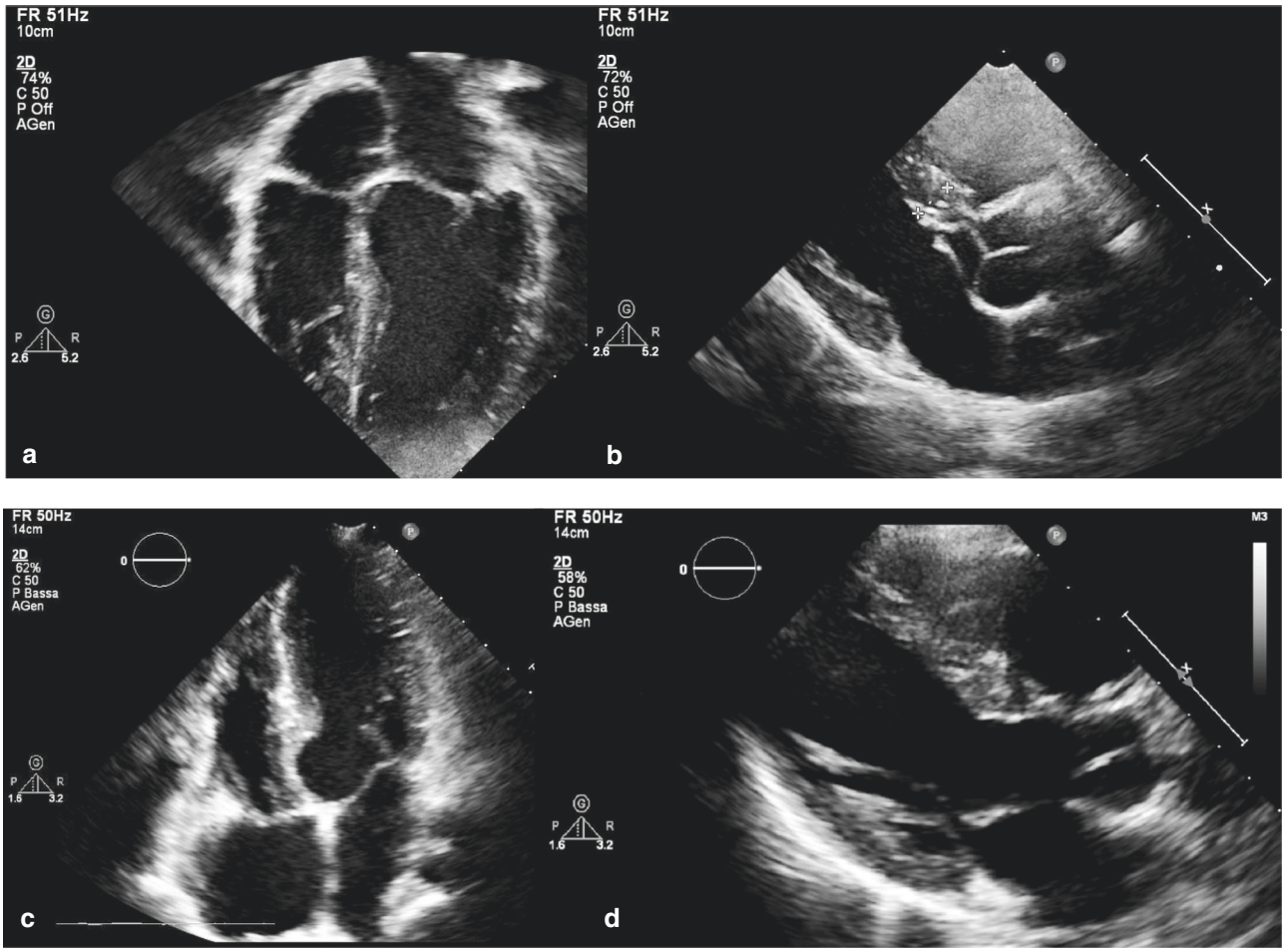

Fig. 2 Sigmoid-shaped ventricular septum in patients with Costello syndrome and cardio-facio-cutaneous syndrome. The figure shows two examples of sigmoid-shaped ventricular septum morphology observed by echocardiography in apical 4-chamber (**a**, **c**) and parasternal long-axis (**b**, **d**) views in Costello syndrome (*HRAS*, top frames) and in cardio-facio-cutaneous syndrome (*BRAF*, bottom frames) patients. It is noteworthy that the rest of the ventricular septum is not hypertrophied in these patients.

DATA AVAILABILITY

The data supporting the findings of this study are included in the article.

REFERENCES

1. Kauffman, H. et al. Genotype-phenotype association by echocardiography offers incremental value in patients with Noonan syndrome with multiple lentigines. *Pediatr. Res.* **90**, 444–451 (2021).
2. Pandit, B. et al. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. *Nat. Genet* **39**, 1007–1012 (2007).
3. Razzaque, M. A. et al. Germline gain-of-function mutations in RAF1 cause Noonan syndrome. *Nat. Genet* **39**, 1013–1017 (2007).
4. Gripp, K. W. et al. Costello syndrome: clinical phenotype, genotype, and management guidelines. *Am. J. Med. Genet A* **179**, 1725–1744 (2019).
5. Sarkozy, A., Digilio, M. C. & Dallapiccola, B. Leopard syndrome. *Orphanet J. Rare Dis.* **3**, 13 (2008).
6. Prendiville, T. W. et al. Cardiovascular disease in Noonan syndrome. *Arch. Dis. Child.* **99**, 629–634 (2014).
7. Roberts, A. E., Allanson, J. E., Tartaglia, M. & Gelb, B. D. Noonan syndrome. *Lancet* **381**, 333–342 (2013).
8. Pierpont, M. E. M. et al. Cardio-facio-cutaneous syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* **134**, e1149–e1162 (2014).
9. Leoni, C. et al. Genotype-cardiac phenotype correlations in a large single-center cohort of patients affected by RASopathies: clinical implications and literature review. *Am. J. Med. Genet Pt A* **188**, 431–445 (2022).
10. Authors/Task Force members et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur. Heart J.* **35**, 2733–2779 (2014).

AUTHOR CONTRIBUTIONS

A.B.D. performed the acquisition and interpretation of data, drafted the manuscript, and made substantial contributions, including assisting with re-drafting the paper and revising it critically for important intellectual content. R.B. contributed to data collection, managed literature research, drafted and corrected the article. C.L. contributed to data collection and reviewed the drafts of the manuscript. M.T. and G.Z. contributed to revising the article critically for important intellectual content. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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