Response to Calgani *et al*.

To the Editor: We appreciate the commentary by Dr Calcagni and colleagues[1] regarding our article entitled "Genotype and Phenotype in Patients With Noonan Syndrome and a *RIT1* Mutation."[2] The authors share their own experience with particular respect to the cardiovascular phenotype in nine patients with *RIT1* mutation. *RIT1* mutations accounted for 6% of cases in their patient cohort, thus confirming that *RIT1* is one of the four most common genes associated with Noonan syndrome. The authors also confirmed a high rate of cardiac and lymphatic involvement in their patients. Two additional series of patients with *RIT1* mutations comprising 14 and 44 affected individuals, respectively, have also been reported.[3,4] Including these recently published studies, 94% of a total of more than 120 reported *RIT1* mutation-positive individuals had cardiac abnormalities, with pulmonary stenosis (64%), hypertrophic cardiomyopathy (45%), and septal defects (39%) being the most frequent.

Notably, Dr Calcagni and colleagues observed one affected infant with severe obstructive hypertrophic cardiomyopathy necessitating heart transplantation. Despite the high overall frequency of hypertrophic cardiomyopathy in *RIT1*-associated Noonan syndrome, such a severe disease expression with a life-threatening or fatal course in infancy still seems to be quite unusual compared to patients with *RAF1* mutations. Another patient had a partial atrioventricular canal defect, a type of heart defect that has not been reported previously in *RIT1*-associated Noonan syndrome but is known to belong to the spectrum of less common cardiac anomalies in RASopathies. Three patients in their small cohort had postnatal chylothorax or lymphedema, providing additional evidence that *RIT1* mutations confer a particular risk to lymphatic complications. This communication further underlines the importance of a thorough cardiologic follow-up and awareness of lymphatic anomalies in patients with Noonan syndrome in general and in those with *RIT1* mutations specifically.

DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Calcagni G, Baban A, Lepri FR, et al. Congenital heart defects in Noonan syndrome and *RIT1* mutation. *Genet Med* e-pub ahead of print 29 Sept, 2016.
2. Kouz K, Lissewski C, Spranger S, et al. Genotype and phenotype in patients with Noonan syndrome and a *RIT1* mutation. *Genet Med* e-pub ahead of print 21 April, 2016.
3. Cavé H, Caye A, Ghedira N, et al. Mutations in RIT1 cause Noonan syndrome with possible juvenile myelomonocytic leukemia but are not involved in acute lymphoblastic leukemia. *Eur J Hum Genet* 2016;24:1124–1131.
4. Yaoita M, Niihori T, Mizuno S, et al. Spectrum of mutations and genotype-phenotype analysis in Noonan syndrome patients with RIT1 mutations. *Hum Genet* 2016;135:209–222.

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