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Natural history of *MRAS*-related Noonan syndrome: Evidence of mild adult-onset left ventricular hypertrophy and neuropsychiatric features

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Abstract

Gain of function pathogenic variants in *MRAS* have been found in a small subset of pediatric subjects presenting with Noonan syndrome (NS) associated with hypertrophic cardiomyopathy (HCM) and moderate to severe intellectual disability. These variants are considered to confer a high-risk for the development of severe HCM with poor prognosis and fatal outcome. We report on the natural history of the first adult subject with NS carrying the recurrent pathogenic p.Thr68Ile amino acid substitution. Different from what had previously been observed, he presented with a mild, late-onset left ventricular hypertrophy, and a constellation of additional symptoms rarely seen in NS. The present case provides evidence that HCM does not represent an obligatory, early-onset and severe complication in subjects with *MRAS* variants. It also adds new data about late-onset features suggesting that other unexpected complications might be observed in adult subjects providing anticipatory guidance for individuals of all age.

KEYWORDS
genotype–phenotype correlations, natural history, Noonan syndrome, RASopathies

1 | INTRODUCTION

The term "RASopathies" refers to a group of genetic conditions caused by upregulated RAS signaling through the mitogen-activated protein kinase (MAPK) pathway (Tartaglia & Gelb, 2010). This class of diseases represents one of the most frequent nonchromosomal disorders affecting development. Noonan syndrome (NS [MIM PS163950]), the most common entity among the RASopathies, is mainly characterized by short stature, a wide spectrum of congenital heart defects (CHDs), and a distinctive facial gestalt (e.g., relative macrocephaly, hypertelorism with downslanted palpebral fissures, ptosis, and low-set posteriorly rotated ears), associated with a recognizable pattern of features, including short stature, pectus anomalies, low posterior hairline, and a broad/webbed neck (Roberts, Allanson, Tartaglia, & Gelb, 2013; Tartaglia, Gelb, & Zenker, 2011). Subjects with NS show an increased risk for bleeding disorders and certain

malignancies, and may have variable developmental delay/intellectual disability (DD/ID), cognitive deficits and behavioral abnormalities, as well (Zenker, 2022). CHDs include a high prevalence of pulmonic valve stenosis (PVS) and hypertrophic cardiomyopathy (HCM), the latter occurring in approximately 20% of the general NS population (Roberts et al., 2013). Many of these features are shared with other RASopathies (e.g., cardiofaciocutaneous syndrome [MIM PS115150], Mazzanti syndrome [MIM PS607721], Costello syndrome [MIM 218040], Legius syndrome [MIM 611431], and neurofibromatosis type I [MIM 162200]) (Tartaglia, Aoki, & Gelb, 2022).

Usually, HCM has an early-onset, with a greater rate of congestive heart failure, left ventricular outflow obstruction, and earlier mortality with respect to other pediatric forms of HCM (Lioncino et al., 2022). NS has been associated with pathogenic variants in more than 12 genes encoding proteins with a role in the RAS-MAPK signaling pathway (Tartaglia et al., 2022), and is mainly transmitted as an autosomal dominant trait with a high proportion of de novo mutations. Rare recessive forms associated with biallelic inactivating variants in *LZTR1* and *SPRED2* have been recently identified, as well (Johnston et al., 2018; Motta et al., 2021).

MRAS (MIM 608435) encodes a small monomeric GTPase of the RAS family controlling multiple signaling pathways including the MAPK and PI3K-AKT cascades (Nakhaei-Rad et al., 2018; Wennerberg et al., 2005). Gain-of-function (GoF) variants in *MRAS* have been found in six pediatric subjects presenting with NS (Higgins et al., 2017; Motta et al., 2020; Pires et al., 2021; Suzuki et al., 2019). All of them had moderate to severe ID and showed severe HCM, which was fatal in two cases during the first months of life (Motta et al., 2020; Pires et al., 2021). Here, we describe the natural history of the first adult subject with the recurrent p.Thr68Ile substitution presenting with NS, who showed ID and developed mild late-onset left ventricular hypertrophy associated with a rare cardiac malformation (i.e., interatrial septal aneurism [IASA]) and mitral valve prolapse. He also presented with additional clinical features previously unreported in *MRAS*-related NS and extremely rare in the overall NS population, which recommend a specific long-term follow-up.

2 | CLINICAL REPORT

The proband is a 40-year-old man, the first son of nonconsanguineous healthy parents. He has two healthy brothers and two sisters. The mother had five first-trimester miscarriages during her reproductive life. He was born at term by Cesarean section because of multiple umbilical cord wrapping around the neck, after an uneventful pregnancy. His birth weight was 3,300 g (−0.42 *SD*, 34° centile), birth length and occipital-frontal circumference (OFC) not being reported. He had psychomotor delay: head control was achieved at 4 months, he sat autonomously at 8 months, walked alone at 15 months, and pronounced his first words at 4 years. At 5 years, slight abnormalities in the EEG pattern without clinical relevance were noted. He subsequently suffered from complex partial seizures at 14 years, for which he was pharmacologically treated with carbamazepine and partially controlled. At 7 years and 7 months, growth parameters were as follows: height 119 cm (−1.15 *SD*, 12th centile), weight 23.5 kg (−0.30 *SD*, 38th centile), and OFC 55 cm (+2 *SD*, 98th centile). At 14 years, right convex scoliosis, dorsal kyphosis, and pectus carenatum were documented. At 19 years, he developed psychiatric symptoms with easily provoked outburst, heteroaggressive and autoaggressive behavior, foul language, destructive and inappropriate social behavior, autistic closure with a diagnosis of schizophrenic psychosis, which was pharmacologically treated with multidrug therapy. At 20 years, a lipoma at the right forearm with axillary reactive lymph nodes was surgically removed.

At last observation (39 years), he had broad forehead, laterally sparse bushy eyebrows, ptosis, downslanted palpebral fissures, low-set posteriorly rotated ears, bulbous nasal tip, upturned nostrils, prominence of nasolabial sulci, long deep philtrum, M-shaped upper lip with full lower lip, pointed chin, mild short/webbed neck, and pectus carinatum. A clinical diagnosis of NS was made. The echocardiogram revealed mild hypertrophic left ventriculum, with a ventricular pump function within the normal range (ejection fraction 66%), IASA, and mitral valve prolapse.

3 | MOLECULAR ANALYSES

Parallel sequencing using a multigene panel including all known genes implicated in RASopathies (see Supplemental Methods of Appendix S1) revealed a heterozygous pathogenic variant, c.203C>T (NM_001085049.3), in exon 3 of *MRAS*, predicting the substitution of a threonine residue by isoleucine at codon 68 (p.Thr68Ile), which had previously been reported as a de novo event in three individuals with NS (Higgins et al., 2017; Motta et al., 2020; Pires et al., 2021). The variant was validated by Sanger sequencing, which also confirmed its presence in genomic DNA extracted from cultured fibroblasts. Parental DNA specimens were not available for segregation analysis. Since the occurrence of the unusual psychiatric features, exome sequencing was also performed using DNA from peripheral blood leukocytes (Supplemental Methods of Appendix S1), which excluded the occurrence of additional clinically relevant variants in genes implicated in neurobehavioral and psychiatric disorders (Table S1).

4 | DISCUSSION

Here, we report on the first adult individual carrying the recurrent pathogenic c.203C>T change (p.Thr68Ile) in *MRAS* and showing mild cardiac findings associated with a constellation of unusual features in NS. The p.Thr68Ile substitution has previously been reported in three other individuals showing severe neonatal/early-onset HCM. This report highlights the variability in cardiac presentation of pathogenic *MRAS* variants, and profile the natural history of NS caused by a GoF variant in this gene.

MRAS is highly homologous to other GTPases of the RAS family mutated in RASopathies (i.e., *HRAS*, *NRAS*, *KRAS*, Rand *RRAS2*). The

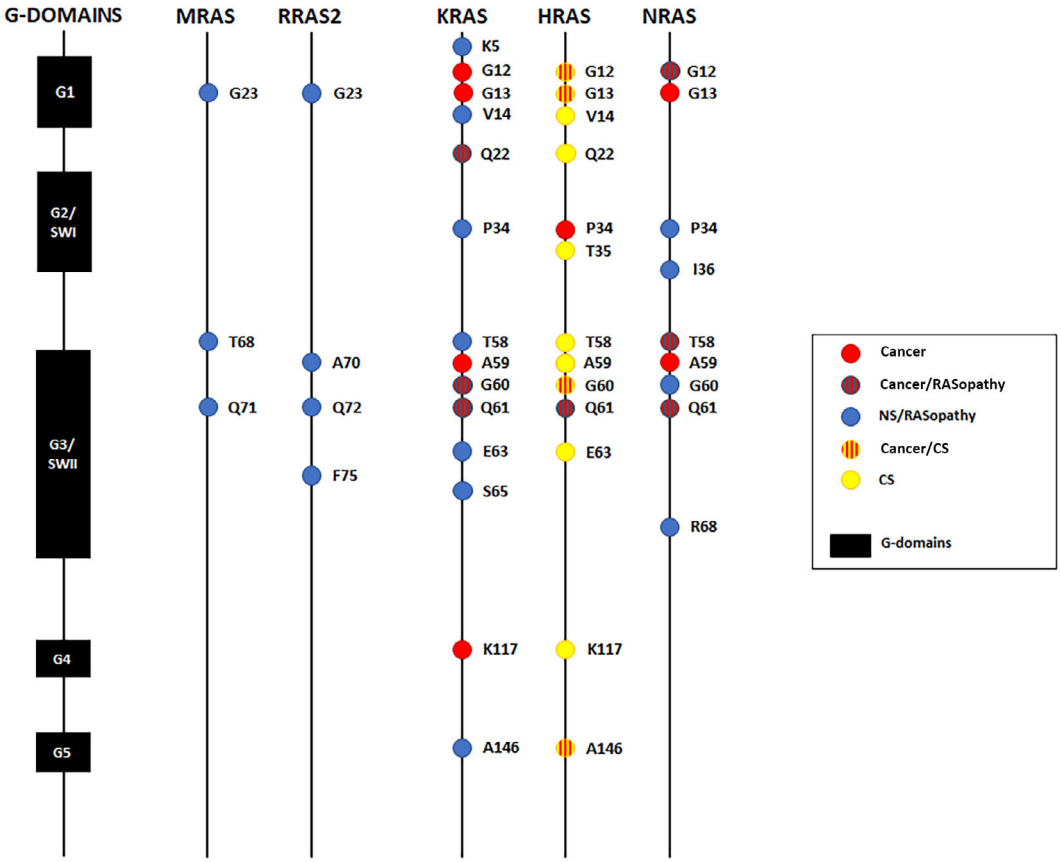

FIGURE 1 Affected amino acid residues of RAS GTPases implicated in RASopathies. Residues of MRAS mutated in Noonan syndrome and those affected in other RAS GTPases implicated in RASopathies are shown together with the major functional motifs/domains characterizing these proteins. Only likely pathogenic/pathogenic variants are reported. Residues affected by somatic mutations contributing to oncogenesis are also shown. Homologous residues are aligned. CFCS, cardiofaciocutaneous syndrome; CS, Costello syndrome; NS, Noonan syndrome.

recurrent pathogenic changes found in *MRAS* have also been found at homologous residues in other *RAS* genes (Figure 1). These changes can be either associated at germline level with NS and other RASopathies (i.e., cardiofaciocutaneous syndrome and Costello syndrome) or, somatically, with different types of tumors (Figure 1). Although the small number of individuals carrying pathogenic *MRAS* variants, our case supports the definition of a mutational hotspot, being the fourth one found heterozygous for the p.Thr68Ile substitution. Variants at just two other *MRAS* residues (Gly23 and Gln71) have been identified, indicating the occurrence of a narrow spectrum of missense variants causing NS.

MRAS interacts with SHOC2 and the catalytic subunit of protein phosphatase 1 (PP1C) to form a heterotrimeric holoenzyme with phosphatase activity (Rodriguez-Viciana, Oses-Prieto, Burlingame, Fried, & McCormick, 2006). RAF proteins are major RAS effectors that, under basal conditions, are maintained in an autoinhibited conformation through 14–3–3 protein binding. The dephosphorylation of the inhibitory Ser259 residue in RAF1 (Ser365 in BRAF) by the MRAS–SHOC2–PP1C holophosphatase results in the partial dissociation of the RAF–14–3–3 protein complex, favoring stable RAF–RAS binding and activation of the kinase (Liau et al., 2022). The Thr68Ile substitution is located in a region that does not directly interact with the ternary complex MRAS–SHOC2–PP1C, but has been demonstrated to maintain the GTPase in its active GTP-bound conformation and has been proved to promote a more stable translocation of the SHOC2–PP1C complex to the plasma membrane, leading to an enhanced activation of the MAPK pathway (Liau et al., 2022; Motta et al., 2020; Young et al., 2018).

We report on the oldest individual affected with *MRAS*-related NS providing an overview of the clinical presentation and natural history of the disorder. In particular, he showed psychomotor and speech delay, adolescent seizures (onset at 14 years), psychiatric symptoms, late-onset cardiac involvement, mild musculoskeletal abnormalities, and a lipoma at the right forearm. The clinical presentation of the subject offers a unique opportunity to re-evaluate the clinical presentation and natural history of *MRAS*-related NS. The subject showed mild late-onset left ventricular hypertrophy. This finding is striking in contrast with what has previously been reported in other *MRAS*-related NS individuals who presented with very early-onset HCM, characterized by a severe and progressive course including cardiac arrest in the newborn period, eventually leading to cardiac failure and premature death in two subjects (Table 1). The previously reported homogeneity of the cardiac phenotype is in contrast with the overall prevalence of HCM in NS, thus it was acknowledged that variants in *MRAS* are likely

TABLE 1 Clinical features of the subjects with clinical diagnosis of Noonan syndrome and pathogenic variants in *MRAS*

	Present case	Higgins et al. (2017)		Suzuki et al. (2019)	Motta et al. (2020)		Pires et al. (2021)	Total
Age	40 years	17 years	6 years	15 months	27 months	Newborn	2 months	
Amino acid substitution	Thr68Ile	Gly23Val	Thr68Ile	Gln71Arg	Thr68Ile	Gly23Arg	Thr68Ile	
Outcome	Alive	Alive	Alive	Alive	Alive	Exitus (2 mo)	Exitus (2 mo)	
Short stature	+	+	NR	+	+	−	−	4/6
DD/ID	+	+	+	+	+	NA	NA	5/5
Facial features								
Broad forehead	+	+	+	+	NR/NA	+	+	6/6
Hypertelorism	+	+	+	+	+	+	+	7/7
Bushy eyebrows, laterally sparse	+	+	+[a]	+	NR/NA	NR/NA	−	4/5
Downslanted palpebral fissures	+ (mild)	−	+	+	NR/NA	+	+	5/6
Ptosis	+	+ (mild)	+	+	+	+	−	6/7
Depressed nasal bridge	−	−	+[a]	+	+	NR/NA	+	4/6
Short nose	+ (mild)	−	+[a]	+	+	NR/NA	+[a]	5/6
Bulbous nose	+	+	+[a]	+	+	NR/NA	+[a]	6/6
Anteverted nostrils	+	+	+[a]	+	+	NR/NA	+	6/6
Full drooping cheeks	+	+	+[a]	+	+	NR/NA	+[a]	6/6
Increased nasolabial folds	+	+	+[a]	−	+	NR/NA	+[a]	5/6
Long philtrum	+	−	+[a]	+	+	NR/NA	+	5/6
Smooth/deep philtrum (S/D)	D	−	S	D	S	NR/NA	D	5/6
M shaped upper lip	+	NA	+[a]	+	NR/NA	NR/NA	+	4/4
Full lower lip	+	+	+[a]	+	Small mouth	NR/NA	+	5/6
Pointed chin	+	Retrognatia	+	Retrognatia	Retrognatia	NR/NA	Retrognatia	6/6
Low set ears	+	+	+	+	NR/NA	+	NR	5/5
Short/webbed neck	+	−	NR	NR	NR/NA	+	NR	2/3
Sparse hair	−	−	+	−	+	NR/NA	+	3/6
Cardiac findings	Adult-onset LVH, IASA, MVP	Early-onset HCM (myectomy)	Severe early-onset HCM, PVS, ASD	Early-onset HCM (severe cardiac arrest)	Early-onset progressive HCM, ASD	Early-onset progressive HCM	Early-onset progressive HCM (myectomy), LVAA, ASD	7/7

Abbreviations: ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; IASA, interatrial sept aneurism; LVAA, left ventricular apical aneurism; LVH, left ventricular hypertrophy; MVP, mitral valve prolapse; NR/NA, not reported/not assessed; PVS, pulmonic valve stenosis.

[a]Evaluated from clinical pictures.

to confer a high-risk for the development of severe HCM with poor prognosis and fatal outcome. To the best of our knowledge, the present subject represents the first report of *MRAS*-related NS who shows mild cardiac involvement (IASA and mild mitral valve prolapse). IASA is an unusual CHD; it has rarely been seen in NS subjects, who show ventricular septum aneurysms more frequently (Otsuka et al., 2006). This finding has a relevant importance in long-term follow-up, being IASA associated with a higher risk for cerebrovascular events (Gallet et al., 1985). It is possible that other *MRAS*-related NS individuals may not have been evidenced with IASA due to their young age or premature death. Of note, the p.Thr68Ile change has been found twice in patients with HCM and other associated CHDs: atrial septum defect (ASD) and PVS (Higgins et al., 2017) and ASD with left ventriculum apical aneurism (LVAA) (Pires et al., 2021). Among them, LVAA seems to be the most functionally related anomaly with IASA.

The present subject presented with complex partial seizures at 14 years. Recurrent seizures have rarely been reported in NS individuals (Romano et al., 2010), but are much more represented in CFCS and, less frequently, in Mazzanti syndrome caused by pathogenic variants in *BRAF*, *MAP2K1*, *MAP2K2*, *SHOC2*, and *PPP1CB* (Battaglia et al., 2021; Motta et al., 2022; Pierpont et al., 2022). All these proteins physically interact with MRAS (i.e., forming the MRAS–SHOC2–PP1C complex) and/or are tiers of the MAPK cascade, highlighting a common molecular mechanism strictly related to MAPK signaling dysregulation in the pathogenesis of seizures.

The subject was also affected with severe psychosis diagnosed in his twenties. Major psychiatric disorders are described as sporadic cases in NS, typically with a mid-life onset and usually presenting with co-occurring ID (Verhoeven, Wingbermühle, Egger, van der Burgt, & Tuinier, 2008). Although we cannot definitely exclude the co-occurrence of different neurological and psychiatric conditions in the same individual, dedicated surveillance in *MRAS*-related NS subjects after puberty could be eventually considered, to exclude late-onset presentation.

The proband was also diagnosed with a large lipoma at the right forearm with axillary reactive lymph nodes, which was surgically treated at 20 years. Lipomas are a rare finding in RASopathies. The review of the literature evidenced one individual with *NRAS*-related NS and a cerebral lipoma (Altmüller et al., 2017) and one case of dominantly inherited *LZTR1* pathogenic variant in a NS individual showing a thoracic lipoma (Farncombe, Thain, Barnett-Tapia, Sadeghian, & Kim, 2022). On the other hand, somatic mutations in *HRAS* have recently been reported in vascular malformation/overgrowth syndromes (VMOS) characterized by congenital aberrant vascular structures combined with overgrowth of surrounding tissues, whose characterization may also include histological description ascribed to lipomas (Eijkelenboom et al., 2019). Most of the identified variants are known pathogenic substitutions with oncogenic behavior, mainly located at residues 12, 13, 61, and 146. In seven cases, a somatic duplication of 7–10 amino acid residues within the switch II region was identified. Previously, two unrelated subjects affected with mild CS and carrying an overlapping in-frame duplication (p.Glu63_Asp69dup) have been described (Lorenz et al., 2013; Xu, Wang, Lin, & Yu, 2015). A similar somatic and an addition germinal insertion in *KRAS* have been found in one VMOS and in one NS individual, respectively (Eijkelenboom et al., 2019). They are all located very near to or comprising the Thr58 residue, which is homologous to the Thr68 residue of MRAS. All these variants have been proved to act as weakly but constitutively activating substitutions determining an increased affinity for the RAS binding domain of RAF proteins. Although it would have been interesting to more accurately classify the nature of the lesion that was histologically identified as lipoma, soft tissue MRI could not be performed in order to verify a possible vascularization. Unfortunately, residual specimens were not available for further analyses due to long time from the first evaluation.

The present report emphasizes the relevance of reaching a molecular diagnosis in adult patients in terms of generating new knowledge. The evolution of phenotypes in rare diseases is one of the most challenging diagnostic difficulties in clinical practice. The vast majority of genetic diagnoses obtained through genomic sequencing are mostly achieved in childhood to late adolescence, and due to the low prevalence of individual rare diseases, very little is known about their natural history and clinical spectrum during adulthood. Although RASopathies are relatively frequent conditions, some of them are caused by rare pathogenic variants in recently identified genes, with very few subjects described, leading to uncertainty about prognosis. Pathogenic *MRAS* variants have been commonly recognized as conferring a high-risk for HCM and ID with a severe prognosis. The present case provides evidence that HCM does not represent an obligatory, early-onset, and severe complication in subjects with *MRAS* variants, even in individuals with the recurrent p.Thr68Ile substitution. It also adds new data about late-onset features suggesting that other unexpected complications might be observed in adult subjects providing anticipatory guidance for individuals of all age.

The profiling of the natural history in rare diseases is also of great value in long-term follow-up and managing of concomitant diseases whose course might be exacerbated by the pre-existing genetic disorder, eventually improving their healthcare outcomes. In this specific case, the presence of IASA suggests a higher risk for cerebrovascular events, recommending high blood pressure accurate monitoring and treatment.

AUTHOR CONTRIBUTIONS

Manuela Priolo: Conceptualization, writing - original draft preparation; Patient enrollment and clinical data collection and analysis; Data curation. **Cecilia Mancini:** Exome sequencing analysis; Targeted resequencing and data validation. **Francesca Clementina Radio:** Clinical data collection and analysis; Data curation. **Luigi Chiriatti:** Targeted resequencing and data validation.

Andrea Ciolfi: Exome sequencing analysis; Data curation. **Camilla Cappelletti:** Exome sequencing analysis; Targeted resequencing and data validation. **Viviana Cordeddu:** Exome sequencing analysis. **Letizia Pintomalli:** Targeted resequencing and data validation. **Alfredo Brusco:** Targeted resequencing and data validation. **Corrado Mammi:** Patient enrollment and clinical data collection. **Marco Tartaglia:**

Conceptualization, writing - original draft preparation; Data curation. All authors: Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (M. P. and M.T.). The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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