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# In Response to: Pediatric Myelodysplastic Syndrome with Germline RRAS Mutation: Expanding the Phenotype of RASopathies

***To the Editor:***

In response to the case report by Catts et al,[1] we present a second patient with myelodysplastic syndrome (MDS) and the same *de novo* germline *RRAS* variant. The female patient was born with pulmonary subvalvular and valvular stenosis, which was surgically corrected at age 3. She had normal growth and development and attended regular education. She presented with frequent nosebleeds and menorrhagia at age 15 without probable cause. Two years later she presented with fatigue and persistent menorrhagia, she had low platelets and was diagnosed with MDS with monosomy 7. The patient was treated with an allogeneic stem cell transplantation (matched unrelated donor). During treatment she presented with pain and paralysis of the lower extremities making her confined to a wheelchair, diagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP). Revision of a chest computed tomography made before the stem cell transplantation showed thickened nerves, indicating pretreatment myelinization abnormalities. After treatment with intravenous immunoglobulins, the patient could walk independent, but paresis was not completely resolved.

Because of the congenital heart disease, unclassified bleeding disorder and MDS, the patient was referred to a clinical geneticist who suspected Noonan syndrome (NS). Physical examination revealed no typical physical features. NS gene panel testing was negative, and SNP array analysis was normal. Trio whole exome sequencing revealed a *de novo* heterozygous germline *RRAS* variant, c.116_118dup, p.Gly39dup. This variant was confirmed by Sanger sequencing in DNA derived from a blood sample taken at age 1, excluding an MDS-related somatic mutation. A highly similar case was reported by Au et al.[2] They described a 23-year-old male with subvalvular pulmonary stenosis and concurrent acute demyelinating neuropathy and MDS with monosomy 7. Genetic testing was declined by the family. The patient reported by Catts et al[1] was born with craniosynostosis, mild dysmorphic features and developed MDS with monosomy 7 at age 7. A third patient with this *de novo* variant is a 16-year-old girl with dysmorphic facial features resembling NS and short stature. Her medical history revealed a pulmonary stenosis, delayed motor development, feeding difficulties, and acute myeloid leukemia suspected to represent a blast crisis of juvenile myelomonocytic leukemic at age 13.[3] This author also reported a 51-year-old woman with an *RRAS* c.163G > A, p.Val55Met variant. Physical examination showed dysmorphic facial features, suggesting NS, and she developed an unspecified bone tumor during childhood.

These cases show a diversity of symptoms in patients with germline *RRAS* variants partially overlapping with clinical symptoms of NS. In the patient reported here, the demyelinating neuropathy was striking. *RRAS* plays an essential role in the differentiation, proliferation, and survival of oligodendrocytes responsible for axon myelination, which might suggest a causal relation.[4] Four patients developed a childhood malignancy, including three patients with a hematologic malignancy. This may indicate a higher penetrance for cancer in patients with germline *RRAS* variants compared with other NS (like) genes. We support the recommendation by Catts et al to add *RRAS* to the list of genes tested when a RASopathy is suspected. Additionally, we recommend including *RRAS* in pediatric cancer predisposition gene panels.


**Nienke van Engelen, MD***
**Illja Diets, PhD†**
**Dorine Bresters, PhD***
**Janneke C. van den Bergen, PhD***
**Alexander F.J.E. Vrancken, PhD‡**
**Roland P. Kuiper, PhD***
**Marjolijn C.J. Jongmans, PhD*§**
*Princess Máxima Center for Pediatric Oncology
‡Department of Neurology, Brain Centre Rudolf Magnus, University Medical Centre
§Department of Genetics, University Medical Center Utrecht, Utrecht
†Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands



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