Severe congenital neutropenia, SRP54 pathogenicity, and a Framework for Surveillance

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March 26, 2023

Received: 28 October 2022 | Revised: 10 January 2023 | Accepted: 6 February 2023

DOI: 10.1002/ajmg.a.63156

CASE REPORT

AMERICAN JOURNAL OF medical genetics PART A WILEY

Severe congenital neutropenia, *SRP54* pathogenicity, and a framework for surveillance

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Abstract

Severe congenital neutropenia (SCN) is a rare disorder, often due to pathogenic variants in genes such as *ELANE*, *HAX1*, and *SBDS*. *SRP54* pathogenic variants are associated with SCN and Shwachman-Diamond-like syndrome. Thirty-eight patients with *SRP54*-related SCN are reported in the literature. We present an infant with SCN, without classic Shwachman-Diamond syndrome features, who presented with recurrent bacterial infections and an *SRP54* (c.349_351del) pathogenic variant. Despite ongoing granulocyte colony-stimulating factor therapy, this patient has no evidence of malignant transformation. Here we establish a framework for the future development of universal guidelines to care for this patient population.

KEYWORDS
severe congenital neutropenia, *SRP54*, surveillance

1 | INTRODUCTION

Severe congenital neutropenia (SCN) is a rare disorder with a prevalence of approximately 8.5 cases per million people. Early severe and recurrent bacterial infections with profound neutropenia (absolute neutrophil count <500 cells/μL) and arrested maturation of myelopoiesis in the bone marrow are characteristic of SCN (Donadieu et al., 2013). Treatment for SCN includes granulocyte colony-stimulating factor (G-CSF), which promotes neutrophil maturation and decreases infection risk. Unfortunately, patients with SCN are at increased risk for developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) (Rosenberg et al., 2010), and G-CSF dosing/response is correlated with increased risk for leukemogenesis (Donadieu et al., 2005; Rosenberg et al., 2006). Hematopoietic stem cell transplant (HSCT) is often considered in patients who are refractory to high-dose G-CSF (Rosenberg et al., 2006). To date, more than 20 identifiable genes are associated with SCN, including *ELANE*, *HAX1*, and *SBDS* (Donadieu et al., 2017). Pathogenic variants in *ELANE* are the most prevalent, comprising 50% of all SCN cases. While pathogenic variants in other known SCN genes comprise approximately 20% of cases, 30% of SCN patients do not have an identifiable known genetic predisposition (Dale et al., 2000; Donadieu et al., 2017; Xia et al., 2009). Genetic testing in SCN patients is vital, as it provides important insight into additional risks for MDS/AML or other extra-hematologic manifestations and aids in the decision-making for cascade testing of family members.

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by bone marrow failure (BMF), exocrine pancreatic insufficiency, skeletal abnormalities, and immune dysfunction (Nelson & Myers, 2018; Shwachman et al., 1964). Similar to SCN, SDS with biallelic SBDS pathogenic variants also portends an increased risk for MDS/AML (8.1%–20% in previous studies), although the exact risk is undetermined (Nelson & Myers, 2018). *SBDS* pathogenic variants are present in 75%–89% of SDS patients (Boocock et al., 2003; Kuijpers et al., 2005); however, new pathogenic variants in other genes are continually being discovered (Stepensky et al., 2017; Tummala et al., 2016).

Abbreviations: AML, acute myelogenous leukemia; ANC, absolute neutrophil count; B-ALL, B-cell acute lymphoblastic leukemia; BMF, bone marrow failure; FISH, fluorescence in situ hybridization; G-CSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplant; MDS, myelodysplastic syndrome; PID, primary immunodeficiency; SCN, severe congenital neutropenia; SDS, Shwachman-Diamond syndrome.

Previously presented as a poster abstract "*SRP54*, a Novel Severe Congenital Neutropenia and Shwachman-Diamond-Like Syndrome Pathogenic Variant" at the American Society of Pediatric Hematology/Oncology Annual Meeting. May 2022. Pittsburgh, PA.

Recently, *SRP54* pathogenic variants have been associated with SCN and SDS-like disease, with phenotypes including exocrine pancreatic insufficiency, neurodevelopmental delay, and skeletal dysplasia (Bellanne-Chantelot et al., 2018; Carapito et al., 2017; Carden et al., 2018; Erdos et al., 2022; Goldberg et al., 2020; Manabe et al., 2022; McCarthy et al., 2022; Saettini et al., 2020; Tamura et al., 2021). *SRP54* is a 54-kDa signal recognition particle GTPase protein. *SRP54* pathogenic variants are associated with increased protein flexibility, impaired GTP binding, and complex formation with the *SRP* receptor. This leads to protein secretion defects that impair granulocyte differentiation, causing apoptosis and autophagy (Juaire et al., 2021). To date, there are two reports of malignant transformation in individuals with *SRP54* pathogenic variants (Calvo et al., 2022; Sabulski et al., 2022). Here, we present a patient with *SRP54* pathogenic variant and SCN, along with a literature review, and propose surveillance recommendations for MDS/AML and other associated complications.

2 | METHODS

Patient demographics, clinical presentation, disease course, genetic results, and treatment response were reviewed using the electronic health record. A literature review of *SRP54*-related SCN was conducted via PubMed search using the terms "*SRP54*" and "neutropenia."

3 | CASE PRESENTATION

A 2-month-old infant was admitted to the pediatric intensive care unit with pneumonia requiring positive pressure ventilatory support. On admission, white blood cell count, hemoglobin, and platelet count were 14.5 $\times$ 10^3/μL, 9.9 g/dL, and 524 $\times$ 10^3/μL, respectively. The differential was remarkable for an absolute neutrophil count (ANC) of zero. As he recovered from the initial illness, his ANC spontaneously recovered to within the normal range. However, after recovery, the patient again presented with perianal abscesses due to *Enterobacter*, *Enterococcus*, and *Klebsiella* species requiring drainage, and ANC was found to be 0. He was treated acutely with three doses of G-CSF at 5 mg/kg, demonstrating improvement in ANC to 3.3 $\times$ 10^3/μL. However, upon discontinuing G-CSF, ANC again decreased to zero for 3 months. Due to concerns for ongoing severe infections, prophylactic G-CSF at 5 μg/kg was started at 5 months of age, and ANC normalized 2 weeks later. Initial bone marrow evaluation was delayed until 8 months of age to allow for growth and to decrease potential complications with general anesthesia. Bone marrow pathology review demonstrated hypocellular (60% cellularity) trilineage hematopoiesis, decreased absolute granulocyte number with left-shifted maturation, and no significant dysgranulopoiesis (Figure S1a–c). Flow cytometry was negative for leukemic blasts, and chromosome analysis demonstrated 46, XY karyotype. Further workup, including a primary pmmunodeficiency (PID) panel, revealed several heterozygous variants (*CLPB*, *FERMT*, *PRKDC*, *UNC93B1*) of unknown significance.

On subsequent hematology follow-up, his weight and height were noted to be less than the 3rd percentile. Due to the concerns for failure to thrive, an expanded workup for BMF syndromes was pursued. At 20 months of age, a BMF panel identified a pathogenic variant, c.349_351del (p.Thr117del) in *SRP54*. Repeat bone marrow evaluation at 23 months of age demonstrated improved cellularity (90%–100%), relative myeloid hypoplasia, and left-shifted granulopoiesis without malignancy. SDS expanded workup revealed no evidence of exocrine pancreatic insufficiency (no history of diarrhea, evaluated by pediatric gastroenterology, and pancreatic elastase was within normal limits) or skeletal dysplasia. His neurodevelopment has been normal thus far. The patient is now 4 years old and has been treated with daily G-CSF at 5–11 μg/kg with ANC within or near the normal range (1.2–5.4 $\times$ 10^3/μL). He is followed with annual surveillance bone marrow evaluations, which include chromosome analysis, MDS fluorescence *in situ* hybridization panel, and next-generation sequencing with a targeted myeloid malignancy panel.

The patient's family history is unremarkable. Genetic testing was recommended for the parents who tested negative for the *SRP54* pathogenic variants, suggesting that this variant arose *de novo* in the patient. The patient's two younger siblings had normal blood counts.

4 | DISCUSSION

SRP54 pathogenic variants were first described by Carapito et al. (2017). A year later, Bellanne-Chantelot et al. (2018) reported a large cohort of 23 SCN patients with *SRP54* pathogenic variants. Since then, additional case reports have been published, adding to the current literature on this rare genetic finding. Importantly, when considering a genetic workup for SCN, there is considerable overlap between PID and BMF syndromes. The case presented highlights the evolution of SCN pathogenicity and emphasizes the need for comprehensive genetic testing for patients with SCN. Many laboratories are now including *SRP54* in their PID and BMF panels, but the clinician must ensure a proper understanding of gene panel limitations when selecting testing.

Including our patient, 39 published cases of *SRP54*-related SCN have been reported (Table 1). Thirty-two (82%) have a history of severe or recurrent infections. Of the seven patients without a history of infection, four were family members identified during the proband's workup. Many patients were noted to have SDS-like features, including exocrine pancreatic insufficiency and neurodevelopmental delay. Most patients required G-CSF (87%) 2–30 μg/kg/day, with the majority responding. However, despite high-dose G-CSF, nine patients (23%) required HSCT—seven due to refractory neutropenia and two for subsequent leukemia diagnosis. Most patients remained alive post-HSCT. One patient died due to transplant-related complications (Calvo et al., 2022; Sabulski et al., 2022).

Patients with *SRP54* pathogenic variants display notable clinical differences from classical SDS. Most patients with *SRP54* and SCN

TABLE 1 39 reported patient cases from the current literature (including our patient) with *SRP54*-related severe congenital neutropenia.

Patient	Age at dx	Sex	Symptoms				ANC at dx (cells/μL)	G-CSF max dose (μg/kg/day)	Outcome	*SRP54* variant (inheritance)
			Severe or recurrent infections	Pancreatic insufficiency	Psychomotor, developmental delay, or autistic behaviors	Other symptoms				
1 (Carapito et al., 2017)	Newborn	M	+	+	+	ASD/VSD, dysmorphic features[a]	280	Unknown dose	HSCT at 4 y, alive at 6 y	c.677G>A, p.Gly226Glu (de novo)
2 (Carapito et al., 2017)	6 m	F	+	+	–	–	20	Unknown dose	HSCT at 1 y, died at 16 m of age from VOD	c.343A>G, p.Thr115Ala (de novo)
3 (Carapito et al., 2017)	4 y	M	+	–	+	–	760	5	Responding to G-CSF, alive at 18 y of age	c.349_351del, p.Thr117del (de novo)
4 (Carden et al., 2018)	Newborn	M	+	+	+	DiGeorge, VSD/IAA, FTT	<500	Unknown dose	HSCT at 32 m of age, alive at 3 y of age	c.349_351del, p.Thr117del (de novo)
5 (Bellanne-Chantelot et al., 2018)	9.8 m	M	+	–	–	–	270	5	Alive at 8 y of age	c.337G>C p.Gly113Arg (de novo)
6 (Bellanne-Chantelot et al., 2018)	4.6 m	M	+	+	–	–	443	20	Alive at 3 y of age	c.349_351del, p.Thr117del (de novo)
7 (Bellanne-Chantelot et al., 2018)	1.7 m	F	+	–	–	–	440	5	Alive at 15 y of age	c.349_351del, p.Thr117del (dominant: patient and father)
8 (Bellanne-Chantelot et al., 2018)	2.1 y	M	–	–	–	–	100	No G-CSF	Alive at 44 y of age	
9 (Bellanne-Chantelot et al., 2018)	10.6 m	M	+	–	+	–	190	50	HSCT at 1.5 y of age, alive at 11 y of age	c.349_351del, p.Thr117del (unknown)
10 (Bellanne-Chantelot et al., 2018)	5 y	M	–	–	–	Osteoporosis and type 2 diabetes	530	20	Alive at 32 y of age	c.349_351del, p.Thr117del (de novo)
11 (Bellanne-Chantelot et al., 2018)	Newborn	M	+	–	–	–	45	15	Alive at 10 y of age	c.349_351del, p.Thr117del (de novo)
12 (Bellanne-Chantelot et al., 2018)	10.1 m	F	–	–	–	–	120	10	Alive at 15 y of age	c.349_351del, p.Thr117del (de novo)
13 (Bellanne-Chantelot et al., 2018)	1 m	M	+	–	–	IUGR, GH deficiency	250	5	Alive at 24 y of age	c.349_351del, p.Thr117del (unknown)

(Continues)

TABLE 1 (Continued)

Patient	Age at dx	Sex	Symptoms				ANC at dx (cells/μL)	G-CSF max dose (μg/kg/day)	Outcome	*SRP54* variant (inheritance)
			Severe or recurrent infections	Pancreatic insufficiency	Psychomotor, developmental delay, or autistic behaviors	Other symptoms				
14 (Bellanne-Chantelot et al., 2018)	4.2 m	M	+	–	–	–	230	10	Alive at 11 y of age	c.349_351del, p.Thr117 (de novo)
15 (Bellanne-Chantelot et al., 2018)	12.7 m	M	+	–	–	–	360	5	Alive at 7 y of age	c.349_351del, p.Thr117del (de novo)
16 (Bellanne-Chantelot et al., 2018)	1.3 y	M	+	–	–	–	90	5	Alive at 39 y of age	c.349_351del, p.Thr117del (de novo)
17 (Bellanne-Chantelot et al., 2018)	Newborn	F	+	–	–	–	100	20	Alive at 3 y of age	c.349_351del, p.Thr117del (de novo)
18 (Bellanne-Chantelot et al., 2018)	Newborn	M	+	–	–	–	110	5	Alive at 6 y of age	c.349_351del, p.Thr117del (dominant)
19 (Bellanne-Chantelot et al., 2018)	20 y	F	–	–	–	–	345	No G-CSF	Alive at 28 y of age	
20 (Bellanne-Chantelot et al., 2018)	4.2 m	F	+	–	+	–	435	5	Alive at 17 y of age	c.353G > A, p.Cys118Tyr (dominant: patient, father, and brother)
21 (Bellanne-Chantelot et al., 2018)	2.8 m	M	+	–	+	–	960	5	Alive at 46 y of age	
22 (Bellanne-Chantelot et al., 2018)	8.3 m	M	–	–	–	–	1090	No G-CSF	Alive at 21 y of age	
23 (Bellanne-Chantelot et al., 2018; Calvo et al., 2022)	Newborn	F	+	–	+	–	215	10	B-ALL dx at 10 y. S/p HSCT, in remission 7 m post HSCT	c.407G>A, p.Cys136Tyr (de novo)
24 (Bellanne-Chantelot et al., 2018)	2.9 m	F	+	–	+	Short stature, obesity	144	30	Alive at 32 y of age	c.407G>A, p.Cys136Tyr (unknown)

TABLE 1 (Continued)

Patient	Age at dx	Sex	Symptoms				ANC at dx (cells/μL)	G-CSF max dose (μg/kg/day)	Outcome	*SRP54* variant (inheritance)
			Severe or recurrent infections	Pancreatic insufficiency	Psychomotor, developmental delay, or autistic behaviors	Other symptoms				
25 (Bellanne-Chantelot et al., 2018)	9 m	M	+	+	+	IUGR	106	5	Alive at 43 y of age	c.668C>A, p.Ala223Asp (de novo)
26 (Bellanne-Chantelot et al., 2018)	Newborn	M	+	−	+	−	220	50	HSCT at 6 m of age, alive at 1.5 y of age	c.677G>A, p.Gly226Glu (de novo)
27 (Bellanne-Chantelot et al., 2018)	1 m	M	+	+	+	IUGR, short stature, bone dysplasia	92	30	Alive at 25.6 y of age	c.821G>A, p.Gly274Asp (de novo)
28 (Saettini et al., 2020)	5 y	M	+	+	+	−	550	3	Responding to G-CSF, alive at 13 y of age	c.349_351del, p.Thr117del (de novo)
29 (Goldberg et al., 2020)	8 m	F	+	−	−	−	180	5	Responding to G-CSF, alive at 8 y of age	c.342_344del, p.T115del (de novo)
30 (Goldberg et al., 2020)	6 m	M	+	−	−	−	100	7.5	Responding to G-CSF, alive at 2 y of age	c.342_344del, p.Thr115del (dominant: patient, father, paternal uncle, and paternal aunt)
31 (Goldberg et al., 2020)	Unknown	M	+	−	−	−	100–600	2	Responding to G-CSF, other info unknown	
32 (Goldberg et al., 2020)	Unknown	M	+	−	−	−	200	Unknown G-CSF status	Unknown	
33 (Goldberg et al., 2020)	Unknown	F	−	−	−	−	Mild neutropenia (illnesses)	Unknown G-CSF status	Unknown	
34 (Tamura et al., 2021)	2 m	F	+	−	+	−	0	30	HSCT at 8 m of age, normal blood counts at 22 m of age	c.674G>A, p.Gly225Asp (de novo) c.821G>A, p.Gly274Asp (de novo)
35 (McCarthy et al., 2022)	Newborn	M	+	+	−	Short stature, congenital vertebral abnormalities	40	60	1st HSCT at 1 y of age, 2nd HSCT 13 m later. Alive at 7 y of age	c.331G > T, p.Gly111Trp (de novo)
36 (Manabe et al., 2022)	4 y	F	+	−	−	−	70	3	Responding to G-CSF, alive at 7.1 y of age	c.349_351del, p.Thr117del (de novo)
37 (Erdos et al., 2022)	11 y	F	+	+	−	Dolichocolon	<300	5	Responding to G-CSF, cyclic neutropenia	c.349_351del, p.Thr117del (de novo)

(Continues)

TABLE 1 (Continued)

Patient	Age at dx	Sex	Symptoms			ANC at dx (cells/μL)	G-CSF max dose (μg/kg/day)	Outcome	*SRP54* variant (inheritance)
			Severe or recurrent infections	Pancreatic insufficiency	Psychomotor, developmental delay, or autistic behaviors	Other symptoms			
38 (Sabulski et al., 2022)	2 m	M	−	−	+	−	0	3	Responding to G-CSF. AML dx at 15 y of age. In remission 9 m post HSCT	c.349_351del, p.Thr117del (de novo)
39	2 m	M	+	−	−	FTT	0	11	Responding to G-CSF, alive at 4 y of age	c.349_351del, p.Thr117del (de novo)

Note: Newborn is defined as under one month of age.

Abbreviations: ANC, absolute neutrophil count; ASD, atrial septal defect; dx, diagnosis; F, female; FTT, failure to thrive; G-CSF, granulocyte-colony stimulating factor; GH, growth hormone; HSCT, hematopoietic stem cell transplantation; IAA, interrupted aortic arch; IUGR, intrauterine growth restriction; m, months; M, male; VOD, veno-occlusive disease; VSD, ventricular septal defect; y, years.

[a]Low-set, asymmetric ears, thinning hair, frontal angioma, mandibular microretrognathism, a high-arched palate, small teeth, and a pectus carinatum.

TABLE 2 *SRP54* pathogenic variant surveillance recommendations.

Testing	Age of onset	Frequency
Complete blood count with peripheral blood smear review	At diagnosis	Every 3–4 months
Bone marrow evaluation (unilateral aspirate and biopsy) including immunophenotyping, histology, conventional karyotype, FISH for MDS-associated chromosomal aberrations, next-generation sequencing for myeloid malignancy associated pathogenic variants, i.e., *RUNX1*, *CSF3R*	At diagnosis	Every 1–3 years, based on peripheral blood counts, previous bone marrow results, and G-CSF use (if any abnormalities or G-CSF use, obtain annually)
Immunodeficiency workup	At diagnosis	N/A
Pancreatic testing (fecal elastase)	At diagnosis	Follow up as needed
Neuropsychological assessment	5 years	Follow up as needed
Skeletal survey	At diagnosis	Follow up as needed
Hematopoietic stem cell transplant consultation	Based on bone marrow results and G-CSF dose	N/A
Biological parental testing for *SRP54* pathogenic variant	At patient diagnosis	N/A

Abbreviations: FISH, fluorescence in situ hybridization; G-CSF, granulocyte colony-stimulating factor; MDS, myelodysplastic syndrome.

were diagnosed latr, with a median age of 4.2–6 months versus 1–1.3 years for SDS (Cesaro et al., 2020; Ginzberg et al., 1999). Unlike most SDS patients with exocrine pancreatic insufficiency (~90%) (Ginzberg et al., 1999), only 23% (9/39) of the patients with *SRP54* pathogenic variants and SCN had clinical or laboratory evidence of pancreatic insufficiency. While skeletal abnormalities, especially metaphyseal dysostosis, can occur in approximately half of SDS patients (Burroughs et al., 2009), only 5% (2/39) of *SRP54* patients had skeletal dysplasia. Additionally, neurocognitive delays often manifesting in SDS (76% of adults and 65% of children) (Perobelli et al., 2012) were less frequent in *SRP54* pathogenic variant patients (14/39, 36%).

The current literature lacks standard guidelines and expert consensus recommendations for managing *SRP54* pathogenic variants. Two reports published in 2022 described the first known malignant transformations in patients with *SRP54*-related SCN, one with B-cell acute lymphoblastic leukemia (Calvo et al., 2022) and the other with

AML (Sabulski et al., 2022). Interestingly, both patients also harbored *RUNX1* and *CSF3R* cytogenetic abnormalities, possibly associated with leukemogenesis in SCN (Skokowa et al., 2014). A previously reported French cohort of 231 SCN patients demonstrated an increased risk for leukemic transformation with a higher average/cumulative G-CSF dose. The exact "safe" dose to minimize malignant transformation risk is unclear, (Donadieu et al., 2005) and referral for HSCT consultation should be considered for patients refractory to "high-dose" G-CSF (≥8 μg/kg/day).

Considering *SRP54* pathogenic variants give rise to a hybrid condition with features of both SDS and SCN, we propose creating surveillance recommendations that include aspects of both entities (Table 2). While clinical history should be considered, given the limited data available on affected individuals with *SRP54* pathogenic variant, these recommendations serve as a framework for monitoring. They incorporate regular monitoring of peripheral blood counts, bone marrow surveillance, and associated symptom awareness. Referral for HSCT consultation should be made for patients requiring prolonged higher dose G-CSF treatment (≥8 μg/kg/day) and/or evidence of clonal evolution on bone marrow. The decision to undergo transplant should be made on an individual basis in consultation with a multidisciplinary BMF team with specific expertise in nonmalignant stem cell transplantation. Familial cascade genetic testing for biological parents is recommended to rule out familial *SRP54* pathogenic variants. Additionally, given the rarity of this condition, participation in local or national IRB-approved research protocols allowing for the collection of additional specimens for future research should be encouraged.

5 | CONCLUSION

SRP54 pathogenic variants are associated with a novel SCN syndrome and display some congruence with the extra-hematopoietic features of SDS, manifesting as a hybrid SDS/SCN-like disease. Due to its rarity, there are no consensus management guidelines for surveillance. We report a patient with *SRP54*-associated SCN who lacks SDS-like features. Additional reports of similar patients and longitudinal follow-up of currently reported patients will expand the knowledge of this rare entity and provide further guidance for clinicians and families.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. 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.

How to cite this article: Fan, E. M., Vagher, J., Meznarich, J. A., Ubico, E. M., Goteti, S., Peterson, D., Rayes, A., & Maese, L. D. (2023). Severe congenital neutropenia, *SRP54* pathogenicity, and a framework for surveillance. *American Journal of Medical Genetics Part A*, 1–8. https://doi.org/10.1002/ajmg.a.63156