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Expanded Phenotypic and Hematologic Abnormalities Beyond Bone Marrow Failure in *MECOM*-Associated Syndromes

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Abstract

The *MECOM* gene encodes multiple protein isoforms that are essential for hematopoietic stem cell self-renewal and maintenance. Germline *MECOM* variants have been associated with congenital thrombocytopenia, radioulnar synostosis and bone marrow failure; however, the phenotypic spectrum of *MECOM*-associated syndromes continues to expand and novel pathogenic variants continue to be identified. We describe nine unrelated patients who add to the previously known phenotypes and genetic defects of *MECOM*-associated syndromes. As each subject presented with unique *MECOM* variants, the series failed to demonstrate clear genotype to phenotype correlation but may suggest a role for additional modifiers that affect gene expression and subsequent phenotype. Recognition of the expanded hematologic and non-hematologic clinical features allows for rapid molecular diagnosis, early identification of life-threatening complications, and improved genetic counseling for families. A centralized international publicly accessible database to share annotated *MECOM* variants would advance their clinical interpretation and provide a foundation to perform functional *MECOM* studies.

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Author Contribution Statement: MMLC, AAB, ESR, AK and TAN contributed to the conception and design of the manuscript. MMLC, AAB, ESR, AK, ZA, JH, TJ, RGR, VGS, DAW and TAN helped acquisition, analysis, and interpretation of patient data. KD applied ACMG classification to assign variant pathogenicity. AAB analyzed molecular sequencing data to map variant locations. MMLC, AAB, ESR, KD and TAN drafted the initial manuscript and AK, ZA, JH, TJ, RGR, VGS, and DAW contributed to edits and revisions. All authors read and approved the final manuscript.

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Keywords

bone marrow failure; inherited bone marrow failure syndrome; *MECOM*; thrombocytopenia; radioulnar synostosis; aplastic anemia

INTRODUCTION

In pediatric bone marrow failure (BMF), the timely identification of pathogenic variants influences treatment decisions, secondary cancer screening, and counseling for families. Phenotypic diversity between and within known inherited BMF syndromes (IBMFS), however, challenges a provider's ability to target certain genes for analysis based on history and physical examination. As identification of new genes associated with BMF expands our definition of known IBMFS, re-examining the phenotype of these disorders is essential for accurate diagnosis.

The *MECOM* gene (Mendelian Inheritance in Man (MIM):165215), comprised of the myelodysplasia syndrome 1 (*MDS1*) and ecotropic viral integration 1 site (*EVI1*) complex loci, encodes multiple protein isoforms that regulate hematopoietic stem cell self-renewal and maintenance [Zhang et al., 2011; Buonamici et al., 2003]. *EVI1* encodes a 1051 amino acid protein, containing 10 zinc finger motifs, and is highly conserved between mice and humans with 94% homology [Buonamici et al., 2003; Hirai, 1999]. *MDS1* adds 188 amino acids encoded by alternative exons at the 5' end of the *EVI1* product (Figure 1) [Hirai, 1999]. *MECOM* expression is required for self-renewal of both embryonic and adult hematopoietic stem cells, as demonstrated in mouse models [Zhang et al., 2011; Kataoka and Kurokawa, 2012]. Furthermore, *MECOM* transcription factors are expressed at high levels in the embryonic heart, lungs, limb buds, nasal cavity, and urinary tract, suggesting an important role in multi-organ development [Buonamici et al., 2003; Perkins et al., 1991].

Overexpression of *MECOM* has been noted in 5–10% of acute myeloid leukemia, several solid tumors, and gene therapy-induced myelodysplastic syndrome (MDS) (MIM:614286) and is generally associated with a poor prognosis [Buonamici et al., 2003; Koos et al., 2011; Jazaeri et al., 2010; Stein et al., 2010; Liang and Wang, 2020]. In contrast, genomic variants that reduce *MECOM* expression have been implicated in the development of BMF [Zhang et al., 2011]. Several loss-of-function (LOF) variants and deletions have been previously reported in association with *MECOM*-related syndrome, supporting haploinsufficiency as a likely mechanism of disease [Germeshausen et al., 2018; Veken et al., 2018; Bouman et al., 2016; Nielsen et al., 2012; Niihori et al., 2015; Kurokawa et al., 1998]. Pathogenic *MECOM* variants (mutations) have previously been reported to cause syndromes involving congenital thrombocytopenia and radioulnar synostosis (Radioulnar Synostosis and Amegakaryocytic Thrombocytopenia or RUSAT) (MIM:616738) [Niihori et al., 2015, 2022]. Recently several case series reported *MECOM* variants in patients with cytopenias and varying systemic anomalies including renal, cardiac, limb, sensorineural hearing loss, and B-cell deficiency [Niihori et al., 2015; Germeshausen et al., 2018; Bluteau et al., 2018; Nielsen et al., 2012; Walne et al., 2018]. Germeshausen et al. coined the term *MECOM*-associated syndrome for this heterogenous group with congenital *MECOM* variants demonstrating a broad

phenotypic spectrum [Germeshausen et al., 2018]. Our objective was to further characterize the phenotypic spectrum of *MECOM*-associated syndrome using a cohort of patients with *MECOM* mutations identified at four North American institutions.

MATERIALS AND METHODS

With institutional review board approval, we performed a retrospective review of eight unrelated patients with *MECOM* alterations referred to Hematology services at Boston Children's Hospital (n=2), Children's Hospital Colorado (n=2), University of Utah (n=2) and Texas Children's Hospital (n=2). Clinical, laboratory, and genetic data were collected on patients and available family members (four of eight patients). Platforms for detecting genomic variants by CLIA-certified genetic testing laboratories included chromosomal microarray, targeted next-generation sequencing panels, exome sequencing (ES) and genome sequencing (GS) (Table 1). Platforms for confirming inheritance of variants included trio ES, trio GS, or targeted Sanger sequencing (Table 1).

RESULTS

Clinical characteristics of the eight patients are outlined in Table 2 and summarized in Supplementary Table 1. Seven of the patients were identified under the age of two years and had multiple malformations that required expedited evaluation. The remaining patient was diagnosed at 6 years of age and his diagnostic evaluation was triggered by persistent and evolving pancytopenia. Further evaluation revealed he had RUSAT. Within our full *MECOM*-associated syndrome cohort, skeletal abnormalities included radioulnar synostosis (n=5), clinodactyly (n=3), and radial hypoplasia (n=1) (Table 2). Additional anomalies included craniofacial [micro- or macrocephaly (head circumference below or 2 standard deviations above the mean for age and gender; equivalent to 3% or 97% on standardized nomogram for age and gender (Supplementary Table 1)), low set and posteriorly rotated ears, bifid epiglottis, micrognathia (n=1 each)], cardiac/vascular [patent ductus arteriosus (n=2), patent foramen ovale (n=2), ventricular septal defect, aortic root dilation, interrupted aortic arch, truncus arteriosus, single umbilical artery, (n=1 each)], pulmonary/airway [laryngomalacia, pulmonary arteriovenous malformation (AVM), (n=1 each)], umbilical hernia (n=1), hepatosplenomegaly (n=1), recurrent intussusception (n=1), renal insufficiency (n=1), malrotated and hypoplastic kidney (n=1), B-cell lymphopenia (n=1) and impaired growth or development [failure to thrive (n=2), developmental delay (n=4), hypotonia (n=1), hearing loss (n=2)] (Table 2 and Figure 2).

Hematologic phenotypes varied considerably as well (Table 2 and Supplementary Table 1). Six patients presented with congenital thrombocytopenia. Patient 1 demonstrated congenital amegakaryocytic thrombocytopenia (MIM:604498) but died in early infancy from surgical complications. Patients 2, 3, 4, 5, and 8 underwent successful hematopoietic stem cell transplant (HSCT). Patient 5 demonstrated a new gain of chromosome 8 (trisomy 8) cytogenetic clone prior to HSCT. Patients 6 and 7 had mild and no thrombocytopenia respectively and have demonstrated clinical stability.

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The *MECOM* (transcript variant NM_004991.4) alterations detected included heterozygous whole- or partial-gene deletions, missense variants and splice site variants (Table 1, Figure 1, and Supplementary Table 2). The deletions included a 111 kb deletion within *MECOM* that contained exons 3–17, a 3.98 kb deletion of *MECOM* exon 5, and a 4.1 Mb deletion spanning several genes including *MECOM* (of note, the *TERC* gene was not included within this deletion) (Patients 1, 4 and 5). Four missense variants were identified including p.Thr944Arg, p.Tyr949Cys and p.Arg950Thr (Patients 3, 6 and 7). These variants are localized to zinc finger region 2 (8th, 9th and 10th zinc finger motifs), a known hotspot region for *MECOM*-associated syndrome [Germeshausen et al., 2018; Shen et al., 2022; Niihori et al., 2015; Ripperger et al., 2018]. While two of the missense variants appear as novel, the p.Tyr949Cys variant has been previously reported in a Kuwaiti child with RUSAT [Al-Abboh et al., 2022]. Two splice site variants were identified including c.2850–1G>A and c.2849+1G>T (Patients 2 and 8). These splicing consensus region variants alter intron 12 consensus splice donor and acceptor sequences and are predicted to disrupt splicing [scSNV, ADA Boost score = 1] (Supplementary Table 2). Of note, patient 8 also carried a heterozygous, hypomorphic variant in *RBM8A* (c.–21G>A) (MIM:605313) associated with autosomal recessive thrombocytopenia absent radius (TAR) syndrome (MIM:274000); a second *RBM8A* null alteration was not reported and therefore the *MECOM* variant was attributed as the likely cause of progressive BMF.

The parents of four of the eight patients (patients 2, 3, 4 and 7) underwent next-generation sequencing or Sanger sequencing to confirm inheritance of the finding. All four cases involving parental testing determined the respective *MECOM* alteration to be *de novo*; inheritance of the remaining cases remain unknown. Three of the mothers, two of whom did not have genetic testing themselves, had recurrent prior miscarriages without a specific diagnosis, and one had a congenital single kidney and bicornuate uterus.

Each *MECOM* alteration was classified via the American College of Medical Genetics and Genomics (ACMG) guidelines and determined to be pathogenic or likely pathogenic (Supplementary Table 2) [Richards et al., 2015].

DISCUSSION

RUSAT was first described in 1989 by Dokal et al [Dokal et al., 1989]. This association was initially suspected to be autosomal dominant because multiple family members exhibited this similar musculoskeletal and hematologic phenotype [Dokal et al., 1989]. In 2000, Thompson and Nguyen identified pathogenic homeobox A11 (*HOXA11)* (MIM:142958) gene variants in a cohort of patients with RUSAT; adding *HOXA11* to the growing list of familial thrombocytopenia disorders with predisposition to BMF [Thompson and Nguyen, 2000]. More recently, Niihori et al. identified patients with RUSAT in which *HOXA11* variants were absent and *de novo* missense variants in *MECOM* were identified [Niihori et al., 2015; Bluteau et al., 2018]. The phenotypical findings associated to *MECOM* variants were expanded by Bluteau et al. and Germeshausen et al. who reported children with BMF without radioulnar synostosis and additional patients who presented with a spectrum of non-hematologic abnormalities including cardiac, renal, and musculoskeletal abnormalities [Bluteau et al., 2018; Germeshausen et al., 2018]. Shen et al, localized these variants within

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the ninth zinc finger motif of EVI1, providing further insight into specific locus of the gene that is more associated to specific phenotypical features [Shen et al., 2022]. Functional experiments in the study by Shen et al. showed alterations in the TGF-beta pathway. This pathway is also affected in patients with hereditary hemorrhagic telangiectasia that can present with AVM [Shen et al., 2022; Kurokawa et al., 1998; Fernández-L et al., 2006].

Our case series further expands the phenotypic spectrum of *MECOM*-associated syndrome and demonstrates there is a subset of patients who lack radioulnar synostosis but express a spectrum of additional congenital anomalies, revealing a broader clinical phenotype than RUSAT syndrome alone. Bifid epiglottis, micro-retrognathia, laryngomalacia, splenomegaly, recurrent intussusception, renal malrotation and insufficiency, hypotonia, pulmonary AVM, aortic root dilation, truncus arteriosus and single umbilical artery, have not previously been reported in *MECOM*-associated syndrome. Table 2 summarizes the various organ systems currently identified to be impacted in the spectrum of *MECOM*-associated syndrome [Bluteau et al., 2018; Germeshausen et al., 2018; Niihori et al., 2015, 2022; Kjeldsen et al., 2018; Osumi et al., 2018; Lord et al., 2018; Veken et al., 2018; Walne et al., 2018]. Cardiac abnormalities can be life-threatening and influence care in early infancy. Patients with hypogammaglobulinemia and B-cell lymphopenia are at higher risk of bacterial and fungal infections which can delay HSCT and impact overall survival especially if there is organ damage prior HSCT. Consistent with our findings, other investigators have reported recurrent miscarriages in mothers of patients with *MECOM*-associated syndrome [Nielsen et al., 2012; Germeshausen et al., 2018]. Additionally, Germeshausen et al. reported that two fetuses that did not survive had hypocellular bone marrows [Germeshausen et al., 2018].

Five of eight patients, varying from infants to an older child, progressed to severe aplastic anemia (SAA) and underwent successful HSCT. Patient 5 acutely developed a somatic trisomy 8 clone. This karyotype abnormality was also reported in one patient described by Bluteau et al. [Bluteau et al., 2018]. This clone has historically been strongly associated with pediatric MDS and acute myeloid leukemia. Myelodysplastic and leukemia transformation have been reported in only a small number of patients with *MECOM* variants. Even though the significance of this abnormal finding is unclear, it may help identify patients with potential to undergo leukemic evolution and require expedited HSCT [Savage and Dufour, 2017; Ripperger et al., 2018].

This case series also expands the molecular spectrum of *MECOM*-associated syndrome. While zinc finger 2 remains a hotspot, the deletions highlight that *MECOM*-associated syndrome can arise as a result of haploinsufficiency. Patient 5 demonstrates a large 4.1 Mb deletion that, in additional to complete deletion of the MECOM locus, additionally deletes *BCHE*, *GOLIM4*, *PDCD10*, *SERPINI1*, *SERPINI2*, *WDR49*, and *ZBBX*. *PDCD10* haploinsufficiency has been associated to cerebral cavernous malformations which was not reported in our patient [Bergametti et al., 2005]. It remains possible that the patient's phenotype as presented in the manuscript could partially be related to another gene in the deletion. The variable phenotypes observed in *MECOM*-associated syndrome may suggest additional modifiers that affect genetic expression either of *MECOM* itself or of its transcription network that is critical for enabling effective hematopoietic stem cell self-renewal [Voit et al., 2021]. A deeper understanding of the mechanisms through which

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these phenotypes vary and how they impact hematopoietic stem cell function will not only provide insights into this rare disorder but will more broadly inform our understanding of stem cell biology, which could also be valuable.

MECOM variants should be considered in the differential diagnosis of congenital thrombocytopenia and BMF, even in the absence of radioulnar synostosis. Family history of other congenital abnormalities and prior unexplained miscarriages may increase suspicion of *MECOM* variants in specific patients. Should a pathogenic or likely pathogenic *MECOM* variant be identified, serial peripheral blood counts should be considered to monitor for progression to SAA or MDS. To screen for non-hematologic complications, consider bilateral forearm radiographs, careful ongoing screening for developmental delay, hearing and failure to thrive, and, given the frequency of renal and cardiac anomalies, a baseline renal ultrasound and echocardiogram. A baseline bone marrow evaluation with karyotype and cytogenetics appears appropriate because of the documented risk of progression to SAA and cytogenetic transformation in a few reported cases associated with hematologic malignancy [Ripperger et al., 2018], and patient 5 in this case series who demonstrated cytogenetic transformation. Genetic counseling is recommended to conduct pre- and post-test counseling, guide cascade testing of family members and related HSCT donor candidates, review inheritance and reproductive chances regarding *MECOM*-related syndrome and provide family planning education and resources. Even in cases of *de novo* *MECOM* alterations, targeted testing of siblings should be considered given rare possibility of germline mosaicism. Given HSCT is often a therapeutic option for this cohort, it may be beneficial to consider cord blood collection and banking of molecularly unaffected, HLA-matched siblings.

A centralized international publicly accessible database to share annotated *MECOM* variants would advance the clinical interpretation of *MECOM* variants and provide a foundation to perform functional *MECOM* studies. Efforts to curate variants and determine their pathogenicity are important as they allow a better classification, when we have an increasing number of VUS detected [Wu et al., 2020]. We advocate for *MECOM* inclusion on targeted sequencing and del/dup panels for inherited BMF syndromes and encourage providers to consider the diagnosis in the setting of congenital thrombocytopenia. We provide further evidence that *MECOM*-associated syndrome is a broad spectrum of diseases with BMF representing just one common phenotype. Further study of the role of *MECOM* in BMF and organogenesis is needed to increase our understanding of this syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

All subject retrospective data including genetic variants are provided openly within the tables of the manuscript. Any additional data that support the findings of this study are available from the corresponding author upon reasonable request

Abbreviation Definition

AVM	arteriovenous malformation
BMF	bone marrow failure
EVI1	ecotropic viral integration 1 site
ES	exome sequencing
GS	genome sequencing
HSCT	hematopoietic stem cell transplant
MDS1	myelodysplasia syndrome 1
IBMFS	inherited bone marrow failure syndromes
MDS	myelodysplastic syndrome
MIM	Mendelian Inheritance in Man
MSD	Matched sibling donor
RUSAT	radioulnar synostosis with amegakaryocytic thrombocytopenia
SAA	severe aplastic anemia

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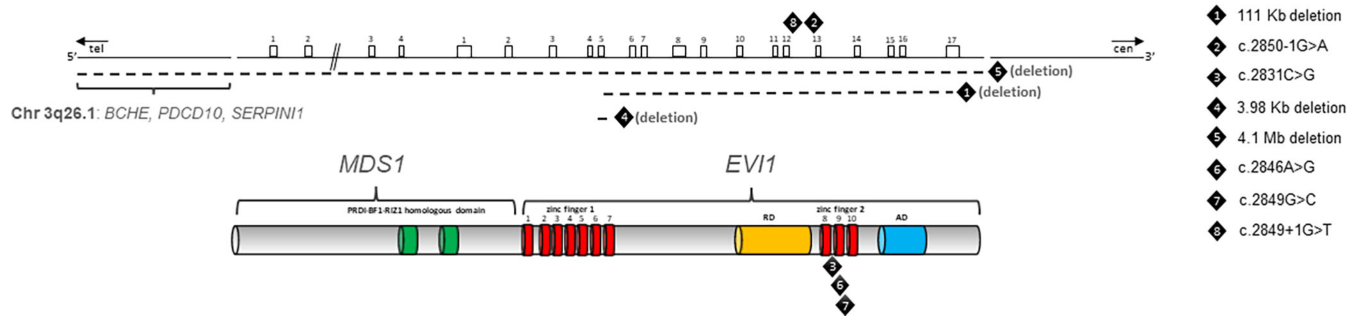

Figure 1:

MECOM; the gene symbol of *MDS1* and *EVI1* complex locus on chromosome 3q26.2. *EVI1* gene structure with 17 exons indicated and MDS1-EVI1 isoform expression product. Location of patient variants identified by black diamonds 1–8. AD: acidic domain in blue; PR: positive regulatory domain (PRDI-BF1-RIZ1 homologous domain) in green; RD: repressor domain in orange.

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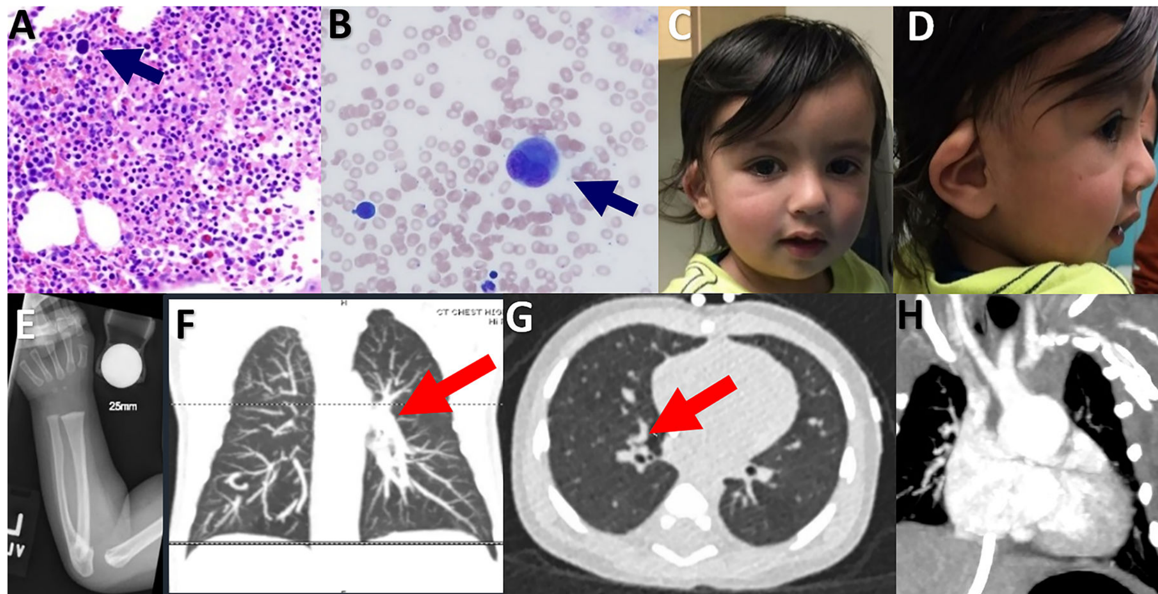

Figure 2:

Phenotypic features of patients with MECOM variations within our cohort include 2A) Bone marrow biopsy from patient 2 (c.2850–1G>A), H&E stain, 40x, decreased megakaryocytes with occasional hypolobated nuclei. 2B) Bone marrow aspirate smear from patient 2, 60X, showing a hypolobated megakaryocyte. 2C, 2D) Abnormal and low-set pinna in patient 5 (deletion whole gene). 2E) Forearm radiographs of patient 5 demonstrating bilateral dislocated, deformed radius with proximal osseous fusion to ulna. 2F, 2G) CT angiogram of patient 2 demonstrating multiple pulmonary arteriovenous malformations (c.2850–1G>A). 2H) Truncus arteriosus in patient 1 (deletion exons 4 to 17).

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Table 1:

MECOM variants identified in cohort

		Genome build					Transcript NM_004991.4 (17 exons)			
Patient (method)	**De novo variants (Parental testing)**	**GRCh37/hg19**	**GRCh38/hg38**	**REF**	**ALT**	**Type**	**CDS change**	**Position**	**Protein change**	**Variant Classification**
1 (CMA)	Not Assessed	Chr3:168744704–168855633	Chr3:169026916–169137845	N/A	N/A	Deletion	111 kb deletion	Intron 3 to transcript end	DEL exons 4 to 17	Pathogenic
2 (trio WES)	Confirmed *de novo* (trio WES)	Chr3:168813034	Chr3:169095246	C	T	Splice Site	c.2850–1G>A	Intron 12	N/A	Pathogenic
3 (NGS panel)	Assumed *de novo*[*] (Sanger sequencing)	Chr3:168818691	Chr3:169100903	G	C	Missense	c.2831C>G	Exon 12	p.Thr944Arg	Likely Pathogenic
4 (trio WGS)	Confirmed *de novo* (tiro WGS)	Chr3:168842211–168846192	Chr3:169124423–169128404	N/A	N/A	Deletion	3.98 kb deletion	Intron 4 to intron 5	DEL exon 5	Pathogenic
5 (CMA)	Not Assessed	Chr3:165310746–169396070	Chr3:165592958–169678282	N/A	N/A	Deletion	4.1 Mb deletion	Whole gene	DEL whole gene	Pathogenic
6 (NGS panel)	Not Assessed	Chr3:168818676	Chr3:169100888	T	C	Missense	c.2846A>G	Exon 12	p.Tyr949Cys	Likely Pathogenic
7 (NGS panel)	Assumed *de novo*[*] (Sanger sequencing)	Chr3:168818673	Chr3:169100885	C	G	Missense	c.2849G>C	Exon 12	p.Arg950Thr	Likely Pathogenic
8 (NGS panel)	Not Assessed	Chr3:168818672	Chr3:169100884	C	A	Splice Site	c.2849+1G>T	Intron 12	N/A	Pathogenic

Only the genome build used by the clinical lab for deletion mapping is shown.

REF: the allele in the reference genome; ALT: any other allele found at that locus. Chr: Chromosome

CMA: chromosomal microarray; WES: whole exome sequencing: WGS: whole genome sequencing; NGS: next generation sequencing; CDS: coding sequence; DEL: deletion

[†]Genes included in patient 5's deletion include: *BCHE*, *GOLIM4*, *MECOM*, *PDCD10*, *SERPINI1*, *SERPINI2*, *WDR49*, *ZBBX*

[*]Assumed *de novo* as paternity and maternity were not confirmed.

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Table 2:

Patient demographics, clinical characteristics, and literature review.

Patients Characteristics	1	2	3	4	5	6	7	8	Current cohort n= 8	Cohort + literatu (PR) n=46	
Demographics	3-week F	2-month M	2-month F	7-month F	2-year M	2-year F	2-year M	6-year M			
	Caucasian	Caucasian	Caucasian	Mixed race	Indian	Chinese	Caucasian	Caucasian			
Clinical characteristics											
Head/ear/nose/throat											
Macrocephaly	-	+	-	-	-	-	-	-	1	2	*g*
Microcephaly	-	-	-	+	-	-	-	-	1	2	*h*
Micrognathia *	+	-	-	-	-	-	-	-	1	1	n/a
Retrognathia *	+	-	-	-	-	-	-	-	1	1	n/a
Ear abnormalities (low-set ears, posterior rotated ears, other non-specific)	+	-	-	-	+	-	-	-	2	3	*h*
Bifid epiglottis *	-	-	-	-	-	-	+	-	1	1	n/a
Facial dysmorphism	+	-	-	-	+	-	+	-	3	7	*b,e,g,h*
Cleft palate	-	-	-	-	-	-	-	-	0	2	*a,c*
Cardiac/Vascular											
Patent ductus arteriousus	-	+	-	+	-	-	-	-	2	4	*d,f*
Atrial septal defect	-	-	+	+	-	-	-	-	2	5	*c,d,e*
Ventricular septal defect	-	-	-	-	+	-	-	-	1	2	*c*
Truncus arteriosus *	+	-	-	-	-	-	-	-	1	1	n/a
Tetralogy of Fallot	-	-	-	-	-	-	-	-	0	3	*b,c,h*
Aortic root dilation *	-	-	-	-	-	-	+	-	1	1	n/a
Pulmonary stenosis	-	-	-	-	-	-	-	-	0	2	*b,e*
Single umbilical artery *	+	-	-	-	-	-	-	-	1	1	n/a
Myocardial atrophy	-	-	-	-	-	-	-	-	0	1	*b*
Interrupted aortic arch, aortic coartaction	+	-	-	-	-	-	-	-	1	2	*c*
Moya Moya disease	-	-	-	-	-	-	-	-	0	1	*h*
Respiratory											
Laryngomalacia *	-	-	-	-	-	-	+	-	1	1	n/a
Pulmonary arteriovenous malformation *	-	+	-	-	-	-	-	-	1	1	n/a
Pulmonary bleeding	-	-	-	-	-	-	-	-	0	1	*f*
Gastrointestinal											
Umbilical hernia *	-	-	-	+	-	-	-	-	1	1	n/a
Hepatomegaly	-	-	-	+	-	-	-	-	1	2	*c*
Splenomegaly *	-	-	-	+	-	-	-	-	1	1	n/a

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Demographics	3-week F	2-month M	2-month F	7-month F	2-year M	2-year F	2-year M	6-year M			
	Caucasian	Caucasian	Caucasian	Mixed race	Indian	Chinese	Caucasian	Caucasian			
Clinical characteristics											
Head/ear/nose/throat											
Recurrent intussusception *	-	-	-	+	-	-	-	-	1	1	n/a
Genitourinary											
Renal hypoplasia	-	-	-	+	-	-	-	-	1	2	*b*
Renal malrotation *	-	-	-	+	-	-	-	-	1	1	n/a
Cystic kidney	-	-	-	-	-	-	-	-	0	1	*c*
Renal calyceal dilation/ double ureter/megaureter	-	-	-	-	-	-	-	-	0	2	*c*
Renal insufficiency *	-	-	-	+	+	-	-	-	2	2	n/a
Nephrocalcinosis	-	-	-	-	-	-	-	-	0	1	*e*
Testicular hydrocele	-	-	-	-	-	-	-	-	0	1	*a*
Neurological											
Subnormal gyrification	-	-	-	-	-	-	-	-	0	1	*g*
Wide peripheral cerebrospinal fluid spaces	-	-	-	-	-	-	-	-	0	1	*g*
Musculoskeletal											
Clinodactyly	+	-	+	-	-	+	-	-	3	9	*a,c,i*
Thumb abnormalities	-	-	-	-	-	+	-	-	1	4	*b,c*
Brachyomesophalangy	-	-	-	-	-	-	-	-	0	2	*a,c*
Brachydactyly	-	-	-	-	-	-	-	-	0	3	*c,g,h*
Overlaping fingers	-	-	-	-	-	-	-	-	0	2	*a,e*
Clubfoot	-	-	-	-	-	-	-	-	0	4	*b,g,h,i*
Toe malposition	-	-	-	-	-	-	-	-	0	1	*c*
Radial hypoplasia *	-	-	-	+	-	-	-	-	1	1	n/a
Radio ulnar synostosis	-	-	+	-	+	+	+	+	5	25	*a,b,c,e,h,*
Floating elbow	-	-	-	-	-	-	-	-	0	1	c
Acetabular/hip dysplasia	-	-	-	-	-	-	-	-	0	2	*c,e*
Small patellae	-	-	-	-	-	-	-	-	0	1	*c*
Skin, nail, hair											
Dystrophic nails	-	+	-	-	-	-	-	-	1	2	*h*
Growth and development											
Failure to thrive/Short stature *	-	+	-	+	-	-	-	-	2	2	n/a
Developmental delay	-	+	-	+	+	-	+	+	5	7	*a,c*
Hypotonia *	-	-	-	-	+	-	-	-	1	1	n/a

Patients Characteristics	1	2	3	4	5	6	7	8	Current cohort n= 8	Cohort + literatu (PR) n=46	
Demographics	**3-week F**	**2-month M**	**2-month F**	**7-month F**	**2-year M**	**2-year F**	**2-year M**	**6-year M**			
	Caucasian	**Caucasian**	**Caucasian**	**Mixed race**	**Indian**	**Chinese**	**Caucasian**	**Caucasian**			
Clinical characteristics											
Head/ear/nose/throat											
Hearing impairment	-	-	-	-	+	-	-	+	2	9	*a,c,h*
Gynecomastia in infancy	-	-	-	-	-	-	-	-	0	1	*c*
Precocious puberty	-	-	-	-	-	-	-	-	0	1	*c*
Hematologic/Immunologic											
Recurrent infections	-	-	-	+	-	-	-	-	1	6	*c,f,g*
AA/hypocellular bone marrow	+	+	+	+	+	-	-	+	6	36	*a,b,c,d,e,f,g*
B-cell lymphopenia/ Hypogammaglobulinemia	-	-	-	+	-	-	-	-	1	3	*c*
Congenital thrombocytopenia	+	+	+	-	-	+	-	+	5	37	*a,b,c,d,e,f,g*
Trisomy 8/ Myelodysplasia	-	-	-	-	+	-	-	-	1	3	*b,h*
Clinical course	Died of cardiac surgery complications	MSD HSCT (5 months) Fully engrafted	MUD HSCT (7 months) Fully engrafted	MUD HSCT (8 months) Fully engrafted	MUD HSCT (2 years) Fully engrafted	Clinically stable	Clinically stable	MUD HSCT (7 years) Fully engrafted			

Shaded areas show phenotypical findings described in our cohort. . PR: Previously Reported. Indicates phenotypical characteristics described by Niihori et al. 2015

[(a)] (n=3), Bluteau et al. 2018

[(b)] (n=6), Germeshausen et al. 2018

[(c)] (n=12), Kjeldsen el al.

[(d)] (n=1), Lord et al. 2018

[(e)] (n=1), Osumi et al. 2018

[(f)] (n=1), van der Veken et al. 2018

[(g)] (n=1), Walne et al. 2018

[(h)] (n=7), Niihori et al. 2022

[(i)] (n=6).

AA: aplastic anemia; CAMT: congenital amegakaryocytic thrombocytopenia; F: female; HSCT: hematopoietic stem cell transplant; M: male; MSD: matched sibling donor; MUD: matched unrelated donor; n/a: not available; PR: previously reported

[*] Not previously described

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