



# A de novo *SFMBT1* pathogenic variant identified in a boy with Poland syndrome

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**Abstract** Poland syndrome is a rare developmental disorder characterized by unilateral, complete or partial, absence of the pectoralis major (and often minor) muscle, accompanied with ipsilateral hand malformations. To date, no clear genetic cause has been associated with Poland syndrome, although familial cases have been reported. We report the employment of trio exome investigation and the identification of a heterozygous de novo pathogenic variant in the *SFMBT1* gene, a transcription factor associated with transcriptional repression during development, in a 14-yr-old boy with Poland syndrome. We further demonstrate by means of cDNA sequencing and western blot analysis that this variant results in *SFMBT1* exon 10 skipping and a lower concentration of the *SFMBT1* wild-type protein. To our knowledge, the heterozygous pathogenic *SFMBT1* variant identified in association with this condition is novel as it has not been elsewhere described in the literature and it can be incorporated to the limited reported cases published.

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**Ontology term:** unilateral absence of pectoralis major muscle

Published by Cold Spring Harbor Laboratory Press

doi:10.1101/mcs.a006168

## INTRODUCTION

### Poland Syndrome (PS)

Poland syndrome (PS) is a rare developmental disorder typically characterized by congenital, unilateral hypoplasia to complete agenesis of the pectoralis major muscle and mammary gland (Poland 1841) associated with ipsilateral upper limb defects—commonly brachysyndactyly and syndactyly (Al-Qattan 2001), breast and nipple anomalies, hypoplasia of the pectoral subcutaneous tissue and regional muscles (Cochran et al. 1981; David and Winter 1985; Zhu et al. 2012), absence of pectoral and axillary hair, and possibly chest wall defects and other ipsilateral upper limb malformations (Catena et al. 2012). Other features may include Moebius syndrome, dextrocardia (in left-sided PS), rib defects (Torre et al. 2010), hemivertebrae, Sprengel anomaly, and lung herniation (Chandran et al. 2013). Familial PS cases show significant variability in phenotypic expression (Parano et al. 1995; Baban et al. 2012; Yiyit et al. 2015). The incidence of the condition is estimated to be 1:20,000 to 1:50,000 (Freire-Maia et al. 1973) with a male preponderance and features more commonly affecting the right side (Torre et al. 2010).

### Pathogenesis

The pathogenesis of Poland syndrome is understudied and to date remains elusive. A favored hypothesis is that during the sixth week of gestation, subclavian artery blood supply disruption occurs. This disruption is thought to involve the vertebral arteries and their branches, thus unilaterally reducing perfusion to the affected side (Bavinck and Weaver 1986). This alleged vascular hypothesis is supported by reports of observed decreased vascularization of the arms, opacification of the aortic arch (Bouvet et al. 1978), and iliac artery disruption (Gonda et al. 2018) in studied PS cases. An alternative hypothesis is the involvement of genes regulating the development of the pectoral girdle muscles during embryogenesis (Valasek et al. 2011).

The use of drugs such as misoprostol by the mother during pregnancy that might be involved in vascular disruption (Rosa et al. 2007) has provided credence for a vascular pathogenesis in PS cases.

### Genetics of Poland Syndrome

Most of the Poland syndrome cases are sporadic, although familial cases have been reported (David and Winter 1985; Parano et al. 1995; Baban et al. 2012; Yiyit et al. 2015), indicative of an autosomal dominant or a polygenic mode of inheritance (Romanini et al. 2018; Baldelli et al. 2020). PS has also been suggested to be the result of a mosaic event during embryogenesis, with the severity of the phenotype depending on the time the mutation occurred (van Steensel 2004).

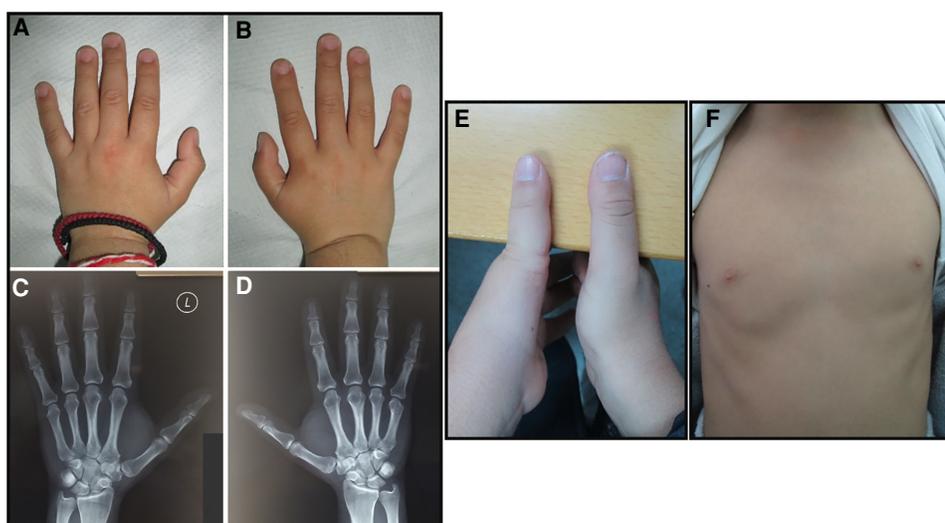
PS has no clear genetic association and the involvement of genes that regulate development, and affect particularly chest wall muscles and skeleton structures, has been proposed. A few studies have attempted to elucidate the genetic cause of this condition by comparative genomic hybridization (CGH). Candidate genes identified were involved in cell growth and differentiation (Vaccari et al. 2014) and skeletal and muscle anomalies (Tassano et al. 2015).

### Poland Syndrome and Malignancy

Poland syndrome has rarely been linked to development of malignancies including breast cancer (Yesilkaya et al. 2011; Huang et al. 2018), hematological malignancies (Sackey et al. 1984), solid tumors, and other types of cancer (Shaham et al. 1992), indicating a predisposition to tumor formation and perhaps a tumor-suppressor gene involvement.

### SFMBT1 Gene

The *SFMBT1* gene is located on Chromosome 3 and encodes for a protein (96 kDa) responsible for transcription regulation (Wu et al. 2007; Lin et al. 2013; Zhang et al. 2013). *SFMBT1* (Scm-like with four MBT domains protein 1) belongs to the MBT family of proteins, comprised of four MBT domains (Usui et al. 2000) that create a propeller-like structure (Wang et al. 2003) crucial for the protein's biological activity (Wu et al. 2007). The gene is known as a corepressor that regulates gene expression epigenetically by recruiting histone-modifying factors, compressing chromatin, and thus repressing transcription (Zhang et al. 2013). Recent studies have specifically demonstrated its role in myogenesis (Lin et al. 2013) as well as in tumor formation (Liu et al. 2020) and progression (Tang et al. 2013; Jiang et al. 2016), and hypertension (Yang et al. 2012). Testes, endocrine glands, and blood are tissues that highly express *SFMBT1* (Uhlén et al. 2015). *SFMBT1* is also highly expressed in skeletal muscles specifically in undifferentiated myoblasts, and this expression starts diminishing during muscle differentiation (Lin et al. 2013). There is limited understanding as to the full spectrum of *SFMBT1* function.



**Figure 1.** Photographs of the proband showing a mildly hypoplastic left thumb (A,B,E) along with corresponding PA (posterior, anterior) hand X-rays (C,D). Photograph showing the mild hypoplasia of the left pectoralis major muscle with slightly smaller left nipple (F).

## RESULTS

### Clinical Presentation

An 8-yr-old boy was referred for a clinical genetics evaluation because of a history of mildly hypoplastic left thumb and mildly dysplastic aortic valve with mild aortic regurgitation. He was born to healthy, nonconsanguineous parents of Cypriot descent. Review of the family history was noncontributory for digital or other developmental anomalies. He was the product of his mother's second pregnancy following a natural conception.

On examination, he was facially nondysmorphic with no facial asymmetry. His OFC (occipitofrontal circumference) was on the sixth centile, his height was on the 36th centile, and his weight was on the 38th centile. He had mild, left-sided hypoplasia of the pectoralis major muscle and mildly hypoplastic left thumb (Fig. 1A–F). He also had bilateral conjunctival nevi, right larger than left. Cardiovascular examination revealed a 2/6, soft systolic heart murmur. His abdomen was soft and nontender with no renal angle tenderness. Neurology examination was unremarkable.

Echocardiography revealed bicuspid aortic valve with mild to moderate aortic regurgitation. Ophthalmology evaluation was unremarkable apart from the presence of conjunctival nevi. Normal or negative investigations included full blood count, urea and electrolytes, liver function tests, lipid profile, plasma glucose, karyotype analysis, mitomycin C (MMC) analysis with no evidence of increased chromosome breaks, array-CGH analysis, and abdominal ultrasound scan. Examination of parents revealed normal hands and no asymmetry of the pectoralis major muscles.

Exome analysis was initially performed on peripheral blood of the affected case. The identified variant was confirmed by Sanger sequencing followed by trio exome analysis on parental samples and a secondary proband sample (buccal swab).

### **SFMBT1 c.1049-2A > T p.(Gly350Valfs\*4) De Novo Variant Detection**

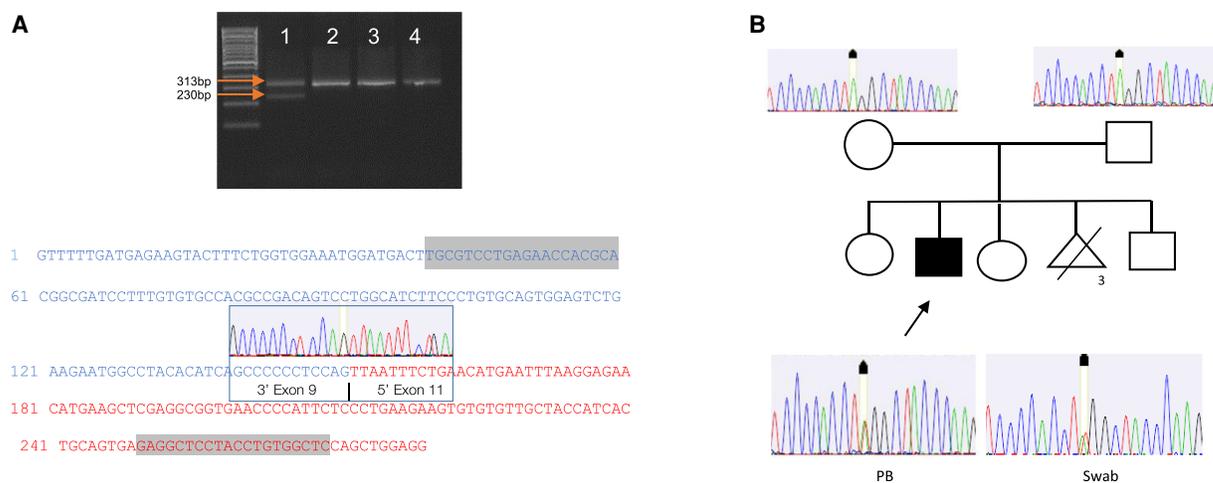
We identified a heterozygous *SFMBT1* variant, c.1049-2A > T, 2 bp located upstream of exon 10, at an acceptor splice site of this gene (Table 1). The variant results in the skipping

**Table 1.** The *SFMBT1* c.1049-2A > T p.(Gly350Valfs\*4) de novo variant

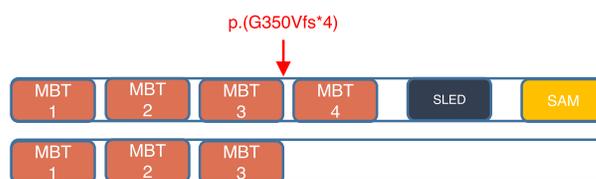
Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/dbVar ID	Genotype	ClinVar ID	Parent of origin	Observed effect
<i>SFMBT1</i>	Chr 3	<i>g.52960131T&gt;A</i>	p.? Our prediction: p.(Gly350Valfs*4)	Missense at splice site	Truncating	No dbSNP ID	Heterozygous	Absent from ClinVar novel	De novo	Lower concentration of the SFMBT1 wild-type protein

of exon 10 at the RNA level as demonstrated by *SFMBT1* cDNA sequencing (Fig. 2A). The c.1049-2A > T variant is absent from gnomAD exomes, gnomAD genomes (Karczewski et al. 2020), and from a DNA pool of 5000 healthy individuals of Cypriot origin (unpubl. data, P Costeas, et al.). In addition, seven computational softwares that take into account the site's conservation and splicing impact (BayesDel, addAF, DANN, EIGEN, FATHMM-MKL, MutationTaster, and scSNV-Splicing) (Kopanos et al. 2019) predict this variant has an effect on SFMBT1 protein function. Trio exome sequencing revealed that the variant was absent from both parents' peripheral blood samples and is thus likely to have occurred de novo (Fig. 2B). The presence of the variant was confirmed by next-generation sequencing (NGS) in a swab sample from the patient.

We hypothesized that the skipped exon results in a truncated SFMBT1 protein p.(Gly350Valfs\*4) that lacks its fourth MBT domain and the domains located downstream (Fig. 3), predicted to have a molecular weight of 40 kDa. Protein analysis, using western blotting for the SFMBT1 protein in peripheral blood mononuclear cells (PBMCs), revealed a



**Figure 2.** (A) (Top) cDNA exon 10-skipping specific polymerase chain reaction (PCR) revealed the exon-skipping effect of the *SFMBT1* c.1049-2A > T in the proband sample (wild-type SFMB1 product expected size: 313 bp and exon 10-skipped PCR product expected size: 230 bp) (100-bp ladder). 1: Proband, 2: mother, 3: father, 4: negative control (IVS-0000 Polyclonal control DNA). (Bottom) cDNA sequence of exon 9 (in blue) and 11 (in red) depicted along with the primers binding site (highlighted in gray). Chromatogram depicts the 3' site of exon 9 followed by the 5' site of exon 11, demonstrating the complete deletion of exon 10 at the cDNA level. (B) Family tree of the proband (indicated with arrow), his parents, and his healthy siblings. Sanger sequencing images display the location of the c.1049-2A > T variant. Parents are homozygous for the wild-type allele A and the proband is heterozygous A > T both in the blood and the buccal swab samples.



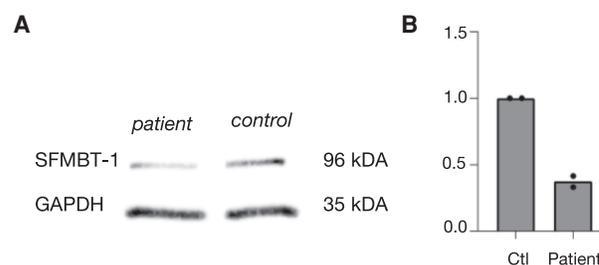
**Figure 3.** (Top) Wild-type SFMBT1 protein. SFMBT1 protein is comprised of four tandem MBT repeats, a SLED, and a SAM domain. (Bottom) Predicted mutant SFMBT1 protein lacking the fourth MBT domain and the SLED and SAM domains located downstream. The red arrow indicates the location of the mutation on the protein level.

significant reduction (an ~60% reduction) in the expression of the 96-kDa common isoform of the protein in our patient compared to a control sample (Fig. 4); however, we could not confirm the presence of this truncated SFMBT1 protein because of the presence of a band of similar molecular size of uncertain identification in both the patient and control samples.

Differential diagnoses of conditions involving hand anomalies (Duane-radial ray syndrome, OMIM #607323), hand anomalies and congenital heart defects (Holt–Oram syndrome, OMIM #142900), Adams–Oliver syndrome (OMIM #100300, #614219, #614814, #615297, #616028, #616589), hand anomalies, and occasionally heart involvement (IVIC syndrome OMIM #147750) were excluded. No pathogenic/likely pathogenic/uncertain significance variants were identified in *SALL4*, *TBX5*, *ARHGAPP31*, *NOTCH1*, and *RBPJ*, which represent the key genes associated to the conditions mentioned above.

## DISCUSSION

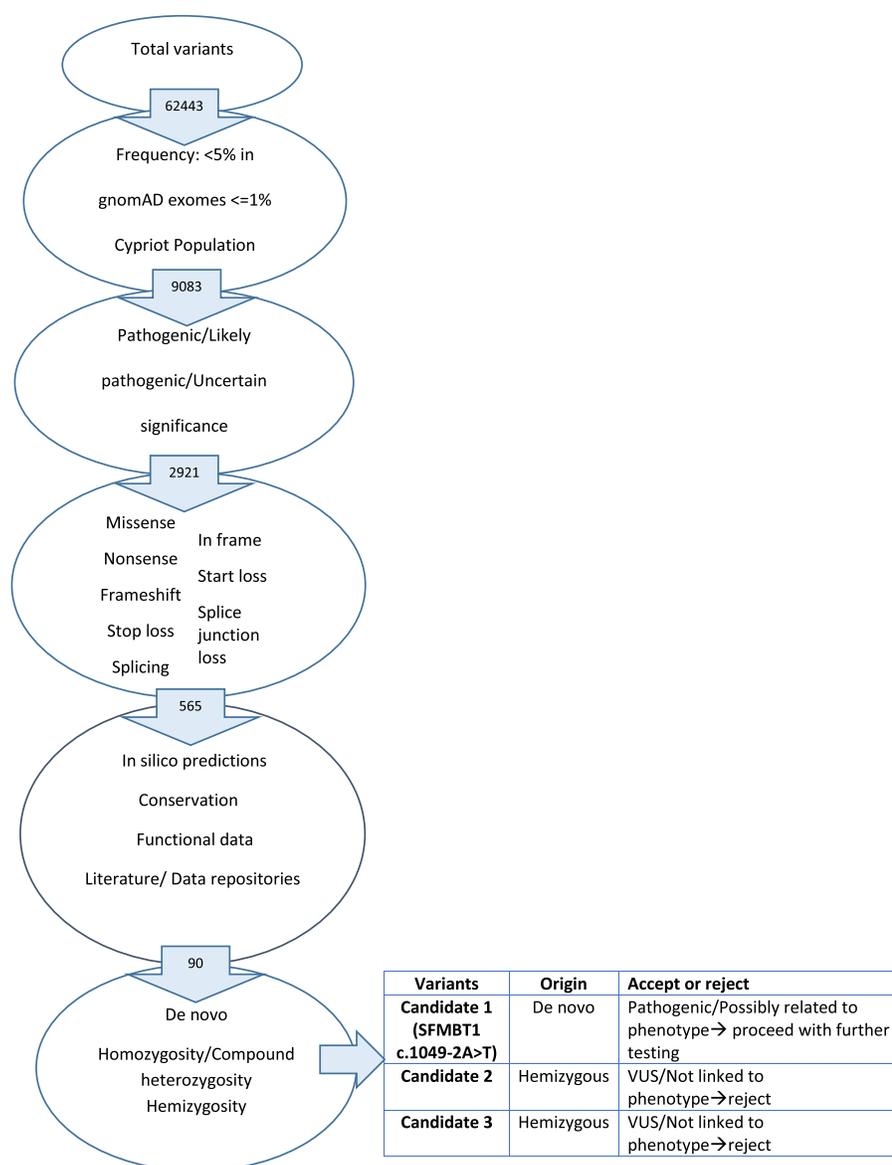
Deciphering the genetic etiology of Poland syndrome has proven challenging mainly because most cases are sporadic and due to the unique pattern of developmental defects observed. Although many cases seem to have a clear parent-to-offspring trait transmission indicative of a dominant inheritance, incomplete penetrance, skipping of generations, and variable expressivity among relatives is also evident (Parano et al. 1995; Baban et al. 2012). The sporadic nature of PS also denotes the high possibility of de novo events in more than one gene in affected individuals either in the context of genetic heterogeneity or due to an oligogenic mode of inheritance.



**Figure 4.** (A) Western blot showing the signal for SFMBT-1 wild-type protein (96 kDa) and housekeeping gene *GAPDH* (30–40 kDa) for the patient and the healthy control. (B) Plot showing the fold change in SFMBT1 expression compared to the control. A significant reduction (60%) of the expression of the 96-kDa wild-type SFMBT1 protein isoform is observed in the patient compared to the control; the mean of two experiments is shown as well as the individual values (black dots) of expression from two independent experiments.

SFMBT1 is a gene with low tolerance for variants that alter its function (Karczewski et al. 2020) and in which such variants cannot be sustained and are rather depleted from a population (SFMBT1 intolerance score to loss of function, LOEUF = 0.324, and GnomAD data shows extremely rare deleterious variants with pLI score = 0.94).

Our study revealed the presence of a de novo SFMBT1 splicing variant that is predicted to be pathogenic. We have demonstrated that this variant results in exon skipping at the RNA level, and we have detected a significantly lower expression of the 96-kDa



**Figure 5.** The filtering algorithm of the variants identified on the exome trio analysis was based on the variant's population frequency, overall predicted pathogenicity (based on ACMG guidelines), type of variant, more specific pathogenicity prediction based on in silico prediction tools, information available in the public repositories and literature, and finally the inheritance mode of each disease and the origin (parental or de novo) of the identified variants. The number of variants resulting from each filtering step is displayed on the arrows.

SFMBT-1 wild-type protein isoform in the patient relative to a control. The actual presence of the truncated SFMBT1 protein, predicted to be 40 kDa, could not be confirmed because of the presence of a similar molecular size band of uncertain identification. We can hypothesize that the lower expression of the SFMBT1 wild-type protein compared to the control is the result of a mutated *SFMBT1* mRNA also being generated, but possibly undergoing nonsense-mediated decay (NMD). NMD hypothesis is also supported by the fact that the variant is not located in the last exon or the last 50 bp of the penultimate exon (Abou Tayoun et al. 2018).

Poland syndrome is believed to result from a mesodermal defect of vascular origin that injures the subclavian artery (Bavinck and Weaver 1986). *SFMBT1* regulates the expression and interacts with key genes involved in heart muscle and artery development (*PWWP2A*, *SIX2*) (Zhang et al. 2013) as well as myogenic differentiation (*MYOD*, *SIX2*) (Lin et al. 2013). Specifically, *PWWP2A*, a transcriptional regulator, plays a significant role during embryogenesis in neural cell migration and differentiation (Pünzeler et al. 2017), and these neural crest cells are crucial for cardiovascular development. Ablation of the cardiac neural crest cells results in heart defects including aortic artery defects (Kirby and Waldo 1995). *SIX2* is a homeobox transcription factor and a critical component of pathways involved in heart muscle morphogenesis and skeletal myogenic differentiation (Relaix et al. 2013). Finally, *MYOD*, a transcriptional activator, is the cornerstone of the skeletal muscle cell differentiation pathway (Megeny et al. 1996). *SFMBT1* directly interacts with *MYOD* in undifferentiated myoblasts to suppress *MYOD*-dependent transcription and to prevent the muscle cell differentiation (Lin et al. 2013).

The contribution of genetic factors in the development of Poland syndrome is currently unclear, but we propose that such factors can play an important role in the pathogenesis of this disorder. In this case report, we present a patient with a significant reduction in the expression of SFMBT1, a common protein isoform that is very likely the result of the identified *SFMBT1* splicing variant. We suggest that such a reduced expression could have a negative impact on the functional capacity and efficiency of *SFMBT1*, enhancing abnormal differentiation or even abolishing differentiation of certain progenitor cells. We can hypothesize that at some point during embryogenesis a mutant *SFMBT1* with a compromised function results in a developmental defect, either of the aortic arch involving the subclavian artery or—later in gestation—during myoblast differentiation that could be associated with the Poland syndrome phenotype. In addition, although the variant was present in the buccal cells of this patient, we do not exclude the possibility of mosaicism, as the change might have occurred very early in development. Further molecular studies on clinically identified Poland syndrome cases and delineation of the molecular pathways of *SFMBT1* will shed light on Poland syndrome genetic etiology and *SFMBT1* involvement and help in understanding and treating manifestations of this condition.

## METHODS

DNA and RNA extraction from peripheral blood was performed using QIAcube automated system (QIAGEN). Concentration of genetic material was quantified on Nanodrop 2000 (Thermo Fisher Scientific). SureSelect Exome V7 panel (Agilent Technologies) was used on DNA for NGS on NextSeq platforms (Illumina) according to manufacturer's protocol. NM transcript selection (NM\_016329.4) followed Human Genome Variation Society (HGVS) recommendations. FASTQ generation was performed using bcl2fastq by Illumina. Coverage of at least 20× was obtained for identified variants with an average region coverage of 99 reads, and the reported variant was confirmed by Sanger sequencing and was also confirmed in a buccal swab sample (Table 2). Alignment on hg19, variant calling, and classification of

**Table 2.** Sequencing coverage information and validation method for the SFMBT variant

Sequence read length	Sequence read type	Coverage of reported variant in proband	Coverage of reported variant in mother	Coverage of reported variant in father	Confirmation with another method	Confirmation in another tissue
151	Paired end	68	97	114	Sanger sequencing	Buccal swab

variants was performed on VarSome Clinical (Saphetor). The algorithm used to perform the exome filtering is displayed in Figure 5. Information on differential diagnoses was retrieved from OMIM (Hamosh et al. 1999). Sanger sequencing was performed on a 3500 Genetic Analyser (Thermo Fisher Scientific), and alignment was done on DNABaser software (Heracle BioSoft SRL). The variant reported was classified according to the American College of Medical Genetics and Genomics (ACMG) recommendations (Richards et al. 2015).

Reverse transcription PCR via PrimeScript RT Reagent Kit (Perfect Real TIME Takara) on RNA for cDNA generation was utilized for an exon-skipping investigation, followed by amplification with sequence-specific primers flanking exons adjacent to the one being investigated for skipping, and the resulting cDNA PCR products were visualized by electrophoresis on 2% agarose gel. Elucidation of the exact splicing breakpoint was performed by cutting the gel band resulting from the exon-skipped allele, submerging it in nuclease-free water overnight, reamplifying it, and finally sequencing it using Sanger. Prediction of the splice variant's effect on the protein level was performed with the ExPasy translation tool (<https://web.expasy.org/translate/>). PBMCs from the patient and controls were isolated using a Ficoll density gradient, followed by red blood cell lysis and cell counting before downstream whole-cell lysate preparation. PBMCs were homogenized in lysis (RIPA buffer, Sigma-Aldrich) to prepare whole-cell lysate in the presence of protease inhibitors (cComplete, Mini Protease Inhibitor Cocktail, Roche and phenylmethylsulfonyl fluoride [PMSF], Roche). For SFMBT-1 and GAPDH analysis, samples were probed overnight with the following primary antibodies: rabbit anti-human SFMBT-1 (antibodies-online ABIN553782) and mouse anti-human GAPDH (Cell Signaling 97166S). Primary antibodies were washed and blot was probed with the following secondary antibodies: IRDye 800CW-conjugated donkey anti-rabbit antibody and IRDye 680RD-conjugated anti-mouse antibody for 45 min at room temperature before washing and visualizing blot on a Vilber Fusion FX6 instrument. The total intensity of each band was determined using ImageJ (<https://imagej.nih.gov/ij/>). The background-corrected intensity of SFMBT1 was then normalized to the background-corrected intensity of housekeeping gene GAPDH, before determining the fold change between the patient and the control.

## ADDITIONAL INFORMATION

### Data Deposition and Access

The variant has been deposited in the Leiden Open Variation Database (LOVD) (<https://databases.lovd.nl/shared/screenings/0000383951>) under accession number 00382737.

### Ethics Statement

The data included in this paper resulted from diagnostic testing of a consented patient referred to our laboratory for Poland syndrome genetic investigation. All genetic and clinical

data included in this publication were identified in the context of this diagnostic investigation, and as this is not a research project, no bioethics approval was required. The mother of the patient has been appropriately informed by the referring physician about the purpose, scope, type, and significance of the planned genetic and other test(s) requested and has provided written consent. Informed written patient's consent (in this case, maternal consent) for the use of their genetic and clinical results in a publication ensuring anonymity has been obtained.

### Acknowledgments

We are very grateful to the family for their help and collaboration. The authors also thank Dr. George A. Tanteles for his collaboration on the phenotypic characteristics of the family involved.

### Competing Interest Statement

The authors have declared no competing interest.

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Received November 25, 2021;  
accepted in revised form  
April 1, 2022.

### Author Contributions

A.M. was responsible for the design of the study, performed experiments and the collection and analysis of the data, and drafted the manuscript. P.D. performed the western blot experiments and edited the manuscript. M.K. performed the western blot experiments. P.G., Y.K., A.E., G.H., M.I., and J.C. contributed to the genetic investigation and editing of the manuscript. G.A.T. and P.C. conceived the study, participated in its design, and edited the manuscript. G.A.T. has done the clinical examination and collection of phenotypic data of the participant. All authors have read and approved the final manuscript.

### REFERENCES

- Abou Tayoun AN, Pesaran T, DiStefano MT, Oza A, Rehm HL, Biesecker LG, Harrison SM. 2018. ClinGen Sequence Variant Interpretation Working Group (ClinGen SVI). Recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion. *Hum Mutat* **39**: 1517–1524. doi:10.1002/humu.23626
- Al-Qattan MM. 2001. Classification of hand anomalies in Poland's syndrome. *Br J Plast Surg* **54**: 132–136. doi:10.1054/bjps.2000.3505
- Baban A, Torre M, Costanzo S, Gimelli S, Bianca S, Divizia MT, Sénès FM, Garavelli L, Rivieri F, Lerone M, et al. 2012. Familial Poland anomaly revisited. *Am J Med Genet A* **158A**: 140–149. doi:10.1002/ajmg.a.34370
- Baldelli I, Baccarani A, Barone C, Bedeschi F, Bianca S, Calabrese O, Castori M, Catena N, Corain M, Costanzo S, et al. 2020. Consensus based recommendations for diagnosis and medical management of Poland syndrome (sequence). *Orphanet J Rare Dis* **15**: 201. doi:10.1186/s13023-020-01481-x
- Bavinck JN, Weaver DD. 1986. Subclavian artery supply disruption sequence: hypothesis of a vascular etiology for Poland, Klippel-Feil, and Möbius anomalies. *Am J Med Genet* **23**: 903–918. doi:10.1002/ajmg.1320230405
- Bouvet JP, Leveque D, Bernetieres F, Gros JJ. 1978. Vascular origin of Poland syndrome? A comparative rheographic study of the vascularisation of the arms in eight patients. *Eur J Pediatr* **128**: 17–26. doi:10.1007/BF00496922
- Catena N, Divizia MT, Calevo MG, Baban A, Torre M, Ravazzolo R, Lerone M, Sénès FM. 2012. Hand and upper limb anomalies in Poland syndrome: a new proposal of classification. *J Pediatr Orthop* **32**: 727–731. doi:10.1097/BPO.0b013e318269c898
- Chandran S, Revanna KG, Ari D, Rana AA. 2013. Lung herniation: an uncommon presentation of Poland's syndrome in a neonate at birth. *BMJ Case Rep* **2013**: bcr2013200106. doi:10.1136/bcr-2013-200106
- Cochran JH Jr, Pauly TJ, Edstrom LE, Dibbell DG. 1981. Hypoplasia of the latissimus dorsi muscle complicating breast reconstruction in Poland's syndrome. *Ann Plast Surg* **6**: 402–404. doi:10.1097/00000637-198105000-00010
- David TJ, Winter RM. 1985. Familial absence of the pectoralis major, serratus anterior, and latissimus dorsi muscles. *J Med Genet* **22**: 390–392. doi:10.1136/jmg.22.5.390
- Freire-Maia N, Chautard EA, Opitz JM, Freire-Maia A, Quelce-Salgado A. 1973. The Poland syndrome—clinical and genealogical data, dermatoglyphic analysis, and incidence. *Hum Hered* **23**: 97–104. doi:10.1159/000152560

- Gonda K, Tachiya Y, Hatakeyama Y, Momma T, Tamaoki T, Maejima Y, Rokkaku Y, Saji S, Shimomura K, et al. 2018. Poland syndrome accompanied by internal iliac artery supply disruption sequence: a case report. *J Med Case Rep* **12**: 312. doi:10.1186/s13256-018-1823-8
- Hamosh A, Scott AF, Amberger J, Valle D, McKusick VA. 1999. Online Mendelian Inheritance in Man (OMIM). *Hum Mutat* **15**: 57–61. doi:10.1002/(SICI)1098-1004(200001)15:1<57::AID-HUMU12>3.0.CO;2-G
- Huang Y, Pang H, Jin S, Han X, Liu X, Yang L, Zuo S, Li J, Meng D. 2018. Clinical characteristics of Poland's syndrome associated with breast cancer: two case reports and a literature review. *J Cancer Res Ther* **14**: 1665–1669. doi:10.4103/jcrt.JCRT\_814\_17
- Jiang Z, Song Q, Zeng R, Li J, Li J, Lin X, Chen X, Zhang J, Zheng Y. 2016. MicroRNA-218 inhibits EMT, migration and invasion by targeting SFMBT1 and DCUN1D1 in cervical cancer. *Oncotarget* **7**: 45622–45636. doi:10.18632/oncotarget.9850
- Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, Collins RL, Laricchia KM, Ganna A, Birnbaum DP, et al. 2020. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* **581**: 434–443. doi:10.1038/s41586-020-2308-7
- Kirby ML, Waldo KL. 1995. Neural crest and cardiovascular patterning. *Circ Res* **77**: 211–215. doi:10.1161/01.RES.77.2.211
- Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Albarca Aguilera M, Meyer R, Massouras A. 2019. VarSome: the human genomic variant search engine. *Bioinformatics* **35**: 1978–1980. doi:10.1093/bioinformatics/bty897
- Lin S, Shen H, Li JL, Tang S, Gu Y, Chen Z, Hu C, Rice JC, Lu J, Wu L. 2013. Proteomic and functional analyses reveal the role of chromatin reader SFMBT1 in regulating epigenetic silencing and the myogenic gene program. *J Biol Chem* **288**: 6238–6247. doi:10.1074/jbc.M112.429605
- Liu X, Simon JM, Xie H, Hu L, Wang J, Zurlo G, Fan C, Ptacek TS, Herring L, Tan X, et al. 2020. Genome-wide screening identifies SFMBT1 as an oncogenic driver in cancer with VHL loss. *Mol Cell* **77**: 1294–1306.e5. doi:10.1016/j.molcel.2020.01.009
- Megeney LA, Kablar B, Garrett K, Anderson JE, Rudnicki MA. 1996. MyoD is required for myogenic stem cell function in adult skeletal muscle. *Genes Dev* **10**: 1173–1183. doi:10.1101/gad.10.10.1173
- Parano E, Falsaperla R, Pavone V, Toscano A, Bolan EA, Trifiletti RR. 1995. Intrafamilial phenotypic heterogeneity of the Poland complex: a case report. *Neuropediatrics* **26**: 217. doi:10.1055/s-2007-979758
- Poland A. 1841. Deficiency of the pectoral muscles. *Guy's Hospital Reports* **VI**: 191–193.
- Pünzeler S, Link S, Wagner G, Keilhauer EC, Kronbeck N, Spitzer RM, Leidescher S, Markaki Y, Mentele E, Regnard C, et al. 2017. Multivalent binding of PWWP2A to H2A.Z regulates mitosis and neural crest differentiation. *EMBO J* **36**: 2263–2279. doi:10.15252/embj.201695757
- Relaix F, Demignon J, Laclef C, Pujol J, Santolini M, Niro C, Lagha M, Rocancourt D, Buckingham M, Maire P. 2013. Six homeoproteins directly activate Myod expression in the gene regulatory networks that control early myogenesis. *PLoS Genet* **9**: e1003425. doi:10.1371/journal.pgen.1003425
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, et al. 2015. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* **17**: 405–424. doi:10.1038/gim.2015.30
- Romanini MV, Calevo MG, Puliti A, Vaccari C, Valle M, Senes F, Torre M. 2018. Poland syndrome: a proposed classification system and perspectives on diagnosis and treatment. *Semin Pediatr Surg* **27**: 189–199. doi:10.1053/j.sempedsurg.2018.05.007
- Rosa RF, Travi GM, Valiatti F, Zen PR, Pinto LL, Kiss A, Graziadio C, Paskulin GA. 2007. Poland syndrome associated with an aberrant subclavian artery and vascular abnormalities of the retina in a child exposed to misoprostol during pregnancy. *Birth Defects Res A Clin Mol Teratol* **79**: 507–511. doi:10.1002/bdra.20366
- Sackey K, Odone V, George SL, Murphy SB. 1984. Poland's syndrome associated with childhood non-Hodgkin's lymphoma. *Am J Dis Child* **138**: 600–601.
- Shaham D, Ramu N, Bar-Ziv J. 1992. Leiomyosarcoma in Poland's syndrome. A case report. *Acta Radiol* **33**: 444–446. doi:10.1177/028418519203300513
- Tang M, Shen H, Jin Y, Lin T, Cai Q, Pinard MA, Biswas S, Tran Q, Li G, Shenoy AK, et al. 2013. The malignant brain tumor (MBT) domain protein SFMBT1 is an integral histone reader subunit of the LSD1 demethylase complex for chromatin association and epithelial-to-mesenchymal transition. *J Biol Chem* **288**: 27680–27691. doi:10.1074/jbc.M113.482349
- Tassano E, Mirabelli-Badenier M, Veneselli E, Puliti A, Lerone M, Vaccari CM, Morana G, Porta S, Gimelli G, Cuoco C. 2015. Clinical and molecular characterization of a patient with interstitial 6q21q22.1 deletion. *Mol Cytogenet* **8**: 31. doi:10.1186/s13039-015-0134-7
- Torre M, Baban A, Buluggiu A, Costanzo S, Bricco L, Lerone M, Bianca S, Gatti GL, Sénès FM, Valle M, et al. 2010. Dextrocardia in patients with Poland syndrome: phenotypic characterization provides insight into the pathogenesis. *J Thorac Cardiovasc Surg* **139**: 1177–1182. doi:10.1016/j.jtcvs.2009.08.024

- Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, et al. 2015. Proteomics. Tissue-based map of the human proteome. *Science* **347**: 1260419. doi:10.1126/science.1260419
- Usui H, Ichikawa T, Kobayashi K, Kumanishi T. 2000. Cloning of a novel murine gene *Sfmbt*, Scm-related gene containing four MBT domains, structurally belonging to the Polycomb group of genes. *Gene* **248**: 127–135. doi:10.1016/S0378-1119(00)00131-1
- Vaccari CM, Romanini MV, Musante I, Tassano E, Gimelli S, Divizia MT, Torre M, Morovic CG, Lerone M, Ravazzolo R, et al. 2014. De novo deletion of Chromosome 11q12.3 in monozygotic twins affected by Poland syndrome. *BMC Med Genet* **15**: 63. doi:10.1186/1471-2350-15-63
- Valasek P, Theis S, DeLaurier A, Hinitz Y, Luke GN, Otto AM, Minchin J, He L, Christ B, Brooks G, et al. 2011. Cellular and molecular investigations into the development of the pectoral girdle. *Dev Biol* **357**: 108–116. doi:10.1016/j.ydbio.2011.06.031
- van Steensel MA. 2004. Poland anomaly: not unilateral or bilateral but mosaic. *Am J Med Genet A* **125A**: 211–212. doi:10.1002/ajmg.a.20392
- Wang WK, Tereshko V, Boccuni P, MacGrogan D, Nimer SD, Patel DJ. 2003. Malignant brain tumor repeats: a three-leaved propeller architecture with ligand/peptide binding pockets. *Structure* **11**: 775–789. doi:10.1016/S0969-2126(03)00127-8
- Wu S, Trievel RC, Rice JC. 2007. Human SFMBT is a transcriptional repressor protein that selectively binds the N-terminal tail of histone H3. *FEBS Lett* **581**: 3289–3296. doi:10.1016/j.febslet.2007.06.025
- Yang HC, Liang YJ, Chen JW, Chiang KM, Chung CM, Ho HY, Ting CT, Lin TH, Sheu SH, Tsai WC, et al. 2012. Identification of *IGF1*, *SLC4A4*, *WVVOX*, and *SFMBT1* as hypertension susceptibility genes in Han Chinese with a genome-wide gene-based association study. *PLoS One* **7**: e32907. doi:10.1371/journal.pone.0032907
- Yesilkaya Y, Dizdar O, Altundag K. 2011. Ipsilateral breast cancer in a patient with Poland's syndrome. *Am Surg* **77**: 234–235. doi:10.1177/000313481107700229
- Yiyit N, Işitmançıl T, Öksüz S. 2015. Clinical analysis of 113 patients with Poland syndrome. *Ann Thorac Surg* **99**: 999–1004. doi:10.1016/j.athoracsur.2014.10.036
- Zhang J, Bonasio R, Strino F, Kluger Y, Holloway JK, Modzelewski AJ, Cohen PE, Reinberg D. 2013. SFMBT1 functions with LSD1 to regulate expression of canonical histone genes and chromatin-related factors. *Genes Dev* **27**: 749–766. doi:10.1101/gad.210963.112
- Zhu L, Zeng A, Wang XJ, Liu ZF, Zhang HL. 2012. Poland's syndrome in women: 24 case studies and literature review. *Chin Med J (Engl)* **125**: 3283–3287.