# Syndromes predisposing to leukemia are a major cause of inherited cytopenias in children

Oded Gilad,[1,2] Orly Dgany,[3] Sharon Noy-Lotan,[3] Tanya Krasnov,[3] Joanne Yacobovich,[1,2] Ron Rabinowicz,[1,2] Tracie Goldberg,[1] Amir A. Kuperman,[4,5] Abed Abu-Quider,[6] Hagit Miskin,[7,8] Noa Kapelushnik,[2,9] Noa Mandel-Shorer,[10,11] Shai Shimony,[2,12,13] Dan Harlev,[14] Tal Ben-Ami,[8,15] Etai Adam,[16] Carina Levin,[11, 17] Shraga Aviner,[18] Ronit Elhasid,[2,19] Sivan Berger-Achituv,[2,19] Lilach Chaitman-Yerushalmi,[20] Yona Kodman,[1] Nino Oniashvilli,[1] Michal Hameiri-Grosman,[1] Shai Izraeli,[1,2] Hannah Tamary[1,2,3] and Orna Steinberg-Shemer[1,2,3]

[1]Department of Hematology-Oncology, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Pediatric Hematology Laboratory, Felsenstein Medical Research Center, Petach Tikva, Israel; [4]Blood Coagulation Service and Pediatric Hematology Clinic, Galilee Medical Center, Nahariya, Israel; [5]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel; [6]Pediatric Hematology, Soroka University Medical Center, Ben-Gurion University, Beer Sheva, Israel; [7]Pediatric Hematology Unit, Shaare Zedek Medical Center, Jerusalem, Israel; [8]Faculty of Medicine, Hebrew University, Jerusalem, Israel; [9]Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel; [10]Department of Pediatric Hematology-Oncology, Ruth Rappaport Children's Hospital, Rambam Healthcare Campus, Haifa, Israel; [11]Rappaport Faculty of Medicine, Technion-Institute of Technology, Haifa, Israel; [12]Rabin Medical Center, Institute of Hematology, Davidoff Cancer Center, Beilinson Hospital, Petach-Tikva, Israel; [13]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [14]Pediatric Hematology-Oncology Department, Hadassah University Medical Center, Jerusalem, Israel; [15]Pediatric Hematology Unit, Kaplan Medical Center, Rehovot, Israel; [16]Pediatric Hematology-Oncology Department, Sheba Medical Center, Tel Hashomer, Israel; [17]Pediatric Hematology Unit and Research Laboratory, Emek Medical Center, Afula, Israel; [18]Department of Pediatrics, Barzilai University Medical Center, Ashkelon, affiliated to Ben Gurion University, Beer-Sheva, Israel, [19]Department of Pediatric Hemato-Oncology, Tel Aviv Medical Center Tel Aviv, Israel and [20]Genoox, Health Care Technology, Tel Aviv, Israel.

**Correspondence:** H. Tamary
htamary@tauex.tau.ac.il

**Received:** September 30, 2021.
**Accepted:** March 10, 2022.
**Prepublished:** March 17, 2022.

**https://doi.org/10.3324/haematol.2021.280116**

**Supplementary Table 1 – Gene list of the latest version of our next-generation sequencing panel (n=226)**

| Category (n) | Gene list |
|---|---|
| **DNA repair /Chromosomal instability (36 genes)** | *ALDH2, BLM, BRCA1, BRCA2, BRCC3, BRIP1, COX4I1, ERCC1, ERCC4, ERCC6L2, FAAP100, FAAP24, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FANCW(RFWD3), HES1, MAD2L2, NBN, NHEJ1, PALB2, PRKDC, RAD50, RAD51, RAD51C, RNF168, SLX4, UBE2T, XRCC2* |
| **Telomere maintenance (20 genes)** | *ACD, CTC1, DKC1, GAR1, GRHL2, NAF1, NHP2, NOP10, PARN, RTEL1, STN1, TCAB1, WRAP53, TERC, TERT, TINF2, TIN2, TPP1, TRF1, TRF2* |
| **Diamond Blackfan Anemia (DBA) (23 genes)** | *FLNB, FLVCR1, HEATR3, RPL5, RPL9, RPL11, RPL15, RPL26, RPL27, RPL31, RPL35A, RPS7, RPS8, RPS10, RPS14, RPS17, RPS19, RPS24, RPS26, RPS27, RPS28, RPS29. TSR2* |
| **Schwachman Bodian Diamond syndrome (SBDS) (4 genes)** | *SBDS, DNAJC21, EFL1, SRP54* |
| **Congenital neutropenia (28 genes)** | *ACKR1/DARC promotor, AK2, C16ORF57, CLPB, CSF3R, CXCR2, CXCR4, EIF2AK3, ELANE, G6PC3, GFI1, GINS1, HAX1, JAGN1, LAMTOR2, RAC2, RBSN, SLC37A4, SMARCD2, STK4, TAZ, TCIRG1, USB1, VPS13B, VPS33B, VPS45, WAS, WIPF1* |
| **Cancer predisposition (43 genes)** | *ATM, ATR, ATRX, BNIP3, BNIP3L, BRAF, CBL, CDKN1B, CDKN2A, CEBPA, CHEK2, DDX41, EPCAM, GATA2, IKZF1, KIT, KRAS, LIG4, LZTR1, MET, MLH1, MRE11A, MSH2, MSH6, NF1, NRAS, NSD1, PAX5, PIK3CA, PMS2, POT1, PTPN11, RAF1, RIT1, SHOC2, SAMD9, SAMD9L, SOS1, SOS2, SRSF2, TP53, WRN, WT1* |
| **Inherited thrombocytopenia/ Bleeding disorders (68 genes)** | *ACTN1, ABCG5, ABCG8, ADAMTS13, ADRA2A, ANKRD26, ANO6, AP3B1, AP3D1, BLOC1S3, BLOC1S6, C6ORF25, CYCS, DIAPH1, DTNBP1, ETV6, F2R, F2RL3, FERMT3, FLI1, FLNA, FYB, GALE, GATA1, GFI1B, GNE, GP1BA, GP1BB, GP6, GP9, HOXA11, HPS1, HPS3, HPS4, HPS5, HPS6, ITGA2, ITGA2B, ITGB3, JAK2, MASTL, MECOM, MEIS1, MPL, MYH9, NBEA, NBEAL2, ORAI1, P2RY12, PLA2G4A, PLAU, PRKACG, PTGS1, PTPRJ, RASGRP2, RBM8A, RUNX1, SH2B3, SLFN14, SRC, STIM1, TBXA2R, TBXAS1, THPO, TPM4, TRPM7, TUBB1, VWF* |
| **Others (4 genes)** | *ADA2/CECR1, MYSM1, SRP72, RMRP* |

**Supplementary Table 2 – Clinical and demographic characteristics of the patients**

| | Number of Patients (%) | Ethnicity (%) | | Consanguinity (%) | Family history of cytopenias (%) | Congenital anomalies (%) |
|---|---|---|---|---|---|---|
| | | Jewish | Non-Jewish | | | |
| Study population | 189 | 102 (54%) | 87 (46%) | 55 (29.1%) | 56 (29.6%) | 54 (28.6%) |
| Genetically diagnosed | 59 (31.2%) | 33 (32.4%) | 26 (29.9%) | 14/59 (23.7%) | 20/59 (33.9%) | 23/59 (39%) |
| No genetic diagnosis | 130 (68.2%) | 69 (67.6%) | 61 (70.1%) | 41/130 (31.5%) | 36/130 (27.7%) | 31/130 (23.8%) |
| P value (comparing diagnosed/undiagnosed) | | | | 0.39 | 0.61 | 0.038 |
| **Referral diagnosis** | | | | | | |
| IBMFS | 48 | 20 (41.7%) | 28 (58.3%) | 21 (43.8%) | 20 (41.7%) | 34 (70.8%) |
| MDS | 26 | 18 (69.2%) | 8 (30.8%) | 6 (23.1%) | 6 (23.1%) | 5 (19.2%) |
| Isolated thrombocytopenia | 33 | 23 (69.7%) | 10 (30.3%) | 6 (18.2%) | 18 (54.6%) | 4 (12.1%) |
| Isolated neutropenia | 51 | 26 (51%) | 25 (49%) | 17 (33.3%) | 10 (19.6%) | 9 (17.6%) |
| SAA | 31 | 15 (48.4%) | 16 (51.6%) | 5 (16.1%) | 2 (6.5%) | 2 (6.5%) |

Non-Jewish – Mainly Arabs (Muslims, Christians, and Druze).

Abbreviations - IBMFS – Inherited Bone Marrow Failure Syndromes; MDS – Myelodysplastic Syndrome, SAA – Severe Aplastic Anemia

## Supplementary Table 3: Molecular diagnoses

| Patient | Disease | *Gene* | Inheritance | HGVS Coding | HGVS Protein | Type of Mutation | Highest MAF (dbSNPrs) | ClinVar (Accession) | Classification | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| 5612 | FA | *FANCA* | AR | NM_000135.4: c.3749_3750insT-Hm | NP 000126.2: p.Cys1251LeufsTer27 | Frameshift | 0 | | Pathogenic | This paper |
| 5409 | FA | *FANCA* | AR | 1. NM_000135.2: c.2172-2173 insG-Ht<br>2.NM_000135.4: c.891_893+1delCTGG-Ht | 1. NP 000126.2: p. Ser725Valfs*69 | 1. Frameshift<br>2.Splice site | 0<br>0 | | Pathogenic<br>Pathogenic | 1,2 |
| 4840 | FA | *FANCA* | AR | NM_000135.2: c.4069 4070insT-Hm | NP 000126.2: p.Ala1357ValfsTer68 | Frameshift | 0 | | Pathogenic | 1 |
| 5011 | FA | *FANCA* | AR | NM 000135.2: c.1361_1374delinsGAG -Hm | NP 000126.2: p.Ala454GlyfsTer27 | Frameshift | 0 | | Pathogenic | This paper |
| 4118* | FA | *FANCA* | AR | NM_000135: c.3490C>T-Hm | NP_000126.2 p. Pro1164Ser | Missense | 0 (rs545772434) | RCV001256293 | Likely pathogenic | This paper |
| 4139* | FA | *FANCA* | AR | NM_000135: c.4261-2A>C-Hm | | Splice site | 0.000016 (rs915983602) | RCV000673853 | Pathogenic | 1 |
| 4034* | FA | *FANCA* | AR | NM_000135.4): c.3382C>T-Hm | NP_000126.2 p.Gln1128Ter | Frameshift | 0 (rs1439817346) | RCV000673853 | Pathogenic | 3 |
| 3013* | FA | *FANCA* | AR | NM_000135.4: c.3788_3790delTCT- Hm | NP_000126.2: p.Phe1263del | In frame deletion | 0.0000997 (rs397507553) | RCV000033896 | Pathogenic | 4 |
| 3950* | FA | *FANCA* | AR | NM_000135.4: c.3788_3790delTCT- Hm | NP_000126.2: p.Phe1263del | In frame deletion | 0.0000997 (rs397507553) | RCV000033896 | Pathogenic | 4 |
| 5295* | FA | *FANCA* | AR | NM_000135.4: c.2172dupG- Hm | NP_000126.2: p.Ser725ValfsTer69 | Frameshift | 0 (rs1555547955) | RCV000670729 | Pathogenic | 2 |
| 3167 | FA | *BRCA1* | AR | NM_007300.4: c.1115G>A – Hm | NP_009231.2: p.Trp372Ter | Nonsense | 0.00000398 (rs397508838) | RCV000241007 | Pathogenic | 5 |
| 5115 | FA | *FANCE* | AR | NM 021922.2: c.1114-8G>A -Hm | | Splice site | 0 (rs878854342) | VCV000008711 | Pathogenic | 6 |
| 4294 | DC | *TERT* | AD | NM_198253.3: c.2834_2842delACTACTCCA insCACCT-Ht | NP_937983.2: p.Asp945AlafsTer35 | Frameshift | 0 | | Likely pathogenic | This paper |
| 4324 | DC | *TERC* | AD | NR_001566: r.172A>G -Ht | | Single Nucleotide Variant-RNA | 0 | | Likely pathogenic | This paper |
| 3884 | DC | *WRAP53* | AR | NM_001143990.1: c.936c>G-Hm | NP_001137462.1: p.Cys312Trp | Missense | 0 | | Likely pathogenic Variant not found in GnomAD . Mixed predictions. | This paper |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 4336 | DC | *TINF2* | AD | NM_001099274.3: c.813dupA-Ht | NP_001092744.1: p.Trp272MetfsTer5 | Frameshift | 0 | | Pathogenic | This paper |
| 5484 | DBA | *RPS19* | AD | NM_ 001022.4: c.384_385delAA -Ht | NP 001013.1: p.Asp130SerfsTer23 | Frameshift | 0 (rs869066130) | RCV000703435 | Pathogenic | 7 |
| 4528* | DBA | *RPS19* | AD | NM_001022.3: c.98G>A-Ht | NP_001013.1: p.Trp33Ter | Nonsense | 0 (rs104894716) | RCV001237459 | Pathogenic | 8 |
| 4337* | DBA | *RPS19* | AD | NM_001022.4): c.184C>T-Ht | NP_001308413.1: p.Arg62Trp | Missense | 0 (rs104894711) | RCV001065746 | Pathogenic | 9 |
| 4335* | DBA | *RPS19* | AD | NM_001022.4): c.184C>T-Ht | NP_001308413.1: p.Arg62Trp | Missense | 0 (rs104894711) | RCV001065746 | Pathogenic | 9 |
| 4236* | DBA | *RPS19* | AD | NM_001022.3: c.98G>A-Ht | NP_001013.1: p.Trp33Ter | Nonsense | 0 (rs104894716) | RCV001237459 | Pathogenic | 8 |
| 3449* | DBA | *RPS19* | AD | NM_001022.3: c.134T>C-Ht | NP_001013.1: p.Leu45Pro | Missense | 0 | | Likely pathogenic | This paper |
| 579 | DBA | *RPS10* | AD | NM_001202470.2: c.71A>G-Ht | NP_001189399.1: p.Lys24Arg | Missense | 0.000342 (rs201147592) | | Likely pathogenic | This paper |
| 5496 | DBA | *RPS26* | AD | NM_001029.5: c.23delA-Ht | NP 001020.2: p.Asn8MetfsTer37 | Frameshift | 0 | | Likely pathogenic | This paper |
| 5810 | DBA | *RPS28* | AD | NM_001031.4: c.2T>C -Ht | NP_001022.1: p.Met1Thr | Start loss | 0 | | Pathogenic | This paper** |
| 3969 | DBA | *RPL15* | AD | NM_001253379.2: c. 29T>C – Ht | NP_001240308.1: p.Leu10Pro | Missense | 0 | | Likely pathogenic | 11 |
| 5541 | DBA like | *CECR1* | AR | NM_001282225.1: c.1397_1403del-Hm | NP 001269154.1: p.Lys466ThrfsTer2 | Frameshift | 0.0000398 (rs754904956) | | Pathogenic | 12 |
| 5112 | BMF | *MYSM1* | AR | NM_001085487.2: c.2329-2A>G-Hm | | Splice site | 0 | | Likely pathogenic | 13 |
| 3941 | BMF | *ERCC6L2* | AR | NM_020207.4: c.3525+2T>G – Hm | | Splice site | 0 | RCV001004901 | Pathogenic | This paper |
| 5467 | MDS | *SAMD9L* | AD | NM_152703: c.4736A>G-Ht | NP_689916: p.Tyr1579Cys | Missense | 0 | | Likely pathogenic | This paper |
| 5096 | MDS | *SAMD9L* | AD | NM_152703.4: c.4045C>G-Ht | NP_689916.2: p.Pro1349Ala | Missense | 0 | | Likely pathogenic | This paper |
| 5371 | MDS | *SAMD9L* | AD | NM_152703.2: c.2957G>A -Ht | NP 689916.2: p.Arg986His | Missense | 0 (rs769611275) | | Likely pathogenic | 14 |
| 5418 | MDS | *ERCC6L2* | AR | NM 001010895.2: c.535A>G- Hm | NP 001010895.1: p.Lys179Glu | Missense | 0.00000399 (rs775665068) | | Likely pathogenic | This paper |
| 5249 | MDS | *ERCC6L2* | AR | NM_020207.7: c.3492+2T>G Hm | | Splice site | 0 | | Pathogenic | 15 |
| 4261 | MDS | *ANKRD26* | AD | NM_001256053.1: c.3G>A -Ht | NP_001242982.1: p.Met1Ile | Start loss | 0.000268 (rs199683454) | | Likely pathogenic | 16 |
| 4674 | IT | *MYH9* | AD | NM_002473.6: c.287C>T -Ht | NP_002464.1: p.Ser96Leu | Missense | 0 (rs121913657) | RCV000790352 | Pathogenic | 17 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 4814 | IT | *MYH9* | AD | NM_002473.5: c.4270G>A -Ht | NP_002464.1: p.Asp1424Asn | Missense | 0 (rs80338831) | RCV000790358 | Pathogenic | 18 |
| 5016 | IT | *MYH9* | AD | NM_002473.4: c.5797C>T -Ht | NP 002464.1: p.Arg1933Ter | Nonsense | 0.000004 (rs80338835) | RCV000790363 | Pathogenic | 19 |
| 3870 | IT | *MYH9* | AD | NM_002473.6: c.287C>T-Ht | NP_002464.1: p.Ser96Leu | Missense | 0 (rs121913657) | RCV000790352 | Pathogenic | 20,21 |
| 5688 | IT | *MYH9* | AD | NM_002473.5: c.4641G>T-Ht | NP_002464.1: p.Glu1547Asp | Missense | 0.000326 (rs752832018) | | Likely pathogenic | This paper |
| 5437 | IT | *ACTN1* | AD | NM_001130004.1: c.1019C>T -Ht | NP_001093.1: p.Thr340Met | Missense | 0 | RCV001003912 | Likely pathogenic | 21 |
| 4774 | IT | *ACTN1* | AD | NM_001130004.1: c.1019C>T-Ht | NP_001093.1: p.Thr340Met | Missense | 0 | RCV001003912 | Likely Pathogenic | 21 |
| 5487 | IT | *CYCS* | AD | NM_018947.5 : c.274A>G-Ht | NP_061820.1: p.Arg92Gly | Missense | 0 | | Likely pathogenic | This paper |
| 4440 | IT (GPS) | *NBEAL2* | AR | NM_015175.3: c.7225-1G>C-Hm | | Splice site | 0 | RCV000991418 | Pathogenic | This paper |
| 5566 | IT-MDS | *ANKRD26* | AD | c.-134G>A -Ht | | 5UTR variant | 0 (rs863223318) | RCV000023838 | Pathogenic | 22 |
| 3867 | IT-MDS | *ANKRD26* | AD | NM_014915.2: c.-127A>G –Ht | | 5UTR variant | 0 rs1589393799 | RCV000851620 | Pathogenic | 23 |
| 3610 | IT-MDS | *ANKRD26* | AD | NM_014915.3: c.-128G>T-Ht | | 5UTR variant | 0 rs1589393809 | RCV001003522 | Pathogenic | 22 |
| 5433 | IT-MDS | *ANKRD26* | AD | NM_001256053: c.-134G>A -Ht | | 5UTR variant | 0 (rs863223318) | RCV000023838 | Pathogenic | 22 |
| 5275 | IT-MDS | *ETV6* | AD | NM_001987.4: c.1103T>G -Ht | NP 001978.1: p.Phe368Cys | Missense | 0 | | Likely pathogenic | This paper |
| 5419 | IT-MDS | *ETV6* | AD | NM_001987.4 c.1104C>G-Ht | NP 001978.1: p.Phe368Leu | Missense | 0 | | Likely pathogenic | This paper |
| 5214 | IT-MDS | *RUNX1* | AD | NM_001001890.2: c.532+1_532+10delGTAAGTGCAT -Ht | | Splice site | 0 | | Pathogenic | This paper |
| 5878 | Galactosemia 3 | *GALE* | AR | NM_000403.3: c.151C>T –Hm | NP_000394.2: p.Arg51Trp | Missense | 0.0000199 (rs780517804) | | Pathogenic | 24 |
| 3881 | CN | *JAGN1* | AR | NM_032492.3: c.3G>A -Hm | NP_115881.3 p.Met1Ile | Start loss | 0.0000383 (rs587777727) | RCV000144162 | Pathogenic | 25 |
| 4452 | CN | *SRP54* | AD | NM_003136.3: c.349_351delACA | NP_003127.1: p.Thr117del | In frame deletion | 0.000013 rs1555354198 | RCV000731602 | Pathogenic | 26 |
| 4041** | CN | *SRP54* | AD | NM_003136.3: c.349_351delACA | NP_003127.1: p.Thr117del | In frame deletion | 0.000013 rs1555354198 | RCV000731602 | Pathogenic | 26 |
| 5750* | CN/SBDS | *SBDS* | AR | 1. NM_016038: c. 183_184 delTAinsCT - Ht<br>2. NM_016038: c.258+2 t>c: splice site - Ht | 1. NP_057122.2: p.Lys62Ter<br>2. Splice variant | 1. stop codon<br>2. Splice site | 1. 0 (rs113993991)<br>2. 0.00388 (rs113993993) | 1. RCV000003195<br>2. RCV000255013 | 1. Pathogenic<br>2. Pathogenic | 27,28 |
| 4633* | CN/SBDS | *SBDS* | AR | 1. NM_016038: c. 183_184 delTAinsCT - Ht | 1. NP_057122.2: p.Lys62Ter | 1. stop codon | 1. 0 (rs113993991) | 1. RCV000003195<br>2. RCV000255013 | 1. Pathogenic<br>2. Pathogenic | 27,28<br>29 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 2. NM_016038: c.258+2 t>c:Ht- | | 2. Splice site | 2. 0.00388 (rs113993993) | | | |
| 3734** | CN/FHLH | *UNC13D* | AR | NM_199242.2: c.679C>T- Hm | NP_954712.1: p.Arg227Cys | Missense | 0.00088 rs754974092 | | Likely pathogenic | This paper |
| 5203 | BMF | *GATA2* | AD | NM_001145661.1: c.1186C>T -Ht | NP 116027.2: p.ArgR396Trp | Missense | 0 | RCV000984829 | Likely Pathogenic | 30 |

BMF – Bone Marrow Failure; FA – Fanconi Anemia; DBA – Diamond Blackfan Anemia; DC – Dyskeratosis Congenita, GPS – Gray Platelet Syndrome; CN - Congenital Neutropenia; SBDS - Schwachman Bodian Diamond syndrome; FHLH - Familial Hemophagocytic Lymphohistiocytosis; HGVS-Human Genome Variation Society; MAF-Minor Allele Frequency; Hm – Homozygous; Ht- Heterozygous; IT –Inherited Thrombocytopenia; IT-MDS – Inherited Thrombocytopenia with elevated risk for myelodysplastic syndrome /acute myeloid leukemia ; AR – Autosomal Recessive ; AD – Autosomal Dominant

*Diagnosed through Sanger sequencing, **Diagnosed through whole exome sequencing
**A different variant in the same amino acid was reported as pathogenic in Grippp et al.[10]

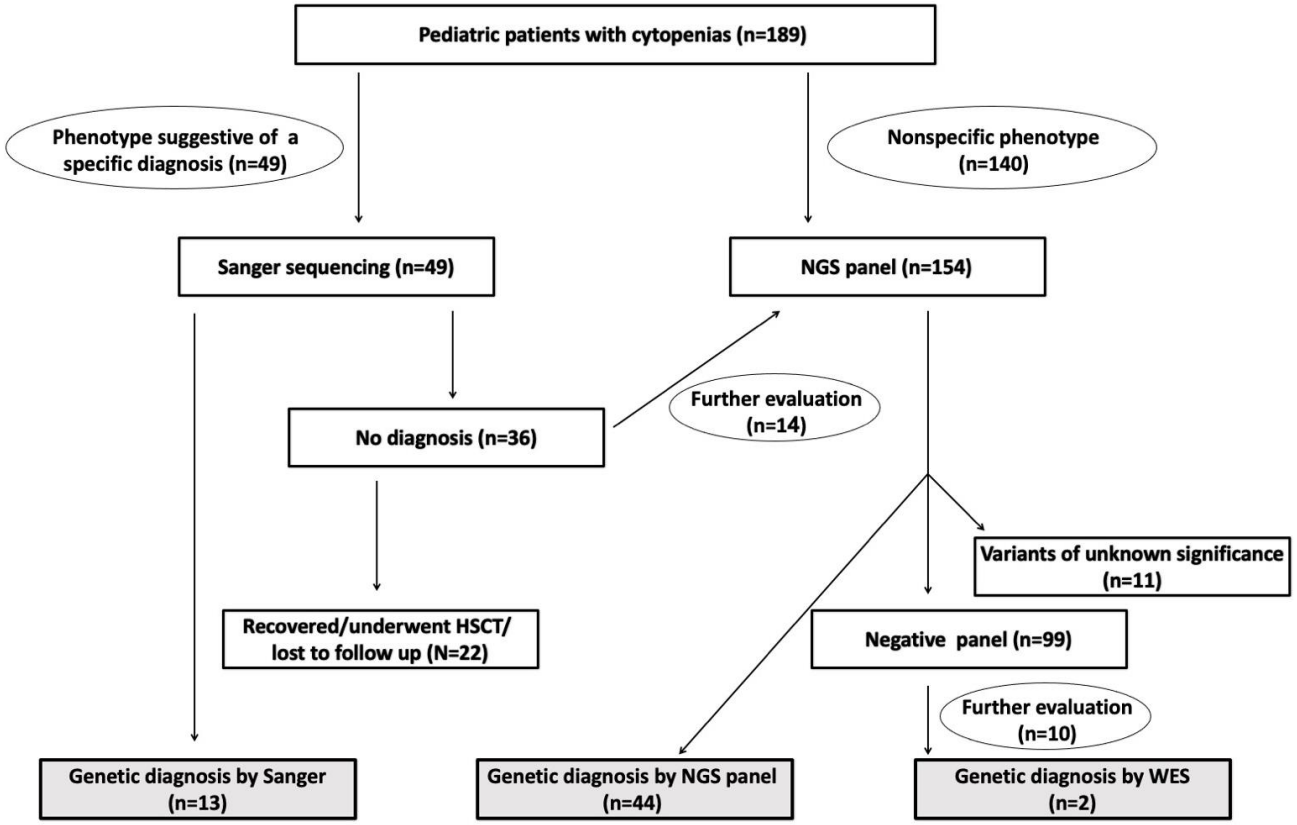
**Supplementary Table 4: Variants of unknown significance found in our cohort**

| Patient | Disease | Gene | Inheritance | HGVS Coding | HGVS Protein | Type of Mutation | Highest MAF (dbSNP rs) | ClinVar (Accession) |
|---|---|---|---|---|---|---|---|---|
| 4716 | DBA | *RPS7* | AD | NM_001011.4: c.79C>A -Ht | NP_001002.1: p.Leu27Ile | Missense | 0.000196 (rs758369264) | |
| 3704 | CN | *CSF3R* | AR | 1. NM_156039.3: c.1071G>C- Ht<br>2. NM_156039.3: c.689C>T-H | 1. NP_000751.1: p.Lys357Asn<br>2. NP_000751.1: p.Pro230Leu | 1. Missense<br>2. Missense | 0<br>0 | |
| 5332 | SAA | *SAMD9L* | AD | NM_152703.2: c.505G>C-Ht | NP 689916.2: p.Asp169His | Missense | 0.000104 (rs144605831) | |
| 5451 | CN | *TCIRG1* | AD | NM 006019.3: c.1138G>A-Ht | NP 006010.2: p.Val380Met | Missense | 0.0000247 | |
| 4998 | Myeloproliferative/ Lymphoproliferative neoplasms | *DDX41* | AD | NM_016222.3: c.1549G>A - Ht | NP_057306.2: p.Val517Ile | Missense | 0.01 | |
| 5466 | Radioulnar Synostosis with amegakaryocytic thrombocytopenia | *MECOM* | AD | NM_004991.4: c.1945G>C-Ht | NP_004982.2 p.Glu649Gln | Missense | 0 | |
| 5171 | Bleeding Disorder, Platelet-Type 16 | *ITGB3* | AD | NM 000212.2: c.2105A>G-Ht | NP 000203.2: p.Lys702Arg. | Missense | 0 | |
| 5429 | CN | *CSF3R* | AR | NM 000760.3: c.79G>A-Hm | NP 000751.1: p.Gly27Arg | Missense | 0.0000269 | RCV000523671 |
| 5291 | Bleeding Disorder, Platelet-Type14 | *TBXAS1* | AD | NM 001061.4: c.725G>A-Ht | NP 001052.2: p.Arg242Gln | Missense | 0.000289 | |
| 4804 | Macrothrombocytopenia | *ITGB3** | AD | NM_000212.2: c.985A>G -Ht | NP_000203.2: p.Asn329Asp | Missense | 0.000135 (rs201550717) | RCV000295402 |

DBA – Diamond Blackfan Anemia; CN –Congenital Neutropenia; SAA – Severe Aplastic Anemia; HGVS-Human Genome Variation Society; MAF-Minor Allele Frequency; AR – Autosomal Recessive; AD – Autosomal Dominant; Hm – Homozygous; Ht-Heterozygous

*A different change in this position was described by Owaidah.[31]

**Supplementary Figure 1**



**Legend**

**Supplementary Figure 1-Genetic workflow of children with persistent cytopenias.** The figure outlines the genetic work-up of patients included in this study. NGS – Next Generation Sequencing; WES – Whole Exome Sequencing; HSCT – Hematopoietic Stem Cell Transplantation.

References: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