Natural history of GATA2 deficiency in a survey of 79 French and Belgian patients

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Pedigree	Exon	Nucleotide change / protein effect	Mutation type	Age at first manifestation (years)	MDS/AL	Karyotype	Treatment	Infections	Post HSCT and post chemotherapy infections	Other features	Vital status (age, years)
P1*	2	c.[140T>G;142T>C ; 145T>C;177C>G] / p.[Val47_Phe49 delinsGLL;Y59*]	NS	22	MDS	Trisomy 8		Axillar abscess, genital warts			A(24)
P2*	Int 2	c.229+13_229+14 insGCCins203_229 +13; p.?	SD	19	MDS	Trisomy 8	HSCT	Cutaneous and genital warts (CIN III)			A(35)
P2 (brother)	Int 2	na	SD	21	MDS	Monosomy 7, Trisomy 1, 46XY, +1, der(1;7)(q10;p10), del(20)(q12)	HSCT	Pyocyanic infection, Pulmonary and medullary tuberculosis, Pneumonia Genital / cutaneous warts, Labial HSV			D(25) (HSCT)
P2 (mother)	Int 2	c.229+13_229+14 insGCCins203_229 +13; p.?	SD	44	MDS	Nl		Pyelonephritis, genital warts, Dermo-hypodermitis, pneumonia		Rheumatisms, Miscarriage, Epidermoid carcinoma	A(56)
P2 (sister)	Int 2	na	SD	18	MDS	Monosomy 7 with complex chr 6 abnormality		CMV pneumonia *E. coli* pneumonia, Pyoderma gangrenosum septicemia			D(22) (bacterial infection)
P3*	3	c.317_318del / p.S106Cfs*78	FS	29	Nl	Nl	EPO	Salpingitis, mycobacteriosis (*M. kansasii)* leg amputation		Psoriatic arthritis Hypoparathyroi-dism, Interstitial lung disease (PAP), Hepatosiderosis	A(42)
P4*	3	c.353del / p.Val618fs	FS	11	MDS	Monosomy 7	HSCT	na			A(15)
P5*	3	c.423C>A / p.Y141*	NS	13	MDS	Monosomy 7	HSCT	Genital warts, facial dermo-hypodermitis, Zoster	sinusitis bronchitis post HSCT		A(44)
P6*	3	c.437del / p.G146fs	FS	17	MDS	Nl		Pneumonia, colitis, salpingitis/ abscess and peritonitis EBV infection		Urinary system malformation (ureteral reflux)	A(18)
P6 (father)	3	na	FS	26	MDS			Mycobacteriosis (*M.kansasii)*		Metastatic adenocarcinoma	D(32) (adenocarcinoma)
P7*	3	c.538G>T / p.E180*	NS	20	MDS	Nl		Cutaneous warts		Urinary system malformation	A(22)
P8* *(6)*	3	c.610C>T / p.R204*	NS	19	MDS, AML4	Trisomy 1q Der9 t(1;9)(q12;q1 2), r(9)(q12 ;q ?3 4), 11q23(2)	GCSF , Interferon , EPO, Chemotherapy	EBV infection, cutaneous warts, mycobacteriosis (*M. avium)*, Zoster, CMV (hemophagocytic syndrome)			D(26) (chemotherapy)
P9* *(6)*	3	c.670G>T / p.E224*	NS	10	MDS	Nl	GCSF	Cutaneous and genital warts			A(20)
P10*	4	c.890A>G / p.N297S	MS	22	MDS , AML0	Inv 3	Chemotherapy HSCT		Mucormycosis post HSCT		D(23) (HSCT)
P11*	4	c.915_916del / p.W306Afs*77	FS	4	MDS	Monosomy 7, 45, XY, -7[7], 46, XY [18], +mar1, +mar2	HSCT	Pneumonia, Staphylococcal and mycobacterial osteomyelitis			A (15)
P12*	4	c.937C>T / p.H313Y	MS	21	MDS, Undifferen-tiated acute leukemia	Del5 Del7 T8 Add 10 Del12 Monosomy 18, Monosomy 21	HSCT	Viral meningitis skin HSV	Hemophagocytic syndrome and lymphoproliferative disease EBV-related post-HSCT		D(57) (EBV)

P13*	4	c.941_951del/ p.Y314Cfs*66	FS	18	MDS	Monosomy 7	HSCT	Flu infection			A(23)
P14*	4	c.944T>C / p.L315P	MS	1	Nl			Buttock abscess			A(8)
P15* *(6)*	4	c.988C>T / p.R330*	NS	8	AML2	46XY, +1, der (1;7)(q10;p10),9qh+ c[15], 46,XY, 9qh+c[5] : trisomy 1q, monosomy 7q)	Chemotherapy	Cutaneous warts	Aspergillosis post-chemotherapy		D(18) (chemotherapy)
P15 (brother) *(6)*	4	c.988C>T / p.R330*	NS	14	Nl	Nl		Meningococcemia			A(23)
P15 (father) *(6)*	4	c.988C>T / p.R330*	NS		Nl	Nl					A(60)
P15 (brother) *(6)*	4	c.988C>T / p.R330*	NS	17	MDS	46,XY,+1,der(1;7)(q 10;p10) [2] / 45,XY,-21 [1] / 46,XY, [8]	HSCT	Recurrent otitis, Pneumonia, Cutaneous warts			A(25)
P15 (paternal uncle) *(6)*	4	c.988C>T / p.R330*	NS	19	na			Cutaneous and genital warts		Aortic dissection	D(36) (aortic dissection)
P16*	Int 4	c.1017+572C>T	Regulatory	22	MDS	der(Y)t(Y;1)(q11.23 ;q21)		Pneumonia, cutaneous warts			A(43)
P16 (brother)	Int 4	c.1017+572C>T	Regulatory	32	ND					Migraine, Transient ischemic attack	A(39)
P17*	5	c.1018_1028del / p.S340Kfs*40	FS	10	MDS	Nl	HSCT	Mycobacteriosis (*M. genavense)*			A(42)
P17 (daughter)	5	c.1018_1028del / p.S340Kfs*40	FS	9	Nl			Pneumonia		Premature	A(16)
P18*	5	c.1020_1029dup / p.R344Gfs*43	FS	27	MDS	Nl	EPO	Pneumonia		Lymphedema PAP	A(30)
P19*	5	c.1023del / p.A342Pfs*45	FS	11	Nl (transient pancytopenia)	Nl	GCSF	Sinusitis, leg folliculitis, Mycobacteriosis (*M. kansasii*), Aspergillosis, cutaneous and genital warts			D(27) (mycobacteriosis)
P19 (sister)	5	c.1023del / p.A342Pfs*45	FS	11	Nl	Nl		cutaneous warts, Pyelonephritis Mycobacteriosis (*M.kansasii)*			A(28)
P20*	5	c.1023dup / p.A342Rfs*42	FS	24	MDS	Nl	HSCT	Buttock abscess, recurrent pneumonia, subcutaneous abscess, genital and cutaneous warts, septic shock			D(43) (bacterial infection)
P21*	5	c.1045T>C / p.C349R	MS	20	MDS	46,XY,der(3)t dic(1;3)(p11; p25)	HSCT	Cutaneous warts, viral meningitis, oral HSV, mycobacterial pulmonary infection		Erythema nodosum	A(20)
P22*	5	c.1060A>C / p.T354P	MS	15	MDS	Nl	HSCT	Cutaneous warts, buccal HSV, recurrent sinusitis		Granulomatous dermatitis lupus-like	A(19)
P23*	5	c.1061C>G / p.T354R	MS	21	MDS	46,XX [20] / 92,XXXX [2]		Genital warts, pneumonia, pulmonary aspergillosis, mycobacteriosis (*M. avium)*, mucormycosis		Sarcoidosis hemophagocytic syndrome	D(24) (mycobacteriosis)
P24*	5	c.1070C>T / p.T357I	MS	25	MDS	Nl		ENT infections, bronchitis, genital warts		Takayasu's disease Cervical dysplasia	A(33)

P25*	5	c.1076T>C / p.L359S	MS	61	MDS	46,XX,del(5)(q2?3q3?3) [18] / 46,XX [2]	EPO Chemotherapy, HSCT	Bacterial septic shock	peritonitis post-HSCT	Lymphedema Conn's syndrome hypothyroidism	D(63) (HSCT)
P25 (brother)	5	na	MS	61	MDS /AML2	Nl	Chemotherapy , Vidaza, HSCT	Pneumonia, septic shock,	Candidiasis post HSCT		D(63) (HSCT)
P26 (daughter)	5	c.1077_1082dup / p.Trp360_Arg361dup	In-frame duplication		na						A(10)
P26*	5	na	in-frame duplication	37	MDS	47,XX,+8 [1] / 46,XX [24]		Cutaneous warts, pneumonia, meningitis			A (42)
P27*	5	c.1081C>G / p.R361G	MS	23	Nl			Aspergillosis / Tuberculosis		Lymphedema	D(29) (mycobacteriosis)
P28*	5	c.1082G>A / p.R361H	MS	20	MDS	Nl		Cutaneous warts, cystitis, vulvar mycosis by *Candida* spp.		Psoriasis, Interstitial lung disease (PAP), transient cerebral palsy	A(21)
P29*	5	c.1082G>A / p.R361H	MS	25	MDS, AML	45,XY,-7 [7] / 46,XY [24]	Chemotherapy	Cutaneous warts, tuberculosis , Staphylococcal septicemia,	aspergillosis post-chemotherapy		D(31) (chemotherapy)
P30*	5	c.1084C>T / p.R362*	NS	8	MDS	46,XX,del(20)(q11) [8] / 46,XX [12]	HSCT	Cutaneous warts, oral HSV			A(30)
P31*	5	c.1084C>T / p.R362*	NS	21	MDS	Nl		Cutaneous warts , inguinal folliculitis with recurrent scrotal abscess, recurrent perineal abscess , pneumonia		Polymalformative syndrome	A(25)
P32*	5	c.1084C>T / p.R362*	NS	10	MDS	46,XY,+8 [14] / 46,XY [6]		Pulmonary tuberculosis, dermo-hypodermitis		Lymphedema, Psoriasis, Pulmonary Segmental edema, sarcoidosis like disease	A(34)
P33*	5	c.1084C>T / p.R362*	NS	11	MDS	Nl		Dermo-hypodermitis		Lymphedema, Aphthous stomatitis	A(12)
P34*	5	c.1085G>C / p.R362P	MS	17	MDS , AML	48 XY, +8, +8 [17]; 46 XY [1]	Chemotherapy	Cutaneous and genital warts, tight boil, chronic hepatitis B, arm abscess			D(38) (chemotherapy)
P34 (brother)	5	c.1085G>C / p.R362P	MS	17	MDS, AML	Monosomy 7	Chemotherapy	Dermo-hypodermitis		Lymphedema	D(23) (chemotherapy)
P35*	5	c.1103_1104del / p.P368Rfs*15	FS	43	Nl			Progressive multifocal leuco-encephalopathy			D(43) (JC virus)
P36* *(6)*	5	c.1114G>A / p.A372T	MS	13	AML5	Monosomy 7 , trisomy 15, Trisomy 20 t(11;19)	Chemotherapy	Pneumonia, labial HSV, H1N1 Influenza	aspergillosis post-chemotherapy	Vesicular lithiasis	D(18) (H1N1 influenza)
P37*	5	c.1114G>A / p.A372T	MS	42	MDS	trisomy 8	EPO	Dermo-hypodermitis, esophageal candidiasis, arthritis, pneumonia		Lymphedema Breast cancer Deep vein thrombosis sweet syndrome	D(72) (bacterial infection)
P37 (son)	5	na	MS	18	CMML	Monosomy 7	Chemotherapy HSCT	Pneumonia			D(19) (HSCT)
P38*	5	c.1114G>A / p.A372T	MS	20	AML 2	?der(7)?r(7)(?p ?q) [22] del7 q in Fish	HSCT	Pneumonia EBV-related			D(21) (HSCT)
P39*	5	c.1118G>A / p.C373Y	MS	17	MDS	Tri1 Monosomy 15		Recurrent otitis pneumonia, cutaneous warts		Interstitial lung disease Lymphedema Erythema nodosum Panniculitis	A(20)

P40*	5	c.1142del / p.Asn381Metfs*6	FS	14	MDS	Nl		Cutaneous warts, pneumonia, Influenza A (hemophagocytic syndrome), pyocyanic infection, aspergillosis, candidiasis, streptococcus sepsis			A(28)
P41*	Int 5	c.1143+5G>C / p.?	SD	11	MDS	Trisomy 8	HSCT	Recurrent pneumonia. genital warts			A(18)
P42*	6	c.1154C>A / p.P385Q	MS	18	MDS	Nl		Disseminated mycobacteriosis (*M. avium*), pneumonia, genital warts		Lymphedema, Rosacea Poncet's disease	A(43)
P42 (sister)	6	c.1154C>A / p.P385Q	MS	17	MDS	Nl	HSCT	Vulvar abscess, genital and cutaneous warts, sinusitis, pelvic cellulitis, aspergillosis		CIN2, Lymphedema	A(39)
P42 (son)	6	c.1154C>A / p.P385Q	MS		na						A(15)
P42 (sister)	6	c.1154C>A / p.P385Q	MS	24	ALL T	Monosomy 7	Chemotherapy	Vulvar cellulitis, Septic shock	candidiasis post chemotherapy	Rheumatoid purpura Deep vein thrombosis	D(24) (chemotherapy)
P43* *(6)*	6	c.1162A>G / p.M388V	MS	12	MDS	Monosomy 7q Trisomy 8	HSCT				A(20)
P43 (mother) *(6)*	6	c.1162A>G / p.M388V	MS	44	MDS	Trisomy 8		Genital warts (major surgery), cutaneous HSV, pneumonia, Aspergillosis		Rosacea, Genital carcinoma, Myocardial infarction	D(56) (HPV-related carcinoma)
P44*	6	c.1186C>T / p.R396W	MS	9	MDS	Monosomy 7	HSCT	Bronchitis	Aspergillosis post-HSCT	Atypical Kawasaki syndrome with arthritis, hemophagocytic syndrome	D(10) (HSCT)
P45*	6	c.1186C>T / p.R396W	MS	9	MDS, AML 4	Monosomy 7, Monosomy 21	Chemotherapy HSCT			asthenia	A (10)
P45 (brother)	6	c.1186C>T / p.R396W	MS	7	MDS	Nl	Chemotherapy	na		premature	A (7)
P45 (mother)	6	na	MS	25	MDS			na		na	A (39)
P46* *(6)*	6	c.1187G>A / p.R396Q	MS	16	MDS	Trisomy 8	HSCT x 2	Chronic EBV replication		Pulmonary embolism Factor V Leiden mutation	A(21)
P46 (mother) *(6)*	6	c.1187G>A / p.R396Q	MS	23	AML M2	Nl	Chemotherapy	Recurrent gingivitis	Aspergillosis post-chemotherapy	Rosacea Miscarriage	D(37) (chemotherapy)
P46 (brother) *(6)*	6	c.1187G>A / p.R396Q	MS	6	MDS	Monosomy 7	HSCT	Chronic EBV replication pneumonia		premature	A(11)
P46 (brother) *(6)*	6	c.1187G>A / p.R396Q	MS	13	AML M2	Trisomy 11 Monosomy 7	Chemotherapy HSCT	ENT infections, recurrent pneumonia		Tight fibroma Factor V Leiden mutation	A(19)
P47*	6	c.1192C>T / p.R398W	MS	0	JMML	Nl		Bronchiolitis			A(4)
P48*	6	c.1193G>A / p.R398Q	MS	19	MDS	Nl	HSCT	Pneumonia, cellulitis, mycobacteriosis, hemophagocytic syndrome		Splenic vein thrombosis, Rectal adenoma (low grade dysplasia)	A(40)
P48 (son)	6	c.1193G>A / p.R398Q	MS		na						A(13)
P48 (daughter)	6	c.1193G>A / p.R398Q	MS		na						A(8)
P49*	6	c.1193G>A / p.R398Q	MS	25	MDS	Trisomy 8	GSCF	Mycobacteriosis (*M. chelonae* and *M. avium)*			A(31)

P50*	2-6	c.1-?_1443+?del / p.0?	Whole gene deletion	18	MDS	Nl		Pilonidal cyst abscess, amygdala phlegmon, toxoplasmosis, orchiepididymitis, hepatitis A			A(25)
P51* *(6)*	2-6	c.1-?_1443+?del / p.0?	Whole gene deletion	13	MDS	Monosomy 7 Trisomy 8	Vidaza HSCT	Pyelonephritis, pneumonia	oral and genital HSV post HSCT	Urinary system malformation, lymphedema	A(18)
P52*	2-6	del3q21	Whole gene deletion	2	MDS AML	Monosomy 7	Vidaza	Oral HSV, cutaneous warts, staphylococcal folliculitis, pneumonia		Poly-malformation Behavioral disorder	A(21)
P53*	2-6	c.1-?_1443+?del / p.0?	Whole gene deletion	18	AML	Monosomy 7	Chemotherapy	Pericarditis		Mental retardation Hypospadias	D(25) (chemotherapy)

Supplemental Table 1. Clinical and biological presentation of 79 patients with a *GATA2* mutation.

▪ P= Pedigree, * =proband

▪ *(6)* Patients of the French Chronic Neutropenia Registry previously described in Pasquet and al. Blood 2013.

▪ mutation type : FS = Frameshift, MS =Missense, NS = Nonsense, SD = Splice defect ; karyotype: Nl = normal

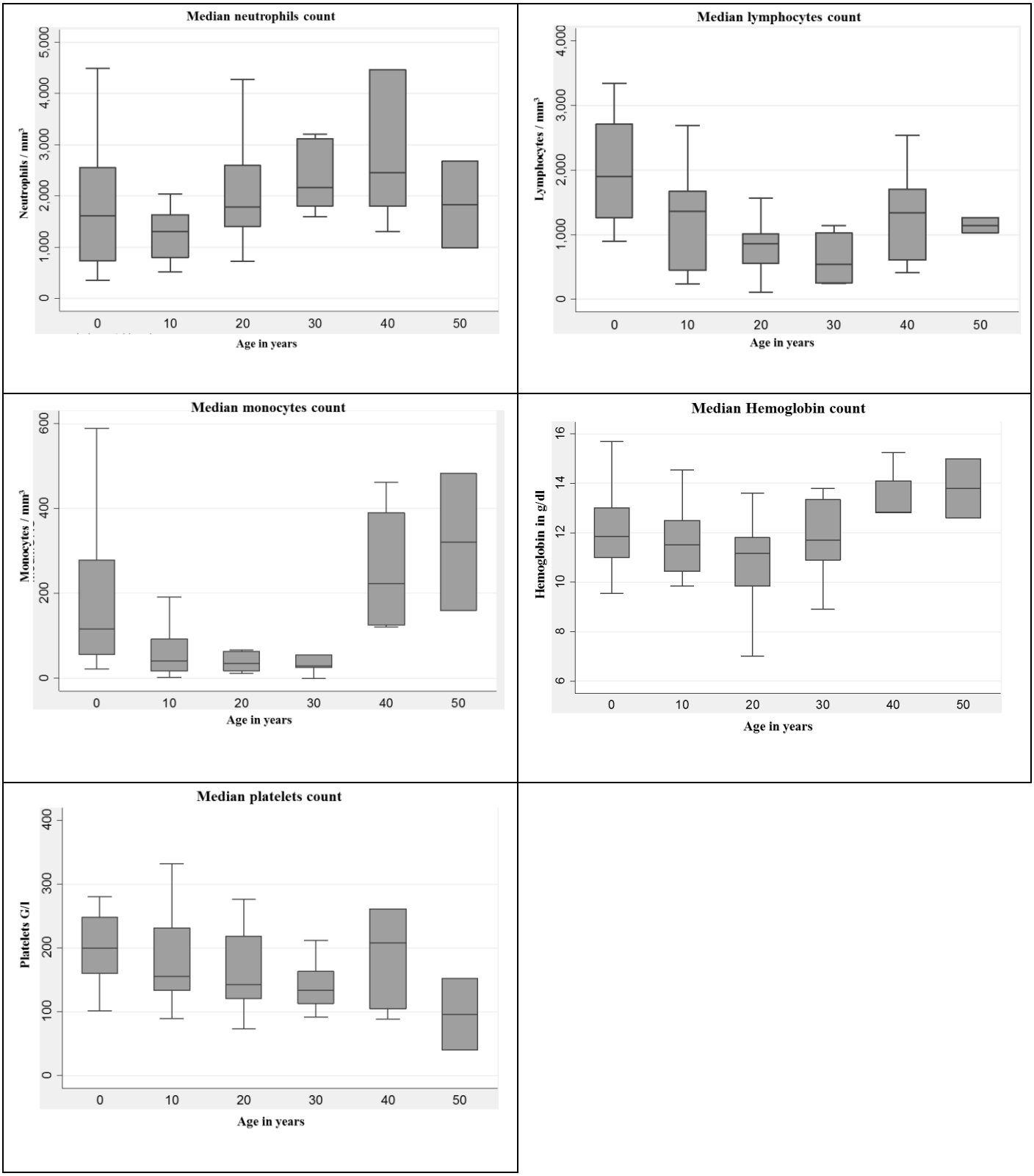
▪ Vital status: A = alive, D = dead

▪ AL= Acute leukemia, ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, CIN = cervical Intraepithelial Neoplasia, CMML= chronic myelomonocytic leukemia, CMV = cytomegalovirus, EBV = EpsteinBarr virus, EPO = erythropoietin, GCSF = granulocyte-colony-stimulating factor, HSCT = hematopoietic stem-cell transplantation, HSV = herpes simplex virus, Int = intron, ITP = idiopathic thrombocytopenic purpura, JMML: juvenile myelo-monocytic leukemia, MDS = myelodysplasia, na = not analyzed, PAP= pulmonary alveolar proteinosis, ZF1 = first zinc finger, ZF2= second zinc finger

Patient Pedigree	Mutation	Age at diagnosis	Age at last FU	Symptomatic Relatives	Median Neutrophils /mm^3	Median Monocytes /mm^3	Median Lymphocytes /mm^3	Median platelets G/L	Median Hb g/dL
P15 (father)	c.988C>T / p.R330*	56	60	4	2679	482	1266	152	15
P26*	c.1077_1082dup / p.Trp360_Arg361dup	10	10	1	2600	Na	Na	175	11.6
P42 (son)	c.1154C>A / p.P385Q	14	15	3	Na	Na	Na	Na	Na
P48 (son)	c.1193G>A / p.R398Q	11	13	1	4290	600	1953	228	12.8
P48 (daughter)	c.1193G>A / p.R398Q	6	8	1	2550	588	2983	269	12.1

Supplemental Table 2. Asymptomatic patients characteristics. Only one patient is a aged >40 years old among the asymptomatic patients.

FU = Follow Up ; Na = Not available ; Hb= haemoglobin



Supplemental Figure 1. Blood counts and immunogical testing in 49 patients before any leukemia or authentified myelodysplasia.

Box plot of the median hematological counts sorted by aged categories. Absolute neutrophil, lymphocyte, monocyte counts (cells/mm^3), hemoglobin (g/dl), platelets (G/l).