Journal of Clinical Immunology (2023) 43:2192–2207
https://doi.org/10.1007/s10875-023-01583-8

ORIGINAL ARTICLE

A Nationwide Study of GATA2 Deficiency in Italy Reveals Novel Symptoms and Genotype–phenotype Association

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Received: 5 June 2023 / Accepted: 10 September 2023 / Published online: 14 October 2023

Abstract

GATA2 deficiency is a rare disorder encompassing a broadly variable phenotype and its clinical picture is continuously evolving. Since it was first described in 2011, up to 500 patients have been reported. Here, we describe a cohort of 31 Italian patients (26 families) with molecular diagnosis of GATA2 deficiency. Patients were recruited contacting all the Italian Association of Pediatric Hematology and Oncology (AIEOP) centers, the Hematology Department in their institution and Italian societies involved in the field of vascular anomalies, otorhinolaryngology, dermatology, infectious and respiratory diseases. Median age at the time of first manifestation, molecular diagnosis and last follow-up visit was 12.5 (age-range, 2–52 years), 18 (age-range, 7–64 years) and 22 years (age-range, 3–64), respectively. Infections (39%), hematological malignancies (23%) and undefined cytopenia (16%) were the most frequent symptoms at the onset of the disease. The majority of patients (55%) underwent hematopoietic stem cell transplantation. During the follow-up rarer manifestations emerged. The clinical penetrance was highly variable, with the coexistence of severely affected pediatric patients and asymptomatic adults in the same pedigree. Two individuals remained asymptomatic at the last follow-up visit. Our study highlights new (pilonidal cyst/sacrococcygeal fistula, cholangiocarcinoma and gastric adenocarcinoma) phenotypes and show that lymphedema may be associated with null/regulatory mutations. Countrywide studies providing long prospective follow-up are essential to unveil the exact burden of rarer manifestations and the natural history in GATA2 deficiency.

Keywords GATA2 Deficiency · Primary Immunodeficiency Diseases · Myelodysplastic Syndrome · Hearing Loss, Sensorineural · Lymphedema

Introduction

GATA2 deficiency is a rare autosomal genetic disease due to heterozygous germline variants (familial or de novo) in the *GATA2* gene [1]. The *GATA2* gene encodes a transcription factor that plays a critical role in the hematopoietic development [2].

Four independent groups described GATA2 deficiency in 2011, reporting different clinical phenotypes: monocytopenia and mycobacterial infections syndrome (MonoMAC) [3]; dendritic cell, monocyte, B, and natural killer (NK) lymphoid (DCML) deficiency [4]; familial myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) [5]; Emberger syndrome (primary lymphedema with MDS) [6]. Currently, up to 500 patients have been described [7] with 3 national cohorts being published [8–10]. Age at disease onset ranges from early childhood to late adulthood. Clinical presentations span from asymptomatic/paucisymptomatic to life-threatening events or phenotypes that significantly affect the quality of life [8]. The clinical hallmarks include hematologic and infectious phenotypes [1]. The hematological presentation can be variable, encompassing cytopenia and bone marrow (BM) hypocellularity as well as myeloid neoplasms (74–81%) [8, 9, 11], being *GATA2* the most common pediatric germline predisposing MDS mutation [12]. Infections are common (71–82%) [8, 10]

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due to immune dysfunction [13], characterized mainly by B lymphocytopenia (86–100%), NK lymphocytopenia (78–82%) and monocytopenia (49–78%) [8–10, 14]. Additional clinical manifestations, such as lymphedema (11–15%), pulmonary alveolar proteinosis (PAP, 3.8–18%), sensorineural deafness (1.3–43%), dermatological, autoimmune or vascular features, obstetric complications and genito-urinary tract alterations, have been described [10]. Although case reports or small cohorts are fundamental in describing novel or rare clinical findings, they may mislead about the prevalence of a peculiar sign/symptom in a rare/ultra-rare disease.

Germline *GATA2* variants can be located in both coding and non-coding regions, such as enhancer elements [15]. Three main categories have been described: null (60% of cases), missense (30%) and intronic variants (4–10%) [7, 16]; in addition, synonymous variants [17] have been reported. The majority of the pathogenic variants are disease-causing through haploinsufficiency [18] caused by a premature translation termination or decreased *GATA2* transcript level, either through truncating (nonsense), frameshift, splicing mutations, mutation in the conserved intronic enhancer or copy number variations (duplications or deletions), or by disrupting protein–protein interaction or DNA binding (missense mutations). However a gain-of-function activity has been reported [19]. To date, there is no definite evidence regarding a clear genotype–phenotype correlation [7] and the individual penetrance of each phenotype is incomplete [20].

Given the risk of progression to MDS/AML (39% at the age of 20), the treatment of choice as well as the only cure for GATA2 deficiency is allogeneic hematopoietic stem cell transplantation (HSCT) [21], which can reverse immune-hematological manifestations and PAP [22, 23]. Nonetheless, the lack of definite genotype–phenotype correlations makes the decision about who and when to transplant rather difficult. HSCT outcome depends on the burden of comorbidities at the time of the procedure [21] and, in case of MDS, is independent of *GATA2* germline mutations thus suggesting the application of standard MDS algorithms and protocols [24]. Early preemptive HSCT has been proposed even in young individuals without cytopenia, karyotypic abnormalities, myelodysplasia or clinically relevant immunodeficiency [10, 24]. Recently, increasing evidence that somatic alterations may frequently occur in *GATA2*-mutated cells has been brought to attention. Two large cohorts have described the somatic landscape of GATA2 deficiency showing that accumulation of at least 1 additional somatic mutation may occur in up to 66% of the patients. Frequently mutated genes (*STAG2*, *ASXL1*, *EZH2* and *SETBP1*) are different from non-GATA2 MDS/AML. Further evidence will define the role of these events in leukemic progression and in patient management.

To broaden the knowledge about GATA2 deficiency and to improve the diagnostic-therapeutic management of patients with GATA2 deficiency, we describe a cohort of 31 Italian patients with GATA2 deficiency.

Methods

Patients

All the Italian Association of Pediatric Hematology and Oncology (AIEOP) centers were contacted by email. AIEOP centers were also asked to contact the Hematology Department in their institution to retrieve data of additional adult patients. In addition, given the clinical manifestations of GATA2 deficiency, Italian Society of Pediatric Infectious Diseases (SITiP), Italian Society for the Study of Vascular Anomalies (SISAV), Italian Society of Otorhinolaryngology and Head and Neck Surgery (SIOeChCF), Italian Society for Respiratory Diseases in Children (SIMRI) and Italian Society of Pediatric Dermatology (SIDerP) were contacted in order to identify any additional GATA2-deficient individual.

All the patients with a pathogenic, likely pathogenic, or variants of unknown significance (VUS) in the *GATA2* gene according to the criteria defined by the American College of Medical Genetics, along with a compatible phenotype, were enrolled in this study.

Further information on methods is detailed in the supplemental data.

Results

Between January and December 2022, 31 patients (13 males), belonging to 26 families, with molecular diagnosis of GATA2 deficiency were enrolled in the study. All the patients had white/caucasian ethnicity. Phenotypical presentation led to diagnosis in 26/31 (84%) individuals, while 5/31 (16%) were identified by family screening (Table 1). Among the latter group, 3 patients (P23, P24 and P25) did not show any signs/symptoms before the molecular diagnosis.

Clinical Features

Patients' median age at onset of symptoms (see Supplemental Data for detailed description of Methods) was 12.5 years (range 2–52 years) (Tables 1 and 2) with twenty-three patients (74%) having less than 18 years of age. The median age at the time of the molecular diagnosis was 18 years (range 7–64 years). The diagnostic delay (time between age at onset of symptoms and molecular diagnosis) had a median of 4 years (range 0–32 years), but, excluding those who had onset of the disease before the first description of GATA2

Table 1 Overview of the clinical and biological features of the Italian GATA2-deficient patients

	N/included patients (%)
Sex	
Males	13/31 (42%)
Age at onset of symptoms	
Median, years (range)	12.5 (2–52)
Signs/symptoms at onset	
Severe/recurrent infections	12/31 (39%)
MDS/AML	7/31 (23%)
Peripheral cytopenias	5/31 (16%)
Lymphedema	3/31 (10%)
Autoimmune features	1/31 (3%)
Pulmonary alveolar proteinosis	0/31 (0%)
Age at molecular diagnosis	
Median, years (range)	18 (7–64)
Type of variant	
Null	16/31 (52%)
Missense	13/31 (42%)
Intronic	2/31 (6%)
Time between onset and molecular diagnosis	
Median, years (range)	4 (0–32)*
Indication for molecular analysis	
Presence of suggestive signs/symptoms	26/31 (84%)
Family screening	5/31 (16%)
Family screening	
Performed, complete	16/26 (62%)
Not performed	8/26 (31%)
Performed, incomplete**	2/26 (8%)
Treatment	
Watch and wait strategy	10/31 (32%)
Bacterial prophylaxis	2/31 (6%)
Fungal prophylaxis	0/31 (0%)
Viral prophylaxis	0/31 (0%)
Ig supplementation	0/31 (0%)
Hypomethylating therapy	2/31 (6%)
HSCT	17/31 (55%)
Last follow-up	
Median age, years (range)	22 (3–64)
Alive	24/31 (77%)

*After 2011, Median, years (range): 1 year (0–6 years)

**The screening was not performed in all the first degree relatives of the patient

Abbreviations: *AML* acute myeloid leukemia, *HSCT* hematopoietic stem cell transplantation, *MDS* myelodysplastic neoplasm

deficiency (2011) the median was 1 year. The event-free survival was 23% at the age of 20 and 16% at the age of 40 whereas the overall survival was 90% at the age of 20 and 78% at the age of 40 (Fig. 1A and B).

The main signs/symptoms at onset were severe/recurrent infections (39%), MDS/AML (23%) and cytopenias (16%) (Table 1). The prevalence of these manifestations increased during the follow-up and additional clinical manifestations occurred (Figs. 1C-F and 2).

In the whole cohort of GATA2 patients, monocytopenia, B- and NK-cell deficiency were respectively 82% (23/28), 80% (16/20) and 60% (12/20). In patients without hematological malignancies or in whom we obtained data before the onset of MDS/AML, complete blood count (CBC) with differential and lymphocyte subsets frequently revealed monocytopenia (77%, 10/13), B- and NK-cell lymphocytopenia (73% [8/11] and 45% [5/11], respectively). IgG levels were within normal ranges in all these patients (0/11). One individual (P9) had both IgA and IgM deficiency and three out of 11 had isolated IgA deficiency (absolute IgA deficiency in P6, partial in P1 and P3) (Tables 2 and 3).

Different myeloid neoplasms were observed: childhood MDS with low blasts (cMDS-LB) (9/31, which evolved to AML in P11 and P30), childhood MDS with increased blasts (cMDS-IB) (4/31), AML (4/31), MDS with low blasts (MDS-LB) (3/31) and MDS with increased blasts (MDS-IB) (1/31). Monosomy 7 (6/31) and trisomy 8 (6/31) were the two most frequent karyotype abnormalities, and always associated with the development of a myeloid neoplasm, except for one patient with trisomy 8 (P9) whose BM biopsy was consistent with BM failure (i.e. hypocellular marrow with cytopenia and absence of cyto-morphological alterations consistent with hematological neoplasm). One GATA2-deficient patient (P14), who developed cMDS-LB, had a supernumerary isochromosome 1.

Targeted next generation sequencing (NGS) analysis for somatic mutations associated with myeloid neoplasms was performed in 16/31 of the patients, resulting positive in 4/16 of cases (i.e. *EZH2* and *MECOM* variants in one individual each, *ASXL1* in two patients).

A summary of the patients' clinical characteristics at the last follow-up is given in Fig. 2 and Table 4. Cytopenias (11/13), myeloid neoplasms (21/31) and infections (19/31) [25, 26] were frequent. Infections were frequently bacterial (14/31) and viral (13/31), while mycobacteriosis was less frequent (4/31) and fungal infections were completely absent. Specifically, upper (6/31; 19%) and lower (7/31; 23%) respiratory tract infections were commonly reported and evolved in sepsis in three individuals. Isolated bacteria were *Streptococcus Pneumoniae*, *Mycoplasma Pneumoniae*, *Pseudomonas Aeruginosa*, *Acynetobacter Baumanii*. Among viruses, Respiratory Syncytial Virus, Influenza A virus subtype H1N1, Cytomegalovirus and Epstein Barr Virus (EBV) were detected. Out of the four patients who had skin infections, three had abscesses with one case evolving in fasciitis, hemothorax and disseminated intravascular coagulation. Varicella zoster virus (VZV) infection was reported in three patients, one of whom had disseminated disease and another one with persistent fever and thrombocytopenia.

Table 2 Detailed description of the clinical and biological features of the Italian GATA2-deficient patients

Patient	Gender	Age at molecular diagnosis	Age at the last FUP	Status	Molecular investigation	c.DNA	Protein	Familial GATA2	If yes, relative	Familial MDS/AML	If yes, relative	Relatives with other malignancies	If yes, relative
1	M	21	21	Alive	NGS	c.1187G>A	p.Arg396Gln	No		No		No	
2	F	19	22	Alive	NGS	c.380_383dupACC	p.Ser129Profs*57	NP		No		No	
3	F	16	18	Alive	NGS	c.503_504insGCTC	p.His169Leufs*17	Yes	Father	No		Yes	Paternal grandfather, maternal cousin
4	F	17	20	Alive	NGS	c.1017+572C>T		NP		Yes	Second-degree maternal cousin, great aunt	Yes	Mother
5	M	7	7	Alive	NGS	c.1215g>T	p.Lys405Asn	NP		No		No	
6	M	16	18	Alive	WES	c.112C>T	p.Gln38Ter	No		No		No	
7	M	18	18	Alive	NGS	c.919C>T	p.Arg307Trp	NP		No		No	
8	M	17	26	Alive	Sanger	c.1084C>T	p.Arg362X	No		No		No	
9	F	14	16	Alive	Sanger	c.G1079A	p.Trp360X	No		No		No	
10	F	16	21	Alive	NGS	c.1084C>T	p.Arg362X	No		No		Yes	Mother, grandmother
11	M	17	26	Alive	NGS	c.1186C>T	p.Arg396Trp	No		No		No	
12	M	8	12	Alive	NGS	c.1215G>T	p.Lys405Asn	Yes	Mother	No		No	
13	F	21	24	Alive	WES	c.1186C>T	p.Arg396Trp	No		No		No	
14	M	11	19	Alive	NGS	c.414_417delCTCT	p.Ser139CysfsX78	No		No		No	
15	F	18	24	Alive	NGS	Intron 4 deletion		No		No		No	
16	M	18	22	Alive	NGS	c.1084C>G	p.Arg362Gly	No		No		No	
17	F	23	24	Dead	Sanger	c.1186C>T	p.Arg396Trp	NP		No		No	
18	F	22	22	Dead	WES	c.1046G>A	p.Cys349Tyr	Yes	Father	Yes	Paternal grandfather, paternal aunt	Yes	Father
19	F	Post-mortem	4	Dead	WES	Stop codon	Unknown	FM		No		No	
20	F	9	9	Dead	WES	Stop codon	Unknown	IS	Sister	Yes	Twin sister	No	
21	F	64	64	Dead	Sanger	c.1057C>T	p.Gln353Ter	IS		No		No	
22	F	46	46	Alive	NGS	c.1186C>T	p.Arg396Trp	NP		No		No	
23	M	43	43	Alive	Sanger	c.503_504insGCTC	p.His169Leufs*17	FM		No		No	
24	F	45	49	Alive	Sanger	c.1215G>T	p.Lys405Asn	FM		Yes	Son	No	
25	M	54	54	Dead	WES	c.1046G>A	p.Cys349Tyr	FM		Yes	Father, sister	No	
26	F	26	26	Alive	NGS	c.1009C>T	p.Arg337X	NP		Yes	Mother, sister	NA	
27	F	19	19	Alive	NGS	c.1150A>G	p.Arg384Gly	No		No		No	
28	M	52	56	Alive	WES	c.372_373insT	p.Pro125Serfs*60	NP		NA		No	
29	F	36	36	Alive	NGS	c.1009C>T	p.Arg337X	FM		Yes	Daughter, brother	Yes	Father
30	F	10	10	Dead	Sanger	c.1009C>T	p.Arg337X	Yes	Mother	Yes	Mother, uncle	Yes	Maternal grandfather
31	M	7	19	Alive	Sanger	c.257_258delGC	p.Cys85fs	No		No		No	

Table 2 (continued)

Patient	Age at first manifestation	Onset before 2011	HSM	Bleeding diathesis	Thrombosis	Infections				Deafness	Lymphedema	PAP	Warts	AI	Other
						Bacterial	Viral	Fungal	Mycobacteriosis						
1	10	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes
2	16	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes
3	2	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No
4	17	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
5	3	No	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	No
6	15	No	Yes	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
7	17	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
8	5	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No
9	13	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes	No	No
10	16	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No
11	17	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No
12	3	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No
13	15	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
14	6	Yes	Yes	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No
15	14	No	Yes	Yes	No	Yes	No	No	No	No	No	No	No	No	No
16	18	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No
17	12	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No
18	11	Yes	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No
19	2	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No
20	6	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No
21	32	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No
22	45	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No
23	Familial screening	No	No	No	No	No	No	No	No	No	No	No	No	No	No
24	Familial screening	No	No	No	No	No	No	No	No	No	No	No	No	No	No
25	Familial screening	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
26	11	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
27	9	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No
28	52	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	No	Yes
29	32	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No
30	9	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No
31	6	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No

Patient	MDS/AML	Age at MDS/AML	BM karyotype	Somatic mutations	Variant and VAF	First CBC, age	Hb	MCV	WBC	ANC	L	Mo	PLT
							g/dl	fl	cells/mcl				
1	cMDS-LB	14	46,XY	EZH2	p.Lys10Glu, VAF 49.4%	12	13.2	91.9	2210	270	1870	0	182000
2	cMDS-LB	17	46,XX	ASXL1	p.Gly646Trpfs*12, VAF 10.8%	17	12.4	92.3	2530	620	1740	140	112000
3	cMDS-LB	16	46,XX	ASXL1	p.Lys982Serfs*2, VAF 15.5%	14	13.3	92.4	3220	1480	1620	30	204000

Table 2 (continued)

4	cMDS-IB	17	45,XX,-7	Np		17	9.3	95.7	1130	260	770	40	65000
5	No	NA	NA	Np		7	13.0	77.5	5870	2780	2230	450	385000
6	No	NA	NA	Np		15	10.1	72.7	1720	820	750	50	106000
7	No	NA	NA	Np		17	16.1	80,5	3100	400	1540	640	48000
8	No	NA	NA	Np		17	12.2	93.6	5290	2120	2980	30	191000
9	No	NA	47,XX,+8	Np		13	11.6	91.0	4330	3820	330	90	19000
10	cMDS-IB	16	46,XX	No		16	10.0	84.0	1040	320	620	20	206000
11	cMDS-LB	17	46,XY	Np		18	9.9	84.0	810	150	550	10	12000
12	cMDS-IB	12	46,XY	No		8	12.8	80.0	4340	2200	1620	170	353000
13	MDS-LB	20	47,XX,+8	No		20	11.4	105.0	2400	930	1380	30	72000
14	cMDS-LB	10	47,XX,+1(1)	No		10	9.1	89	1950	570	1300	10	125000
15	AML	14	46,XX	MECOM	c.3437C>T, VAF 52%	14	8.9	83	1680	140	1000	100	88000
16	AML	18	46,XY	No		18	9.0	91	1230	760	350	40	194000
17	No	NA	46,XX	No		12	10.0	101.8	3070	875	2048	28	210000
18	cMDS-LB	12	47,XX,+8	No		12	11.8	103.6	4410	1960	2150	280	93000
19	AML	2	46,XX	Np		2	4.9	103.4	1510	50	NA	NA	168000
20	cMDS-IB	8	45,XX,-7	Np		8	5.0	96.9	1020	210	760	50	229000
21	MDS-LB	39	47,XX,+8	No		64	9.0	88	1350	1180	100	10	32000
22	No	NA	46,XX	Np		46	8.0	91.7	1300	900	100	0	116000
23	No	NA	NA	Np		43	17.2	96.9	8290	5490	1850	830	255000
24	No	NA	NA	Np		49	13.3	80.0	4000	1900	1800	200	250000
25	No	NA	NA	Np		NA	NA	NA	NA	NA	NA	NA	NA
26	cMDS-LB	11	45,XX,-7	Np		NA	NA	NA	NA	NA	NA	NA	NA
27	AML	19	45,XX,-7	No		19	11.8	110	2700	530	1190	760	100000
28	MDS-IB	52	47,XY,+8	No		52	8.3	127	3090	1670	1210	50	6000
29	MDS-LB	36	47,XX,+8	No		36	12.2	89.3	3120	1760	1290	50	117000
30	cMDS-LB	9	45,XX,-7	Np		9	6.5	79	3600	590	2491	50	137000
31	cMDS-LB	9	45,XX,-7	No		7	13.8	85	4540	1271	3087	32	191000
Patient	**CD3+**	**CD3+ CD4+**	**CD3+ CD8+**	**CD19+**	**CD3-CD16+ CD56+**	**IgG**	**IgA**	**IgM**	**Prophylaxis**			**IgRT**	**Other**
	cells/mcl					**mg/dl**			**Bacterial**	**Fungal**	**Viral**		
1	1305	665	550	55	160	865	50	85	No	No	No	No	Hypomethylating therapy
2	1356	506	658	47	38	1197	137	156	No	No	No	No	
3	1465	720	654	59	203	884	51	92	No	No	No	No	
4	NA	NA	NA	NA	NA	803	81	227	No	No	No	No	
5	1567	934	509	631	336	985	173	103	No	No	No	No	
6	681	178	216	17	58	1217	<4	97	No	No	No	No	
7	1120	357	230	262	42	991	155	88	No	No	No	No	
8	2175	938	1218	3	799	1307	126	80	Yes	No	No	No	
9	938	501	412	20	49	676	69	33	Yes	No	No	No	
10	595	285	290	12	12	839	95	114	No	No	No	No	

Table 2 (continued)

11	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	
12	921	567	291	369	291	917	147	66	No	No	No	No	
13	1053	540	452	34	40	887	175	73	No	No	No	No	
14	1153	481	649	18	114	758	51	117	No	No	No	No	
15	NA	NA	NA	NA	NA	791	146	196	No	No	No	No	
16	NA	NA	NA	NA	NA	579	121	22	No	No	No	No	
17	1900	1075	735	36	290	1300	170	331	No	No	No	No	
18	1956	860	1096	6	129	794	71	36	No	No	No	No	
19	NA	NA	NA	NA	NA	810	80	55	No	No	No	No	
20	NA	NA	NA	NA	NA	715	79	63	No	No	No	No	
21	75	47	28	4	0.1	1040	168	262	No	No	No	No	
22	55	37	17	2	0	1274	117	361	No	No	No	No	
23	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	
24	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	
25	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	
26	NA	NA	NA	NA	NA	NA	NA	NA	No	No	No	No	
27	NA	NA	NA	NA	NA	812	76	181	No	No	No	No	
28	1760	690	750	140	110	1720	296	139	No	No	No	No	Hypomethylating therapy
29	538	436	134	16	50	1160	115	240	No	No	No	No	
30	1668	573	1056	82	29	780	94	176	No	No	No	No	
31	2487	1457	742	176	39	819	80	75	No	No	No	No	

Patient	HSCT	Indication	Donor	Conditioning regimen
1	No			
2	No			
3	No			
4	Yes	c-MDS-IB	Haploidentical family donor	MAC
5	No			
6	Yes	Cytopenia	Haploidentical family donor	MAC
7	No			
8	Yes	Immunodeficiency, severe infections	Identical family donor	RIC
9	Yes	Cytopenia	Haploidentical family donor	MAC
10	Yes	cMDS-IB	Haploidentical family donor	MAC
11	Yes	AML	MUD	MAC
12	No			
13	No			
14	Yes	cMDS-LB	Haploidentical family donor	MAC
15	No			
16	Yes	AML	Haploidentical family donor	MAC
17	Yes	Cytopenia	MUD	Unknown

Table 2 (continued)

18	Yes	cMDS-LB	Haploidentical family donor	Unknown	
19	Yes	AML	Unknown	MAC	
20	Yes	cMDS-IB	MUD	MAC	
21	No				
22	No				
23	No				
24	No				
25	No				
26	Yes	cMDS-LB	MUD	MAC	
27	Yes	AML	Haploidentical family donor	MAC	
28	No				
29	Yes	MDS-LB	MUD	MAC	
30	Yes	cMDS-LB	Identical family donor	MAC	
31	Yes	cMDS-LB	Identical family donor	MAC	

Abbreviations:*AI* autoimmune manifestations; *ANC* absolute neutrophil count; *AML* acute myeloid leukemia, *BM* bone marrow; *CBC* complete blood count; *cMDS-IB* childhood myelodysplastic syndrome with increased blast; *cMDS-LB* childhood myelodysplastic syndrome with low blast; *F* female; *FM* Family member identified by means of familial screening; *FUP* follow-up visit; *Hb* hemoglobin; *HSCT* hematopoietic stem cell transplantation; *HSM* hepatosplenomegaly; *IC* incomplete screening; *IgRT* immunoglobulin replacement therapy; *L* lymphocytes; *M* male; *Mo* monocytes; *MAC* myeloablative conditioning; *MCV* mean corpuscular volume; *MDS* myelodysplastic syndrome; *MDS-IB* myelodysplastic syndrome with increased blast; *MDS-LB* myelodysplastic syndrome with low blast; *MUD* matched unrelated donor; *NA* not available; *NP* not performed; *NGS* next generation sequencing; *PAP* pulmonary alveolar proteinosis; *PLT* platelets; *RIC* reduced intensity conditioning; *VAF* variant allele frequency; *WBC* white blood cells; *WES* whole exome sequencing

Macrophage activation syndrome (MAS) occurred in one patient with active EBV infection. Human papillomavirus (HPV) infection occurred in four individuals, one showing warts and three condyloma acuminata. Out of the three patients with anogenital warts, hysterectomy was performed in P21 due to persistent HPV infection. Parvovirus B19 infection resulted in anemia (P6) or polyarticular arthritis (P31) in one individual each. Mycobacteriosis was reported in four patients, of whom two showed disseminated disease (lymph nodes, lung, liver) caused by *M. Avium* (P21) and *M. Tuberculosis* (P28), respectively. *M. Kansasii* and *M. Avium* were detected in lymph nodes of P1 and P22.

In addition, bleeding diathesis (10/31; nine of whom had thrombocytopenia), hepatosplenomegaly (7/31), lymphedema (7/31), autoimmunity (4/31, solely represented by autoantibody positivity in P17 and P30, whereas associated with erythema nodosum and persistent fever in P22 and alopecia areata in P31), warts (4/31), pulmonary alveolar proteinosis (4/31, three of whom with monocytopenia), BM failure (3/31), sensorineural deafness (3/31, in two cases presented as congenital deafness), thrombosis (3/31) and myelofibrosis (1/31) [27] were reported. Finally, we describe two cases of pilonidal cyst/sacrococcygeal fistula, two cases of solid tumors (one cholangiocarcinoma and one gastric adenocarcinoma, respectively) and one case of autoinflammatory syndrome (fever, arthralgias and elevated levels of inflammatory markers, unresponsive to steroid and anti-IL-1 treatments).

Molecular Findings

Out of the 31 patients included in our cohort, sixteen were diagnosed by means of targeted NGS panels, eight by means of Sanger sequencing and the remaining seven by means of whole exome sequencing (WES).

Nineteen different *GATA2* pathogenic (14 variants), likely pathogenic (2 variants) or variants of uncertain significance (VUS; 3 variants) were detected in 29 patients (two patients had confirmed *GATA2* variants, but local clinicians were unable to retrieve data; Fig. 3B). Specifically, *GATA2* sequencing revealed 19 different mutations, among which 14 were recurrent [7, 28] and 5 (p.Gln38Ter; p.Cys85fs; p.Pro125Serfs*60; p.Gln353Ter; p.Arg384Gly) were novel. The majority of *GATA2* variants (13/29) were located within the zinc-finger 2 (ZF2) domain of the GATA2 protein. Four patients carried mutations in the zinc-finger 1 (ZF1) domain (Fig. 3A). Null and missense mutations were the most frequent (52% and 42%, respectively), whereas intronic variants were found in 6% of the cohort (Table 1). Of note, one patient (P26), who presented with MDS when she was 11 years old and underwent HSCT at the age of 12, along with *GATA2* mutation (c.1009C > T/p.Arg337X), carried one additional pathogenic variant (c.1468 + 2 T > C) in the *MPL* gene (NM_005373.3).

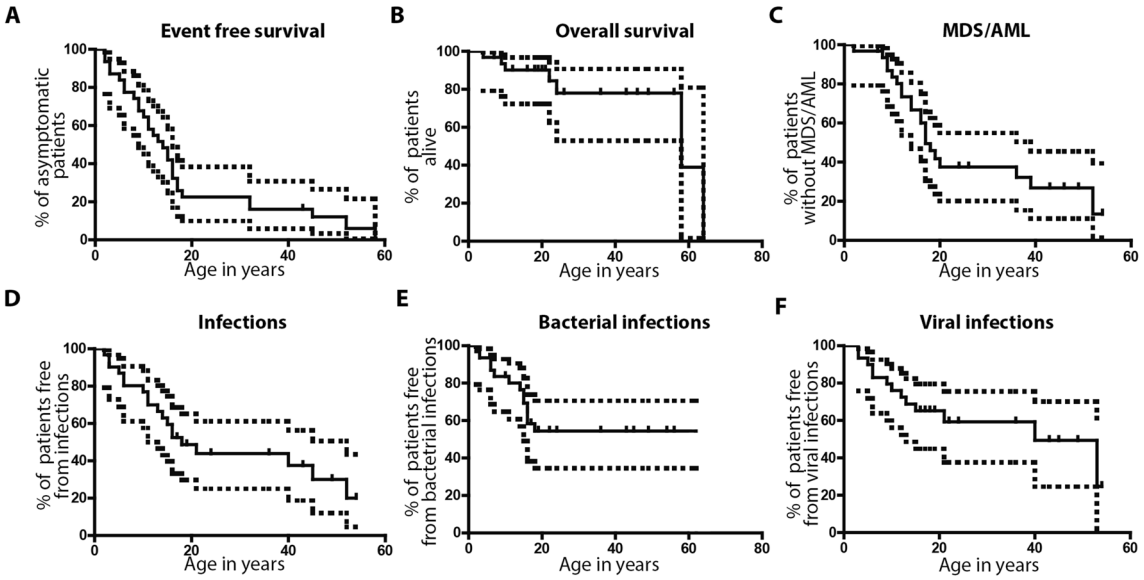

Fig. 1 Onset of illness, survival, hematologic and infection events. Kaplan Meier curves for event free survival (**A**), overall survival (**B**), onset of MDS/AML (**C**), severe/recurrent (**D**), bacterial (**E**) and viral (**F**) infections. Dotted lines show 95% confidence intervals

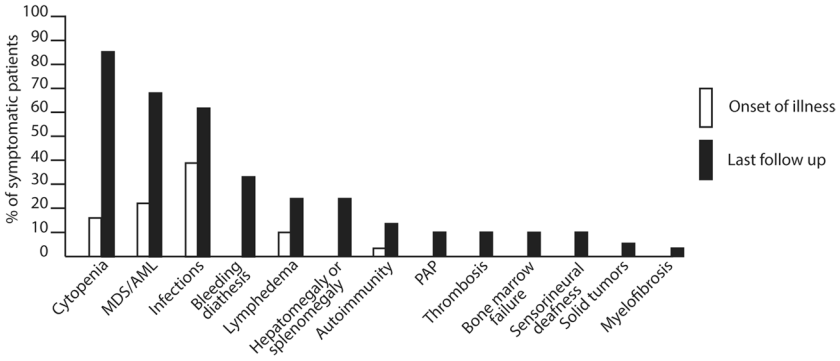

Fig. 2 Comparison of the clinical features between onset and the last follow-up in the GATA2-deficient patients

Family screening was performed in 18 out of 26 probands (Table 1). In 2 patients (P20 and P21) the screening was incompletely performed: P20's homozygous twin sister (P19) received a genetic diagnosis post-mortem, but it was not possible to establish whether the mutation was familial/hereditary or de novo, as the patients' father was wild-type, whereas the patients' mother declined to be investigated; P21 was diagnosed during late adulthood and only her son was studied (negative), but no further molecular tests were performed in the rest of her family. In the remaining 16 patients the family screening was completely performed and identified additional GATA2 relatives in 4 out of 16 (25%) families (P3, P12, P18 and P30): P3's father and P12's mother were completely asymptomatic either at the time of genetic analysis or at the last follow-up. P18's father died of cholangiocarcinoma 4 years after the molecular diagnosis. Although P18's paternal grandfather died of AML at the age of 35 and her paternal aunt died of AML at the age of 12, no samples were available and therefore were precluded further testing. P30's mother had a previous history of lymphedema and warts, her maternal grandfather was affected by lymphedema and her maternal uncle died of AML at the age of 13. Similarly to P18's relatives, no samples were available to confirm a molecular diagnosis of GATA2 deficiency.

Treatment and Clinical Outcome

Ten out of 31 patients underwent a watch and wait strategy and did not receive any treatment. Considering only treatments given before the onset of MDS and excluding treatments at the time or after HSCT, antibiotic prophylaxis was given in 2 patients (trimethoprim/sulfamethoxazole) twice a day once a week. No patient received Ig replacement therapy (IgRT). In two patients with MDS (P1 and P28), hypomethylating therapy, namely azacytidine, was given. HSCT

Table 3 Hemato-immunological alterations in GATA2-deficient patients at the time of diagnosis

Haemato-immunological data*	*N*/included patients (%)
Complete blood count	
Anemia	6/13 (46%)
Neutropenia	7/13 (54%)
Lymphocytopenia	3/13 (23%)
Monocytopenia	10/13 (77%)
Thrombocytopenia	4/13 (31%)
Lymphocyte subsets	
T CD3 + lymphocytopenia	4/11 (36%)
T CD4 + lymphocytopenia	5/11 (45%)
T CD8 + lymphocytopenia	4/11 (36%)
B CD19 + lymphocytopenia	8/11 (73%)
NK CD3-CD16 + CD56 + lymphocytopenia	5/11 (45%)
Immunoglobulins	
IgG deficiency	0/11 (0%)
IgA deficiency	4/11 (36%)
IgM deficiency	1/11 (9%)

*Patients without hematological malignancies or in whom were obtained data before the onset of MDS/AML are included

Table 4 Clinical phenotype of GATA2-deficient patients at the last follow-up

Clinical characteristics	*N*/included patients (%)
Haemato-immunological	
-Cytopenias	11/13 (85%)*
-MDS/AML	21/31 (68%)
-Bleeding diathesis	10/31 (32%)
-Hepato-splenomegaly	7/31 (23%)
-Autoimmunity	4/31 (13%)
-Thrombosis	3/31 (10%)
-Bone marrow failure	3/31 (10%)
-Myelofibrosis	1/31 (3%)
Infections	19/31 (61%)
-Bacterial infections	14/31 (45%)
-Viral infections	13/31 (42%)
-Fungal infections	0/31 (0%)
-Mycobacteriosis	4/31 (13%)
-Warts	4/31 (13%)
Other	
-Lymphedema	7/31 (23%)
-Pulmonary alveolar proteinosis	4/31 (13%)
-Sensorineural deafness	3/31 (10%)
New clinical features?	
-Pilonidal cyst/sacro-coccygeal fistula	2/31 (6%)
-Solid tumors	2/31 (6%)
-Autoinflammatory syndrome	1/31 (3%)

*Patients without hematological malignancies or in whom were obtained data before the onset of MDS/AML are included

Abbreviations: *AML* acute myeloid leukemia, *MDS* myelodysplastic neoplasm

was performed in the majority of patients (55%) (Table 1). HSCT's details are shown in Table 5. Clinical features that led to HSCT were myeloid neoplasia (13/17) and BM failure (3/17), whereas one patient (P8) underwent HSCT due to immunodeficiency (i.e. severe infections and decreased IgM and IgA). The median age at the time of HSCT was 17 years (range 3–36 years) and median time between molecular diagnosis and HSCT was 6 months. Seventy-one percent of patients (12/17) were alive and in good clinical conditions at the last follow-up visit. The overall survival was 56% at 36 months (Figure S1).

The median age at the last follow-up was 22 years (range 3–64 years) and 24/31 patients of the whole cohort were alive. Out of the 24 alive patients, twelve patients had undergone HSCT. One patient (P5) was lost to follow-up. Among the eleven patients who have not undergone HSCT, two (P12 and P13) are currently scheduled for HSCT, nine are regularly followed through clinical and laboratory monitoring (seven underwent a watch and wait strategy and two were given hypomethylating therapy). Out of the 9 patients in whom HSCT was not scheduled yet, P23 and P24 were asymptomatic at the last follow-up.

Seven out of 31 patients died. 5/31 patients died after HSCT: four patients due to relapse of hematological neoplasia (AML relapsed 3, 4 and 6 months post-HSCT in P17, P19 and P30, respectively; AML secondary to MDS 5 months post-HSCT in P20), whereas P18 died of HSCT-related complications (multi-organ failure associated with *Aspergillus Flavus* pneumonia during the engraftment of second HSCT performed due to primary graft failure). Among the remaining two deceased patients, P21 died of multi-organ failure without having undergone HSCT, while P25 died of cholangiocarcinoma. The median age at the time of death was 22 years (range 4–64 years).

Discussion

This national, multicenter and retrospective observational study provides an overview of the clinical-laboratory features, genetic characteristics, treatment options and outcomes of 31 Italian patients with molecular diagnosis of GATA2 deficiency.

In keeping with previous reports [8, 9], in our cohort the most frequent manifestations at onset are severe/recurrent infections (39%). When clinicians evaluate patients with severe/recurrent infections, first-line diagnostic tests usually include CBC with differential and immunoglobulin levels. Cytopenia (either anemia, neutropenia, monocytopenia or thrombocytopenia) are frequent early findings in

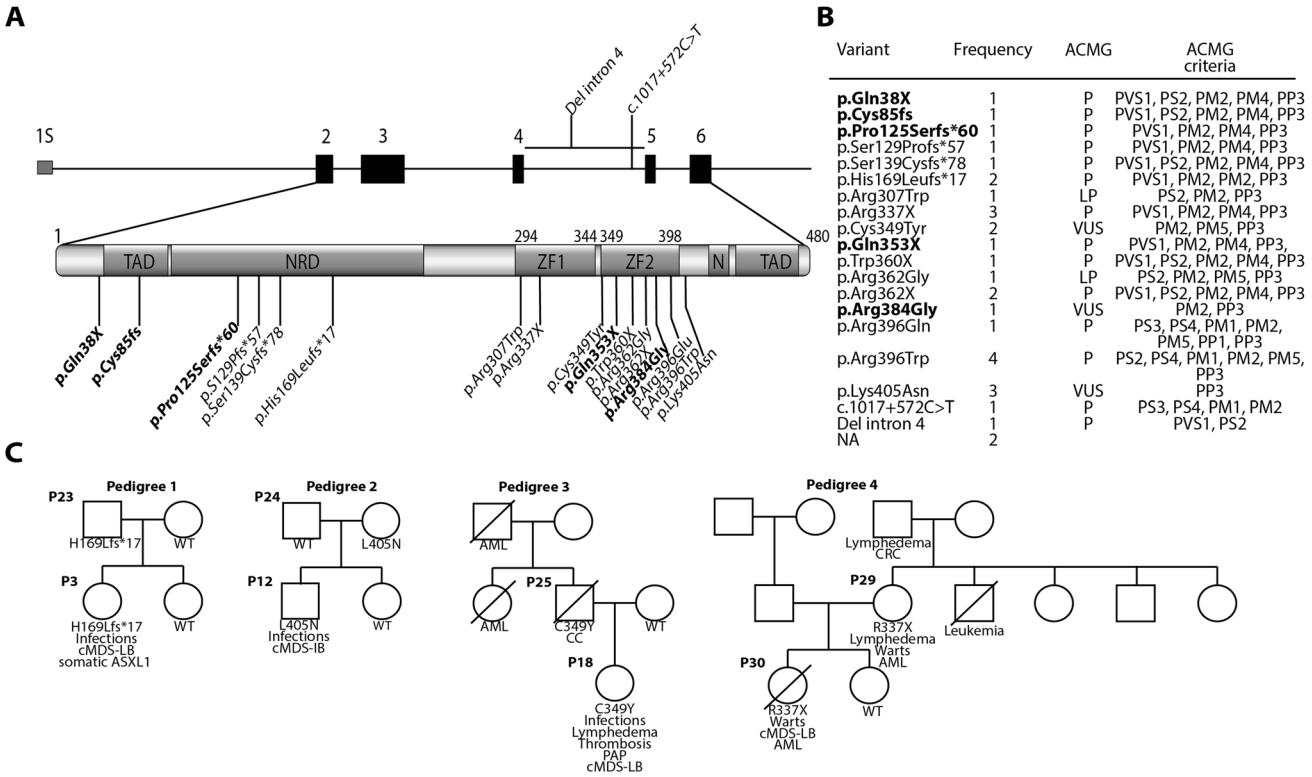

Fig. 3 *GATA2* mutations and familial GATA2 deficiency. **A** Schematic representation (not in scale) of the *GATA2* locus (top) with indication of the deletion and intronic regulatory mutation detected in the described cohort. At the bottom, GATA2 protein domains with localization of the mutations' predicted effect at the protein level. **B** Frequency of the reported variants. Novel mutations are depicted in bold. **C** Pedigree description. Circles represent females and squares males. Parents are connected by a single horizontal line, and vertical lines indicate their offspring. Offspring are connected by a horizontal line. Siblings are placed from left to right. If a patient is dead, a diagonal line is placed over the circle or square. Patients tested are indicated by the result of the GATA2 screening. The absence (wild-type, WT) or presence of a GATA2 mutation (protein variation) is indicated below the symbol of the patient tested. Gene annotation: *GATA2* (NM_032638.4). Abbreviations: ACMG = American College of Medical Genetics and Genomics. CC = cholangiocarcinoma. CRC = colorectal cancer. LP = likely pathogenic. N = nuclear localization signal. NA = not available. NRD = negative regulatory domain. P = pathogenic. TAD = trans-activation domain. VUS = variant of uncertain significance. ZF = zinc-finger domain

GATA2 patients [28]. Even if immunoglobulin levels are adequate, which often occurs in GATA2 deficiency, we strongly suggest investigating lymphocyte subsets which may show hallmarks of GATA2 deficiency (B and NK cell deficiency). Finally, opportunistic infections (non-tuberculous mycobacteria, fungal infection and HPV) should prompt clinicians to exclude GATA2 deficiency. Hematological neoplasms (23%) or cytopenias (16%) were frequently reported. Yet, due to the variable clinical penetrance, the phenotype is often incomplete (Fig. 4) [20]. Manifestations rarely reported at the time of the diagnosis (i.e. lymphedema, autoimmunity and pulmonary alveolar proteinosis) increase their prevalence during the follow-up. It is therefore crucial to suspect GATA2 deficiency even in individuals with incomplete phenotype.

Comparing our results with the two largest published cohorts [8, 9], we report a higher percentage of lymphedema (in our cohort 23% vs 11%-15%). The prevalence of PAP in our cohort (13%) is close to what has been reported by Spinner (18%), yet data from Donadieu (3.8%) greatly diverge. It remains unclear the precise burden of sensorineural deafness because, as suggested by Spinner, aminoglycoside exposure may act as a confounding factor in case of non-congenital presentation. Of note, once the diagnosis was established, congenital deafness was considered part of the clinical picture of GATA2 deficiency in two adolescents in our cohort. Despite this significant percentage, *GATA2* sequencing is not currently included in NGS panels for congenital deafness [29]. We therefore recommend investigating *GATA2* in patients with bilateral congenital deafness not attributable to other etiology (e.g. infections or drug exposure). As regards autoimmunity, our data are superimposable with the literature [9]. In some cases autoimmunity is solely represented by autoantibody positivity: we suggest laboratory monitoring in order to clarify whether increased autoimmune conditions may be anticipated by antibody positivity. We report no cases of miscarriage, idiopathic hypothyroidism and urinary tract

Table 5 Hematopoietic stem cell transplantation in GATA2-deficient patients: indication, donor, conditioning and outcome

HSCT	*N*/included patients (%)
Indication	
-cMDS-LB	4/17 (24%)
-cMDS-IB	3/17 (18%)
-AML	5/17 (29%)
-MDS-LB	1/17 (6%)
-Cytopenia/Bone marrow failure	3/17 (18%)
-Immunodeficiency	1/17 (6%)
Donor	
-Identical	3/17 (18%)
-Haploidentical	8/17 (47%)
-MUD	5/17 (29%)
-NA	1/17 (6%)
Conditioning	
MAC	14/15 (93%)
RIC	1/15 (7%)
Post-HSCT outcome	
Alive	12/17 (71%)
Time between HSCT and last follow-up	
Median time, years (range)	2 (0–14)

Abbreviations:*AML* acute myeloid leukemia *cMDS-IB* childhood myelodysplastic neoplasm with increased blasts, *cMDS-LB* childhood myelodysplastic neoplasm with low blasts, *HSCT* hematopoietic stem cell transplantation, *MDS-LB* myelodysplastic neoplasm with low blasts, *MUD* matched unrelated donor, *NA* not available *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning

malformations. Considering that demographic data of our cohort are similar to those already reported, such differences may occur when evaluating small cohorts of patients with rare disease. One patient with GATA2 deficiency and myelofibrosis was described in 2021 [30]. We here report another patient, already described as having Pediatric Immune MyeloFibrosis [27] thus reinforcing myelofibrosis as a GATA2 BM manifestation.

Four new possible clinical features of GATA2 deficiency are described here, namely pilonidal cyst/sacrococcygeal fistula, cholangiocarcinoma, gastric adenocarcinoma and autoinflammatory syndrome. Pilonidal cyst/sacrococcygeal fistula (two cases) may be incidental as this manifestation is very common in the young adult population (prevalence 0.7%, peak of incidence between 15 and 30 years) [31]. Although rarer than hematological neoplasms, solid tumors have already been reported [8, 9, 32]. Reduced viral clearance and defective immunosurveillance, which may be underlying mechanisms of cholangiocarcinoma, are part of the picture of GATA2 immunodeficiency and may promote sclerosing cholangitis [33], a known risk factor for cholangiocarcinoma [34]. Unfortunately, it was not possible to obtain further clinical, anamnestic and laboratory data, so it is not known whether this patient has undergone a complete infectious disease work-up and his immuno-hematological status. We believe that cholangiocarcinoma and gastric adenocarcinoma (the second solid tumor we have reported) should be included among the solid tumors (breast cancers, skin cancers, pancreas adenocarcinoma, renal cell carcinoma, locally invasive desmoid tumor of the chest wall, epidermoid carcinoma) which may affect GATA2-deficient patients [8, 9]. Lastly, it is conceivable that the autoinflammatory syndrome one of our patients has experienced could be related to the underlying myelodysplastic neoplasm.

Our hemato-immunological data are consistent with those previously described [8–10, 28]. Monocytopenia and CD19 + lymphocytopenia are the most important hemato-immunological features.

GATA2 deficiency is severely associated with myeloid neoplasms, with a 68% (21/31) frequency of MDS/AML in our study. This percentage, lower than those reported by Donadieu (86%) [9] and Spinner (84%) [8], could be partly explained by the lower age of our patients at the last follow-up (22 years), compared to Spinner (30 years). Patients' median age in the French cohort (24.5 years) is similar to that of our cohort. Donadieu reports a higher

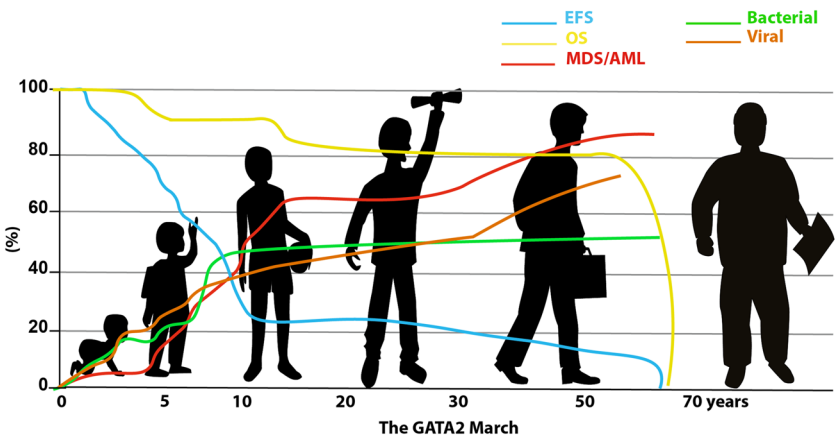

Fig. 4 The GATA2 march in the Italian cohort

risk of leukemia in case of missense mutations (14 out of 38) compared with null mutations (2 out of 28). We may speculate that a different composition of the type of variants could explain our results. Since null variants have a higher frequency in our cohort, the lower percentage of myeloid neoplasms could be explained by the proportionally lower frequency of missense mutations described here. However, we are aware that the genotype–phenotype correlation between missense mutations and higher risk of leukemia was not confirmed by Homan [7].

Similarly to what was stated by Wlodarski [11], most GATA2-deficient patients develop MDS, while a rather small subset presents directly with AML. GATA2-related MDS has a significant risk of evolution to AML or chronic myelomonocytic leukemia (CMML). Progression to AML has been reported in 14–16% of MDS-patients [8, 9] and, in line with these percentages, among patients with MDS, we observed a progression to AML in 12% (2/17) of cases. We report no cases of acute lymphoblastic leukemia, juvenile myelomonocytic leukemia and CMML, which were previously described [8, 9]. These hematological disorders seem to be rarely associated with GATA2 deficiency and only larger international cohorts may unveil their exact prevalence.

Null and missense variants were the most frequent types of variants [16]. Nonetheless, in the presence of strong clinical suspicion and negative exon analysis, patients should also be screened for intronic lesions, since genetic analysis of the only coding sequence could lead to a misdiagnosis [16]. Three variants are frequently represented in our cohort. The p.Arg396Trp (4 individuals, 4 families) and the p.Arg337X (3 individuals, 2 families) are already known to be recurrent pathogenic variants [24]. The p.Lys405Asn (3 individuals, 2 families), affecting an amino acid located C-terminal to the ZF2 domain, was previously found in only one Norwegian and one Italian individual each [10, 35]. The Lys405Asn is reported in 5 carriers in the general population (GnomAD) and in silico tools predict it either as disease causing (MutationTaster) or possibly damaging (PolyPhen) with a combined annotation dependent depletion (CADD) score of 26.6. Since functional studies have not been performed and authors reported it as either pathogenic [35] or probably benign, the interpretation of this variant remains controversial.

Family screening was not routinely performed in our cohort. Yet, it identified completely asymptomatic adult patients. Since family screening is essential to exclude potential HSCT donors and to identify patients exhibiting incomplete phenotypes, we advocate a more extensive implementation among families with GATA2 deficiency, although the best management for healthy carriers has not been well defined yet [21].

Germline *GATA2* mutations are not sufficient per se for the development of clonal disease, as not all patients progress to a malignant neoplasm. Yet, certain additional cytogenetic and molecular alterations trigger disease evolution and are recurrently found in patients with GATA2 deficiency (i.e., monosomy 7 and trisomy 8) and should point towards GATA2 deficiency [11]. Interestingly, in one patient we describe the presence of a supernumerary isochromosome 1, which has never been previously reported.

The four somatic variants found in our cohort are all known to affect genes (*EZH2*, *MECOM* and *ASXL1*) involved in the development of MDS/AML [36]. In keeping with this, all the four patients were affected by hematological neoplasia (cMDS-LB in three cases, AML in one individual). Notably, *ASXL1* mutations are encompassed among the most frequent recurrent somatic mutations in GATA2-MDS patients [37]. As it has been previously demonstrated that somatic mutations in leukemia-related genes lead to leukemic transformation and inferior outcome [11, 16, 35], periodic evaluation of somatic driver mutations may be useful as they may serve as prognostic markers and guide the HSCT strategy [24].

HSCT is the only curative treatment for GATA2 deficiency, which is burdened by a mortality rate of 35% at the age of 40 [9]. In our cohort, the majority of patients suffered from myeloid neoplasms, which were the main indication for HSCT, and more than half of them underwent HSCT. The rate of HSCT in our study is higher compared to what has been reported in the French cohort (28/79; 35%). In recent years there has been a debate over proper timing and indications for HSCT in GATA2 patients. We may speculate that this discussion has increased the rate of HSCT we observe in our cohort. Preemptive HSCT has been proposed in patients with MDS and GATA2 deficiency, irrespective of their hematological presentation [24]. With only 17 patients transplanted, our data do not allow definitive conclusions on this topic. As more GATA2 patients are described, indications for HSCT may now include severe infections due to the underlying immune defect. Here we report that, in one individual, immunodeficiency led to the decision of performing HSCT thus increasing the long-term survival before developing serious infections or secondary organ damage [24]. Similarly, severe immunodeficiency in the absence of myelodysplastic-leukemic changes was also considered an indication for HSCT in two patients in the Norwegian cohort [10]. As more GATA2 patients are described, indications for HSCT may now include severe, recurrent or opportunistic infections due to the underlying immune defect.

Given the heterogeneity of the conditioning regimen, disease severity and HSCT indications, the overall survival rate of 56% at 36 months observed in our cohort of transplanted patients appears almost comparable to that reported in previous series [8, 9, 12]. We did not observe increased susceptibility to unexpected transplant-related toxicity after HSCT, which is in line with previous reports [12, 24]. Indeed, disease progression was the cause of death of 4 out of 5 patients who died after HSCT.

HSCT is associated with a regression of PAP and pulmonary hypertension and with the resolution of condylomas and cervical cancer in situ [24–26]. Thrombotic complications and transplant-associated microangiopathy have been reported post-HSCT [21, 24]. We are aware these events may be frequently associated with HSCT. Yet, *GATA2* is expressed in endothelial cells [38] and therefore it remains to be elucidated whether HSCT may revert the risk of vascular manifestations.

Regarding symptoms at onset, type and distribution of infections, hemato-immunological characteristics and post-HSCT outcome, there is no obvious genotype–phenotype correlation. Particularly, even among individuals belonging to the same family or carrying the same mutation, the variability of the clinical phenotype points towards an exclusion of a genotype–phenotype correlation. Interestingly, through the analysis of over 400 patients with GATA2 deficiency, Homan [7] observed that lymphedema was never found in patients with missense mutations, concluding that the association between lymphedema and null/regulatory mutations is the only genotype–phenotype correlation in GATA2 deficiency. However, we reported 4 missense mutations out of the 7 cases of lymphedema described in our cohort thus proving that lymphedema does indeed occur in patients with missense mutations. This observation underlines that in rare diseases even a few patients can change what was known up to that point [39].

Furthermore, as more and more patients are described, it cannot be a priori excluded a dual molecular diagnosis scenario [40, 41]. In fact, one patient of our cohort (P26) received a dual molecular diagnosis, as variants in the *GATA2* and in the *MPL* genes were found through NGS. In this case, both the conditions have been effectively treated by HSCT. Yet, the conditioning regimen could have been modified in case of concomitant *GATA2* mutations and solid tumor predisposing conditions (i.e. Fanconi Anemia or radiosensitive conditions) [41].

The study has some limitations: (i) given its retrospective nature and the different Italian Association of Pediatric Hematology and Oncology (AIEOP) centers involved, it was not possible to obtain for each patient all the data required in the Case Report Form (CRF) and there is no uniformity in the diagnostic-therapeutic management of the patients (different targeted NGS panels were adopted either for diagnostic purposes or for monitoring the occurrence of somatic variants); (ii) the clinical spectrum is necessarily limited due to the referral bias, therefore some manifestations, such as pulmonary alveolar proteinosis, lymphedema and sensorineural deafness, are probably underestimated; (iii) some asymptomatic patients may not have been included in the study, decreasing their actual prevalence; (iv) although synonymous variants have been recently associated with GATA2 deficiency [17], we report no synonymous variants in our cohort. As most of the patients were investigated before the paper of Kozyra [17], it is conceivable that synonymous variants were deemed silent and therefore filtered out during the analysis; (v) a longer follow-up is needed to better understand the natural history of the disease.

Conclusions

Our series represents the third largest national cohort after the ones described by Donadieu and Spinner (79 and 57 patients, respectively) [8, 9] and provides a representative overview of GATA2 deficiency.

Our results emphasize some key points: (i) *GATA2* regulatory region should be sequenced, considering that germline variants located in the intronic transcriptional enhancer elements may cause GATA2 deficiency [18]; (ii) family screening should be offered to all first degree relatives, as identification of asymptomatic GATA2-deficient patients could allow to exclude potential HSCT donors and to investigate risk factors that may explain the phenotypic difference; (iii) HSCT should be considered in case of patients with immunodeficiency without myeloid neoplasms, as performing HSCT before patients develop malignancies or severe/recurrent infections causing organ failure is likely to increase the long-term survival [24]; (iv) *GATA2* should be included in targeted gene panels for congenital deafness. Furthermore, new (pilonidal cyst/sacrococcygeal fistula, cholangiocarcinoma and gastric adenocarcinoma) phenotypes can be associated with GATA2 deficiency. Lastly, our data shows that lymphedema may be associated with null and regulatory mutations [7].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-023-01583-8.

Acknowledgements The Authors thank the patients and families for their participation in this study. We thank the Italian Society for Pediatric Research (SIRP) for supporting this study. VS is partially supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) IG-26537-2021.

Author's Contributions Francesco Saettini designed the work and coordinated the project. Francesco Saettini and Samuele Roncareggi analyzed data. Samuele Roncareggi wrote the manuscript. All authors contributed with clinical, immunological, and molecular data. All authors approved the final version of the manuscript.

Data Availability Not applicable.

Declarations

Ethics Approval The study was approved from the local hospital Ethical Committee and was conducted in accordance with the 1964 Helsinki Declaration.

Consent to Participate Informed consent was collected from all patients or their legal guardians.

Consent for Publication Informed consent was collected from all patients or their legal guardians.

Conflict of Interest The authors declare no competing interests.

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