Published in final edited form as:
J Allergy Clin Immunol. 2014 July ; 134(1): 223–226. doi:10.1016/j.jaci.2014.01.041.

Presence of hypogammaglobulinemia and abnormal antibody responses in 1 GATA2 deficiency

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Keywords

GATA2; hypogammaglobulinemia

To the editor

GATA2 encodes a transcription factor that regulates stem cell homeostasis. Mutations in *GATA2* result in a diverse clinical phenotype that includes myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), decreased monocytes, B cells, and NK cells, opportunistic infections, and lymphedema.[2] Previous studies have noted normal immunoglobulin levels and detectable bone marrow plasma cells in patients with GATA2 mutations.[1,3–6] We report 2 patients with hypogammaglobulinemia and defective antibody responses associated with an autosomal dominant mutation in *GATA2*.

Patient 1 presented at 3 years of age with recurrent otitis media and sinusitis. He had a normal lymphocyte and monocyte counts, platelet number, and hematocrit. He had IgG_2 and IgA deficiency, absent tetanus and low PRP (52 ng/mL, protective >1000 ng/ml) antibody titers. Tetanus and Hib vaccine boosters resulted in protective tetanus (0.4 IU/mL) and PRP (>1200 ng/mL) titers. Two years later, his tetanus titer was undetectable, his PRP decreased to 185 ng/mL, and his IgG level was decreased at 444 mg/dL (normal 600 – 1500 ng/mL), prompting IVIG initiation. At 10 years of age, IVIG was discontinued to reassess his antibody response. His tetanus titer increased from 0.14 to 0.27 IU/mL after a booster, but

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waned within one year to 0.03 IU/mL. At 14 years of age, his PRP titer increased significantly after the Hib vaccine, but he failed to respond to repeated vaccinations of tetanus, Prevnar, and Pneumovax; additionally, his IgG was low and IgA was undetectable (Table 1). He developed pneumonia and pan-sinusitis in the setting of absent B cells and $CD4^+$ T cell lymphopenia (Table I); therefore, IVIG was restarted. He had absent tonsils, which had been barely visible on previous exams. No mutations were found in *TACI*, *PNP*, *ADA*, *BTK*, or *SH2D1A*. At 16 years of age, he developed persistent warts on his hands and severe bronchiectasis. Sputum cultures were positive for *Mycobacterium kansasii*. Lymphocyte proliferation to mitogens and antigens was normal, but the counts of NK cells, monocytes, and platelets were low (Table I). Progressive respiratory decline led to his death at 22 years of age.

Patient 2, the mother of Patient 1, was well until 48 years of age, when her son was 18 years old. She developed diarrhea, anemia, and leukopenia, attributed to a viral illness causing bone marrow suppression. Although the anemia resolved, she had persistent neutropenia, monocytopenia, and thrombocytopenia. Immune evaluation revealed $CD4^+$ T and B cell lymphopenia, nearly absent NK cells, and monocytopenia (Table I). She had low IgG, normal IgA and IgM, low pneumococcal and PRP titers, and a normal tetanus titer (Table I). Pneumovax and Hib vaccinations caused no significant increase in pneumococcal titers, but her PRP titer normalized to >9000 ng/mL. IVIG was started; since then, she has had no significant infections. Lymphocyte proliferation two years later was normal to mitogens and present to antigens (Table I). Analysis of B cells revealed a deficiency of IgD^+CD27^- naïve B cells, markedly increased IgD^+CD27^+ marginal zone (MZ)-like B cells, and a normal percentage of switched IgD^-CD27^+ memory B cells (Fig. 1A), suggesting skewed differentiation of transitional B cells toward MZ-like B cells or/and impairment of naïve B cell survival. Stimulation of sorted $CD19^+$ B cells with anti-CD40+IL-21 resulted in IgM and IgG secretion comparable to a control (Fig. 1B), indicating that class-switching downstream of CD40 was intact.

Whole exome sequencing on both patients identified a heterozygous mutation in *GATA2* (c. C1061T) that was confirmed by Sanger sequencing. The mutation results in a.a. change from threonine to methionine at position 354 (T354M) in the second zinc finger domain[7] and is predicted to be damaging to protein function by both Polyphen (score 0.997) and SIFT (score 0). The T354M mutation does not affect GATA2 expression or nuclear localization, but significantly impairs GATA2 binding to DNA and to the transcription factor PU.1, resulting in a dominant negative effect on transcriptional activation.[7] The phenotypes associated with the T354M mutation include autosomal dominant MDS/AML, MDS with pancytopenia, multilineage cytopenias, and opportunistic infections.[2, 7–9] One patient with this mutation had one episode of parainfluenza and mycoplasma with normal immunoglobulins,[6] another had pneumonias limited to childhood [6], and three others had mycobacterial and viral infections.[2, 3, 8] Four individuals were healthy into adulthood.[7] Patient 1 presented with IgG_2 and IgA deficiency and an abnormal vaccine response, which has not been previously reported in patients with *GATA2* mutations.

No additional mutations were found through whole exome sequencing that would account for the hypogammaglobulinemia seen in both patients. The normal immunoglobulin levels

in patients with *GATA2* mutations have been attributed to the presence of plasma cells. However, atypical plasma cell morphology has been reported in patients with different mutations in *GATA2*.[2, 5, 8] GATA2 may therefore be important for a normal plasma cell population. Our patients illustrate the broad spectrum of clinical presentation inherent in this disease. Patient 1 had an initially mild clinical presentation, with recurrent otitis media and sinusitis, but eventually developed warts and mycobacterial infections despite normal proliferation to mitogens and antigens (Table I). Patient 2 had no history of recurrent infections despite her impaired lymphocyte proliferation to antigens. Thus in our patients, as in others,[6] the same *GATA2* mutation can result in different phenotypes. This may be due to differences in modifier genes, environmental exposures, and epigenetic factors.

This report highlights the importance of considering mutations in *GATA2* in patients with hypogammaglobulinemia particularly in the setting of abnormal lymphocyte subsets and monocyte counts.

Acknowledgments

Supported by NIH (AI-076210 and AI094017 (RSG), The Manton Foundation (LDN), and a Manton Foundation Pilot Award (JC).

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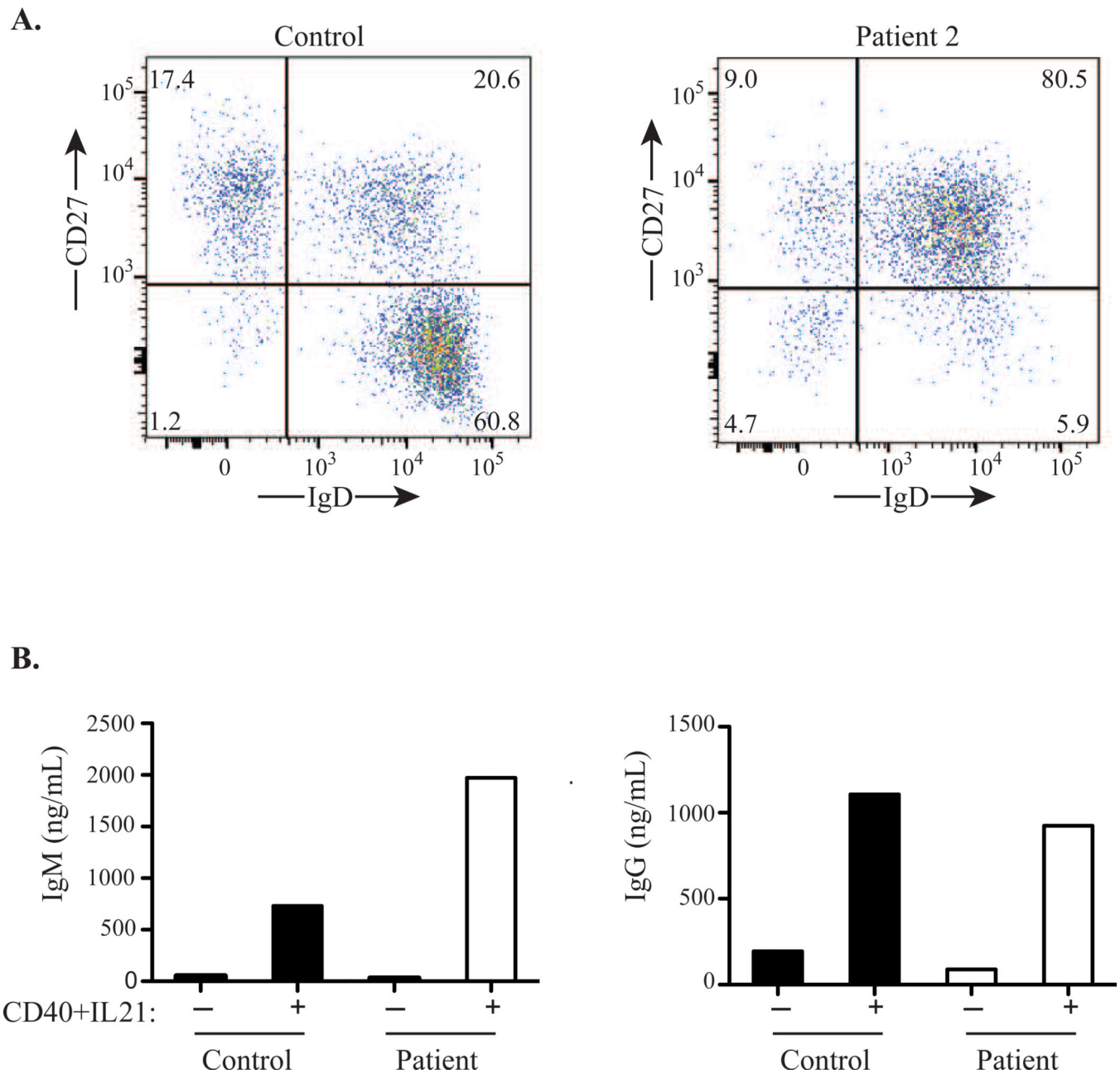

Figure 1.

(A) B cell subpopulations in Patient 2 and a control. (B) IgM and IgG production from sorted CD19+ B cells isolated from Patient 2 and a control stimulated with anti-CD40+IL21.

Table I

Immune profiles

	Patient 1		Patient 2	
	14 years	17 years	48 years	50 years
Immunoglobulins (mg/dL)[1]				
IgG (639 – 1344)	260	886	560	1122 on IVIG
IgG1 (240 – 1118)	ND	ND	329	ND
IgG2 (124 – 549)	ND	ND	82	ND
IgG3 (21 – 134)	ND	ND	64	ND
IgG4 (7 – 89)	ND	ND	<1	ND
IgA (70 – 312)	<7	<5	104	89
IgM (34 – 210)	12	<4	220	195
Vaccine titers (normal range)				
Pneumococcal IgG (Positive: > 1μg/mL, normal > +7/14 serotypes)	Absent; +1/14 after booster	ND	+3/14	ND
Tetanus IgG, IU/ml (0.15 – 7.0 IU/mL)	0.03; 0.02 after booster	ND	2.75	ND
Polysaccharide ribose phosphate, ng/mL (>1000 ng/mL)	131; >9000 after booster	ND	460	ND
Lymphocytes, cells/mL (normal range)[2]				
CD3+ (1000 –2600)	770	871	1139	1257
CD3+CD4+ (530 – 1500)	237	299	330	428
CD3+CD8+ (330 – 1100)	494	547	742	801
CD4+/CD8+ ratio (0.9 – 3.7)	0.48	0.52	0.44	0.53
CD19+ (110 – 570)	0	0	39	59
IgD−CD27+ (5 – 21%)	ND	ND	9.7	ND
IgD+CD27+ (8.7 – 18.7%)	ND	ND	81	ND
IgD+CD27− (57.7 – 79.7 %)	ND	ND	4.6	ND
CD16+/CD56+ (90 – 600)	104	20	2	2
Hemogram				
Monocytes, cells/mL (200 – 900)	252	41	90	75
Neutrophils, cells/mL (2,730 – 6,680)	10,970	3,050	1,470	1,110
Platelets, cells/mL (168,000 – 339,000)	256,000	162,000	144,000	141,000
Proliferation, cpm (normal control on test day)				
Phytohemagglutinin	ND	255,173 (227,256)	ND	174,994 (112,915)
Concanavalin A	ND	127,955 (127,472)	ND	127,538 (57,266)
Pokeweed mitogen	ND	66,517 (112,473)	ND	35,255 (77,049)
Background	ND	462 (1,430)	ND	342 (231)
Tetanus	ND	37,464 (71,042)	ND	5,285 (90,686)
Diptheria	ND	5,769 (6,687)	ND	2446 (68,326)

	Patient 1		Patient 2	
	14 years	17 years	48 years	50 years
Background	ND	166 (2,594)	ND	561 (647)

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ND: Not done