

GATA2 deficiency associated with copy number variation: A reference for considering inborn errors of immunity

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Clinical Implications

Patients with chromosomal deletions or duplications, also known as copy number variants, may have associated inborn errors of immunity. This communication provides a clinical reference tool for the rapid identification of the cytogenetic location of genes associated with inborn errors of immunity.

Deletions and duplications of chromosomal DNA fragments, alongside inversions and translocations, are collectively termed copy number variants (CNVs). A significant contribution to human genome variability can be attributed to CNVs, which are estimated to account for 4.8% to 9.7% of the human genome.¹ Copy number variants have three potential implications: no phenotypic effect, an adaptive trait, or underlying disease. Mechanisms implicated in CNV-associated disease include gene dosage, gene disruption, gene fusion, and long-range regulation effects.

Certain CNVs have definitively been associated with inborn errors of immunity (IEIs), most notably 22q11.2 deletion syndrome, with resultant haploinsufficiency of coding genes with key roles, including *TBX1*. 22q11.2 deletion syndrome may be confirmed by several diagnostic modalities including fluorescence in situ hybridization, chromosomal microarray analysis, and multiplex ligation-dependent probe amplification. The relationship between most CNVs and IEI has not been clearly defined. Indeed, targeted gene sequencing panels do not routinely list the cytogenetic location of causative genes. Here, we report a case of GATA2 deficiency associated with a CNV and provide a resource for easy identification of the cytogenetic location of known genes associated with IEI.

A 6-year-old girl was evaluated for recurrent sinopulmonary and urinary tract infections. She had a 2-week hospitalization with respiratory syncytial virus bronchiolitis at age 2 months, chest x-ray confirmed lobar pneumonia at age 4 years, and recurrent gram-negative *Enterobacteriaceae* urinary tract infections. Medical history was notable for vesicoureteral reflux, developmental delay, and a *de novo* 3q13.33-q21.3 deletion, confirmed by chromosomal microarray analysis. Surgical history was remarkable for adenotonsillectomy at age 3 years. Physical examination demonstrated dysmorphic facies, microcephaly, and low-set ears. Initial laboratory evaluation revealed T- and B-cell lymphopenia (CD4⁺ cells 351/mm³ and CD8⁺ cells 312/mm³, CD19⁺ cells 247/mm³). Absolute monocyte count was normal (0.3/mm³). IgG was low for age at 381 mg/dL, but IgM and IgA were normal. Neutrophil oxidative burst and total hemolytic complement were normal. Vaccine titers were low but responded

robustly to booster vaccination. The patient underwent ureteral reimplantation and received trimethoprim-sulfamethoxazole prophylaxis, and then was asymptomatic. Upon discontinuation of antibiotic prophylaxis, the course was complicated by viral gastroenteritis and recurrent bilateral lower lobe pneumonia, with parapneumonic effusion requiring chest tube thoracostomy. Infectious etiology was suspected, but cultures remained negative. Repeat immune evaluation demonstrated loss of protective pneumococcal serotypes and reduced switched memory B cells (Table I). Genetic sequencing revealed a heterogeneous pathogenic mutation in *GATA2*, with the entire coding sequence missing. Two genes implicated in IEI are within the patient's known microdeletion, *GATA2* and *SEC61A1*. Whereas *SEC61A1* is associated with hypogammaglobulinemia and absent response to polysaccharide vaccination, normal subpopulations of B and T cells are expected in peripheral blood.² Upon review by a GATA2 deficiency expert, it was determined that the patient's findings were consistent with this diagnosis. Three main types of monoallelic mutations are known to cause GATA2 deficiency: mutations leading to premature translation termination before or within zinc finger domain 2, missense mutations within zinc finger domain 2, and noncoding variants in the enhancer region of intron 4.³

Bone marrow biopsy showed no evidence of dysplasia and computed tomography of the chest was without findings suggestive of bronchiectasis or pulmonary alveolar proteinosis. The patient is currently receiving immunoglobulin replacement therapy and daily azithromycin prophylaxis. GATA2 deficiency is associated with a wide spectrum of clinical phenotypes and variable age of clinical presentation. Most occur in adolescence to early adulthood. This may explain why the patient does not yet have many of the classical features of GATA2 deficiency (Table II).

The use of cytogenetic studies to identify such CNVs has experienced recent exponential growth at least partly attributable to advances in next-generation sequencing technology and less prohibitive cost. Furthermore, genetic testing has become an integral component of the diagnostic evaluation of patients presenting with congenital anomalies, autism spectrum disorders, or unexplained developmental delay, as demonstrated in the patient in this report. The finding of GATA2 deficiency might have been anticipated given its cytogenetic location at 3q21.3, within the patient's identified microdeletion syndrome (Figure 1).⁴ Some commercially available gene panels offer analysis of gene duplication or deletion. If initial testing does not reveal an etiology, it is prudent to request duplication or deletion analysis.

A 2016 European Society for Immunological Disease survey of 16 centers reported that 30% of patients with known chromosomal aberrations evaluated were found to have some form of primary immunodeficiency.⁵ Sinopulmonary infections were the most common presentation prompting evaluation, in which antibody deficiency was the most frequently detected immune abnormality. Importantly, this survey excluded patients with trisomy 21 or 22q11.2 deletion, the two best-described chromosomal deletion syndromes with associated immunodeficiency.

Syndromes with numerical or structural chromosomal abnormalities are considered a distinct group within the classification of

TABLE I. Immune evaluation and dates

Immune parameter	May 2017	September 2017	December 2018	August 2020
WCC (K/ μ L) (reference range, 4-12 K/ μ L)	5.0		6.2	5.3
ALC (K/ μ L) (reference range, 0.6-7.8 K/ μ L)	0.9		2.0	1.2
ANC (K/ μ L) (reference range, 1-6 K/ μ L)	3.9		3.8	3.5
AMC (K/ μ L) (reference range, 0.1-1.8 K/ μ L)	0.3		0.2	0.5
CD3 ⁺ (cells/mm ³) (reference range, (1,400-3,700 cells/mm ³))	741			713
CD4 ⁺ (cells/mm ³) (reference range, 700-2,200 cells/mm ³)	351			340
CD8 ⁺ (cells/mm ³) (reference range, 490-1,300 cells/mm ³)	312			265
CD4/CD8 ratio (reference range, (0.9/2.6))	1.13			1.28
CD19 ⁺ (cells/mm ³) (reference range, 270-860 cells/mm ³)	247			184
CD16/56 ⁺ (cells/mm ³) (reference range, 78-470 cells/ μ L)	384			220
CD45RA (reference range, 250-2,000 cells/ μ L)	123			184
CD45RO (reference range, (100-510 cells/ μ L))	167			152
CD27 ⁺ percentage of CD19 ⁺ B cells (reference range, (6.3% to 52.8%))				7
CD27 ⁺ IgD ⁻ percentage of CD19 ⁺ B cells (reference range, 2.3% to 26.5%)				4
CD27 ⁺ IgD ⁺ percentage of CD19 ⁺ B cells (reference range, 1.7% to 29.3%)				4
CD21 ⁺ CD27 ⁻ percentage of CD19 ⁺ B cells (reference range, 92.1% to 99.6%)				91
CD21 ⁻ CD27 ⁺ percentage of CD19 ⁺ B cells (reference range, 0.2% to 8.6%)				0
T-cell proliferation to mitogens (ConA, PHA, and CD3 ligation)				Normal
IgG (mg/dL) (reference range, 592-1,723 mg/dL)	381		425	672
IgA (mg/dL) (reference range, 33-235 mg/dL)	26		24	58
IgM (mg/dL) (reference range, 36-314 mg/dL)	34		26	36
<i>Streptococcus pneumoniae</i> serotypes	0/23 protective	15/23 protective	6/23 protective	4/23 protective
Tetanus titer protective $\geq$ 0.01 IU/mL	0.54			0.64
Diphtheria titer protective $\geq$ 0.01 IU/mL	0.2			0.16
Hemophilus titer protective $\geq$ 1.00 μ g/mL	0.0	>9.0		8.8
Total hemolytic complement (reference range, 31-60 U/mL)	>60			
DHR	Normal			
HIV	Negative			

ALC, Absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; DHR, dihydrorhodamine; WCC, white cell count. Values less than reference range are highlighted in bold.

IEI.⁶ However, distinct chromosomal aberrations associated with immunodeficiency, other than those classified by the International Union of Immunological Societies (IUIS), have been reported in the literature.⁷ The patient in this report, as in many cases of immunodeficiency, did not present with classical features of GATA2 deficiency such as cutaneous viral skin infection, sensorineural hearing loss, or cytopenias. Awareness of the cytogenetic location of genes implicated in IEI may provide a pivotal additional diagnostic clue for immunologic assessment and diagnosis.

To facilitate easier identification of CNVs that may be associated with primary immunodeficiency, we generated a reference table of known IEI genes and their cytogenetic locations. A commercially available primary immunodeficiency targeted gene panel (TGP) (Invitae, San Francisco, Calif) was cross-referenced against the 2019 IUIS Classification of Inborn Errors of Immunity and the 2020 update.^{6,8} Genes within the TGP but not reported in the IUIS classification were removed. Additional genes reported by IUIS but not within the TGP were included.

TABLE II. Characteristic features of GATA2 deficiency versus patient features

Features	GATA2 deficiency	Index patient
Hematologic	Bone marrow failure, cytopenias involving B, natural killer, dendritic cell, CD4 ⁺ , monocytes, macrophages	B- and T-cell lymphopenia, micromegakaryocytes on bone marrow biopsy
Myeloid neoplasia	AML, MDS, CMML, MPN	Absent
Auditory	Sensorineural hearing loss	Normal hearing
Infectious	Viral, bacterial, non-tuberculous mycobacterial and fungal infections	Recurrent viral URI, <i>Escherichia coli</i> , <i>Klebsiella</i> UTI, suspected bacterial pneumonia with parapneumonic effusion
Lymphatic	Lymphedema	Absent
Pulmonary	Pulmonary alveolar proteinosis	Absent

AML, Acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; URI, upper respiratory infection; UTI, urinary tract infection.

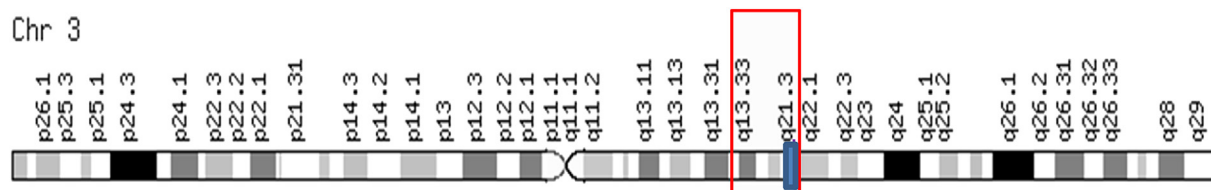


FIGURE 1. Representation of *GATA2* gene (blue rectangle) located within the patient's known microdeletion, q13.33-q21.3 (red box) on chromosome 3 (Chr 3).⁴

A total of 436 genes were cataloged. The Online Mendelian Inheritance in Man database was used to define the cytogenetic location of each gene.⁹ Inheritance pattern was also reported (See Table E1 in this article's Online Repository at www.jaci-inpractice.org).

In the evaluation of possible immunodeficiency, it is imperative for any associated CNV to be analyzed carefully for the potential inclusion of a cytogenetic location incorporating a known causative gene of IEL.

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ONLINE REPOSITORY

TABLE E1. Genes implicated in inborn errors of immunity, arranged in ascending order by cytogenetic location

1p22.1	GFI1	GFI1 deficiency (SCN2)	AD
1p22.3	Bcl10	Bcl10 deficiency	AR
1p31.3	IL12RB2	IL-12 receptor β 2 deficiency	AR
1p31.3	IL23R	IL-23 receptor deficiency	AR
1p31.3	JAK1	JAK1 deficiency	AR LOF
1p32.1	C8A	C8 α deficiency (C8 deficiency, type 1)	AR
1p32.1	MYSM1	MYSM1 deficiency	AR
1p32.2	C8B	C8 β deficiency (C8 deficiency, type II)	AR
1p34.2	CTPS1	CTPS1 deficiency	AR
1p34.3	CSF3R	G-CSF deficiency	AR
1p35.1	AK2	AK2 deficiency (T-B-NK-SCID)	AR
1p35.2	LCK	LCK deficiency	AR
1p36.11	FCN3	Ficolin 3 deficiency	AR
1p36.12	C1QA	C1q deficiency	AR
1p36.12	C1QB	C1q deficiency	AR
1p36.12	C1QC	C1q deficiency	AR
1p36.12	CDC42	Multisystem inflammatory disease	AD
1p36.22	PIK3CD	p110 δ deficiency; activated P110 δ syndrome	AR; AD GOF
1p36.22	MASP2	MASP2 deficiency	AR
1p36.22	MAD2L2	Fanconi anemia type V	AR
1p36.23	TNFRSF9	CD137 deficiency (41BB)	AR
1p36.33	ISG15	ISG15 deficiency	AR
1p36.33	TNFRSF4	OX40 deficiency	AR
1q12.3-q21.1	EPG5	EPG5 deficiency (Vici syndrome)	AR
1q21.1	POLR3C	RNA polymerase III deficiency	AD
1q21.2	VPS45	VPS45 deficiency	AR
1q21.3	ADAR1	ADAR1 deficiency, Aicardi Goutières syndrome	AR
1q21.3	HAX1	HAX1 deficiency (Kostmann disease) (SCN 3)	AR
1q21.3	IL6R	IL-6 receptor deficiency	AR
1q21.3	PSMB4	Proposed CANDLE syndrome	AR
1q21.3	RFX5	MHC class II deficiency Group C	AR
1q21.3	RORC	RORyt deficiency	AR
1q22	LAMTOR2	P14/LAMTOR2 deficiency	AR
1q23.2	COPA	COPA defect	AD
1q23.2	NCSTN	Hidradenitis suppurativa	AD
1q23.3	RCGR3A (CD16)	CD16 deficiency	AR
1q24.2	CD247	CD3 ζ deficiency	AR
1q24.3	FASLG (TNFSF6)	ALPS-FASL	AD
1q25.3	NCF2	CGD	AR
1q31.3	CFH	Factor H deficiency	AR or AD
1q31.3	CFHR1	Factor H-related protein deficiencies	AR or AD
1q31.3	CFHR2	Factor H-related protein deficiencies	AR or AD
1q31.3	CFHR3	Factor H-related protein deficiencies	AR or AD
1q31.3	CFHR4	Factor H-related protein deficiencies	AR or AD
1q31.3	CFHR5	Factor H-related protein deficiencies	AR or AD
1q31.3-q32.1	PTPRC	CD45 deficiency (T-B+NK+SCID)	AR
1q32.1	IL10	IL-10 deficiency	AR
1q32.1	UBE2T	Fanconi anemia type T	AR
1q32.2	CD46	Membrane cofactor protein (CD46) deficiency	AD
1q32.2	CD55	CD55 deficiency (CHAPLE disease)	AR
1q32.2	CD21	CD21 deficiency (common variable immunodeficiency [CVID])	AR
1q42.3	IRF2BP2	IRF2BP2 deficiency	AD
1q42.3	LYST	Chediak Higashi syndrome	AR
1q44	NLRP3	Familial cold autoinflammatory syndrome; Muckle-Wells syndrome; NOMID/CINCA	AD GOF
2p11.2	CD8A	CD8 deficiency	AR

(continued)

TABLE E1. (Continued)

1p22.1	GF11	GF11 deficiency (SCN2)	AD
2p11.2	IGKC	Kappa chain deficiency	AR
2p13.1	MOGS	Mannosyl-oligosaccharide glucosidase deficiency	AR
2p16.1	FANCL	Fanconi anemia type L	AR
2p16.1	REL	c-Rel deficiency	AR
2p16.3	MSH6	MSH6 deficiency	AR
2p21	TTC7A	Immunodeficiency with multiple intestinal atresias	AR
2p22.3	NLRC4	NLRC4-macrophage activating syndrome	AD GOF
2p24.3	NBAS	NBAS deficiency	AR
2p25.1	ADAM17	ADAM17 deficiency	AR
2q11.2	ZAP70	ZAP-70 deficiency/activating mutation	AR LOF/GOF
2q13	RANBP2	Acute necrotizing encephalopathy	AR
2q14.1	IL1RN	Deficiency of IL-1 receptor antagonist	AR
2q14.1	IL36RN	Deficiency of IL-36 receptor antagonist	AR
2q14.2	RNU4ATAC	MOPD1 deficiency (Roifman syndrome)	AR
2q22.1	CXCR4	WHIM syndrome	AD
2q24.2	IFIH1	MDA5 deficiency; Aicardi-Goutières syndrome 7	AR LOF; AD GOF
2q31.1	CDCA7	Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome type 3	AR
2q31.1	WIPF1	WIP deficiency	AR
2q31.2	NFE2L2	Activating <i>de novo</i> mutations in NFE2L2	AD
2q32.2	STAT1	STAT1 GOF; STAT1 LOF	AD GOF; AD/AR LOF
2q33.1	CASP10	ALPS-caspase 10 (ALPS syndrome, type II)	AD
2q33.1	CASP8	ALPS-caspase 8	AR
2q33.1	FADD	FADD deficiency	AR
2q33.2	CTLA4	CTLA4 haploinsufficiency	AD
2q33.2	ICOS	ICOS deficiency	AR
2q35	NHEJ1	Cernunnos/XLF deficiency (T-B-NK+SCID)	AR
2q35	SMARCAL1	Schimke immuno-osseous dysplasia	AR
2q36.1	AP1S3	AP1S3 deficiency	AR
2q37.1	SP110	Hepatic veno-occlusive disease with immunodeficiency	AR
3p14.3	DNASE1L3	Pediatric SLE owing to DNASE1L3 deficiency	AR
3p21.1	PRKCD	PRKCD deficiency	AR
3p21.31	TREX1	TREX1 deficiency (Aicardi-Goutières syndrome 1)	AR
3p22.1	RPSA	Isolated congenital asplenia	AD/AR
3p22.2	MYD88	MyD88 deficiency	AR
3p24.1	TGRBR2	Loeys-Dietz syndrome (TGFB1 deficiency)	AD
3p24.2	TOP2B	Hoffman syndrome (TOP2B deficiency)	AD
3p25.3	IL17RC	IL-17RC deficiency	AR
3p25.3	JAGN1	JAGN1 deficiency	AR
3p25.3	FANCD2	Fanconi anemia type D2	AR
3p26.2	TRNT1	TRNT1 deficiency	AR
3q21.3	GATA2	GATA2 deficiency	AD
3q22.3	DBR1	DBR1 deficiency	AR
3q21.3	SEC61A1	SEC61A1 deficiency	AD
3q26.2	TERC	Dyskeratosis congenita	AD
3q29	RNF168	RNF168 deficiency (RIDDLE syndrome)	AR
3q29	TFRC	TFRC deficiency	AR
4p14	RHOH	RHOH deficiency	AR
4p16.1	WDR1	WDR1 deficiency	AR
4p16.3	SH3BP2	Cherubism	AD
4q12	SRP72	SRP72 deficiency (BMFS1)	AD
4q24	TET2		AR (LOF)
4q24	NFKB1	NFKB1 deficiency	AD
4q25	CFI	Factor I deficiency	AR
4q27	IL21	IL-21 deficiency	AR

(continued)

TABLE E1. (Continued)

1p22.1	GF1	GF1 deficiency (SCN2)	AD
4q28.1	FAT4	Hennekam lymphangiectasia-lymphedema syndrome 2	AR
4q31.3	LRBA	LRBA deficiency	AR
4q35.1	TLR3	TLR3 deficiency	AD; AR
5p13.1	C6	C6 deficiency	AR
5p13.1	C7	C7 deficiency	AR
5p13.1	C9	C9 deficiency	AR
5p13.2	DNAJC21	Shwachman-Diamond syndrome	AR
5p13.2	IL7R	IL-7 receptor α deficiency	AR
5p15.2	OTULIN	Otulipenia/ORAS	AR
5p15.33	TERT	Dyskeratosis congenita	AD/AR
5q11.2	IL6ST	HIES-STAT3-like	AD (DN)
5q11.2	IL6ST	Fatal Stuve-Wiedmann-like syndrome	AR (LOF)
5q11.2	IL6ST	IL-6 signal transducer deficiency	AR
5q12.3	ERBIN (ERBB2IP)	ERBIN deficiency	AD
5q13.1	PIK3R1	P85 deficiency; activated P110 δ syndrome	AR; AD
5q14.1	AP3B1	Hermansky Pudlak syndrome, type 2	AR
5q15	TTC37	Tricho-hepato-enteric syndrome	AR
5q31.1	FNIP1		AR (LOF)
5q31.2	TMEM173	STING-associated vasculopathy infantile-onset	AR
5q32	SPINK5	Comel-Netherton syndrome	AR
5q33.3	IL12B	IL-12p40 (IL-12 and IL-23) deficiency	AR
5q33.3	ITK	ITK deficiency	AR
5q33.3	LSM11	Aicardi-Goutières syndrome	AR (LOF)
5q33.3	HAVCR2	T cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency)	AR
5q35.1	DOCK2	DOCK2 deficiency	AR
5q35.3	NHP2	Dyskeratosis congenita	AR
5q35.3	NOLA2	Dyskeratosis congenita	AR
6p12.2	IL17F	IL-17F deficiency	AD
6p21.31	DEF6	DEF6 deficiency	AR
6p21.31	FANCE	Fanconi anemia type E	AR
6p21.32	PSMB8	CANDLE syndrome	AD and AR
6p21.32	SLC39A7	SLC39A7 (ZIP7) deficiency	AR
6p21.32	TAP1	MHC class I deficiency	AR
6p21.32	TAP2	MHC class I deficiency	AR
6p21.32	TAPBP	MHC class I deficiency	AR
6p21.33	C2	C2 deficiency	AR
6p21.33	CFB	Factor B deficiency or factor B GOF	AR/AD (GOF)
6p21.33	SKIV2L	Tricho-hepato-enteric syndrome	AR
6p21.33	C4A +C4B	Complete C4 deficiency	AR
6p25.2	RIPK1	Autoinflammatory disorder	AD
6p25.2	RIPK1	RIPK1	AR
6p25.3	IRF4	IRF4 haploinsufficiency	AD
6q14.1	PGM3	PGM3 deficiency	AR
6q15	BACH2	BACH2 deficiency	AD
6q21	OSTM1	Osteopetrosis	AR
6q21	TRAF3IP2	ACT1 deficiency	AR
6q21	ZBTB24	ICF type 2	AR
6q23.3	IFNGR1	IFN-gamma receptor 1 deficiency	AR/AD
6q23.3	TNFAIP3	A20 deficiency	AD
6q24.2	STX11	Syntaxin 11 deficiency (FHL4)	AR
7p12.2	IKZF1	IKAROS deficiency	AD DN
7p13	POLD2	Polymerase and deficiency	AR
7p15.2	SNX10	Osteopetrosis	AR
7p22.1	ACTB	β -Actin deficiency	AD

(continued)

TABLE E1. (Continued)

1p22.1	GF1	GF1 deficiency (SCN2)	AD
7p22.1	PMS2	PMS2 deficiency	AR
7p22.2	CARD11	CARD11 GOF	AD GOF
7q11.21	SBDS	Shwachman-Diamond syndrome	AR
7q11.23	NCF1	Autosomal recessive CGD	AR
7q21.11	SEMA3E	CHARGE syndrome	AD
7q21.2	SAMD9	MIRAGE	AD GOF
7q21.2	SAMD9L	Ataxia pancytopenia syndrome	AD GOF
7q22.1	ARPC1B	Arp2/3-mediated filament branching defect	AR
7q22.3	PIK3CG	HLH-like	AR (LOF)
7q31.2	CFTR	Cystic fibrosis	AR
7q31.2	ASZ1 (ALP1)	ALP1 deficiency	AR
7q36.1	XRCC2	Fanconi anemia type U	AR
8p11.21	IKBKB	Anhidrotic Ectodermodyplasia with Immunodeficiency (EDA-ID)	AD GOF
8p21.1	EXTL3	EXTL3 deficiency	AR
8p21.3	SH2D1A	SAP deficiency (XLP1)	XL
8q11.21	MCM4	MCM4 deficiency	AR
8q11.21	PRKDC	DNA PKcs deficiency	AR
8q12.2	CHD7	CHARGE syndrome	AD
8q21.3	NBN (NBS1)	Nijmegen breakage syndrome	AR
8q22.2	VPS13B	Cohen syndrome	AR
8q23.1	ANGPT1	Hereditary angioedema	AD
9p13.3	RMRP	Cartilage hair hypoplasia	AR
9p13.3	FANCG (XRCC9)	Fanconi anemia type G	AR
9p24.3	DOCK8	DOCK8 deficiency	AR
9q22.32	ERCC6L2	ERC6L2 (Hebo deficiency)	AR
9q22.32	FANCC	Fanconi anemia type C	AR
9q22.33	TGFBR1	Loeys-Dietz syndrome (TGFBR deficiency)	AD
9q33.2	C5	C5 deficiency	AR
9q34.3	C8γ	C8γ deficiency	AR
9q34.4	CARD9	CARD9 deficiency	AR
10p13	MCM10		AR (LOF)
10p13	DCLRE1C	DCLRE1C (Artemis) deficiency	AR
Del10p13-p14		Chromosome 10p13-p14 deletions syndrome (10p13-p14DS)	AD
10p15.1	IL2RA	CD25 deficiency	AR
10q11.22	MAPK8	CMC	AD (haploinsufficiency)
10q22.1	PRF1	Perforin deficiency (FHL2)	AR
10q22.1	SLC29A3	SLC29A3 mutation (histiocytosis-lymphadenopathy plus syndrome)	AR
10q22.3	POLR3A	RNA polymerase III deficiency	AD
10q23.31	FAS (TNFRSF6)	ALPS-FAS	AD
10q23.32	PTEN	PTEN deficiency	AD
10q23.33	HELLS	ICF 4	AR
10q24.1	BLNK	BLNK deficiency	AR
10q24.32	NFKB2	NFKB2 deficiency	AD
10q24.33	STN1	Coats plus syndrome	AR
11p11.2	SLC35C1	Leukocyte adhesion deficiency type 2	AR
11p12	RAG1	RAG deficiency (T-B-NK+SCID)	AR
11p12	RAG2	RAG deficiency (T-B-NK+SCID)	AR
11p13	CD59	Membrane attack complex inhibitor (CD59) deficiency	AR
11p14.3	FANCF	Fanconi anemia type F	AR
11p15.4	STIM1	STIM1 deficiency	AR
11p15.4	TRIM22	TRIM22 deficiency	AR
11p15.5	CD81	CD81 deficiency	AR
11p15.5	IRF7	IRF7 deficiency	AR
11q12.1	SERPING1	C1 inhibitor deficiency	AD

(continued)

TABLE E1. (Continued)

1p22.1	GFI1	GFI1 deficiency (SCN2)	AD
11q12.2	MS4A1 (B1 CD20)	CVID (CD20 deficiency)	AR
11q13.1	FERMT3	Leukocyte adhesion deficiency type 3	AR
11q13.1	RELA	RelA haploinsufficiency	AD
11q13.1	RNASEH2C	RNASEH2A deficiency, Aicardi-Goutières syndrome 3	AR
11q13.2	UNC93B1	UNC93B1 deficiency	AR
11q13.4	CLPB	3-methylglutaconic aciduria	AR
11q13.4	IL18BP	IL-18BP deficiency	AR
11q132.	TCIRG1	Osteopetrosis	AR
11q14.2	CTSC	Papillon-Lefevre syndrome	AR
11q22.3	ATM	Ataxia telangiectasia	AR
11q23.3	CD3D	CD3 δ deficiency (T-B+NK+SCID)	AR
11q23.3	CD3E	CD3 ϵ deficiency (T-B+NK+SCID)	AR
11q23.3	CD3G	CD3 γ deficiency (T-B+NK+SCID)	AR
11q23.3	HYOU1	HYOU deficiency	AR
11q23.3	IL10RA	IL-10R deficiency	AR
11q23.3	KMT2A	Wiedemann-Steiner syndrome	AD
11q23.3	SLC37A4 (G6PT1)	Glycogen storage disease Ib, Ic	AR
11q23 del		Chromosome 11q deletion syndrome (Jacobsen syndrome)	AD
11q24.2	TIRAP	TIRAP deficiency	AR
12p13.31	RNU7-1	Aicardi-Goutières syndrome	
12p13.31	AICDA	AID deficiency	AR
12p13.31	C1S	C1s deficiency; C1s periodontal Ehlers-Danlos	AR; AD GOF
12p13.31	CD27	CD27 deficiency	AR
12p13.31	TNFRSF1A	TNF-receptor-associated periodic syndrome	AD
12p13.31	C1r	C1r deficiency; C1r periodontal Ehlers-Danlos	AR; AD GOF
12q12	IRAK4	IRAK4 deficiency	AR
12q13.1-q13.2	NCKAP1L	Immunodeficiency with autoinflammation	AR (LOF)
12q13.12	KMT2D	Kabuki syndrome type I	AD
12q13.3	STAT2	STAT2 GOF	AR (GOF)
12q13.3	STAT2	STAT2 deficiency	AR
12q24.22	MAP1LC3B2	Mollaret's meningitis (HSV2)	AD
12q15	IFNG	MSMD/BCG-osis	AR (LOF)
12q24.11	MVK	Mevalonate kinase deficiency (hyper IgD syndrome)	AR
12q24.11	UNG	UNG deficiency	AR
12q24.13	OAS1	OAS1 deficiency	AD GOF
12q24.31	ORAI1	ORAI1 deficiency	AR
12q24.33	POLE	Polymerase ϵ subunit 1 deficiency (FILS syndrome)	AR
13q12.3	POMP	CANDLE phenotype	AD
13q13.1	BRCA2	Fanconi anemia type D1	AD
13q13.3	RFXAP	MHC class II deficiency group D	AR
13q14.1	TNFSF11	Osteopetrosis	AR
13q14.3	SNORA31	HSV-1 encephalitis	AD
13q14.3	RNASEH2B	RNASEH2A deficiency, Aicardi-Goutières syndrome 2	AR
13q33.1	TPP2	Tripeptidyl-peptidase II deficiency	AR
13q33.3	LIG4	DNA ligase 4 deficiency (T-B-NK+SCID)	AR
14q11.2	CEBPE	Specific granule deficiency	AR
14q11.2	PNP	Purine nucleoside phosphorylase deficiency	AR
14q11.2	SLC7A7	SLC7A7 deficiency	AR
14q11.2	TRAC	TCR α deficiency	AR
14q12	IRF9	IRF9 deficiency	AR
14q12	RNF31	HOIP deficiency	AR
14q12	TINF2	Dyskeratosis congenita	AD
14q13.2	NFKBIA	EDA-ID	AD GOF
14q13.2	SRP54	SRP54 deficiency	AD

(continued)

TABLE E1. (Continued)

1p22.1	GF1	GF1 deficiency (SCN2)	AD
14q21.2	FANCM	Fanconi anemia type M	AR
14q21.3	POLE2	POLE (polymerase ϵ subunit 2) deficiency	AR
14q23.1	PSMA3	Proposed CANDLE syndrome	
14q23.3	MTHFD1	MTHFD1 deficiency	AR
14q24.2	PSEN	Hidradenitis suppurativa	AD
14q32 (mut/del)		Ig heavy chain mutations and deletions	AR
14q32.2	BCL11B	BCL11B deficiency	AD
14q32.32	TRAF3	TRAF3 deficiency	AD
14q32.33	IGHM	Mu heavy chain deficiency	AR
15q13.1	NSMCE3	NSMCE3 deficiency	AR
15q14	NOP10	Dyskeratosis congenita	AR
15q14	RASGRP1	RASGRP1 deficiency	AR
15q14	NOLA3	Dyskeratosis congenita	AR
15q15.1	INO80	INO80 deficiency	AR
15q15.1	RAD51	Fanconi anemia type R	AR
15q21.1	B2M	MHC class I deficiency	AR
15q21.2	SPPL2A	SPPL2a deficiency	AR
15q21.3	RAB27A	Griscelli syndrome type 2	AR
15q24.3	PSTPIP1	PAPA syndrome, hyperzincemia and hypercalprotectinemia	AD
15q25.2	EFL1	Shwachman-Diamond syndrome	AR
15q26.1	BLM	Bloom syndrome	AR
15q26.1	CIB1	CIB1 deficiency (epidermodysplasia verruciformis)	AR
15q26.1	FANCI	Fanconi anemia type I	AR
16p11.2	CD19	CD19 deficiency	AR
16p11.2	CORO1A	Coronin 1A deficiency	AR
16p11.2	LAT	LAT deficiency	AR
16p12.1	IL21R	IL-21 receptor deficiency	AR
16p12.2	PALB2	Fanconi anemia type N	AR
16p13.12	PARN	Dyskeratosis congenita	AR
16p13.12	ERCC4	Fanconi anemia type Q	AR
16p13.13	SOC3	Autoinflammatory syndrome	AD
16p13.13	CIITA	MHC class II deficiency	AR
16p13.3	CLCN7	Osteopetrosis	AR
16p13.3	MEFV	Familial Mediterranean fever	AR LOF and AD
16p13.3	SLX4	Fanconi anemia type P	AR
16q12.1	NOD2	Blau syndrome	AD
16q21	USB1	Clericuzio syndrome (poikiloderma with neutropenia)	AR
16q22.1	CARMIL2	CARMIL2 deficiency	AR
16q22.1	ACD	Dyskeratosis congenita	AD or AR
16q22.1	NFAT5	NFAT5 haploinsufficiency	AD
16q23.1	RFWD3	Fanconi anemia type W	AR
16q23.3	PLCG2	PLC γ 2 associated antibody deficiency and immune dysregulation	AD GOF
16q24.1	IRF8	IRF8 deficiency	AD
16q24.2	CYBA	CGD	AR
16q24.3	FANCA	Fanconi anemia type A	AR
17p11.2	TNFRSF13B	TACI deficiency	AR or AD
17p13.1	CTC1	Coats plus syndrome	AR
17p13.1	TNFSF12	TWEAK deficiency	AD
17p13.1	WRAP53	Dyskeratosis congenita	AR
17p13.1	TNFSF13	CVID	AR (LOF)
17p13.1	TP53	Bone marrow failure syndrome 5	AD
17p13.2	SLP76	Combined immunodeficiency	AR (LOF)
17p13.2	NLRP1	NLRP1 deficiency	AR
		NLRP1 GOF	AD GOF

(continued)

TABLE E1. (Continued)

1p22.1	GF11	GF11 deficiency (SCN2)	AD
17q11.2	FOXN1	FOXN1 haploinsufficiency	AD
		Winged Helix Nude FOXN1 deficiency	AR
17q11.2	SLC46A1	SLC46A1/PCFT deficiency	AR
17q11.2	NOS2	Susceptibility to CMV-induced disease	AR
17q21.2	STAT3	STAT3 GOF mutation	AD GOF
17q21.2	STAT5B	STAT5b deficiency	AD DN/AR
17q21.31	G6PC3	G6PC3 deficiency (SCN4)	AR
17q21.31	MAP3K14	NIK deficiency	AR
17q21.31	PLEKHM1	Osteopetrosis	AR
17q21.31	BRCA1	Fanconi anemia type S	AR
17q21.32	TBX21	MSMD	AR (LOF)
17q22	RAD51C	Fanconi anemia type O	AR
17q23.2	BRIP1	Fanconi anemia type I	AR
17q23.3	CD79B	Igβ deficiency	AR
17q23.3	SMARCD2	SMARCD2 deficiency	AR
17q25.1	UNC13D	UNC13D/Munc14-4 deficiency (FHL3)	AR
17q25.3	C17orf62 (CYBC1)	CGD	AR
17q25.3	CARD14	CARD14 mediated psoriasis	AD
17q25.3	TMC6	EVER1 deficiency	AR
17q25.3	TMC8	EVER2 deficiency	AR
18p11.21	PSMG2	CANDLE syndrome	AR
18p11.31	LPIN2	Majeed syndrome	AR
18q21.32	CCBE1	Hennekam lymphangiectasia-lymphedema syndrome	AR
18q21.32	MALT1	MALT1 deficiency	AR
18q21.33	TNFRSF11A	Osteopetrosis	AR
19p13.11	FCHO1	FCHO1 deficiency	AR
19p13.11	IL12RB1	IL-12 and IL-23 receptor β1 chain deficiency	AR
19p13.11	JAK3	Jak3 deficiency (T-B+NK-SCID)	AR
19p13.11	RFXANK	MHC class II deficiency group B	AR
19p13.13	DNASE2	DNase II deficiency	AR
19p13.13	RNASEH2A	RNASEH2A deficiency, Aicardi-Goutières syndrome 4	AR
19p13.2	POLA1	SPENCD	AR
19p13.2	STXBP2	STXBP2/Munc18-2 deficiency (FHLS)	AD or AR
19p13.2	TYK2	Tyk2 deficiency; P1104a TYK2 homozygosity	AR
19p13.2	ACP5	Spondyloenchondrodysplasia with immune dysregulation	AR
19p13.3	AP3D1	Hermansky-Pudlak syndrome, type 10	AR
19p13.3	C3	C3 deficiency/C3 GOF	AR/ AD (GOF)
19p13.3	CFD	Factor D deficiency	AR
19p13.3	ELANE	Elastase deficiency (severe congenital neutropenia)	AD
19p13.3	TCF3	E47 transcription factor deficiency	AD/AR
19p13.3	TICAM1	TRIF deficiency	AD
19p13.3	CD70	CD70 deficiency	AR
19q13.11	PEPD	Prolidase deficiency	AR
19q13.11	FAAP24	FAAP24 deficiency	AR
19q13.2	ARHGEF1	ARHGEF1 deficiency	AR
19q13.2	CD79A	Igα deficiency	AR
19q13.2	PSENEN	Hidradenitis suppurativa	AD
19q13.2	TGFB1	TGFB1 deficiency	AR
19q13.32	RELB	RelB deficiency	AR
19q13.33	LIG1	Ligase 1 deficiency	AR
19q13.33	POLD1	Polymerase δ1 deficiency	AR
19q13.33	IRF3	IRF3 deficiency	AD
19q13.41	FPR1	Localized juvenile periodontitis	AR
19q13.42	NLRP12	Familial cold autoinflammatory syndrome 2	AD GOF

(continued)

TABLE E1. (Continued)

1p22.1	GFI1	GFI1 deficiency (SCN2)	AD
20p11.2	PAX1	T-B+NK+SCID	AR (LOF)
20p11.21	GINS1	GINS1 deficiency	AR
20p11.21	THBD	Thrombomodulin deficiency	AD
20p11.23	POLR3F	RNA polymerase III deficiency	AD
20p12.3	FERMT1	FERMT1 deficiency	AR
20p13	RBCK1	HOIL1 deficiency	AR
20q11.21	DNMT3B	ICF type 1	AR
20q11.22	ITCH	ITCH deficiency	AR
20q11.22	ZNF341	ZNF341 deficiency	AR
20q11.23	CTNBL1	CVID	AR (LOF)
20q11.23	SAMHD1	SAMHD1 deficiency	AR
20q13.12	ADA	Adenosine deaminase deficient SCID	AR
20q13.12	CD40	CD40 deficiency	AR
20q13.12	STK4	STK4 deficiency	AR
20q13.33	RTEL1	Dyskeratosis congenita	AD/AR
21q22.11	IFNAR1	IFNAR1 deficiency	AR
21q22.11	IFNAR2	IFNAR2 deficiency	AR
21q22.11	IFNGR2	IFN-gamma receptor 2 deficiency	AR
21q22.11	IL10RB	IL-10R deficiency	AR
21q22.3	AIRE	APECED	AR or AD
21q22.3	ICOSLG	ICOSL deficiency	AR
21q22.3	ITGB2	Leukocyte adhesion deficiency type 1	AR
22q11.1	ADA2	VAIHS	AR
22q11.1	IL17RA	IL-17RA deficiency	AR
22q11.21	TBX1	TBX1 deficiency	AD
22q11.21	USP18	USP18 deficiency	AR
22q11.23	IGLL1	Delta5 deficiency	AR
22q12.2	TCN2	Transcobalamin 2 deficiency	AR
22q12.3	CSF2RB	CSF2RB deficiency	AR
22q12.3	HMOX1	Isolated congenital asplenia	AR
22q12.3	IL2RB	CD122 deficiency	AR
22q12.3	NCF4	CGD	AR
22q12.3	APOL1	Trypanosomiasis	AD
22q13.1	RAC2	Rac2 deficiency	AD LOF
22q13.1-q13.2	MKL1	MKL1 deficiency	AR
22q13.2	TNFRSF13C	BAFF receptor deficiency	AR
Xp11.23	CFP	Properdin deficiency	XL
Xp11.23	FOXP3	IPEX	XL
Xp11.23	WAS	X-linked neutropenia/myelodysplasia	XL GOF
Xp11.23	UBA1	Late adulthood onset treatment refractory inflammatory syndrome	XL (somatic LOF)
Xp11.3	KDM6A	Kabuki syndrome type 2	XL (+/- females)
Xp21.1-p11.4	CYBB	CGD	XL
Xp22.12	SH3KBP1	SH3KBP1 (CIIN85) deficiency	XL
Xp22.1-p21.3	POLA1	X-linked reticulate pigmentary disorder	XL
Xp22.2	FANCB	Fanconi anemia type B	XL
Xp22.33	CSF2RA	CSF2RA deficiency	XL
Xq12	MSN	Moesin deficiency	XL
Xq13.1	IL2RG	Gamma chain deficiency (T-B+NK-SCID), CD132 deficiency	XL
Xq21.1	MAGT1	X-linked magnesium EBV and neoplasia	XL
Xq22	ATG4A	Mollaret's meningitis (HSV2)	AD
Xq22.1	BTK	X-linked agammaglobulinemia	XL
Xq25	XIAP	XIAP deficiency (XLP2)	XL
Xq26.3	CD40LG	CD40 ligand (CD154) deficiency	XL
Xq28	ATP6AP1	AtP6AP1 deficiency	XL

(continued)

TABLE E1. (Continued)

1p22.1	GFI1	GFI1 deficiency (SCN2)	AD
Xq28	DKC1	Dyskeratosis congenita	XL
Xq28	G6PD	G6PD deficiency class I	XL
Xq28	TAZ	Barth syndrome (3-methylglutaconicaciduria type II)	XL
Xq28	IRAK1	IRAK1 deficiency	XL
Xq28	IKBKG	Anhidrotic ectodermodyplasia with immunodeficiency	XL

AD, autosomal dominant; ALPS, autoimmune lymphoproliferative; AR, autosomal recessive; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CARMIL2, capping protein regulator and myosin 1 linker 2; CGD, chronic granulomatous disease; CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities and ear abnormalities; CINCA, Chronic infantile neurologic cutaneous articular syndrome; CMC, chronic mucocutaneous candidiasis; DN, dominant negative; GOF, gain of function; HIES, hyper IgE syndrome; HLH, hemophagocytic lymphohistiocytosis; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LOF, loss of function; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MSMD, Mendelian susceptibility to mycobacterial diseases; NK, natural killer; NOMID, Neonatal-onset multisystem inflammatory disease; SCID, severe combined immunodeficiency; SPENCD, Spondyloenchondrodysplasia; TWEAK, TNF-like weak inducer of apoptosis; XL, X-linked.