Letter to the Editor

Application of extensively targeted next-generation sequencing for the diagnosis of primary immunodeficiencies

To the Editor:

Primary immunodeficiencies (PIDs) represent a diverse group of inherited disorders caused by congenital defects of the immune system. The latest International Union of Immunological Societies classification has identified 240 causative genes, and more than 10 new genetic causes of PIDs have been described per year over recent years.[1] A precise molecular diagnosis for patients with PIDs is critical for appropriate management, but a timely and accurate genetic diagnosis in daily clinical practice is difficult. The clinical phenotype can vary in patients with identical genotypes, and more than 1 genotype could produce similar clinical phenotypes. Furthermore, several congenital bone marrow failure syndromes (CBMFSs) can mimic PIDs. For example, patients with Fanconi anemia are reported to have impaired CD8 T-cell and natural killer cell function.[2]

Recent progress in next-generation sequencing (NGS) enables simultaneous sequencing of a massive amount of nucleic acids,[3] and at least 3 studies have reported regarding the clinical application of NGS for the diagnosis of PIDs.[4-6] However, these studies were limited because of incomplete coverage of causative genes and the inability to detect copy number variants (CNVs). In addition, target capture-based NGS enables detection of CNVs, which is occasionally associated with disruption of PID-related genes. Therefore we wished to overcome these limitations by designing a comprehensively targeted sequencing platform that covers 349 causal genes associated with PIDs, CBMFSs, or the 22q11.2 region (Fig 1, *A*).

We studied 97 patients, which included 38 with known PID mutations and 59 without any genetic diagnoses. Genomic DNA was extracted from frozen PBMCs. Patients' characteristics are listed in Table E1 in this article's Online Repository at www.jacionline.org. Written informed consent was obtained from patients or their guardians, and the study was approved by the ethics committee of the Nagoya University Graduate School of Medicine.

A total of 349 genes associated with PIDs, CBMFSs, and the 22q11.2 region were subjected to DNA capture designed by SureDesign (Agilent, Santa Clara, Calif; see Table E2 in this article's Online Repository at www.jacionline.org). PID-related genes were selected on the basis of the 2014 International Union of Immunological Societies classification,[1] the 2014 European Society for Immunodeficiencies meeting (http://esid.org/Working-Parties/Registry/New-ESID-Registry/List-of-diseases-and-genes), and the Resource of Asian Primary Immunodeficiency Diseases (http://web16.kazusa.or.jp/rapid/). CBMFS-related genes included genes associated with Fanconi anemia, dyskeratosis congenita, congenital neutropenia, Shwachman-Diamond syndrome, and chromosome fragility syndromes. In addition to these genes, probes covering 5019 common single nucleotide polymorphisms were included for copy number analysis. The target region included the coding exon plus 10 flanking bases, and boosting was performed with the MaximizePerformance option. As a result, 55,877 probes (2 Mb), covering 99.3% of the target region, were prepared. Target capture, enrichment, and indexing were performed according to the manufacturer's instructions.

Generated libraries were sequenced on a HiSeq 2500 platform (Illumina, San Diego, Calif). The cost of this procedure was approximately $500 US dollars per sample. Copy number analysis was performed by comparing the number of reads covering each exon with unrelated control samples, as previously described.[7]

Putative causative variants were interrogated for 349 candidate genes, following the guidelined published by the American College of Medical Genetics[8]; those variants were considered the causative variants, which were reported to be pathogenic in the literature or were otherwise highly expected to cause the disorders (eg, nonsense, frameshift, and splice site variants). Detected variants were validated by means of Sanger sequencing. Our target sequencing covered 99.1% of the target-coding region with 20 times read coverage (Fig 1, *B*). Our system successfully detected all mutations and CNVs in 38 patients with preceding genetic diagnoses (see Table E3 in this article's Online Repository at www.jacionline.org). Moreover, in 59 patients without genetic diagnoses, we detected 9 diagnostic variants in 8 patients (14%, Table I) affecting the *PIK3CD*, *XIAP* (2 patients each), *RTEL1*, *TERT*, *TYK2*, and 22q11.2 regions.

In patient UPN 64 we detected the 22q11.2 lesion using CNV analysis, which was confirmed by means of fluorescence *in situ* hybridization (Fig 1, *C* and *D*). This patient was a 27-year-old woman who met the European Society for Immunodeficiencies criteria for common variable immunodeficiency (CVID) syndrome. She had no congenital malformation, and family history was unremarkable. At 10 years of age, she began to experience recurrent infections, particularly of the respiratory tract. Laboratory tests revealed hypogammaglobulinemia, and she was subsequently treated with immunoglobulin replacement therapy.

In patient UPN 86 we found a homozygous mutation in *TYK2* (c.1507C>T p.Arg503X). This patient had severe atopic dermatitis, food allergy, and hypereosinophilia with a near-normal IgE level.

Compared with a previous study covering 170 PID-associated genes, our system covered an additional 107 genes associated with PIDs and 30 genes associated with CBMFSs.[4] Furthermore, to improve the performance of CNV detection, we added probes for 45 genes in the 22q11.2 region and 5019 single nucleotide polymorphisms in the entire genome. Although we expanded the target region, our system achieved better sequence coverage compared with a previous study, which established genetic diagnoses in 47 patients. Of note, the previously described assay might miss genetic lesions in 11 of the 47 (23%) patients, including *PIK3CD* (n = 3), *TERT* (n = 2), *RTEL1* (n = 1), *GATA2* (n = 1), and 22q11.2 (n = 4) mutations and deletions, suggesting improved clinical utility of our comprehensively designed target capture.

CVID is the most common PID, representing a heterogeneous group of hypogammaglobulinemias of largely unknown molecular defects. Our system established a genetic diagnosis of 22q11.2 deletion syndrome (22q11.2DS) in a patient with CVID in accordance with a previous study, reporting that a

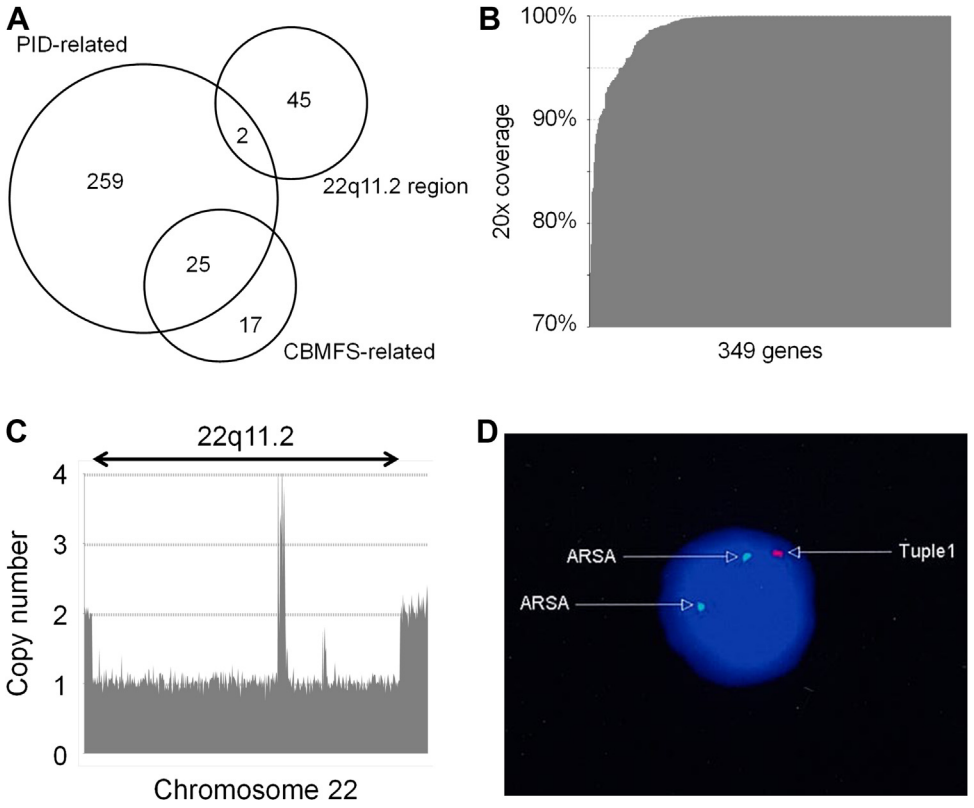

FIG 1. Comprehensively designed target sequencing system. **A,** Venn diagram for gene selection. Two hundred eighty-six genes were associated with PIDs, 42 with CBMFSs, and 47 with the 22q11.2 region. **B,** Read coverage of each gene. The percentage of coverage in each gene with 20× reads is plotted. More than 95% of the target genes are covered with 20× reads in 90% of the coding region. **C,** 22q11.2 deletion detected in patient UPN 64. The estimated copy number of each probe (exon or single nucleotide polymorphism) is plotted along with chromosome 22. **D,** Fluorescence *in situ* hybridization analysis of the same patient. Two ARSA (located near the terminus of 22q) signals *(green)* and one Tuple1 (located in 22q11.2) signal *(red)* were detected in 98% of the observed cells.

TABLE I. Detected mutations in patients without genetic diagnoses

UPN	Clinical diagnosis	Gene	Mutation
47	IgG_2 deficiency	*PIK3CD*	c.3061G>A, p.E1021K
64	CVID	(22q11.2)	Microdeletion
72	DKC	*TERT*	Microdeletion
80	IgG_2 deficiency	*PIK3CD*	c.3061G>A, p.E1021K
86	HES	*TYK2*	c.1507C>T, p.R503X
95	DKC	*RTEL1*	c.2127C>A, p.F709L
		RTEL1	c.102+1G>A, splice site
102	XLP	*XIAP*	c.978-1G>A, splice site
104	HPS	*XIAP*	c.1056+1_4delGTAA, splice site

DKC, Dyskeratosis congenita; *HES*, hypereosinophilic syndrome; *HPS*, hemophagocytic syndrome; *XLP*, X-linked lymphoproliferative disorder.

subgroup of patients with adult 22q11.2DS could have hypogammaglobinemia.[9] Moreover, the incidence of this syndrome is relatively high compared with that of other PIDs. Therefore patients with CVID should always be evaluated for the possibility of 22q11.2DS. In this context our customized design to capture this chromosomal lesion is useful.

Recent studies revealed that newborn screening for T-cell receptor excision circles can efficiently detect infants with severe combined immunodeficiency and complete DiGeorge syndrome (mainly because of 22q11.2DS).[10] Our comprehensive genetic diagnostic system covering virtually all of the PID genes and 22q11.2DS, would provide an effective genetic confirmation test for infants with positive results on T-cell receptor excision circle screening tests, who require precise and rapid genetic diagnoses for appropriate clinical management.

In summary, we developed an NGS-based comprehensive, rapid, and efficient PID diagnostic system that could become a first-line genetic analysis of PID-suspected patients, including infants with positive newborn screening results.

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REFERENCES

1. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol 2014;5:162.
2. Justo GA, Bitencourt MA, Pasquini R, Castelo-Branco MT, Almeida-Oliveira A, Diamond HR, et al. Immune status of Fanconi anemia patients: decrease in T CD8 and CD56dim CD16+ NK lymphocytes. Ann Hematol 2014;93:761-7.
3. Ng SB, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, et al. Targeted capture and massively parallel sequencing of 12 human exomes. Nature 2009;461:272-6.
4. Nijman IJ, van Montfrans JM, Hoogstraat M, Boes ML, van de Corput L, Renner ED, et al. Targeted next-generation sequencing: a novel diagnostic tool for primary immunodeficiencies. J Allergy Clin Immunol 2014;133:529-34.
5. Stoddard JL, Niemela JE, Fleisher TA, Rosenzweig SD. Targeted NGS: a cost-effective approach to molecular diagnosis of PIDs. Front Immunol 2014;5:531.
6. Moens LN, Falk-Sorqvist E, Asplund AC, Bernatowska E, Smith CI, Nilsson M. Diagnostics of primary immunodeficiency diseases: a sequencing capture approach. PLoS One 2014;9:e114901.
7. Sakaguchi H, Okuno Y, Muramatsu H, Yoshida K, Shiraishi Y, Takahashi M, et al. Exome sequencing identifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leukemia. Nat Genet 2013;45:937-41.
8. Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet Med 2008;10:294-300.
9. Bjork AH, Oskarsdottir S, Andersson BA, Friman V. Antibody deficiency in adults with 22q11.2 deletion syndrome. Am J Med Genet A 2012;158A:1934-40.
10. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. JAMA 2014;312:729-38.

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TABLE E1. Patients' characteristics

Clinical diagnosis	Patients with established genetic diagnoses (n = 38)	Patients without genetic diagnosis (n = 59)
SCID	9	1
CGD	6	0
HIGM	4	1
WAS	3	0
22q11.2 DS	3	0
Neutropenia	2	21
DKC	2	4
MSMD	2	0
SDS	2	0
XLA	2	0
WHIMS	1	0
IPEX	1	0
MonoMAC	1	0
CVID	0	9
HLH or XLP	0	8
Periodic fever syndrome	0	4
HHV-6 encephalitis	0	4
IgG_2 deficiency	0	2
HIGE	0	1
Hypereosinophilic syndrome	0	1
Complement deficiency	0	1
Subcutaneous mycosis	0	1
Disseminated BCG infection	0	1

CGD, Chronic granulomatous disease; *DKC*, dyskeratosis congenita; *HIGE*, hyper-IgE syndrome; *HIGM*, hyper-IgM syndrome; *HLH*, hemophagocytic syndrome; *IPEX*, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; *MonoMAC*, autosomal dominant and sporadic monocytopenia and mycobacterial infection; *MSMD*, Mendelian susceptibility to mycobacterial disease; *22q11.2DS*, 22q11.2 deletion syndrome; *SCID*, severe combined immunodeficiency; *SDS*, Shwachman-Diamond syndrome; *WAS*, Wiskott–Aldrich syndrome; *WHIMS*, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; *XLA*, X-linked agammaglobulinemia; *XLP*, X-linked lymphoproliferative disease.

TABLE E2. List of genes in the assay

[PID]	*CD79B*	*IGHG1**	*MSH6**	*SERPING1*	*VPREB1**	*RAD51C**
ACP5	*CD81*	*IGHG2**	*MTHFD1**	*SH3BP2**	*VPS13B**	*SLX4**
ACTB	*CD8A*	*IGHG3**	*MVK*	*SLC29A3**	*WAS*	**[22q11.2]**
ADA	*CEBPE*	*IGHG4**	*MYD88*	*SLC35C1*	*WIPF1**	*AIFM3**
*ADAR**	*CFB**	*IGHM*	*MYO5A**	*SLC37A4*	*ZAP70*	*ARVCF**
AICDA	*CFD*	*IGKC**	*NCF1*	*SLC46A1**	*ZBTB24**	*C22ORF29**
AIRE	*CFH*	*IGLL1*	*NCF2*	*SMARCAL1*	**[PID/CBMFS]**	*C22ORF39**
AK2	*CFHR1**	*IKBKB**	*NCF4**	*SP110*	*ATM*	*CDC45**
AP3B1	*CFHR3**	*IKBKG*	*NFKB2**	*SPINK5*	*BLM*	*CLDN5**
*APC**	*CFHR5**	*IKZF1**	*NFKBIA*	*STAT1*	*C16ORF57**	*CLTCL1**
APOL1	*CFI*	*IL10RA*	*NHEJ1*	*STAT2**	*CTC1**	*COMT**
BLNK	*CFP*	*IL10RB*	*NLRP12*	*STAT3*	*CXCR4*	*CRKL**
*BRCA1**	*CHD7**	*IL12B*	*NLRP3*	*STAT5A**	*DKC1*	*DGCR14**
BTK	*CIITA*	*IL12RB1*	*NOD2*	*STAT5B*	*ELANE*	*DGCR2**
C1QA	*CLCN7**	*IL17F*	*NRAS*	*STIM1*	*G6PC3*	*DGCR6**
C1QB	*CLEC7A**	*IL18*	*ORAI1*	*STK4**	*G6PD*	*DGCR6L**
*C1QC**	*COLEC11**	*IL1RN*	*OSTM1**	*STX11*	*GATA2**	*DGCR8**
C1R	*CORO1A*	*IL21**	*PIK3CD**	*STXBP2*	*GFI1*	*GGTLC3**
C1S	*CR2**	*IL21R**	*PIK3R1**	*TAP1*	*HAX1*	*GNB1L**
C2	*CSF2RA*	*IL2RA*	*PLCG2*	*TAP2*	*NHP2**	*GP1BB**
C3	*CSF3R**	*IL2RG*	*PLDN**	*TAPBP*	*NOP10**	*GSC2**
C4A	*CTSC*	*IL36RN**	*PMS2*	*TAZ**	*POT1**	*HIRA**
C4B	*CYBA*	*IL7R*	*PNP*	*TBK1**	*PRF1*	*KLHL22**
*C4BPA**	*CYBB*	*IRAK4*	*POLE**	*TCF3**	*RTEL1**	*LZTR1**
*C4BPB**	*DCLRE1B**	*IRF8**	*PRKDC*	*TCIRG1**	*SBDS*	*MED15**
C5	*DCLRE1C*	*ISG15**	*PSMB8**	*TCN2**	*SH2D1A*	*MRPL40**
C6	*DNMT3B*	*ITCH**	*PSMB9**	*TERF2IP**	*TERC**	*P2RX6**
C7	*DOCK8*	*ITGB2*	*PSTPIP1*	*THBD**	*TERT**	*PI4KA**
C8A	*ELF4**	*ITK*	*PTPRC*	*TICAM1**	*TINF2**	*PRODH**
C8B	*F12**	*JAGN1**	*RAB27A*	*TIRAP**	*VPS45**	*RANBP1**
*C8G**	*FADD*	*JAK3*	*RAC1**	*TLR3*	*WRAP53**	*RIMBP3**
C9	*FAS*	*KRAS**	*RAC2*	*TMC6*	*XIAP*	*RTN4R**
*CA2**	*FASLG*	*LAMTOR2*	*RAG1*	*TMC8*	**[PID/22q11.2]**	*SCARF2**
*CARD11**	*FCGR1A*	*LCK**	*RAG2*	*TNFRSF11A**	*IL17RA*	*SEPT5**
*CARD14**	*FCGR2A*	*LIG1**	*RASGRP2**	*TNFRSF13B*	*TBX1*	*SERPIND1**
CARD9	*FCGR2B*	*LIG4*	*RB1**	*TNFRSF13C*	**[CBMFS]**	*SLC25A1**
CASP10	*FCGR3A*	*LPIN2*	*RBCK1**	*TNFRSF1A*	*BRCA2**	*SLC7A4**
CASP8	*FCGR3B*	*LRBA**	*RECQL4**	*TNFRSF4**	*BRIP1**	*SNAP29**
*CD177**	*FCGRT*	*LRRC8A**	*RFX5*	*TNFSF12**	*FANCA**	*TANGO2**
CD19	*FCN3*	*LYST*	*RFXANK*	*TP53**	*FANCB**	*THAP7**
CD247	*FERMT3*	*MAGT1**	*RFXAP*	*TRAC**	*FANCC**	*TMEM191B**
*CD27**	*FOXN1*	*MALT1**	*RHOH**	*TRAF3*	*FANCD2**	*TRMT2A**
CD3D	*FOXP3*	*MASP1**	*RMRP**	*TRAF3IP2**	*FANCE**	*TSSK2**
CD3E	*FPR1*	*MASP2*	*RNASEH2A**	*TREX1*	*FANCF**	*TXNRD2**
CD3G	*G6PC**	*MBL2*	*RNASEH2B**	*TTC37**	*FANCG**	*UFD1L**
CD40	*ICOS*	*MCM4**	*RNASEH2C**	*TTC7A**	*FANCI**	*USP41**
CD40LG	*IFNGR1*	*MEFV*	*RNF168**	*TYK2*	*FANCL**	*ZDHHC8**
CD46	*IFNGR2*	*MLPH**	*RORC**	*UNC119**	*FANCM**	
*CD55**	*IGHA1**	*MPO*	*RPSA**	*UNC13D*	*NBN*	
CD59	*IGHA2**	*MRE11A*	*SAMHD1**	*UNC93B1*	*PALB2**	
CD79A	*IGHE**	*MS4A1**	*SEMA3E**	*UNG*	*PIGA*	

*Not included in previous study.

TABLE E3. Mutation, single nucleotide polymorphisms, and CNV detection in patients without genetic diagnoses

Individual ID	Clinical diagnosis	Gene or chromosome	Mutation	Effect	Mutation type	Detected	Comment
3	CGD	*CYBB*	Extensive loss			Yes	Detected by CNV
6	HIGM	*CD40L*	c.500G>A	p.G167E	Missense	Yes	
7	SCN	*ELANE*	c.641G>A	p.G214E	Missense	Yes	
8	SCID	*LIG4*	c.1341G>T	p.W447C	Missense	Yes	
		LIG4	c.1270_1274delAAAAG	p.K424RfsX19	Deletion	Yes	
9	CGD	*CYBB*	c.442C>T	p.Q148X	Nonsense	Yes	
10	SDS	*SBDS*	c.258+2T>C		Splice	Yes	
		SBDS	c.129-1G>A		Splice	Yes	
11	HIGM	*CD40L*	c.617T>C	p.L206P	Missense	Yes	
12	MonoMAC	*GATA2*	c.1042C>T	p.R348X	Nonsense	Yes	
13	MSMD	*STAT1*	c.821G>A	p.R274Q	Missense	Yes	
14	MSMD	*STAT1*	c.821G>A	p.R274Q	Missense	Yes	
16	XLA	*BTK*	c.902_904delACT	p.Y302del	Deletion	Yes	
18	SCN	*ELANE*	c.570G>A		Splice	Yes	Cryptic splice site
19	CGD	*CYBB*	c.271C>T	p.R91X	Nonsense	Yes	
22	WHIMS	*CXCR4*	c.1025C>G	p.S342X	Nonsense	Yes	
23	WAS	*WAS*	c.777+1G>C		Splice	Yes	
26	22q11.2DS	22q11.2	Chromosomal abnormality		Deletion	Yes	Detected by CNV
27	CGD	*CYBB*	c.626A>G	p.H209R	Missense	Yes	
28	SCID	*IL2RG*	c.172C>A	p.P58T	Missense	Yes	
29	CGD	*CYBB*	c.626A>G	p.H209R	Missense	Yes	
30	22q11.2DS	22q11.2	Chromosomal abnormality		Deletion	Yes	Detected by CNV
31	CGD	*CYBB*	c.141+2T>C		Splice	Yes	
32	SCID	*DOCK8*	c.2014G>T	p.E672X	Nonsense	Yes	
33	WAS	*WAS*	c.133-1G>A		Splice	Yes	
35	SCID	*RAG1*	c.1420C>T	p.R474C	Missense	Yes	
		RAG1	c.2195T>C	p.L732P	Missense	Yes	
36	22q11.2DS	22q11.2	Chromosomal abnormality		Deletion	Yes	Detected by CNV
39	SCID	*RAG1*	c.994C>T	p.R332X	Nonsense	Yes	
		RAG1	c.2210G>A	p.R737H	Missense	Yes	
41	HIGM	*CD40LG*	c.767T>C	p.F256S	Missense	Yes	
42	SCID	*RAG1*	c.1420C>T	p.R474C	Missense	Yes	
		RAG1	c.2195T>C	p.L732P	Missense	Yes	
43	WAS	*WAS*	c.360+1G>A		Splice	Yes	
46	SDS	*SBDS*	c.258+2T>C		Splice	Yes	
53	SCID	*JAK3*	c.662T>C	p.L221P	Missense	Yes	
54	SCID	*AK2*	c409.C>T	p.R137X	Nonsense	Yes	
		AK2	c.308G>A	p.R103Q	Missense	Yes	
55	HIGM	*PIK3CD*	c.3061G>A	p.E1021K	Missense	Yes	
61	XLA	*BTK*	c.1750+1G>C		Splice	Yes	
62	SCID	*IL2RG*	Extensive loss			Yes	Detected by CNV
71	IPEX	*FOXP3*	c.1045G>A	p.A349T	Missense	Yes	
85	DKC	*TERT*	c.2045G>A	p.G682D	Missense	Yes	
87	DKC	*DKC1*	c.1058C>T	p.A353V	Missense	Yes	

CGD, Chronic granulomatous disease; *DKC*, dyskeratosis congenita; *HIGM*, hyper-IgM syndrome; *IPEX*, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; *MonoMAC*, autosomal dominant and sporadic monocytopenia and mycobacterial infection; *MSMD*, Mendelian susceptibility to mycobacterial disease; *22q11.2DS*, 22q11.2 deletion syndrome; *SCID*, severe combined immunodeficiency; *SCN*, severe congenital neutropenia; *SDS*, Shwachman-Diamond syndrome; *WAS*, Wiskott-Aldrich syndrome; *WHIMS*, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; *XLA*, X-linked agammaglobulinemia.