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ORIGINAL ARTICLE

Genetic characterization and clinical correlation in a cohort of Turkish patients with immunodeficiency: insights from whole exome sequencing

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ABSTRACT

Background: This retrospective study aims to present the clinical and genetic data of patients diagnosed with immunodeficiency through genetic diagnostic methods. It is essential to investigate the impact of genetic risk factors, such as consanguinity, on immunodeficiency, identify the underlying genetic variants, and assess potential risks. Identifying genetic defects in patients with unknown etiology is critical for accurate diagnosis and effective treatment.

Methodology: Patient histories were evaluated, and detailed clinical findings were recorded. Genetic analyses were performed, identifying eight different variants consistent with autosomal recessive inheritance. The American College of Medical Genetics and Genomics classification criteria were utilized to assess several pathogenic and likely pathogenic variants associated with various immunodeficiency disorders.

Results: Several pathogenic and likely pathogenic variants were identified, related to immunodeficiency disorders such as severe combined ımmunodeficiency due to ADA deficiency and LIG4 syndrome. A significant proportion of patients had a history of consanguinity. The clinical variability observed emphasizes the importance of comprehensive genetic evaluation. Whole exome sequencing (WES) proved effective in uncovering the genetic causes of unexplained immunodeficiency symptoms.

Conclusion: This study highlights the critical role of genetic testing in diagnosing immunodeficiency disorders. WES and next-generation sequencing technologies were particularly useful in identifying the genetic basis of immunodeficiency in patients with unexplained symptoms. Genetic evaluation enables personalized treatment strategies, improving patient management and outcomes. Comprehensive genetic assessments are especially important in populations with high consanguinity rates.

Keywords: Immunodeficiency, consanguinity, whole exome sequencing (WES).

Background

Genetic diagnosis helps identify the origins of diseases, facilitates the development of effective treatment strategies, allows for timely interventions, and enables the assessment of hereditary risks. Today, a variety of technologies and tests have been developed for genetic diagnosis (1). Next-generation sequencing (NGS) technology allows for the rapid sequencing and analysis of many genes simultaneously (2). Whole-exome sequencing (WES) is a technique that targets the protein-coding regions of the genome (3). The human genome consists of 3.2 billion nucleotides and contains approximately 23,500 protein-coding genes. Additionally, there are about 180,000 exons in the human genome; these exons represent about 1% of the genome, totaling approximately 30 million nucleotides (4). The

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human exome contains approximately 85% of known disease-associated variants (3). The emergence of NGS, and particularly WES, has made it possible to diagnose many genetic disorders (5).

Immunodeficiency results from the deficiency or absence of one or more components of the immune system (6). Immunodeficiencies are generally classified into two main categories: primary immunodeficiency and secondary immunodeficiency (7). Primary immunodeficiencies are diseases that arise from monogenic germline mutations in functional genes governing both the innate and adaptive immune systems (8). Secondary immunodeficiency is a condition caused by factors not related to the immune system, resulting in temporary or permanent dysfunction of immune cells or tissues (9).

The aim of this study is to present the variants identified through whole exome sequencing (WES) analysis in immunodeficiency patients, excluding non-genetic causes. The OMIM (Online Mendelian Inheritance in Man) database contains 969 phenotypes related to immunodeficiency, with known molecular bases for these phenotypes. The significance of genetic approaches in immunodeficiency patients is increasing, and studies have shown that 35%-52% of immunodeficiency patients receive a diagnosis through NGS analysis.

In this study, non-genetic etiological causes have been excluded in immunodeficiency patients, emphasizing the importance of genetic evaluation. Additionally, the variability and diversity in the phenotypes of complex diseases associated with immunodeficiency are detailed. The findings support the role of genetic analyses in diagnosing immunodeficiency disorders and provide important insights for clinical practice.

Methods

The aim of this study is to present clinical and genetic data of immunodeficiency patients diagnosed through NGS analysis. This is a single-center cohort retrospective study conducted at the Genetic Disorders Evaluation Center of Istanbul Medipol University. Patient files were reviewed and re-evaluated. The criteria for including patients in this study are as follows:

- Referral to the Genetic Disorders Evaluation Center of Istanbul Medipol University between 2015 and 2024.
- Genetic results obtained through NGS analysis, such as whole exome sequencing (WES).
- Presence of immunodeficiency signs during clinical examination.
- Born as a result of consanguineous marriage.

According to these criteria, a total of nine patients were included in the study. The anamnesis information of the patients was evaluated using the ALIS patient database information system employed by the Genetic Disorders Evaluation Center of Istanbul Medipol University. The onset time and complaints of the patients, consanguinity between the parents, and the existence of similar cases in the family were queried. Detailed clinical examination findings of the patients were reviewed using the patient database information system.

The WES analysis of the patients was performed by contracted institutions. WES was performed with the QIAseq Human Exome Kit and Novaseq 6000 platform (Illumina Inc., San Diego, CA). Alignment to the reference genomes (GRCh38/hg38 for human) was performed using Burrows–Wheeler Aligner (BWA). The identified variants were functionally annotated using ANNOVAR. Variants were reported based on the phenotype of the patients. Attention was focused on variants classified as pathogenic, likely pathogenic, and of uncertain significance. If the gene in which the variant was detected was associated with multiple diseases in the OMIM database, differential diagnosis was conducted based on physical examination and all test results. Possible genetic etiologies responsible for the immunodeficiency signs in the patient were determined.

This study presents the variability of genetic etiology and phenotype in patients with immunodeficiency symptoms. The power of NGS analyses in identifying the etiology of patients with unknown immunodeficiency symptoms was evaluated.

Results

The demographic information, family histories, and clinical findings of the 9 patients included in the study are summarized in Table 1. All patients have a consanguineous marriage. In seven patients, the age of onset of the disease is below 3 years. Five patients have a preliminary diagnosis of primary immunodeficiency. Additionally, various laboratory abnormalities have been detected in most of the patients.

WES analysis was performed on all patients. A total of eight different variants were identified among nine patients. Additionally, the same variant was found in one pair of siblings (Patient numbers: 6 and 7). Variants consistent with the phenotypes of autosomal recessive inheritance are presented in Table 2.

Discussion

This study details the results of genetic analyses in patients exhibiting symptoms of immunodeficiency. The application of genetic testing in patients without an identified organic cause through conventional diagnostic methods represents a significant advancement in the diagnostic process. Particularly, identifying the underlying genetic causes of complex diseases like immunodeficiency allows for a more holistic approach to patient management.

This classification divides genetic variants into five categories: "Pathogenic," "Likely Pathogenic," "Variants of Uncertain Significance (VUS)," "Likely Benign" and "Benign." This framework plays a critical role in genetic counseling processes and disease risk assessments Additionally, the ClinVar and HGMD databases provide systematic presentations of the relationships between genetic variants and diseases, making significant contributions to diagnostic and evaluation processes. The combined use of these three systems allows for a more detailed and comprehensive analysis of genetic variants. This enhances the reliability of the variants and

Table 1. *Summary of patients' demographic, family, and clinical findings.*

Patıent ID	#1	#2	#3	#4	#5	#6	#7	#8	#9
Sex	M	F	M	F	F	F	M	F	M
Age at dıagnosıs (Y)	5	10	7	5	4	12	9	7	23
Age at onset (y)	Congenital	N/A	5 MONTHS	Postnatal/ 15 DAYS	Congenital	5	2	Congenital	2 MONTHS
Consanguıneous marrıge	+	+	+	+	+	+	+	+	+
1st Degree Cousin	N/A	+	N/A	+	+	+	+	N/A	
2nd Degree Cousin	N/A		N/A					N/A	+
3rd Degree Cousin	N/A		N/A					N/A	
From Same Village			N/A					N/A	
Other affected ındıvıduals ın famıly	1 Brother (Ex), 2 Cousin	–	–	–	1 Brother	1 Brother	1 Sister	–	–
Clınıcal features									
Immunodeficiency	+	+	+	+	+	+	+	+	+
Others	Severe Combined Immunodeficiency, Iga ↓, Igm ↓, CD3 ↓, CD4 ↓, CD8 ↓, AST ↑	Primary Immunodeficiency, Lymphopenia, Neutropenia MVC High, Pancreatic Insufficiency, Atrophic Kidney, Abnormal Urinary System, Premature Birth, Short Stature, Growth Retardation, Microcephaly, Developmental Retardation, Joint Hypermobility	Immunodeficiency, Liver Disease, XLP, MAGT_1, STK4, ITK, Coronoin, GATA2, CD27 And MCM4 Deficiency, Regional Seizures, Hepatomegaly, Splenomegaly		Primary Immunodeficiency	Common Variable Immunodeficiency, Combined Immunodeficiency, Lymphoma, CD4 ↓, CD19 ↓, Isohemagglutinin ↑, T And B Cell Proliferation ↓	Primary Immunodeficiencl, Lymphopenia, Iga ↓	Inflammatory bowel disease, ulcerative colitis, eczema, chronic diarrhea, anal abscess, hydronephrosis, short stature	Diabetes mellitus, malabsorption, developmental delay, motor developmental delay, developmental regression

+ / – – Present / Absent; AST – Aspartate Aminotransferase; IgA / IgM – Immunoglobulin A / Immunoglobulin M; ISO (Isohemagglutinin) ; M / F – Male / Female; MAGT1 – Magnesium Transporter 1 gene; MCM4 – Minichromosome Maintenance Complex Component 4, ; MVC (MCV) – Mean Corpuscular Volume; N/A – Not Available ; SCID – Severe Combined Immunodeficiency; STK4 – Serine/Threonine Kinase 4 gene; XLP – X-linked Lymphoproliferative Syndrome; Y – Years.

Table 2. *Genetic results of patients with autosomal recessive inheritance disease.*

Patient ID	Genes	ID	Zygosity	Variant	mutation type	gnomAD frequency (Aggregated - Aggregation of gnomAD exome + genome)	Agmg classification / pathogenicity criteria (ACMG)	Genetic diagnosis	OMIM
#1	ADA	NM_000022.4	Homozygous	c.956_960del (p.Glu319Glyfs*3)	Frameshift	0.0001131	Pathogenic / PVS1, PM3, PM2, PP5	Severe combined immunodeficiency due to ADA deficiency	# 102700
#2	LIG4	NM_206937.2	Homozygous	c.2440C>T (p.Arg814*)	Stop Gain	0.00009549	Pathogenic/ PM3, PVS1, PM2, PS3, PP1, PP5	LIG4 syndrome	# 606593
#3	PEPD	NM_000285.4	Homozygous	c.1359_1361del (p.Glu453del)	In frame /Non Frameshift	0.000004958	VUS /PM2, PM4	Prolidase deficiency	# 170100
#4	ADA	NM_000022.4	Homozygous	c.95+2del	Splice	not found	Likely Pathogenic / PVS1, PM2	Severe combined immunodeficiency due to ADA deficiency, Autosomal recessive; Adenosine deaminase deficiency, partial, Autosomal recessive	# 102700
#5	TYK2	NM_003331.5	Homozygous	c.647del (p.Pro216Argfs*14)	Frameshift	N/A	Pathogenic / PVS1, PM3, PM2, PP5	Immunodeficiency 35	# 611521
#6	RAG2	NM_000536.4	Homozygous	c.104G>C (p.Gly-35Ala)	Missense	0.000003979	Pathogenic / PM3, PM2, PM5, PP3, PM1, PP2, PS3, PP5	Combined cellular and humoral immune defects with granulomas, Omenn syndrome, Severe combined immunodeficiency, B cell-negative	# 233650, # 603554, # 601457
#7	RAG2	NM_000536.4	Homozygous	c.104G>C (p.Gly-35Ala)	Missense	0.000003979	Pathogenic / PM3, PM2, PM5, PP3, PM1, PP2, PS3, PP5	Combined cellular and humoral immune defects with granulomas, Omenn syndrome, Severe combined immunodeficiency, B cell-negative	# 233650, # 603554, # 601457
#8	IL10RA	NM_001558.4	Homozygous	c.133T>G (p.Trp-45Gly)	Missense	not found	Likely Pathogenic / PP3, PM2	Inflammatory bowel disease 28, early onset, autosomal recessive	# 613148
#9	NEUROG3	NM_020999.4	Homozygous	c.10C>T (p.Gln4*)	Stop Gain	not found	Likely Pathogenic / PVS1, PM2	Diarrhea 4, malabsorptive, congenital	# 610370

aids in the development of effective strategies for disease management. Consequently, it provides an effective approach in the fields of genetic counseling and patient monitoring (10).

It is important to note that while this study provides valuable insights into the genetic etiology and clinical features of immunodeficiency in a single-center cohort, it does not fully confirm whether this cohort can be generalized to a larger population or if it could serve as a representative sample for the broader immunodeficiency community. Given that all patients were referred to the Genetic Disorders Evaluation Center at Istanbul Medipol University between 2015 and 2024, the findings may reflect the specific patient population within this particular center and healthcare system. This raises the possibility that findings from this study may not fully represent the immunodeficiency spectrum observed across different regions or healthcare settings. Therefore, further research with multi-center studies or larger cohorts would be beneficial in confirming the broader applicability of the results and understanding the genetic and clinical diversity in the immunodeficiency patient population.

Patient #1 and Patient #4 exhibit similar clinical findings, both showing pathogenic changes in the *ADA* gene. In Patient #1, a homozygous frameshift mutation p.E319Gfs*3 (c.956_960delAAGAG) was identified in the *ADA* (NM_000022.4) gene. This variant is categorized as a "disease-causing mutation" in the HGMD database under accession number CD930882 for "Adenosine deaminase deficiency," and classified as "pathogenic/likely pathogenic" in the ClinVar database under accession number RCV000173618.3 for "Severe combined immunodeficiency (SCID) due to ADA deficiency." According to ACMG criteria (PVS1, PP5, PM2), this variant is classified as "pathogenic"(11).

In Patient #4, a homozygous splice variant c.95+2delT was detected in the *ADA* (NM_000022.4) gene. This variant is classified as “likely pathogenic” based on ACMG criteria (PVS1, PM2, and PP3). Both mutations are consistent with the SCID resulting from “Adenosine deaminase deficiency.”

Severe combined immunodeficiency due to ADA deficiency (OMIM #102700) is an autosomal recessive genetic defect characterized by severe deficiencies in T, B, and NK cells, accounting for 10%-15% of SCID cases. Generally, *ADA* deficiency is diagnosed in infancy, with over 85% of affected individuals showing severe immunodeficiency symptoms, including recurrent opportunistic infections, lymphopenia, and developmental delays within the first six months of life (12). The clinical features of patients with ADA-2 deficiency reported in the literature show similarities with the severe immunodeficiency symptoms exhibited by Patient #1 and Patient #4. This indicates that both patients share common phenotypic characteristics associated with *ADA* deficiency.

Patient #2 presented to our institution with clinical features including primary immunodeficiency, lymphopenia, neutropenia, elevated MVC, pancreatic insufficiency, atrophic kidney, abnormal urinary system, premature birth, short stature, growth delay, microcephaly, developmental delay, and joint hypermobility.

WES analysis revealed a homozygous p.R814X (c.2440C>T) nonsense variant in the *LIG4* (NM_002312.3) gene. This variant is reported in the HGMD database under access number CM014721 as a "disease-causing mutation" for LIG4 syndrome, and in the ClinVar database under rs104894419 as "pathogenic/likely pathogenic" (13). According to ACMG criteria (PVS1, PM2, PP3, and PP5), this variant is classified as "pathogenic." The LIG4 gene is associated with the "LIG4 syndrome" phenotype in the OMIM database (OMIM: #606593).

LIG4 syndrome is characterized by autosomal recessive severe combined immunodeficiency, radi sensitivity, chromosomal instability, pancytopenia, and developmental and growth delays. Some patients with this syndrome have also been reported to exhibit leukemia and dysmorphic facial features (14). In the literature, patients with compound heterozygous variants in the *LIG4* gene have been reported to have a history of chronic infections, microcephaly, growth retardation, leukopenia, anemia, thrombocytopenia, and indications of acute kidney failure (15). Patient #2's clinical findings largely overlap with those reported in the literature for LIG4 syndrome.

Patient #3 is a 7-year-old male from a consanguineous family who presented to our institution at 5 months of age with immunodeficiency, liver disease, X-linked lymphoproliferative syndrome (XLP), deficiencies in MAGT1, STK4, ITK, coronin, GATA2, CD27, and MCM4, regional seizures, hepatomegaly, and splenomegaly. A homozygous c.1359_1361delGGA in-frame deletion was identified in the *PEPD* (NM_000285.3) gene, classified as a “disease-causing mutation” in the HGMD database under access number CD941756 for “Prolidase deficiency” and as “pathogenic” in the ClinVar database under access number rs757386104, with a population frequency (0.00001223, gnomAD) significantly below polymorphism levels(16). Biallelic *PEPD* gene mutations are associated with the “Prolidase deficiency” phenotype in the OMIM database (OMIM: # 170100). The “Prolidase deficiency” phenotype is characterized by cutaneous lesions (painful skin ulcers and telangiectasias), recurrent infections (especially cutaneous and respiratory infections), dysmorphic facial features, developmental delay, intellectual disability, anemia, thrombocytopenia, and hepatosplenomegaly. Clinically, it is heterogeneous among patients, and the severity varies greatly (17). Although the variant identified in this patient is classified as a variant of uncertain significance (VUS) according to current guidelines, the case was included in the study due to the clear phenotypic expression consistent with the associated genotype. The strong genotype-phenotype correlation observed in this patient, along with the clinical features that aligned with the known manifestations of the disorder, supported the inclusion of this case in the study despite the uncertain classification of the variant.

Patient #5 is a 4-year-old female from a consanguineous family who presented to our institution with clinical findings of severe pneumonia and a preliminary diagnosis of primary immunodeficiency. A homozygous

p.P216fs (c.647delC) frameshift mutation was identified in the *TYK2* (NM_003331) gene, reported as “likely pathogenic” in the ClinVar database under access number rs1555719963. In silico analyses predominantly classify this variant as “deleterious.” According to ACMG criteria (PVS1, PM2, PP3, and PP5), it is classified as “pathogenic.” Biallelic *TYK2* mutations are associated with the "Immunodeficiency 35" phenotype (OMIM: 611521), characterized by increased susceptibility to localized or disseminated mycobacterial infections following BCG vaccination, and are a cause of primary immunodeficiency. Some patients also exhibit heightened sensitivity to other intracellular organisms and viral infections. In affected cases, it has been reported that immune system cells are at normal levels, but faulty signaling in specific immunological pathways is observed (18). Additionally, mutations in the *TYK2* gene that affect type 1 interferon levels have been suggested to play a significant role in the severe course of COVID-19 infection (19). In the literature, it has been reported that homozygous and compound heterozygous changes in the *TYK2* gene are associated with disease in patients with recurrent infections (20).

Patient #6 and Patient #7 are two siblings, aged 12 and 9, respectively, who exhibit similar clinical features. Both patients have been found to have a homozygous p.G35A (c.104G>C) missense mutation in the *RAG2* (NM_000536) gene. This mutation is classified in the HGMD database with access number CM141426 as a "disease-causing mutation" for "Hyper-IgM syndrome," and in the ClinVar database with access number rs148508754 as having "Conflicting interpretations of pathogenicity." In silico analyses predominantly characterize the identified variant as "damaging." According to ACMG criteria, the variant is classified as "likely pathogenic" (PM2, PM5, PP2, and PP3). The *RAG2* gene has been associated in the OMIM database with phenotypes such as "Combined cellular and humoral immune defects with granulomas," "Omenn syndrome," and "Severe combined immunodeficiency, B cell-negative" (OMIM: * 179616).

Patient #6 presented with a diagnosis of severe combined immunodeficiency and combined immune deficiency. The patient began experiencing symptoms at the age of 5, including autoimmune hemolytic anemia, recurrent pneumonia, and granulomatous lesions. Two years later, a lymphoma diagnosis was made. Laboratory results showed decreased CD4 levels, decreased CD19 levels, elevated isohemagglutinin levels, and increased T and B cell proliferation.

Patient #7 presented with a preliminary diagnosis of primary immunodeficiency and has shown signs of lymphopenia and IgA deficiency since the age of 2. The clinical features and laboratory results of both patients align with the phenotypes associated with the *RAG2* gene in OMIM, including "Combined cellular and humoral immune defects with granulomas," "Omenn syndrome," and "Severe combined immunodeficiency, B cell-negative."

Considering the autoimmune hemolytic anemia, recurrent pneumonia, and granulomatous lesions observed in Patient #6, their condition aligns closely with the phenotype of Omenn syndrome. Similarly, Patient #7's lymphopenia and IgA deficiency also suggest a potential compatibility with Omenn syndrome. Therefore, both patients may have a likelihood of being associated with Omenn syndrome. The literature frequently reports complex clinical features such as autoimmune conditions, granulomatous lesions, and infections in individuals with RAG2 deficiency, which are similar to the clinical presentations of Patient #6 and Patient #7(21).

Patient #8 is a 7-year-old male from a family with a history of consanguinity, who presented with clinical features of congenital immunodeficiency, inflammatory bowel disease (ulcerative colitis), eczema, an abscess in the anus, and chronic diarrhea. A homozygous p.W45G (c.133T>G) missense mutation was identified in the *IL10RA* (NM_001558.3) gene, which is classified in the HGMD database with access number CM1412394 as a "disease-causing mutation" for "inflammatory bowel disease, very early-onset"(22). According to ACMG criteria, this change is classified as a " likely pathogenic (PM2, PP3), and in silico prediction tools indicate that this variant is "damaging" in variant of likely pathogenicterms of its functional effect. IL10RA gene mutations have been reported to be associated with the phenotype of Inflammatory bowel disease 28, early onset, autosomal recessive in the OMIM database (OMIM: # 613148).

Inflammatory bowel disease (IBD) consists of a group of inflammatory diseases affecting the small and large intestines in genetically susceptible individuals. The main types are ulcerative colitis (UC) and Crohn's disease (CD) (23,24). Most patients experience these diseases during adolescence or adulthood (25). However, they can also manifest in infancy (26). Early-onset inflammatory bowel disease (IBD) can present with a wide range of symptoms, both gastrointestinal and extraintestinal. Gastrointestinal symptoms may include diarrhea with blood and/or mucus, frequent vomiting, growth retardation, and perianal skin tags or fistulas. Systemic and/or extraintestinal symptoms can involve intermittent fevers, arthritis, arthralgia, folliculitis, uveitis, and dermatological manifestations (27).

In a similar study reported in the literature, a child with a different compound heterozygous mutation in the *IL-10RA* gene was also observed to have very early-onset IBD (28). In this study, there are parallels between the gastrointestinal symptoms and extraintestinal signs experienced by the patient and those of Patient #8. Both cases illustrate the broad spectrum of symptoms associated with early-onset IBD. The findings in Patient #8 overlap with similar cases reported in the literature, highlighting the presence of both gastrointestinal and extraintestinal symptoms, which emphasizes the complexity of early-onset IBD. This suggests that *IL10RA* gene mutations play a significant role in the early stages of inflammatory bowel disease.

Patient #9, a 23-year-old male from a consanguineous family, presented with clinical findings that began at 2 months of age, with a preliminary diagnosis of immune deficiency. He also exhibited symptoms of diabetes mellitus, malabsorption, developmental

delay, motor developmental delay, and developmental regression. A homozygous p.Q4* (c.10C>T) stop codon (nonsense) mutation was identified in the *NEUROG3* (NM_020999.3) gene, classified as a "disease-causing mutation" in the HGMD database under access number CM1713951 for "Neonatal diabetes & malabsorptive diarrhoea," and according to ACMG criteria (PVS1, PM2, PP3) as "pathogenic"(29). All in silico prediction tools indicate that this change, which creates an early stop codon, could completely abolish gene expression, yielding "damaging" results. Mutations in the *NEUROG3* gene (OMIM *604882) have been reported in association with congenital malabsorptive diarrhea (OMIM: # 610370), which is characterized by severe malabsorption and the absence of enteroendocrine cells (30). In the literature, a previously reported Turkish case and his cousin were followed for permanent neonatal diabetes mellitus, malabsorption, and neurointestinal dysplasia, where a homozygous c.10C>T variant in the *NEUROG3* gene was identified (29). These findings highlight that the clinical features of Patient #9 are similar to those of other cases with *NEUROG3* mutations in the literature, emphasizing the role of genetic mutation in such complex symptomatology.

Conclusion

This study emphasizes the importance of genetic testing in diagnosing immunodeficiency diseases, highlighting the effectiveness of genetic analyses in identifying the underlying causes of complex diseases. Additionally, this study makes a valuable contribution to the literature by providing more information on the genetic foundations of immunodeficiency diseases and demonstrating that the integration of genetic testing into clinical practice allows for more accurate diagnosis and targeted management of the treatment process.

List of Abbreviations

ACMG	American College of Medical Genetics and Genomics
ADA	Adenosine Deaminase
BWA	Burrows-Wheeler Aligner
CD	Crohn's Disease
CLINVAR	Clinical Variation Database
COVID-19	Coronavirus Disease 2019
GATA2	GATA Binding Protein 2
HGMD	Human Gene Mutation Database
IBD	Inflammatory Bowel Disease
IL10RA	Interleukin 10 Receptor Subunit Alpha
Iga	Immunoglobulin A
Igm	Immunoglobulin M
ITK	IL2-Inducible T-Cell Kinase
LIG4	DNA Ligase 4
MVC	Mean corpuscular volume
MCM4	Minichromosome Maintenance Complex Component 4
NGS	Next-generation sequencing
NEUROG3	Neurogenin 3
OMIM	Online Mendelian Inheritance in Man
PEPD	Peptidase D (Prolidase)
PM	Pathogenic moderate (ACMG criteria)
PP	Pathogenic supporting (ACMG criteria)
PVS	Pathogenic very strong (ACMG criteria)
RAG2	Recombination activating Gene 2
SCID	Severe combined immunodeficiency
STK4	Serine/Threonine Kinase 4
TYK2	Tyrosine Kinase 2
VUS	Variant of uncertain significance
WES	Whole exome sequencing
XLP	X-Linked Lymphoproliferative Syndrome

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