

immunoHIC

genetic diagnosis of immune disorders

PORTFOLIO 2018

www.immunohic.com

About us

Disorders of the immune system refer to a group of diseases in which a part of the immune system is not functional or functions improperly.

To date, more than 450 distinct disorders have been described, each of which is characterized by a specific gene defect. Due to the **complexity** of immunogenetics, our comprehensive approach covers

primary immunodeficiencies (PIDs), encompassing disorders of innate and adaptive immunity, and **immune dysregulation** diseases, including **autoimmune** and **autoinflammatory disorders**, as well as overlapping and syndromic conditions. In addition to their complexity, the prevalence and incidence of these disorders are increasing annually.

WHAT WE OFFER

Our service includes the sequencing, analysis, and interpretation of ~500 different genes related to immune disorders. These genes are grouped within distinct sequencing panels based on the latest recommendations for genetic testing in diseases affecting the immune system and on our expertise on the field. Our high-quality report is what sets us apart.

Service benefits. Our aim is to provide a proper and accurate diagnosis in order to offer the means for personalized medicine, a better **disease understanding**, and improved **patient** management.

immunoHIC, expands the current portfolio of Health in Code, offering a unique and comprehensive genetic diagnostic service for the various disorders that affect the immune system.

OUR COMPANY

immunoHIC follows the model established by Health in Code, which has more than 10 years of experience in the field of genetic diagnosis. Our clinical report, based on genetic data and biomedical interpretation, provides clinicians with detailed scientific content, thus offering the right tools for personalized medicine. We are experts in knowledge management, to which end we use a highly curated database containing information on more than 155,000 individuals reported in the scientific literature as well as data from our patient cohort. The relevance and quality of the information are evaluated by a multidisciplinary team following the recommended best practices for genetic testing and genetic counseling.

Advanced technology

Our laboratory is equipped with the most advanced NGS technology, and our team applies bioinformatics approaches that guarantee the reliability of our results. We can identify disease-related single nucleotide variants (SNVs), small deletions and/or insertions (INDELs), and copy number variations (CNVs). We rely on *nextLIMS*, our state-of-the-art next-generation laboratory management software that controls all end-to-end processes and automatizes sample processing.

Quality

Health in Code's laboratory fulfills the ISO 15189:2013 accreditation for both NGS and Sanger sequencing techniques (ENAC/ILAC assay No. 1211/LE2335). This is the highest quality standard for clinical laboratories, which, in addition to guaranteeing our technical competence, ensures our acceptance at the international level. Our laboratory is a member of the European Molecular Genetics Quality Network (EMQN, EQA UKRAS accredited provider, UK), successfully participates periodically in both technical and interpretative inter-laboratory proficiency testing (EQA schemes), and is qualified to perform high-complexity clinical diagnostic testing.

Multidisciplinary team

We are a multidisciplinary team formed by people with expertise in different areas, including clinicians, geneticists, molecular biologists, bioinformaticians, pharmacists, epidemiologists, and documentalists, among other professionals. Our team also contributes to the development of new areas and services that offer high-quality products in the field of genetic diagnosis and biomedical knowledge management.



DISORDERS OF THE IMMUNE SYSTEM [458 GENES]

Primary Immunodeficiencies (PID) [301 genes]

Primary Antibody Deficiencies (PAD) [41 genes]

Common Variable Immunodeficiency (CVID) [25 genes]
 Agammaglobulinemia [10 genes]
 Hyper-IgM Syndrome (HIGM) [8 genes]

Combined Immunodeficiencies (CID) [37 genes]

Bare Lymphocyte Syndrome (BLS) [13 genes]

Severe Combined Immunodeficiency (SCID) [19 genes]

Severe combined immunodeficiency [T- B+] SCID [11 genes]
 Severe combined immunodeficiency [T- B-] SCID [8 genes]

Syndromes with Combined Immunodeficiency [74 genes]

Dyskeratosis Congenita (DKC) [16 genes]
 Hyper-IgE Syndrome (HIES) [14 genes]
 Ataxia telangiectasia (AT) [1 gene]

Defects in Intrinsic & Innate Immunity [67 genes]

Viral Infections, Predisposition [21 genes]
 Mendelian Susceptibility to Mycobacterial Disease [17 genes]
 Fungal Infections, Predisposition [15 genes]
 Invasive Bacterial Infections, Predisposition [6 genes]
 Cystic fibrosis (CF) [1 gene]

Phagocyte Defects, Congenital [44 genes]

Neutropenia, Syndromic [21 genes]
 Neutropenia, Non-Syndromic [7 genes]
 Chronic Granulomatous Disease (CGD) [6 genes]

Complement System Deficiencies [38 genes]

Atypical Haemolytic Uremic Syndrome (aHUS) [13 genes]
 Disseminated Neisserial Infections [9 genes]
 Systemic Lupus Erythematosus (SLE)-like Syndrome [8 genes]
 Pyogenic Infections, Recurrent [6 genes]
 Hereditary Angioedema (HAE) [2 genes]

Immune Dysregulation Diseases (IDD) [247 genes]

Autoimmune Diseases (AD) [156 genes]

Systemic Lupus Erythematosus (SLE) [69 genes]
 Autoimmune Nephropathy (AN) [52 genes]
 Autoimmune Lymphoproliferative Syndrome (ALPS) [21 genes]
 Autoimmune Enteropathy (AE) [18 genes]
 Autoimmune Polyendocrinopathy (AP) [13 genes]

Autoinflammatory Diseases (AID) [145 genes]

Behçet's Disease [27 genes]
 Inflammatory Bowel Disease (IBD) [26 genes]
 Autoinflammatory Diseases with Recurrent Fever [12 genes]
 Aicardi-Goutières Syndrome (AGS) [7 genes]

Hemophagocytic Lymphohistiocytosis (HLH) [29 genes]

HLH with Epstein Barr Virus Susceptibility [13 genes]

DISORDERS OF THE IMMUNE SYSTEM [458 GENES]

IMMUNE DYSREGULATION DISEASES (IDD) [247 GENES]

Autoimmune Diseases (AD) [156 genes]	Autoinflammatory Diseases (AID) [145 genes]	Hemophagocytic Lymphohistiocytosis (HLH) [29 genes]
Systemic Lupus Erythematosus (SLE) [69 genes]	Behçet's Disease (BD) [27 genes]	HLH with Epstein Barr Virus Susceptibility [13 genes]
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Autoimmune Polyendocrinopathy (AP) [13 genes]		

PRIMARY IMMUNODEFICIENCIES (PID) [301 GENES]

<i>Defects of adaptive immunity</i>				<i>Defects of innate immunity</i>		
Primary Antibody Deficiencies (PAD) [41 genes]	Combined Immunodeficiencies (CID) [37 genes]	Severe Combined Immunodeficiency (SCID) [19 genes]	Syndromes with Combined Immunodeficiency [74 genes]	Defects in Intrinsic & Innate Immunity [67 genes]	Phagocyte Defects, Congenital [44 genes]	Complement System Deficiencies [38 genes]
Common Variable Immunodeficiency (CVID) [25 genes]	Bare Lymphocyte Syndrome (BLS) [13 genes]	T(-)B(+) SCID [11 genes]	Dyskeratosis Congenita (DKC) [16 genes]	Viral Infections, Predisposition [21 genes]	Neutropenia, Syndromic [21 genes]	Atypical Haemolytic Uremic Syndrome (aHUS) [13 genes]
Agammaglobulinemia [10 genes]		T(-)B(-) SCID [8 genes]	Hyper-IgE Syndrome (HIES) [14 genes]	Mendelian Susceptibility to Mycobacterial Disease (MSMD) [17 genes]	Neutropenia, Non-Syndromic [7 genes]	Disseminated Neisserial Infections [9 genes]
Hyper-IgM Syndrome (HIGM) [8 genes]			Ataxia Telangiectasia (AT) [1 gene]	Fungal Infections, Predisposition [15 genes]	Chronic Granulomatous Disease (CGD) [6 genes]	Systemic Lupus Erythematosus (SLE)-like Syndrome [8 genes]
				Invasive Bacterial Infections, Predisposition [6 genes]		Pyogenic Infections, Recurrent [6 genes]
				Cystic Fibrosis (CF) [1 gene]		Hereditary Angioedema (HAE) [2 genes]

Disorders of the Immune System

This comprehensive panel includes more than **450 genes** covering genetic disorders of the immune system. Defects in these genes can cause alterations in immunity. Due to the phenotypic overlap and **complexity** of these disorders, our broad approach to immunogenetics covers two major groups: **Primary Immunodeficiencies (PID)**, including disorders of **innate** and **adaptive** immunity; and **Immune Dysregulation Diseases (IDD)**, encompassing **autoimmune** and **autoinflammatory** disorders. In addition, the panel considers **overlapping** and **syndromic** conditions in these disorders.

Panels included:

> Primary Immunodeficiencies (PID) [301 genes]

> Immune Dysregulation Diseases (IDD) [247 genes]

- Casanova, J. L., & Abel, L. (2007). Primary immunodeficiencies: A field in its infancy. *Science*. <https://doi.org/10.1126/science.1142963>
- Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. *J Autoimmun*. 2009;33(3-4):197-207. doi:10.1016/j.jaut.2009.09.008
- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol*. 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
- Lerner A, Jeremias P, Matthias T. The World Incidence and Prevalencia of Autoimmune Diseases is Increasing. *Int J Celiac Dis*. 2016;3(4):151-155. doi:10.12691/ijcd-3-4-8
- Rezaei N, Bonilla FA, Sullivan KE, De Vries E, Orange JS. An introduction to primary immunodeficiency diseases. *Prim Immunodef Dis Defin Diagnosis Manag*. 2008;1-38. doi:10.1007/978-3-540-78936-9_1

Disorders of the Immune System Panel [458 genes]

ABCB1	CARMIL2	CSF3R	GINS1	ITCH	MYD88	PRKCD	SLC37A4	TMC8
ACD	CASP10	CSK	GUCY2C	ITGAM	MYH9	PRKDC	SLC46A1	TMEM173
ACP5	CASP8	CTC1	HAS2	ITGB2	MYO5A	PRKG1	SLC7A7	TNF
ACTB	CCBE1	CTLA4	HAX1	ITK	MYO5B	PRPS1	SLC9A3	TNFAIP3
ADA	CCDC88B	CTPS1	HELLS	JAGN1	MYSM1	PSEN1	SMARCAL1	TNFRSF11A
ADA2	CCL2	CTSC	HMOX1	JAK1	NBAS	PSENE1	SMARCD2	TNFRSF13B
ADAM17	CCL22	CXCL13	HNF1A	JAK3	NBN	PSMB8	SNX10	TNFRSF13C
ADAR	CCR1	CXCR4	HYOU1	KDM6A	NCF1	PSTPIP1	SP110	TNFRSF1A
ADGRE2	CCR3	CXCR5	ICAM1	KIRREL2	NCF2	PTEN	SPATA5	TNFRSF4
AICDA	CCR5	CYBA	ICOS	KLRC4	NCF4	PTGS2	SPINK5	TNFSF11
AIRE	CCR9	CYBB	IFIH1	KMT2D	NCSTN	PTPN2	SPINT2	TNFSF12
AK2	CD14	DCLRE1B	IFNAR2	KRAS	NEIL1	PTPN22	STAT1	TNFSF13
ANXA11	CD19	DCLRE1C	IFNGR1	LACC1	NEUROG3	PTPRC	STAT2	TNFSF15
AP3B1	CD226	DDX58	IFNGR2	LAMTOR2	NFAT5	PXK	STAT3	TNFSF4
AP3D1	CD247	DGAT1	IGLL1	LAT	NFKB1	RAB27A	STAT4	TNIP1
APOL1	CD27	DGKE	IKBKB	LCK	NFKB2	RAC2	STAT5B	TRAF3
ARID5B	CD3D	DKC1	IKBKG	LIG1	NFKBIA	RAG1	STAT6	TRAF3IP2
ARPC1B	CD3E	DNAJC21	IKZF1	LIG4	NHEJ1	RAG2	STIM1	TREX1
ATG16L1	CD3G	DNASE1	IKZF3	LIMK2	NHP2	RANBP2	STK4	TRIM21
ATG5	CD40	DNASE1L3	IL10	LPIN2	NLR4	RASGRP1	STN1	TRNT1
ATM	CD40LG	DNMT3A	IL10RA	LRBA	NLRP12	RBCK1	STX11	TTC37
ATP6AP1	CD46	DNMT3B	IL10RB	LRRC8A	NLRP3	RECQL4	STXBP2	TTC7A
B2M	CD55	DOCK2	IL12A	LYST	NOD2	REL	TAGAP	TYK2
BANK1	CD59	DOCK8	IL12B	MAGT1	NOP10	RELB	TAP1	UBAC2
BCL10	CD70	E2F1	IL12RB1	MALT1	NPHS1	RFX5	TAP2	UBE2L3
BCL11B	CD79A	EGFR	IL12RB2	MAN2B1	NROB1	RFXANK	TAPBP	UHRF1BP1
BLK	CD79B	ELANE	IL15	MAP3K14	NR4A2	RFXAP	TAZ	UNC119
BLM	CD81	EPCAM	IL15RA	MASP1	NRAS	RHOH	TBK1	UNC13D
BLNK	CD8A	EPG5	IL17F	MASP2	NSMCE3	RMRP	TBX1	UNC93B1
BTK	CDCA7	ERAP1	IL17RA	MBL2	MBL2	AS1	TBX21	UNG
BTNL2	CEBPE	ERCC6L2	IL17RC	MC2R	OAS2	RNASEH2A	TCF3	USB1
C1QA	CFB	ETS1	IL18R1	MC3R	OAS2	RNASEH2B	TCF7	USB1
C1QB	CFD	EXTL3	IL1RN	MCM2	OSTM1	RNASEH2C	TCF7	VPS13B
C1QC	CFH	F12	IL21	MCM4	OTULIN	RNF168	TCIRG1	VPS45
C1QTNF4	CFHR1	FAAP24	IL21R	MCM4	OTULIN	RNF31	TCN2	WAS
C1R	CFHR2	FADD	IL23A	MECP2	PARN	RNU4ATAC	TERC	WDR1
C1S	CFHR3	FAS	IL23R	MEFV	PBX1	RORC	TERT	WIPF1
C2	CFHR4	FASLG	IL2RA	MICA	PDCD1	RP5A	TFRC	WRAP53
C3	CFHR5	FCGR2A	IL2RG	MICB	PDGFR1	RTEL1	TGFB1	XIAP
C4A	CFI	FCGR2B	IL36RN	MKL1	PEPD	SAA1	THBD	XKR6
C4B	CFP	FCGR3A	IL7R	MME	PGM3	SAMD9	THBS1	ZAP70
C5	CFTR	FCN3	INO80	MOGS	PHF11	SAMD9L	THSD7A	ZBTB24
C6	CHD7	FERMT3	IRAK1	MPO	PIK3CD	SAMHD1	TICAM1	ZNF341
C7	CIITA	FOXP3	IRAK4	MRAP	PIK3R1	SATB1	TINF2	
C8A	CLCN7	FOXP3	IRF1	MRC1	PLA2R1	SBDS	TIRAP	
C8B	CLEC16A	FPR1	IRF2BP2	MS4A1	PLOG2	SEC61A1	TLR1	
C8G	CLEC7A	FUT2	IRF3	MSH6	PLEKHM1	SEMA3E	TLR2	
C9	CLPB	G6PC3	IRF5	MSN	PMS2	SERPING1	TLR3	
CALCOCO2	CORO1A	G6PD	IRF7	MST1	PNP	SH2D1A	TLR5	
CARD11	CR2	GATA1	IRF7	MTHFD1	POLE	SKIV2L	TLR7	
CARD14	CSF2RA	GATA2	IRF8	MTHFR	POLE2	SLC11A1	TLR8	
CARD9	CSF2RB	GFI1	IRGM	MTMR3	PRDM1	SLC26A3	TLR9	
			ISG15	MVK	PRF1	SLC35C1	TMC6	

Primary Immunodeficiencies (PID)

Primary immunodeficiency diseases comprise a heterogeneous group of more than **300** distinct hereditary disorders, each of them caused by a different gene defect. Our panel includes those genes that have been associated with a defective **adaptive** or **innate** immune response, either by causing a **specific or combined B or T cell deficiency**, a particular defect of **phagocytes** or **host defences**, or a deficiency of the **complement system**. Clinical manifestations are highly variable; however, most affected individuals share an **increased** vulnerability to **infections** affecting various body systems. The estimated prevalence of PID is about 1 in 1,200 births. The **complexity** and symptom **overlap** found in PID makes **genetic testing** essential for the understanding and diagnosis of the disease and for the management of the patient.

Panels included:

> Primary Antibody Deficiencies
[41 genes]

> Combined Immunodeficiencies
[37 genes]

> Severe Combined
Immunodeficiencies [19 genes]

> Syndromes with Combined
Immunodeficiency [74 genes]

> Defects in Intrinsic and Innate
immunity [67 genes]

> Phagocytes Defects,
Congenital [44 genes]

> Complement System
Deficiencies [38 genes]

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol*. 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
- Bousfiha AA, Jeddane L, Ailal F, et al. Primary immunodeficiency diseases worldwide: More common than generally thought. *J Clin Immunol*. 2013;33(1):1-7. doi:10.1007/s10875-012-9751-7
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- Kobrynski L, Powell RW, Bowen S. Prevalencia and Morbidity of Primary Immunodeficiency Diseases, United States 2001–2007. *J Clin Immunol*. 2014;34(8):954-961. doi:10.1007/s10875-014-0102-8

Primary Immunodeficiencies (PID) Panel [301 genes]

ACD	C8G	CFP	FERMT3	IL2RG	MOGS	PNP	SLC35C1	TLR3
ACP5	C9	CFTR	FOXP1	IL7R	MPO	POLE	SLC37A4	TMC6
ACTB	CARD11	CHD7	FOXP3	INO80	MRC1	POLE2	SLC46A1	TMC8
ADA	CARD9	CIITA	FPR1	IRAK1	MS4A1	PRKDC	SMARCAL1	TNFRSF11A
ADA2	CARMIL2	CLCN7	G6PC3	IRAK4	MSH6	PRPS1	SMARCD2	TNFRSF13B
AICDA	CASP8	CLEC7A	G6PD	IRF2BP2	MSN	PSEN1	SNX10	TNFRSF13C
AIRE	CCBE1	CLPB	GATA1	IRF3	MTHFD1	PSENNEN	SP110	TNFRSF4
AK2	CCL2	CORO1A	GATA2	IRF7	MYD88	PTEN	SPATA5	TNFSF11
AP3B1	CD19	CR2	GF11	IRF8	MYSM1	PTPRC	SPINK5	TNFSF12
AP3D1	CD247	CSF2RA	GIN51	ISG15	NBAS	RAC2	STAT1	TNFSF13
APOL1	CD27	CSF2RB	HAX1	ITGB2	NBN	RAG1	STAT2	TRAF3
ARPC1B	CD3D	CSF3R	HELLS	JAGN1	NCF1	RAG2	STAT3	TRAF3IP2
ATM	CD3E	CTC1	HMOX1	JAK1	NCF2	RANBP2	STAT5B	TRNT1
ATP6AP1	CD3G	CTLA4	HYOU1	JAK3	NCF4	RBCK1	STIM1	TTC37
B2M	CD40	CTPS1	ICOS	KDM6A	NCSTN	REL	STK4	TTC7A
BCL10	CD40LG	CTSC	IFIH1	KMT2D	NFAT5	RELB	STN1	TYK2
BCL11B	CD46	CXCR4	IFNAR2	LAMTOR2	NFKB1	RFX5	TAP1	UNC119
BLM	CD55	CYBA	IFNGR1	LAT	NFKB2	RFXANK	TAP2	UNC93B1
BLNK	CD59	CYBB	IFNGR2	LCK	NFKBIA	RFXAP	TAPBP	UNG
BTK	CD79A	DCLRE1B	IGLL1	LIG1	NHEJ1	RHOH	TAZ	USB1
C1QA	CD79B	DCLRE1C	IKBKB	LIG4	NHP2	RMRP	TBK1	VPS13B
C1QB	CD81	DGKE	IKBKG	LRBA	NOD2	RNF168	TBX1	VPS45
C1QC	CD8A	DKC1	IKZF1	LRRC8A	NOP10	RNF31	TCF3	WAS
C1R	CDCA7	DNAJC21	IL10	LYST	NSMCE3	RNU4ATAC	TCIRG1	WDR1
C1S	CEBPE	DNMT3B	IL10RA	MAGT1	ORAI1	RORC	TCN2	WIPF1
C2	CFB	DOCK2	IL10RB	MALT1	OSTM1	RPSA	TERC	WRAP53
C3	CFD	DOCK8	IL12B	MAP3K14	PARN	RTEL1	TERT	ZAP70
C4A	CFH	ELANE	IL12RB1	MASP1	PGM3	SAMD9	TFRC	ZBTB24
C4B	CFHR1	EPG5	IL17F	MASP2	PHF11	SAMD9L	THBD	ZNF341
C5	CFHR2	ERCC6L2	IL17RA	MBL2	PIK3CD	SBDS	TICAM1	
C6	CFHR3	EXTL3	IL17RC	MC3R	PIK3R1	SEC61A1	TINF2	
C7	CFHR4	F12	IL21	MCM2	PLCG2	SEMA3E	TIRAP	
C8A	CFHR5	FCGR3A	IL21R	MCM4	PLEKHM1	SERPING1	TLR1	
C8B	CFI	FCN3	IL2RA	MKL1	PMS2	SLC11A1	TLR2	

Primary Antibody Deficiencies (PAD)

Primary antibody deficiencies (PAD) are the most common of all primary immune deficiencies (PID), and they are caused by genetic defects that disrupt **B cell development**, B cell differentiation, or **class switch recombination**, ultimately leading to **defective antibody production** and **hypogammaglobulinemia**. PADs include diseases such as agammaglobulinemia, hyper IgM syndrome, common variable immunodeficiency (CVID), and other selective antibody deficiencies (SAD).

Clinical features

- Bacterial infections (respiratory, gastrointestinal, skin)
- Agamma/hypogammaglobulinemia
- Chronic inflammation, autoimmunity can be present
- Onset: infancy (XLA, HIGM); adulthood (CVID)

Prevalence

- 1:500 (IgA deficiency)
- 1:25,000 (CVID)
- 1:200,000 (XLA)
- 1:500,000 (HIGM)
- 55% of all PID

Service benefits and management

- Differential diagnosis: cystic fibrosis, HIV, bronchiectasis, Crohn's disease
- Genetic counselling
- Ig replacement (VIG)
- Antibiotic prophylaxis
- Avoid corticoids in HIGM

Primary Antibody Deficiencies Panel

[41 genes]

<i>AICDA</i>	<i>CD19</i>	<i>CD81</i>	<i>IGLL1</i>	<i>LRBA</i>	<i>NFKB1</i>	<i>PMS2</i>	<i>TNFRSF13C</i>	<i>UNG</i>
<i>ATP6AP1</i>	<i>CD40</i>	<i>CR2</i>	<i>IKZF1</i>	<i>LRRC8A</i>	<i>NFKB2</i>	<i>PTEN</i>	<i>TNFSF12</i>	
<i>BLNK</i>	<i>CD40LG</i>	<i>CTLA4</i>	<i>IL21</i>	<i>MOGS</i>	<i>PIK3CD</i>	<i>SEC61A1</i>	<i>TNFSF13</i>	
<i>BTK</i>	<i>CD79A</i>	<i>CXCR4</i>	<i>INO80</i>	<i>MS4A1</i>	<i>PIK3R1</i>	<i>TCF3</i>	<i>TRNT1</i>	
<i>CARD11</i>	<i>CD79B</i>	<i>ICOS</i>	<i>IRF2BP2</i>	<i>MSH6</i>	<i>PLCG2</i>	<i>TNFRSF13B</i>	<i>TTC37</i>	

Panels included:

> Common Variable Immunodeficiency (CVID) [25 genes]

> Agammaglobulinemia [10 genes]

> Hyper-IgM Syndrome (HIGM) [8 genes]

- Chan H-Y, Yang Y-H, Yu H-H, Chien Y-H, Chiang L-L, Chiang B-L. Clinical characteristics and outcomes of primary antibody deficiency: A 20-year follow-up study. *J Formos Med Assoc.* 2014;113(6):340-348. doi:10.1016/j.jfma.2012.07.005
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- Herriot R, Sewell WAC. Antibody deficiency. *J Clin Pathol.* 2008;61(9):994-1000. doi:10.1136/jcp.2007.051177
- Rezaei N, Bonilla FA, Sullivan KE, De Vries E, Orange JS. An introduction to primary immunodeficiency diseases. *Prim Immunodef Dis Defin Diagnosis, Manag.* 2008:1-38. doi:10.1007/978-3-540-78936-9_1

Common Variable Immunodeficiency (CVID)

Common variable immunodeficiency (CVID) is the most common symptomatic and frequently diagnosed primary immunodeficiency in adults. CVID is an umbrella term that encompasses various genetic disorders that share a common feature: **hypogammaglobulinemia** with **normal** or **low B cell** numbers. The pathophysiology of CVID is caused by a **defective humoral** and cell-mediated response due to B cell differentiation failure, no immunoglobulin production, defective T cell signalling, or an altered B cell-T cell interaction.

Clinical features

- Bacterial infections (respiratory)
- Hypogammaglobulinemia
- Autoimmunity (25% cases)
- Lymphoproliferation and risk of cancer
- Onset: childhood (rare), adulthood (20-40 years)

Prevalence

- 1:10,000 - 1:50,000
- 1:143-1:18,500 IgA deficiency

Service benefits and management

- Differential diagnosis: agammaglobulinemia, SCID, cystic fibrosis, primary ciliary dyskinesia
- Genetic counselling
- Ig replacement (IVIG)
- Antibiotic prophylaxis
- Corticosteroids

Common Variable Immunodeficiency Panel

[25 genes]

ATP6AP1	CR2	ICOS	IRF2BP2	MS4A1	PIK3CD	PTEN	TNFRSF13C	TTC37
CD19	CTLA4	IKZF1	LRBA	NFKB1	PIK3R1	SEC61A1	TNFSF12	
CD81	CXCR4	IL21	MOGS	NFKB2	PLCG2	TNFRSF13B	TRNT1	

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Agammaglobulinemia

Agammaglobulinemia refers to a small group of primary antibody deficiencies characterized by a **severe reduction of all immunoglobulin classes** due to the absence of peripheral B cells. There are at least 8 forms of agammaglobulinemia depending on which gene is defective. However, the common underlying pathological mechanism is a **maturation failure of B lymphocyte** precursors into differentiated B lymphocytes and, ultimately, plasma cells. Hence, immunoglobulins cannot be produced due to the lack of circulating mature B cells. X-linked agammaglobulinemia (XLA), caused by *BTK* mutations, explains most of the cases.

Clinical features

- Bacterial infections
- Agammaglobulinemia
- Onset: neonatal, infancy, childhood

Prevalence

- 1:1,000,000
- 1:100,000 - 1:200,000 (XLA)

Service benefits and management

- Differential diagnosis: CVID, SCID, HIGM, IgA def.
- Genetic counselling
- Ig replacement (IVIG)
- Antibiotic prophylaxis
- Avoid live vaccines

Agammaglobulinemia Panel

[10 genes]

<i>BLNK</i> <i>BTK</i>	<i>CD79A</i>	<i>CD79B</i>	<i>IGHM*</i>	<i>IGKC*</i>	<i>IGLL1</i>	<i>LRRC8A</i>	<i>PIK3R1</i>	<i>TCF3</i>
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* These genes will be sequenced by a complementary technique

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Hyper-IgM Syndrome (HIGM)

Hyper-IgM syndrome (HIGM) is a type of primary antibody deficiency characterized by the **inability** of **B cells** to **switch** from being IgM producing cells to being IgG, IgA, or IgE producing cells (class switch recombination deficiency). As a result, patients have **decreased** levels of immunoglobulin G (**IgG**) or **IgA** and normal to **elevated** levels of **IgM** in blood. Most of reported HIGM cases (70%) are caused by mutations in CD40LG, whereas the remaining 30% are caused by any of the other genes.

Clinical features

- Chronic bacterial Infections
- Elevated IgM in serum
- Lymphoid hyperplasia
- Autoimmunity
- Onset: infancy and childhood, mostly boys

Prevalence

- 1:500,000
- 1:1,000,000 (*AICDA* deficiency)
- 70% (*CD40LG*)

Service benefits and management

- Differential diagnosis: CVID, agammaglobulinemia, CID
- Genetic counselling
- Ig replacement (IVIg)
- Antibiotic prophylaxis
- Avoid corticoids and live vaccines

Hyper-IgM Syndrome Panel

[8 genes]

AICDA

CD40

CD40LG

INO80

MSH6

PIK3R1

PMS2

UNG

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Combined Immunodeficiencies (CID)

Combined immunodeficiencies (CID) are a group of rare and congenital disorders characterized by a critically compromised immune response (not as profound as that found in SCID), which is due to reduced T lymphocyte counts and/or function, with or without defective B lymphocyte function.

Clinical features

- Infections (viral, fungal, bacterial)
- Autoimmunity
- Autoinflammation
- Syndromic features
- Onset: infancy, childhood

Prevalence

- 1 : 75,000 - 1:100,000

Service benefits and management

- Differential diagnosis with SCID
- Genetic counselling
- Bone marrow transplantation
- Gene therapy
- Avoid live vaccines

Combined Immunodeficiencies Panel

[37 genes]

<i>B2M</i>	<i>CASP8</i>	<i>CIITA</i>	<i>IKBKB</i>	<i>MAGT1</i>	<i>RFX5</i>	<i>TAP1</i>	<i>UNC119</i>
<i>BCL10</i>	<i>CD27</i>	<i>CTPS1</i>	<i>IL21</i>	<i>MALT1</i>	<i>RFXANK</i>	<i>TAP2</i>	<i>ZAP70</i>
<i>BCL11B</i>	<i>CD40</i>	<i>DOCK2</i>	<i>IL21R</i>	<i>MAP3K14</i>	<i>RFXAP</i>	<i>TAPBP</i>	
<i>CARD11</i>	<i>CD40LG</i>	<i>DOCK8</i>	<i>LAT</i>	<i>MSN</i>	<i>RHOH</i>	<i>TFRC</i>	
<i>CARMIL2</i>	<i>CD8A</i>	<i>ICOS</i>	<i>LCK</i>	<i>RELB</i>	<i>STK4</i>	<i>TNFRSF4</i>	

Panels included:

- > Bare Lymphocyte Syndrome (BLS) [13 genes]

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Bare Lymphocyte Syndrome (BLS)

Bare lymphocyte syndrome (BLS) is a group of combined immunodeficiencies in which B and T cells do not express the major histocompatibility (HLA) proteins on their surface. There are three types of BLS: BLS I is characterized by low or no expression of HLA class I molecules and a reduced number of functional B and T cells; BLS II is characterized by a reduction or complete loss of HLA class II protein expression on the surface of professional APCs that ultimately leads to a deficit of antibody production, and BLS III is caused by the absence of both HLA class I and class II antigen expression.

Clinical features

- Respiratory tract infections
- Agammaglobulinemia
- BLS II more severe than BLS I
- Onset: infancy, childhood

Prevalence

- BLS I: aprox. 30 cases
- BLS II: aprox. 100 cases

Service benefits and management

- Differential diagnosis: SCID
- Genetic counselling
- Bone marrow transplantation
- Gene therapy

Bare Lymphocyte Syndrome Panel

[13 genes]

<i>B2M</i>	<i>CIITA</i>	<i>MAGT1</i>	<i>RFXANK</i>	<i>TAP1</i>	<i>TAPBP</i>	<i>ZAP70</i>
<i>CD8A</i>	<i>LCK</i>	<i>RFX5</i>	<i>RFXAP</i>	<i>TAP2</i>	<i>UNC119</i>	

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Severe Combined Immunodeficiency (SCID)

SCID represents a group of rare, and potentially **lethal**, primary immunodeficiencies (PIDs) characterized by a **severe defect** in both **T and B lymphocytes**, and in many cases in **natural killer (NK) cells**, which is caused by **mutations** in different genes involved in the **maturation** and function of the T cell, B cell and NK cell lineage.

Clinical features

- Severe life-threatening infections (viral, fungal, bacterial)
- Diarrhoea
- Failure to thrive
- Autoimmunity
- Onset: neonatal, infancy

Prevalence

- 1-9 : 1,000,000
- 40-100 newborns in USA

Service benefits and management

- Differential diagnosis: BLS, agammaglobulinemia
- Genetic counselling
- Bone marrow transplantation
- Gene therapy

Severe Combined Immunodeficiency Panel

[19 genes]

ADA	CD3D	CORO1A	IL2RA	JAK3	PRKDC	RAG2
AK2	CD3E	DCLRE1C	IL2RG	LIG4	PTPRC	
CD247	CD3G	FOXP1	IL7R	NHEJ1	RAG1	

Panels included:

- > Severe Combined Immunodeficiency [T- B+] [11 genes]
- > Severe Combined Immunodeficiency [T- B-] [8 genes]

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol*. 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
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Severe Combined Immunodeficiency [T- B+] (SCID)

This form of SCID is caused by **genetic defects** that result in very low **T lymphocyte counts**, but **normal B lymphocyte levels**. However, **B lymphocyte function** is **impaired** because these B cells have abnormal receptors for growth factors on their cell surfaces. The natural killer lymphocyte compartment may also be affected.

Clinical features

- Severe life-threatening infections (viral, fungal, bacterial)
- Diarrhoea
- Failure to thrive
- Autoimmunity
- Onset: neonatal, infancy

Prevalence

- 1 -9 : 1,000,000
- 40-100 new-borns in USA

Service benefits and management

- Differential diagnosis: BLS, agammaglobulinemia
- Genetic counselling
- Bone marrow transplantation
- Gene therapy

[T- B+] SCID Panel

[11 genes]

<i>CD247</i>	<i>CD3E</i>	<i>CORO1A</i>	<i>IL2RA</i>	<i>IL7R</i>	<i>PTPRC</i>
<i>CD3D</i>	<i>CD3G</i>	<i>FOXP1</i>	<i>IL2RG</i>	<i>JAK3</i>	

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol*. 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
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- Immune deficiency foundation (IDF). Severe Combined Immune Deficiency and Combined Immune Deficiency. <https://primaryimmune.org/about-primary-immunodeficiencies/specific-disease-types/severe-combined-immune-deficiency-and-combined-immune-deficiency>. Accessed April 5, 2018.
- National Human Genome Research Institute (NHGRI). Learning About Severe Combined Immunodeficiency (SCID). <https://www.genome.gov/13014325/learning-about-severe-combined-immunodeficiency-scid/>. Published 2014. Accessed April 5, 2018.
- Rivers, L., & Gaspar, H. B. (2015). Severe combined immunodeficiency: recent developments and guidance on clinical management. *Archives of Disease in Childhood*, 100(7), 667–672. <https://doi.org/10.1136/archdischild-2014-306425>

Severe Combined Immunodeficiency [T- B-] (SCID)

This form of SCID is caused by **genetic defects** that result in the **absence** of **functional** peripheral **T and B lymphocytes**, resulting in recurrent **early onset severe** respiratory viral, bacterial or fungal **infections**, diarrhoea, and **failure to thrive**. The natural killer lymphocyte compartment may also be affected.

Clinical features

- Severe life-threatening infections (viral, fungal, bacterial)
- diarrhoea
- Failure to thrive
- Autoimmunity
- onset: neonatal, infancy

Prevalence

- 1 -9 : 1,000,000
- 40-100 new-borns in USA

Service benefits and management

- Differential diagnosis: BLS, agammaglobulinemia
- Genetic counselling
- Bone marrow transplantation
- Gene therapy

[T- B-] SCID Panel

[8 genes]

ADA

AK2

DCLRE1C

LIG4

NHEJ1

PRKDC

RAG1

RAG2

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol*. 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
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Syndromes with Combined Immunodeficiency

Syndromes with combined immunodeficiency refer to a group of rare and **congenital** disorders characterized by a **compromised response** of the **adaptive immune system**, due to a low T cell and often B cell function, and by **syndromic features, autoimmunity, or inflammation**. More than one body system is usually affected. Examples of syndromes encompassed by this group include **dyskeratosis congenita, hyper-IgE syndrome, Wiskott-Aldrich syndrome, and ataxia-telangiectasia**, among others.

Clinical features

- Recurrent infections
- Autoimmunity
- Inflammation
- Multisystemic
- Aplastic anemia
- Onset: infancy, childhood, adulthood

Prevalence

- 1 :10,000 - 1:1,000,000 (HIES)
- 1:100,000 - 1:1,000,000 (DKC)
- 1:100,000 - 1:1,000,000 (WAS)

Service benefits and management

- Genetic diagnosis and counselling
- Bone marrow transplantation
- Immunosuppressants

Syndromes with Combined Immunodeficiency Panel

[74 genes]

ACD	DCLRE1B	GINS1	MYSM1	PHF11	RNF31	SPATA5	TERC	ZBTB24
ACP5	DKC1	HELLS	NBN	PMS2	RNU4ATAC	SPINK5	TERT	ZNF341
ARPC1B	DNMT3B	IKBKG	NFKBIA	PNP	RTEL1	STAT3	TINF2	
ATM	DOCK2	IL21R	NHP2	POLE	SAMD9	STAT5B	TTC7A	
BLM	DOCK8	KDM6A	NOP10	POLE2	SAMD9L	STIM1	TYK2	
CCBE1	EPG5	KMT2D	NSMCE3	PRPS1	SEMA3E	STK4	USB1	
CDCA7	ERCC6L2	LIG1	ORAI1	RBCK1	SLC46A1	STN1	WAS	
CHD7	EXTL3	MCM4	PARN	RMRP	SMARCAL1	TBX1	WIPF1	
CTC1	FOXP3	MTHFD1	PGM3	RNF168	SP110	TCN2	WRAP53	

Panels included:

> Dyskeratosis Congenita (DKC)
[16 genes]

> Hyper-IgE Syndrome (HIES)
[14 genes]

> Ataxia telangiectasia (AT) [1 gen]

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Immunodeficiencies primarias. *J Clin Immunol.* 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
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Dyskeratosis Congenita (DKC)

Dyskeratosis congenita (DKC) is a **complex** syndrome characterized by **immunodeficiency**, **bone marrow failure**, **somatic abnormalities**, and predisposition to cancer. The **reduced T cell function** results from a **dysfunction of the telomerase complexes**, whose function is to protect the telomeres from degradation. When telomerase complexes do not function correctly, **telomeres** cannot be protected and **degradation** is accelerated. DKC is caused by mutations in the genes encoding the proteins that compose the telomerase and shelterin complexes.

Clinical features

- Recurrent infections
- Nail dystrophy
- Leucoplakia
- Skin pigmentation, grey hair
- Hypogammaglobulinemia
- Cancer predisposition
- Onset: neonatal, infancy, childhood, adolescent, adulthood

Prevalence

- 1 : 100,000 - 1:1,000,000

Service benefits and management

- Genetic diagnosis and counselling
- Anabolic steroids
- Granulocyte stimulation factors
- Bone marrow transplantation

Dyskeratosis Congenita Panel

[16 genes]

<i>ACD</i>	<i>DCLRE1B</i>	<i>NHP2</i>	<i>PARN</i>	<i>SAMD9</i>	<i>STN1</i>	<i>TERT</i>	<i>USB1</i>
<i>CTC1</i>	<i>DKC1</i>	<i>NOP10</i>	<i>RTEL1</i>	<i>SAMD9L</i>	<i>TERC</i>	<i>TINF2</i>	<i>WRAP53</i>

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- Bar, C., Povedano, J. M., Serrano, R., Benitez-Buelga, C., Popkes, M., Formentini, I., ... Blasco, M. A. (2016). Telomerase gene therapy rescues telomere length, bone marrow aplasia, and survival in mice with aplastic anemia. *Blood*, 127(14), 1770–1779. <https://doi.org/10.1182/blood-2015-08-667485>
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- Walne AJ, Bhagat T, Kirwan M, et al. Mutations in the telomere capping complex in bone marrow failure and related syndromes. *Haematologica.* 2013;98(3):334-338. doi:10.3324/haematol.2012.071068

Hyper-IgE Syndrome (HIES)

There are two main forms of hyper-IgE syndromes (HIES) according to the gene defect and mode of inheritance: autosomal dominant (AD-HIES, or Job syndrome), mostly caused by mutations in the *STAT3* gene, which is involved in the maturation of T cells, specifically Th17 cells; and the more severe autosomal recessive form (AR-HIES), which is usually explained by mutations in the *DOCK8* gene, involved in B cell stimulation and in the maintenance of the structure and integrity of T cells and NK cells. However, mutations in other genes explain the less common forms of the disease.

Clinical features

- Respiratory and skin infections
- Eczema
- Elevated IgE levels
- Eosinophilia
- Asthma, allergy, autoimmunity, immunodeficiency (AR-HIES)
- Joint, osseous, dental problems (AD-HIES)
- Onset: neonatal, infancy

Prevalence

- 1:10,000 - 1:100,000 (AD-HIES)
- 1:100,000-1:1,000,000 (AR-HIES)

Service benefits and management

- Genetic diagnosis and counselling
- Bone marrow transplant
- Moisturizing creams
- Antifungals
- Antibiotic prophylaxis
- IVIG therapy

Hyper-IgE Syndrome Panel

[14 genes]

<i>ARPC1B</i>	<i>DOCK8</i>	<i>IL21R</i>	<i>PHF11</i>	<i>STAT3</i>	<i>TYK2</i>	<i>WIPF1</i>
<i>DOCK2</i>	<i>FOXP3</i>	<i>PGM3</i>	<i>SPINK5</i>	<i>STK4</i>	<i>WAS</i>	<i>ZNF341</i>

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Ataxia-telangiectasia (AT)

Ataxia telangiectasia (AT) is a **multisystemic disorder** caused by mutations in the **ATM gene**. *ATM* encodes a protein involved in the **control of cell division by repairing DNA damage**. The ATM protein helps cells to detect damaged or broken DNA strands and coordinates DNA repair by activating specific enzymes, such as p53. **Defects in the ATM gene** lead to a dysfunctional protein, without which, there is **no efficient DNA repair**; therefore, **cells become unstable** and eventually die. **Immune cells** and **cells in the cerebellum** are particularly affected by the loss of a functional ATM protein. Therefore, ataxia and immune deficiency are among the main symptoms of this syndromic condition. In addition, since cells do not respond effectively against DNA damage, **mutations may accumulate in the DNA** and lead to the formation of cancerous tumors.

Clinical features

- Ataxia
- Telangiectasia
- Chorea and myoclonus
- Oculomotor apraxia
- Chronic lung infections
- Increased cancer risk: leukemia and lymphoma
- Onset: Infancy, Childhood

Prevalence

- 1:40.000-100.000

Service benefits and management

- Differential diagnosis: Cerebral palsy, Friedreich ataxia, cogan oculomotor apraxia.
- Genetic counselling
- Physical therapy
- IVIG replacement
- Ionizing radiation and chemotherapy

Ataxia-Telangiectasia Panel

[1 gen]

ATM

• Biton S, Barzilai A, Shiloh Y. The neurological phenotype of ataxia-telangiectasia: solving a persistent puzzle. *DNA Repair (Amst)*. 2008 Jul 1;7(7):1028-38. doi: 10.1016/j.dnarep.2008.03.006. Epub 2008 May 5. Review.

• Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. *DNA Repair (Amst)*. 2004 Aug-Sep;3(8-9):1187-96. Review.

• GeneReviews Ataxia-Telangiectasia. Adam MP, Ardinger HH, Pagon RA, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2018. <https://www.ncbi.nlm.nih.gov/books/NBK26468/>

Defects in Intrinsic & Innate Immunity

Defects in innate and intrinsic immunity are produced by alterations in genes controlling the development, structure, or function of innate immune-related components and cells. Innate immunity is the first line of defence against pathogens, and its alteration results in a varied group of clinical conditions characterized predominantly by increased susceptibility to microbes. These conditions are caused by defects in genes that encode interferons, toll-like receptors, NOD-like receptors, and genes involved in Th1 and Th17 signalling, among other innate immune pathways.

Clinical features

- Severe, recurrent and invasive microbial infections
- Onset: Infancy and adulthood

Prevalence

- Unknown
- ~1.5% of reported PIDs

Service benefits and management

- Genetic diagnosis and counselling
- HSCT
- Recombinant cytokines
- Antimicrobials (treatment & prophylactic)

Defects in Intrinsic & Innate Immunity Panel

[67 genes]

AIRE	CYBB	IL10	IRAK1	MCM2	PSEN1	STAT1	TLR2	TYK2
APOL1	DOCK8	IL10RA	IRAK4	MPO	PSENE1	STAT2	TLR3	UNC93B1
CARD9	FCGR3A	IL10RB	IRF3	MRC1	RANBP2	STAT3	TMC6	ZNF341
CCL2	HMOX1	IL12B	IRF7	MYD88	REL	TBK1	TMC8	
CFTR	IFIH1	IL12RB1	IRF8	NBAS	RORC	TCIRG1	TNFRSF11A	
CLCN7	IFNAR2	IL17F	ISG15	NCSTN	RPSA	TICAM1	TNFSF11	
CLEC7A	IFNGR1	IL17RA	JAK1	OSTM1	SLC11A1	TIRAP	TRAF3	
CXCR4	IFNGR2	IL17RC	MC3R	PLEKHM1	SNX10	TLR1	TRAF3IP2	

Panels included:

- > Viral Infections, Predisposition [21 genes]
- > Fungal Infections, Predisposition [15 genes]
- > Cystic Fibrosis [1 gen]
- > Mendelian Susceptibility to Mycobacterial Disease (MSMD) [17 genes]
- > Invasive Bacterial Infections, Predisposition [6 genes]

- IUIS Scientific Committee. *Primary Immunodeficiency Diseases*. Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6
- Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. *Nat Immunol*. 2015;16(4):343-353. doi:10.1038/ni.3123
- Modell V, Quinn J, Orange J, Notarangelo LD, Modell F. Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network. *Immunol Res*. 2016 Jun;64(3):736-53. doi:10.1007/s12026-016-8784-z.
- Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol*. 2010;125(2 SUPPL. 2):S182-S194. doi:10.1016/j.jaci.2009.07.053

Viral Infections, Predisposition

Predisposition to viral infections comprises PIDs that are caused by defects in antiviral sensing and effector pathways, including Toll-like receptor 3 (TLR-3), type I and III interferons (IFNs), STATs, and interferon-stimulated genes. These pathways are critical for virus recognition and inhibition.

Clinical features

- Herpetic encephalitis (HSE) in childhood
- Susceptibility to CMV, VZV, HPV
- Onset: Infancy, adulthood (rare)

Prevalence

- Rare
- 1-2:500,000 (HSE)

Service benefits and management

- Genetic diagnosis and counselling
- HSCT
- Recombinant IFNs
- Antivirals

Viral Infections, Predisposition Panel

[21 genes]

CCL2	IFIH1	IL10RA	IRF7	STAT2	TLR3	TRAF3
CXCR4	IFNAR2	IL10RB	MCM2	TBK1	TMC6	TYK2
FCGR3A	IL10	IRF3	STAT1	TICAM1	TMC8	UNC93B1

- IUIS Scientific Committee. *Primary Immunodeficiency Diseases*. Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6
- Sancho-Shimizu V, Perez De Diego R, Jouanguy E, Zhang SY, Casanova JL. Inborn errors of anti-viral interferon immunity in humans. *Curr Opin Virol*. 2011;1(6):487-496. doi:10.1016/j.coviro.2011.10.016
- Sullivan, K. E., & Stiehm, E. R. (2014). *Stiehm's Immune Deficiencies*. Elsevier. <https://doi.org/10.1016/C2012-1-01317-3>
- Zhang SY, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis. *Science (80-)*. 2007;317(5844):1522-1527. doi:10.1126/science.1139522

Mendelian Susceptibility to Mycobacterial Disease (MSMD)

Mendelian susceptibility to mycobacterial disease (MSMD) is a PID characterized by genetic defects in the IL-12/ Interferon- γ -dependent signalling pathway, with impairment of the production or the response to IFN- γ . These pathways are critical for granuloma formation and for killing intracellular bacteria.

Clinical features

- Disseminated or recurrent infections with *M. avium*, *M. bovis* BCG, and *M. tuberculosis*
- Persistent, recurrent, or extraintestinal non-typhi salmonellosis, opportunistic infections
- Chronic fever, wasting, hepatosplenomegaly, lymphadenopathy, anaemia
- Onset: infancy, adulthood (rare)

Prevalence

- Rare
- Few families reported

Service benefits and management

- Genetic diagnosis and counselling
- HSCT
- Recombinant IFNs
- Antibiotics

Mendelian Susceptibility to Mycobacterial Disease Panel

[17 genes]

<i>CCL2</i>	<i>IFNGR1</i>	<i>IL12B</i>	<i>IRF8</i>	<i>JAK1</i>	<i>MRC1</i>	<i>SLC11A1</i>	<i>TLR1</i>	<i>TYK2</i>
<i>CYBB</i>	<i>IFNGR2</i>	<i>IL12RB1</i>	<i>ISG15</i>	<i>MC3R</i>	<i>RORC</i>	<i>STAT1</i>	<i>TLR2</i>	

- Bustamante J, Boisson-Dupuis S, Abel L, Casanova J-L. Mendelian susceptibility to mycobacterial disease: Genetic, immunological, and clinical features of inborn errors of IFN- γ immunity. *Semin Immunol.* 2014;26(6):454-470.
- Boisson-Dupuis S, Bustamante J, El-Baghdadi J, et al. Inherited and acquired immunodeficiencies underlying tuberculosis in childhood. *Immunol Rev.* 2015;264(1):103-120. doi:10.1111/imr.12272
- Casanova J-L, Abel L. Genetic Dissection of Immunity to Mycobacteria: The Human Model. *Annu Rev Immunol.* 2002;20(1):581-620. doi:10.1146/annurev.immunol.20.081501.125851
- IUIS Scientific Committee. *Primary Immunodeficiency Diseases.* Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6
- Picard, from Ratcliffe MJH. *Encyclopedia of Immunobiology.* (Ratcliffe MJH, ed.); 2016. <https://www.sciencedirect.com/science/referenceworks/9780080921525>.

Fungal Infections, Predisposition

Predisposition to fungal infections is a PID characterized by defects in genes controlling the sensing and killing of fungi. The affected pathways include the sensors and adaptors C-type lectins, Dectins, CARDs, and Th17-dependent immune effectors.

Clinical features

- Chronic mucocutaneous candidiasis (CMC)
- Invasive fungal infections (CNS candidiasis)
- Onset: infancy, adulthood

Prevalence

- Rare
- 1:100,000 (CMC)

Service benefits and management

- Genetic diagnosis and counselling
- Systemic antifungals

Fungal Infections, Predisposition Panel

[15 genes]

AIRE	CLEC7A	IL12RB1	IL17RA	MPO	RORC	STAT3	ZNF341
CARD9	IL12B	IL17F	IL17RC	REL	STAT1	TRAF3IP2	

- Okada S, Puel A, Casanova J-L, Kobayashi M. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. *Clin Transl Immunol.* 2016;5(12):e114. doi:10.1038/cti.2016.71
- Okada S, Markle JG, Deenick EK, et al. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic RORC mutations. *Science (80-).* 2015;349(6248):606–613. doi:10.1126/science.aaa4282
- Puel A, Cypowyj S, Maródi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol.* 2012 Dec;12(6):616–22. doi: 10.1097/ACI.0b013e328358cc0b
- Romani L. Immunity to fungal infections. *Nat Rev Immunol.* 2004;4(1):11–24. doi:10.1038/nri1255
- Rezaei N, Aghamohammadi A, Notarangelo LD, eds. *Primary Immunodeficiency Diseases.* Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6

Invasive Bacterial Infections, Predisposition

Predisposition to invasive bacterial infections is a PID characterized by defects in genes involved in bacterial sensing and anti-bacterial effector pathways, including the Toll and Toll-IL-1R pathways of cytokine and interferon (IFN) induction. These pathways are important for innate recognition of pyogenic and gram-negative bacteria.

Clinical features

- Pyogenic infections
- Meningitis, arthritis, septicemia
- No fever
- Resistant to other infections
- Onset: infancy

Prevalence

- Rare
- Few families described

Service benefits and management

- Genetic diagnosis and counselling
- Immunoglobulin replacement (IVIG)
- Prophylactic antibiotics

Invasive Bacterial Infections, Predisposition Panel

[6 genes]

HMOX1

IRAK1

IRAK4

MYD88

RPSA

TIRAP

- Casanova J-L, Abel L, Quintana-Murci L. Human TLRs and IL-1Rs in Host Defense: Natural Insights from Evolutionary, Epidemiological, and Clinical Genetics. *Annu Rev Immunol*. 2011;29(1):447-491. doi:10.1146/annurev-immunol-030409-101335
- IUIS Scientific Committee. *Primary Immunodeficiency Diseases*. Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6
- Rezaei N, Aghamohammadi A, Notarangelo LD, eds. *Primary Immunodeficiency Diseases*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6

Cystic fibrosis (CF)

Cystic fibrosis is an **inherited condition** caused by mutations in the **CFTR gene**. This gene encodes a large transmembrane protein that acts as a **channel** for the **transport of chloride ions** through the plasma membrane. Chloride is used to produce sodium chloride, the common salt found in sweat, but is also **important** to control water distribution in tissues, which is necessary **for the production of mucus**. When the CFTR channel is mutated, it cannot regulate the flow of chloride and water across cell membranes. Consequently, mucus-producing cells, such as those covering the hallways of lungs, intestines or the pancreas, produce an **unusually thick and sticky mucus that clogs airways and various ducts**.

Clinical features

- Chronic respiratory problems
- Inflammation, fibrosis and lung cysts
- Recurrent bacterial lung infections
- GI complications (ileus, malnutrition, low insulin),
- Reproductive complications
- Onset: neonatal

Prevalence

- 1 in 2,500 to 31,000

Service benefits and management

- Genetic diagnosis and counseling
- Preventive care
- Prophylactic antibiotics
- Immunizations
- Anti-inflammatory therapy
- CFTR modulators

Cystic Fibrosis Panel

[1 gen]

CFTR

- Gardner J. What you need to know about cystic fibrosis. Nursing. 2007 Jul;37(7):52-5. Review. Citation on PubMed
- Gershman AJ, Mehta AC, Infeld M, Budev MM. Cystic fibrosis in adults: an overview for the internist. Cleve Clin J Med. 2006 Dec;73(12):1065-74. Review. Citation on PubMed
- Accurso FJ. Update in cystic fibrosis 2005. Am J Respir Crit Care Med. 2006 May 1;173(9):944-7. Review. Citation on PubMed or Free article on PubMed Central
- Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med. 2013;368:1963-70.

Phagocyte Defects, Congenital

Clinical conditions resulting from **phagocyte defects** can result from low numbers or impaired function of innate immune cells such as neutrophils, monocytes, macrophages, and dendritic cells. This category includes genes involved in cell development processes, such as proliferation and differentiation, and involved in cell function and motility processes, such as granule production and chemotaxis.

Clinical features

- Infections, disseminated, recurrent
- Poor wound healing
- Susceptibility to myelodysplasia, leukemia, neutropenia
- Onset: infancy

Prevalence

- Rare
- ~10% of all PIDs

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Prophylactic antibacterials
- Immunomodulators
- HSCT

Phagocyte Defects, Congenital Panel

[44 genes]

<i>ACTB</i>	<i>CSF2RA</i>	<i>CYBB</i>	<i>G6PC3</i>	<i>GINS1</i>	<i>LAMTOR2</i>	<i>NCF4</i>	<i>SLC35C1</i>	<i>VPS13B</i>
<i>AP3B1</i>	<i>CSF2RB</i>	<i>DNAJC21</i>	<i>G6PD</i>	<i>HAX1</i>	<i>LYST</i>	<i>NOD2</i>	<i>SLC37A4</i>	<i>VPS45</i>
<i>AP3D1</i>	<i>CSF3R</i>	<i>ELANE</i>	<i>GATA1</i>	<i>HYOU1</i>	<i>MKL1</i>	<i>PGM3</i>	<i>SMARCD2</i>	<i>WAS</i>
<i>CEBPE</i>	<i>CTSC</i>	<i>FERMT3</i>	<i>GATA2</i>	<i>ITGB2</i>	<i>NCF1</i>	<i>RAC2</i>	<i>TAZ</i>	<i>WDR1</i>
<i>CLPB</i>	<i>CYBA</i>	<i>FPR1</i>	<i>GF1</i>	<i>JAGN1</i>	<i>NCF2</i>	<i>SBDS</i>	<i>USB1</i>	

Panels included:

- > Neutropenia, Syndromic [21 genes]
- > Neutropenia, Non-Syndromic [7 genes]
- > Chronic Granulomatous Disease (CGD) [6 genes]

• Andrews T, Sullivan KE. Infections in Patients with Inherited Defects in Phagocytic Function. *Clin Microbiol Rev.* 2003;16(4):597-621. doi:10.1128/CMR.16.4.597-621.2003

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• Murphy K, Weaver C. *Janeway's Immunobiology*; 2017. doi:10.1007/s13398-014-0173-7.2

• Lanini LLS, Prader S, Siler U, Reichenbach J. Modern management of phagocyte defects. *Pediatr Allergy Immunol.* 2017;28(2):124-134. doi:10.1111/pai.12654

Neutropenia, Syndromic

Severe congenital neutropenias are rare paediatric haematological disorders characterized by germline mutations that lead to maturation arrest of granulocytes in the bone marrow. Affected children have an increased risk of infections and leukemic progression. Syndromic conditions present with hematopoietic or extra-hematopoietic manifestations, and affected tissues or organs include the heart (G6PC3 and TAZ), urogenital system (G6PC3), bones and exocrine pancreas (Shwachman-Diamond syndrome), skin (LAMTOR2), and liver (glycogen storage; SLC37A4), among others.

Clinical features

- Infections, disseminated, recurrent
- Poor wound healing
- Extra-hematopoietic manifestations
- Onset: infancy

Prevalence

- Rare

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Prophylactic antibacterials
- G-CSF therapy
- HSCT

Neutropenia, Syndromic Panel

[21 genes]

<i>AP3B1</i>	<i>DNAJC21</i>	<i>GATA2</i>	<i>JAGN1</i>	<i>PGM3</i>	<i>SMARCD2</i>	<i>VPS13B</i>
<i>AP3D1</i>	<i>G6PC3</i>	<i>GINS1</i>	<i>LAMTOR2</i>	<i>SBDS</i>	<i>TAZ</i>	<i>VPS45</i>
<i>CLPB</i>	<i>GATA1</i>	<i>HYOU1</i>	<i>LYST</i>	<i>SLC37A4</i>	<i>USB1</i>	<i>WDR1</i>

• IUIS Scientific Committee. *Primary Immunodeficiency Diseases*. Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6

• Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. *Nat Rev Dis Prim*. 2017;3:17032. doi:10.1038/nrdp.2017.32

Neutropenia, Non-Syndromic

These conditions are characterized by **neutrophil-specific defects** that produce severe **congenital neutropenia (SCN)**. Germline mutations in neutrophil elastase (encoded by *ELANE*) can cause severe congenital neutropenia and cyclic neutropenia, while *HAX1* mutations can produce autosomal recessive congenital neutropenia. Mutations in *CSF3R*, *GFI1*, *WAS*, and *RAC2* produce neutropenia associated with other hematopoietic defects.

Clinical features

- Infections, disseminated, recurrent
- Poor wound healing
- Onset: infancy

Prevalence

- Rare
- Few families described

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Prophylactic antibacterials
- G-CSF therapy
- HSCT

Neutropenia, Non-Syndromic Panel

[7 genes]

CSF3R

ELANE

GFI1

HAX1

MKL1

RAC2

WAS

- Donadieu J, Fenneteau O, Beupain B, Mahlaoui N, Chantelot C. Congenital neutropenia: diagnosis, molecular bases and patient management. *Orphanet J Rare Dis.* 2011;6(1):26. doi:10.1186/1750-1172-6-26
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- Klein C. *Congenital Neutropenia*. Elsevier Inc.; 2014. doi:10.1016/B978-0-12-405546-9.00029-7
- Skokowa J, Dale DC, Touw IP, Zeidler C, Welte K. Severe congenital neutropenias. *Nat Rev Dis Prim.* 2017;3:17032. doi:10.1038/nrdp.2017.32

Chronic Granulomatous Disease (CGD)

Chronic granulomatous disease (CGD) is a disorder of neutrophils, where impaired NADPH oxidase activity is caused by a defect in one of the five protein subunits of the NADPH oxidase complex, resulting in failure to kill certain bacteria and fungi. The proteins of the NADPH oxidase complex are encoded by genes *CYBB*, *CYBA*, *NCF1*, *NCF2*, and *NCF4*. Genetic counselling and specific prognosis are possible after the detection of the disease-causing mutation.

Clinical features

- Infections, disseminated, recurrent
- Colitis
- Onset: infancy to adulthood

Prevalence

- 1:250,000

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- HSCT
- Prophylactic antibacterials / antifungals
- Gene therapy

Chronic Granulomatous Disease Panel

[6 genes]

CYBA *CYBB* *NCF1* *NCF2* *NCF4* *NOD2*

- Åhlin A, Fasth A. Chronic granulomatous disease – conventional treatment vs. hematopoietic stem cell transplantation. *Curr Opin Hematol.* 2015;22(1):41-45. doi:10.1097/MOH.0000000000000097
- Arnold DE, Heimall JR. A Review of Chronic Granulomatous Disease. *Adv Ther.* 2017;34(12):2543-2557. doi:10.1007/s12325-017-0636-2
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- Richardson AM, Moyer AM, Hasadsri L, Abraham RS. Diagnostic Tools for Inborn Errors of Human Immunity (Immunodeficiencies primarias and Immune Dysregulatory Diseases). *Curr Allergy Asthma Rep.* 2018;18(3):19. doi:10.1007/s11882-018-0770-1
- Seger RA. Advances in the diagnosis and treatment of chronic granulomatous disease. *Curr Opin Hematol.* 2011;18(1):36-41. doi:10.1097/MOH.0b013e32834115e7

Complement System Deficiencies

Defects in complement system components increase susceptibility to infection and autoimmune disorders, whereas defects in complement regulatory proteins may lead to serious disorders due to unrestricted activation. The clinical expression of genetically determined deficiencies of the complement system is variable and depends on the role of the deficient component in normal host defence and inflammation. Clinical features are diverse, but cluster into features that align with the known functions of complement: prevention of infection, disposal of apoptotic cells and immune complexes, and protection of endothelial surfaces.

Clinical features

- Infections, disseminated, recurrent
- Inflammation
- Onset: infancy to adulthood

Prevalence

- ~1-10% of PIDs
- 0.03% in the general population

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Vaccination against encapsulated bacteria
- Antibiotics
- Antiinflammatory therapy

Complement System Deficiencies Panel

[38 genes]

<i>C1QA</i>	<i>C2</i>	<i>C6</i>	<i>C9</i>	<i>CFD</i>	<i>CFHR4</i>	<i>F12</i>	<i>MBL2</i>
<i>C1QB</i>	<i>C3</i>	<i>C7</i>	<i>CD46</i>	<i>CFH</i>	<i>CFHR5</i>	<i>FCN3</i>	<i>SERPING1</i>
<i>C1QC</i>	<i>C4A</i>	<i>C8A</i>	<i>CD55</i>	<i>CFHR1</i>	<i>CFI</i>	<i>G6PD</i>	<i>THBD</i>
<i>C1R</i>	<i>C4B</i>	<i>C8B</i>	<i>CD59</i>	<i>CFHR2</i>	<i>CFP</i>	<i>MASP1</i>	
<i>C1S</i>	<i>C5</i>	<i>C8G</i>	<i>CFB</i>	<i>CFHR3</i>	<i>DGKE</i>	<i>MASP2</i>	

Panels included:

- > Atypical Haemolytic Uremic Syndrome (aHUS) [13 genes]
- > SLE-like Syndrome [8 genes]
- > Disseminated Neisserial Infections [9 genes]
- > Pyogenic Infections, Recurrent [6 genes]
- > Hereditary Angioedema (HAE) [2 genes]

- Grumach AS, Kirschfink M. Are complement deficiencies really rare? Overview on prevalence, clinical importance and modern diagnostic approach. *Mol Immunol.* 2014;61(2):110-117. doi:10.1016/j.molimm.2014.06.030
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- Sullivan KE, Stiehm ER. *Stiehm's Immune Deficiencies.* Elsevier; 2014. doi:10.1016/C2012-1-01317-3

Atypical Haemolytic Uremic Syndrome (aHUS)

Complement's Alternative Pathway Deficiency

aHUS is a disease characterized by the triad of **microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury**. aHUS is a consequence of the altered regulation of complement system activation on cell surfaces, leading to endothelial damage mediated by C5 and the complement terminal pathway. Therefore, activating events therefore lead to unrestricted, ongoing complement activity producing **widespread endothelial injury**. Pathogenic mutations include those resulting in loss-of-function in a complement regulatory gene (*CFH*, *CFI*, *CD46*, or *THBD*), gain-of-function in an effector gene (*CFB* or *C3*), or combination of different variants in more than two genes.

Clinical features

- Anaemia, thrombocytopenia and renal disease
- Onset: childhood, adults

Prevalence

- 1:9:100,000

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Plasma Tx
- Eculizumab

Atypical Haemolytic Uremic Syndrome Panel

[13 genes]

C3 CD46	CFB CFH	CFHR1 CFHR2	CFHR3 CFHR4	CFHR5 CFI	G6PD	DGKE	THBD
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Disseminated Neisserial Infections

Complement's Terminal Pathway Deficiency

Defects in genes encoding the terminal components of the complement pathway (**C5 to C9**) predispose for **recurrent systemic neisserial infections** because the clearance of these bacteria is highly dependent on C5b-9-mediated lysis. Additionally, deficiency of **properdin** (encoded by CFP) usually leads to **severe neisserial infections**.

Clinical features

- *Neisseria spp.* infections
- Onset: childhood, adults

Prevalence

- Rare

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Vaccination with polyvalent meningococcal vaccine
- Antibiotics

Disseminated Neisserial Infections Panel

[9 genes]

C5

C6

C7

C8A

C8B

C8G

C9

CFD

CFP

Systemic Lupus Erythematosus (SLE)-like Syndrome

Complement's Classical Pathway Deficiency

The classical pathway of the complement system is activated primarily by immune complexes. The rheumatic diseases seen in complement-deficient patients can result from disordered humoral immunity, since the complement system is important in the generation and expression of an adequate antibody response. It is also partially required for tolerance induction. Rheumatic and autoimmune manifestations occur frequently in C1q- and C3-deficient patients. In addition, some rheumatic disorders may be the consequence of an altered host response to recurrent or chronic viral infections.

Clinical features

- Rheumatic, SLE-like symptoms
- Onset: childhood, adults

Prevalence

- Rare

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Antiinflammatory therapy
- Vaccination
- Prophylactic antibiotics

Systemic Lupus Erythematosus (SLE)-like Syndrome Panel

[8 genes]

C1QA C1QB C1QC C1R C1S C2 C4A C4B

• Casciola-Rosen LA. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med.* 1994;179(4):1317-1330. doi:10.1084/jem.179.4.1317
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Pyogenic Infections, Recurrent

Complement Lectin Pathway Deficiency

Defects in the genes encoding the components of the complement's lectin pathway predispose carriers to recurrent infections. Deficiency of MBL generally increases the risk of any type of infection but is mostly related to an increased frequency of pyogenic infections, including pneumococcal infection and sepsis, particularly in neonates/infants or in patients undergoing immunosuppressive treatment. In addition, primary deficiencies of C3 due to defects in cleavage products of C3 result in severe, recurrent pyogenic infections because of ineffective opsonization of pathogens.

Clinical features

- Recurrent infections
- Severe pyogenic infections
- Onset: childhood, adults

Prevalence

- Unknown
- Few families described

Service benefits and management

- Accurate diagnosis & prognosis
- Complications management
- Targeted treatment
- Vaccination
- Prophylactic antibiotics
- Purified MBL under development

Pyogenic Infections, Recurrent Panel

[6 genes]

C3

CFB

FCN3

MASP1

MASP2

MBL2

Hereditary Angioedema (HAE)

Complement's Classical Pathway Deficiency

Hereditary angioedema is an **inflammatory disorder** characterized by **recurrent and unpredictable attacks of tissue swelling**, which is caused by **mutations** in the ***SERPING1*** (HAE types I, II) or in the ***F12*** gene (HAE type III). ***SERPING1*** encodes the **C1 inhibitor protein**, a key plasma inhibitor of the **Complement, the Fibrinolytic and the Contact Pathways**. In the contact pathway, it blocks the activity of the contact system enzymes, which promote inflammation. When there is not enough functional C1 inhibitor, the **kallikrein-kinin pathway** (Contact pathway) is **affected**; therefore, **bradykinin production is unchecked**. Bradykinin promotes inflammation by increasing the leakage of fluid through the walls of blood vessels into body tissues. **An excess of bradykinin leads to an abnormal tissue accumulation of fluids and episodes of swelling**. In the same way, mutations in the ***F12*** gene will have the same effect, since the **coagulation factor XII** also regulates bradykinin production in the Contact Pathway.

Clinical features

- Tissue swelling
- Digestive problems
- Breathing difficulties
- Erythema marginatum (30%)
- No thrombotic events
- Onset: childhood

Prevalence

- 1:10.000 - 1:150.000

Service benefits and management

- Genetic diagnosis and counselling
- subcutaneous icatibant
- intravenous C1-INH
- Tranexamic acid or danazol
- Corticosteroid, antihistamine or adrenaline treatments are not effective

Hereditary Angioedema Panel

[2 genes]

SERPING1 *F12*

- Nzeako, U. C., Frigas, E. and Tremaine, W. J. (2001) 'Hereditary Angioedema', Archives of Internal Medicine. American Medical Association, 161(20), p. 2417. doi: 10.1001/archinte.161.20.2417.
- Weis, M. (2009) 'Clinical Review of Hereditary Angioedema: Diagnosis and Management', Postgraduate Medicine, 121(6), pp. 113–120. doi: 10.3810/pgm.2009.11.2071.
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Immune Dysregulation Diseases (IDD)

Immune dysregulation diseases comprise a group of disorders that can trigger defective or uncontrolled immune responses and are characterized by **autoimmunity**, episodes of recurrent **autoinflammation**, **dysregulation of lymphocyte homeostasis**, or **hypersensitivity** reactions. These disorders are caused by distinct genetic defects, some of which can also cause immunodeficiency. Prevalence varies between 1:5,000 and 1:100,000 for some diseases. The complexity and symptom overlap makes genetic testing essential for the understanding of the disease, the diagnosis, and anticipation of disease behaviour and patient management.

Panels included:

> Autoimmune Diseases
[156 genes]

> Autoinflammatory Diseases (AID)
[145 genes]

> Hemophagocytic Lymphohistio-
cytosis (HLH) & EBV Susceptibility
[29 genes]

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- Doria A, Zen M, Bettio S, Gatto M, Bassi N, Nalotto L, Ghirardello A, Iaccarino L, Punzi L. Autoinflammation and autoimmunity: bridging the divide. *Autoimmun Rev*. 2012 Nov;12(1):22-30. doi: 10.1016/j.autrev.2012.07.018. Epub 2012 Aug 2.
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Immune Dysregulation Diseases Panel [247 genes]

ABCB1	CALCOCO2	CIITA	GUCY2C	IRF7	MRAP	PDGFRA	SH2D1A	TNF
ACP5	CARD14	CLEC16A	HAS2	IRF8	MST1	PEPD	SKIV2L	TNFAIP3
ADA2	CARD9	CR2	HNF1A	IRGM	MTHFR	PLA2R1	SLC26A3	TNFRSF11A
ADAM17	CARMIL2	CSK	ICAM1	ISG15	MTMR3	PLCG2	SLC7A7	TNFRSF13B
ADAR	CASP10	CTLA4	ICOS	ITCH	MVK	PRDM1	SLC9A3	TNFRSF1A
ADGRE2	CASP8	CTPS1	IFIH1	ITGAM	MYH9	PRF1	SPATA5	TNFRSF4
AIRE	CCDC88B	CXCL13	IKZF1	ITK	MYO5A	PRKCD	SPINT2	TNFSF15
ANXA11	CCL2	CXCR5	IKZF3	KIRREL2	MYO5B	PRKG1	STAT1	TNFSF4
AP3B1	CCL22	CYBB	IL10	KLRC4	NCF1	PSMB8	STAT3	TNIP1
AP3D1	CCR1	DDX58	IL10RA	KRAS	NCF2	PSTPIP1	STAT4	TREX1
APOL1	CCR3	DGAT1	IL10RB	LACC1	NEIL1	PTEN	STAT5B	TRIM21
ARID5B	CCR5	DNASE1	IL12A	LAT	NEUROG3	PTGS2	STAT6	TRNT1
ARPC1B	CCR9	DNASE1L3	IL12B	LCK	NFAT5	PTPN2	STK4	TTC37
ATG16L1	CD14	DNMT3A	IL12RB1	LIMK2	NFKB1	PTPN22	STX11	TTC7A
ATG5	CD226	DOCK8	IL12RB2	LPIN2	NFKBIA	PTPRC	STXBP2	TYK2
BANK1	CD27	E2F1	IL15	LRBA	NLRC4	PXK	TAGAP	UBAC2
BLK	CD40	EGFR	IL15RA	LYST	NLRP12	RAB27A	TAP1	UBE2L3
BTNL2	CD46	EPCAM	IL18R1	MAGT1	NLRP3	RAG2	TBX21	UHRF1BP1
C1QA	CD55	ERAP1	IL1RN	MAN2B1	NOD2	RASGRP1	TCF7	UNC13D
C1QB	CD70	ETS1	IL23A	MASP2	NPHS1	RBCK1	TGFB1	WDR1
C1QC	CFB	FAAP24	IL23R	MBL2	NR0B1	RECQL4	THBD	XIAP
C1QTNF4	CFH	FADD	IL2RA	MC2R	NR4A2	REL	THBS1	XKR6
C1R	CFHR1	FAS	IL36RN	MCM4	NRAS	RNASEH2A	THSD7A	ZAP70
C1S	CFHR2	FASLG	IL7R	MECP2	OAS1	RNASEH2B	TLR5	
C2	CFHR3	FCGR2A	IRAK1	MEFV	OAS2	RNASEH2C	TLR7	
C3	CFHR4	FCGR2B	IRF1	MICA	OTULIN	SAA1	TLR8	
C4A	CFHR5	FOXP3	IRF2BP2	MICB	PBX1	SAMHD1	TLR9	
C4B	CFI	FUT2	IRF5	MME	PDCD1	SATB1	TMEM173	

Autoimmune Diseases (AD)

Disorders of autoimmunity are mainly a consequence of defects during the generation of autoantigen tolerance mechanisms. Genetic burden has been widely related to autoimmune disorders, existing **monogenic forms**, and many genetic risk factors. Our approach focuses on monogenic disorders and also includes genetic alterations that confer **susceptibility** to disease development. Clinical manifestations are frequently characterized by the presence of **autoantibodies**, **tissue damage** without known external cause, or **lymphocyte homeostasis dysregulation**, but they can present with a wide spectrum of symptoms, which makes diagnosis difficult.

Clinical features

- Autoantibodies
- Tissue damage
- Multisystemic
- Lymphocyte homeostasis dysregulation

Prevalence

- ~1:10,000 to 1:100,000 (Monogenic forms)

Service benefits and management

- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation
- Anti-inflammatory therapy
- Immunosuppressors
- Monoclonal antibodies
- Bone marrow transplantation

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Autoimmune Diseases (AD) Panel

[156 genes]

ACP5	C4B	CIITA	FASLG	IRF7	MRAP	PEPD	SKIV2L	TNFRSF13B
ADAR	CARD9	CLEC16A	FCGR2A	IRF8	MTMR3	PLA2R1	SLC26A3	TNFRSF4
AIRE	CASP10	CR2	FCGR2B	ISG15	MYH9	PRDM1	SLC9A3	TNFSF4
APOL1	CASP8	CSK	FOXP3	ITGAM	MYO5B	PRKCD	SPATA5	TNIP1
ARID5B	CCL2	CTLA4	GUCY2C	ITK	NCF1	PRKG1	SPINT2	TREX1
ARPC1B	CCL22	CXCR5	HAS2	KIRREL2	NCF2	PSMB8	STAT1	TRIM21
ATG5	CD226	CYBB	HNF1A	KRAS	NEUROG3	PTEN	STAT3	TTC37
BANK1	CD27	DDX58	ICOS	LAT	NFAT5	PTPN22	STAT4	TYK2
BLK	CD46	DGAT1	IFIH1	LCK	NLRC4	PTPRC	STAT5B	UBE2L3
C1QA	CD55	DNASE1	IKZF1	LRBA	NOD2	PXK	STK4	UHRF1BP1
C1QB	CFB	DNASE1L3	IKZF3	MAN2B1	NPHS1	RAG2	TAP1	XKR6
C1QC	CFH	DNMT3A	IL10	MASP2	NR0B1	RASGRP1	TCF7	ZAP70
C1QTNF4	CFHR1	DOCK8	IL12A	MBL2	NRAS	REL	THBD	
C1R	CFHR2	E2F1	IL12B	MC2R	OAS1	RNASEH2A	THBS1	
C1S	CFHR3	EPCAM	IL2RA	MCM4	OAS2	RNASEH2B	THSD7A	
C2	CFHR4	ETS1	IRAK1	MECP2	PBX1	RNASEH2C	TLR5	
C3	CFHR5	FADD	IRF2BP2	MICB	PDCD1	SAMHD1	TMEM173	
C4A	CFI	FAS	IRF5	MME	PDGFRA	SH2D1A	TNFAIP3	

Panels included:

- > Systemic Lupus Erythematosus (SLE) [69 genes]
- > Autoimmune Nephropathies [52 genes]
- > Autoimmune Lymphoproliferative Syndrome (ALPS) [21 genes]
- > Autoimmune Enteropathy (AE) [18 genes]
- > Autoimmune Polyendocrinopathy (AP) [13 genes]

Systemic Lupus Erythematosus (SLE)

Monogenic forms of lupus are rare and frequently catalogued as **lupus-like** syndromes, which present some clinical features of systemic lupus erythematosus (SLE) and result from T or B **lymphocyte dysregulation, uncontrolled inflammatory responses, or loss of immune tolerance**. Only a few cases of familial lupus have been reported in the literature with disease-causing mutations. Several rare autoimmune disorders can present overlapping phenotypes with SLE. Other immune-related diseases could also increase the predisposition to develop compatible SLE symptomatology. Variant interpretation is **important** in these familial forms, as it can modify patient management and guide genetic counseling.

Clinical features

- Chilblain lupus
- Vasculitis
- Arthralgias
- Chronic autoinflammation
- SLE or lupus-like symptoms
- Multisystemic features

Prevalence

- Unknown (rare monogenic forms).
- ~0.5% of general population (SLE)

Service benefits and management

- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation
- Anti-inflammatory therapy
- Immunosuppressors
- Monoclonal antibodies
- Immunomodulators

Systemic Lupus Erythematosus Panel

[69 genes]

<i>ACP5</i>	<i>C1R</i>	<i>CFH</i>	<i>CTLA4</i>	<i>IFIH1</i>	<i>KRAS</i>	<i>PEPD</i>	<i>SAMHD1</i>	<i>TREX1</i>
<i>ADAR</i>	<i>C1S</i>	<i>CFHR1</i>	<i>CYBB</i>	<i>IKZF1</i>	<i>MAN2B1</i>	<i>PRKCD</i>	<i>STAT1</i>	<i>TRIM21</i>
<i>APOL1</i>	<i>C2</i>	<i>CFHR2</i>	<i>DNASE1</i>	<i>IRAK1</i>	<i>MASP2</i>	<i>PTEN</i>	<i>STAT4</i>	<i>TYK2</i>
<i>BANK1</i>	<i>C3</i>	<i>CFHR3</i>	<i>DNASE1L3</i>	<i>IRF5</i>	<i>MBL2</i>	<i>PTPN22</i>	<i>TLR5</i>	<i>UBE2L3</i>
<i>BLK</i>	<i>C4A</i>	<i>CFHR4</i>	<i>ETS1</i>	<i>IRF7</i>	<i>MICB</i>	<i>RAG2</i>	<i>TMEM173</i>	<i>XKR6</i>
<i>C1QA</i>	<i>C4B</i>	<i>CFHR5</i>	<i>FCGR2A</i>	<i>IRF8</i>	<i>NCF1</i>	<i>RNASEH2A</i>	<i>TNFAIP3</i>	
<i>C1QB</i>	<i>CD46</i>	<i>CFI</i>	<i>FCGR2B</i>	<i>ISG15</i>	<i>NCF2</i>	<i>RNASEH2B</i>	<i>TNFSF4</i>	
<i>C1QC</i>	<i>CFB</i>	<i>CR2</i>	<i>HAS2</i>	<i>ITGAM</i>	<i>PDCD1</i>	<i>RNASEH2C</i>	<i>TNIP1</i>	

- Costa-Reis P, Sullivan KE. Monogenic lupus: it's all new! *Curr Opin Immunol*. 2017 Dec; 49:87-95. doi: 10.1016/j.coi.2017.10.008. Epub 2017 Oct 27.
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Autoimmune Nephropathy (AN)

Autoimmune nephropathies include disorders that are caused by immune responses against kidney structures, producing **glomerulonephritis**, **membranous nephropathy** or **glomerular sclerosis**, among other presentations. There have been described both intrinsic genetic predisposition and external factors in the pathogenesis of AN, including **genetic hereditary defects**, **exposition to proinflammatory agents**, **constitutive activation of complement system**, **autoinflammatory response** and **adaptive immunity alteration**. There are two major autoimmune nephropathies, **primary membranous nephropathy (pMN)**, characterized by subepithelium IgG immune-complexes presence and C3 factor deposits into the peripheral capillary of the glomeruli; and **immunoglobulin A nephropathy (IgAN)** or **Berger's disease**, characterized by IgA deposits affecting the mesangial area of the glomeruli.

Clinical features

- Membranous glomerulopathy
- Nephritis
- Hematuria
- Renal failure
- Immune Complexes deposits
- Autoantibody presence
- C3 nephritic factor positive
- Galactose-deficient IgA

Prevalence

- IgAN. ~1:50,000
- pMN. ~1:100,000

Service benefits and management

- Immunosuppressive and immunomodulators
- Renin-angiotensin blockers
- Corticosteroids
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Nephropathy Panel

[52 genes]

<i>APOL1</i>	<i>C1S</i>	<i>CD46</i>	<i>CFHR5</i>	<i>FAS</i>	<i>ITGAM</i>	<i>NPHS1</i>	<i>STAT4</i>	<i>TNFRSF4</i>
<i>BLK</i>	<i>C3</i>	<i>CFB</i>	<i>CFI</i>	<i>FASLG</i>	<i>KIRREL2</i>	<i>PDGFRA</i>	<i>THBD</i>	<i>TNFSF4</i>
<i>C1QA</i>	<i>C4A</i>	<i>CFH</i>	<i>CTLA4</i>	<i>FCGR2A</i>	<i>MBL2</i>	<i>PLA2R1</i>	<i>THBS1</i>	<i>TNIP1</i>
<i>C1QB</i>	<i>C4B</i>	<i>CFHR1</i>	<i>DNASE1</i>	<i>FCGR2B</i>	<i>MME</i>	<i>PTEN</i>	<i>THSD7A</i>	<i>UBE2L3</i>
<i>C1QC</i>	<i>CARD9</i>	<i>CFHR2</i>	<i>DNASE1L3</i>	<i>HAS2</i>	<i>MTMR3</i>	<i>PTPN22</i>	<i>TLR5</i>	
<i>C1R</i>	<i>CASP10</i>	<i>CFHR3</i>	<i>ETS1</i>	<i>IRF5</i>	<i>MYH9</i>	<i>STAT1</i>	<i>TNFAIP3</i>	

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Autoimmune Lymphoproliferative Syndrome (ALPS)

Autoimmune lymphoproliferative syndrome (ALPS) is a genetic autoimmune disorder that affects the regulation of lymphocyte homeostasis, especially the apoptotic mechanism that occurs during T cell selection. **Genetic testing** is the primary diagnostic method for patients with the following matching criteria: **increased DN T cells + chronic non-malignant, non-infectious lymphadenopathy**. There are other laboratory findings and non-specific abnormalities present in ALPS and ALPS-like patients that increase the complexity of diagnosis.

Clinical features

- Increased DN T cells
- Reduced CD27+ B cells
- Chronic non-malignant, non infectious lymphadenopathy

Prevalence

- Unknown
- At least 650 described pathogenic variants

Service benefits and management

- Bone marrow transplantation
- Immunosuppressor for autoimmunity reactions
- Monoclonal Abs
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Lymphoproliferative Syndrome Panel

[21 genes]

<i>CASP10</i>	<i>FADD</i>	<i>IKZF1</i>	<i>IL2RA</i>	<i>MCM4</i>	<i>NRAS</i>	<i>RASGRP1</i>	<i>SH2D1A</i>
<i>CASP8</i>	<i>FAS</i>	<i>CD27</i>	<i>ITK</i>	<i>LAT</i>	<i>PRKCD</i>	<i>STAT3</i>	<i>TNFAIP3</i>
<i>CTLA4</i>	<i>FASLG</i>	<i>HNF1A</i>	<i>KRAS</i>	<i>LRBA</i>			

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Autoimmune Enteropathy (AE)

Autoimmune enteropathy is a rare autoimmune disorder with early onset, characterized by the presence of circulating autoantibodies directed against gut epithelial cells. A dysfunction of regulatory T cells may lead to autoantibody production, which causes noncoeliac enteropathy (NCE) with villous atrophy. This results in intestinal wall damage. Genetic testing offers differential diagnosis for other overlapping syndromes like congenital diarrhoea and provides alternative options for specific treatments.

Clinical features

- Diarrhoea with malabsorption and anorexia
- Non-coeliac enteropathy villous atrophy
- Auto-Ab against enterocytes and goblet cells
- Lymphocytic infiltration in the cryptic epithelium
- Onset: childhood

Prevalence

- ~1:100,000

Service benefits and management

- Bone marrow transplantation
- Immunosuppressive agents (cyclosporin)
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Enteropathy Panel

[18 genes]

<i>CIITA</i>	<i>CD55</i>	<i>EPCAM</i>	<i>GUCY2C</i>	<i>MYO5B</i>	<i>NFAT5</i>	<i>SKIV2L</i>	<i>SLC9A3</i>	<i>STAT1</i>
<i>CTLA4</i>	<i>DGAT1</i>	<i>FOXP3</i>	<i>IL10</i>	<i>NEUROG3</i>	<i>NLRC4</i>	<i>SLC26A3</i>	<i>SPINT2</i>	<i>TTC37</i>

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Autoimmune Polyendocrinopathy (AP)

Autoimmune polyendocrinopathies are a cluster of endocrine disorders caused by a dysregulated immune response targeted against **endocrine glandular tissue**. Failure of **T cell tolerance** (usually loss of functional T reg cells) prevents the **apoptosis** of autoreactive T cells and, therefore, they are released into circulation. In addition to **IPEX syndrome** (Immune Dysregulation, Polyendocrinopathy, enteropathy, X-linked; caused by **FOXP3** mutations) and **APS-1** (caused by mutations in **AIRE**), there are other syndromes with defects in genes controlling T cell regulation that resemble an IPEX phenotype (IPEX-like syndromes).

Clinical features

- Diabetes mellitus
- Addison disease
- Thyroiditis
- Hepatitis
- Diarrhoea

Prevalence

- ~1:100,000

Service benefits and management

- Bone marrow transplantation
- Immunosuppressive agents
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Polyendocrinopathy Panel

[13 genes]

<i>AIRE</i>	<i>CTLA4</i>	<i>FOXP3</i>	<i>ITCH</i>	<i>MRAP</i>	<i>NROB1</i>	<i>STAT1</i>	<i>STAT3</i>	<i>STAT5B</i>
<i>C/ITA</i>	<i>DOCK8</i>	<i>IL2RA</i>	<i>MC2R</i>					

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Autoinflammatory Diseases (AID)

Autoinflammatory diseases (AID) are immune-related disorders that primarily affect the innate immune system, characterized by recurrent episodes of inflammation. There are monogenic forms of AID with high penetrance, as well as forms that are more prone to be affected by environmental factors, complicating their diagnosis. Both gain-of-function mutations in genes inducing the pro-inflammatory response and loss-of-function mutations in genes controlling the inhibition of the inflammatory response can cause these disorders.

Clinical features

- Inflammation
- Fever
- Arthralgia
- Skin lesions
- Multisystemic

Prevalence

- ~1:5,000 to 1:100,000 (Monogenic forms)

Service benefits and management

- Anti-inflammatory therapy
- Immunosuppressors
- Monoclonal antibodies
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoinflammatory Diseases Panel

[145 genes]

<i>ABCB1</i>	<i>C4A</i>	<i>CD40</i>	<i>DGKE</i>	<i>IL12RB2</i>	<i>LIMK2</i>	<i>NOD2</i>	<i>SERPING1</i>	<i>TNFRSF1A</i>
<i>ADA2</i>	<i>C4B</i>	<i>CD46</i>	<i>EGFR</i>	<i>IL15</i>	<i>LPIN2</i>	<i>NR4A2</i>	<i>SLC9A3</i>	<i>TNFSF15</i>
<i>ADAM17</i>	<i>C5</i>	<i>CD55</i>	<i>ERAP1</i>	<i>IL15RA</i>	<i>MASP1</i>	<i>OAS1</i>	<i>STAT1</i>	<i>TREX1</i>
<i>ADAR</i>	<i>C6</i>	<i>CD59</i>	<i>F12</i>	<i>IL18R1</i>	<i>MASP2</i>	<i>OTULIN</i>	<i>STAT3</i>	<i>TRNT1</i>
<i>ADGRE2</i>	<i>C7</i>	<i>CFB</i>	<i>FAS</i>	<i>IL1RN</i>	<i>MBL2</i>	<i>PLCG2</i>	<i>STAT4</i>	<i>TTC7A</i>
<i>AIRE</i>	<i>C8A</i>	<i>CFD</i>	<i>FASLG</i>	<i>IL23A</i>	<i>MEFV</i>	<i>PSMB8</i>	<i>STAT6</i>	<i>UBAC2</i>
<i>ANXA11</i>	<i>C8B</i>	<i>CFH</i>	<i>FCN3</i>	<i>IL23R</i>	<i>MICA</i>	<i>PSTPIP1</i>	<i>TAGAP</i>	<i>UBE2L3</i>
<i>ARPC1B</i>	<i>C8G</i>	<i>CFHR1</i>	<i>FOXP3</i>	<i>IL2RA</i>	<i>MST1</i>	<i>PTGS2</i>	<i>TAP1</i>	<i>WDR1</i>
<i>ATG16L1</i>	<i>C9</i>	<i>CFHR2</i>	<i>FUT2</i>	<i>IL36RN</i>	<i>MTHFR</i>	<i>PTPN2</i>	<i>TGFB1</i>	<i>XIAP</i>
<i>BTNL2</i>	<i>CALCOCO2</i>	<i>CFHR3</i>	<i>GUCY2C</i>	<i>IL7R</i>	<i>MVK</i>	<i>PTPN22</i>	<i>THBD</i>	
<i>C1QA</i>	<i>CARD14</i>	<i>CFHR4</i>	<i>ICAM1</i>	<i>IRF1</i>	<i>NCF1</i>	<i>RBCK1</i>	<i>TLR7</i>	
<i>C1QB</i>	<i>CCDC88B</i>	<i>CFHR5</i>	<i>IFIH1</i>	<i>IRF2BP2</i>	<i>NEIL1</i>	<i>RNASEH2A</i>	<i>TLR8</i>	
<i>C1QC</i>	<i>CCR1</i>	<i>CFI</i>	<i>IL10</i>	<i>IRF5</i>	<i>NFKB1</i>	<i>RNASEH2B</i>	<i>TLR9</i>	
<i>C1R</i>	<i>CCR3</i>	<i>CFP</i>	<i>IL10RA</i>	<i>IRF8</i>	<i>NFKBIA</i>	<i>RNASEH2C</i>	<i>TMEM173</i>	
<i>C1S</i>	<i>CCR5</i>	<i>CTLA4</i>	<i>IL10RB</i>	<i>IRGM</i>	<i>NLRC4</i>	<i>SAA1</i>	<i>TNF</i>	
<i>C2</i>	<i>CCR9</i>	<i>CXCL13</i>	<i>IL12A</i>	<i>KLRC4</i>	<i>NLRP12</i>	<i>SAMHD1</i>	<i>TNFAIP3</i>	
<i>C3</i>	<i>CD14</i>	<i>CXCR5</i>	<i>IL12RB1</i>	<i>LACC1</i>	<i>NLRP3</i>	<i>SATB1</i>	<i>TNFRSF11A</i>	

Panels included:

- > Behcet Disease (BD) [27 genes]
- > Inflammatory Bowel Disease (IBD) [26 genes]
- > Autoinflammatory Diseases with Recurrent Fever [12 genes]
- > Aicardi-Goutières Syndrome (AGS) [7 genes]

• IUIS Scientific Committee. Primary Immunodeficiency Diseases. Vol 118. (Rezaei N, Aghamohammadi A, Notarangelo LD, eds.). Berlin, Heidelberg: Springer Berlin Heidelberg; 2017. doi:10.1007/978-3-662-52909-6

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Behçet's disease (BD)

Behçet disease (BD) is a chronic inflammatory disease characterized by common manifestations that include **uveitis**, **refractory oral and genital ulcers**, skin lesions and other alterations that may affect the **gastrointestinal tract**, **CNS**, **vasculature**, **joints**, **kidney** or **lung**. There is a **positive family history** in more than **30%** of the families affected by BD. Although there exists an association between EB and HLA-B haplotypes, this has been only described in less than 20% of cases, suggesting the involvement of other genetic factors. In addition to predisposing genetic polymorphisms, **monogenic forms** have been described associated to genes like *TNFAIP3*, *NLRP3*, *NLRC4*, *NOD2* or *MEFV*, taking the name of **Behçet's-like** phenotype in cases of autoinflammatory diseases with overlapping symptoms of BD. Defects in genes associated to BD would affect the production of IFN, IL-7, TNF, inflammasome generation and other proinflammatory pathways.

Clinical features

- Oral ulcers
- Genital ulcers
- Uveitis
- Skin lesions
- Vasculitis
- CNS alterations
- arthritis
- Increase of circulating proinflammatory cytokines

Prevalence

- 1-10:100.000
- ~1:1.000 (Turkish population)

Service benefits and management

- Immunomodulators
- Antiinflammatories
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Behçet Disease Panel

[27 genes]

<i>CCR1</i>	<i>ERAP1</i>	<i>FUT2</i>	<i>IL12A</i>	<i>IRAK1</i>	<i>KLRC4</i>	<i>MICA</i>	<i>NLRP3</i>	<i>TNFAIP3</i>
<i>CCR3</i>	<i>FAS</i>	<i>ICAM1</i>	<i>IL12RB2</i>	<i>IRAK4</i>	<i>LIMK2</i>	<i>NEIL1</i>	<i>NOD2</i>	<i>TNFRSF1A</i>
<i>DCLRE1C</i>	<i>FASLG</i>	<i>IL10</i>	<i>IL23R</i>	<i>IRF8</i>	<i>MEFV</i>	<i>NLRC4</i>	<i>STAT4</i>	<i>UBAC2</i>

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Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a heterogeneous group of chronic inflammatory disorders affecting the gastrointestinal tract. **There are three main phenotypes that include Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU).** Defects of the gut microbiome, environmental factors, and immunological and genetic defects (Th cell dysregulation, impaired autophagy, or chronic inflammatory signalling) are associated with IBD development. IBD usually occurs in young adults, but cases with childhood and neonatal onset are frequently characterized by a more severe phenotype. It is estimated that 25%-30% of pediatric IBD patients have a positive family history, supporting the indication for genetic testing. Our approach focuses on **monogenic disorders** and also includes genetic alterations that confer **susceptibility** for disease development.

Clinical features

- Villous atrophy
- Diarrhoea
- Bowel inflammation
- Mucosal eosinophilia
- Multisystemic abnormalities

Prevalence

- Unknown for monogenic forms
- ~1:1,000 (CD)
- ~1:1,000 (CU)

Service benefits and management

- Monoclonal antibodies against IL-12
- Immunomodulators
- Anti-inflammatory drugs
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Inflammatory Bowel Disease Panel

[26 genes]

<i>ABCB1</i>	<i>ARPC1B</i>	<i>EGFR</i>	<i>IL10</i>	<i>IL23R</i>	<i>MST1</i>	<i>PTPN2</i>	<i>SPINT2</i>	<i>TTC7A</i>
<i>ADAM17</i>	<i>CALCOCO2</i>	<i>EPCAM</i>	<i>IL10RA</i>	<i>IRF5</i>	<i>NOD2</i>	<i>PTPN22</i>	<i>STAT3</i>	<i>XIAP</i>
<i>ATG16L1</i>	<i>CCDC88B</i>	<i>GUCY2C</i>	<i>IL10RB</i>	<i>IRGM</i>	<i>OTULIN</i>	<i>SLC9A3</i>	<i>TNFSF15</i>	

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Autoinflammatory Diseases with Recurrent Fever

This panel groups **autoinflammatory diseases with recurrent non-infectious febrile episodes** as common manifestation, including familial Mediterranean fever, familial cold urticaria, familial periodic fever, and Majeed syndrome. Genes in this panel are important **modulators of innate immunity** intervening in several processes such as **inflammasomes production, apoptosis, TNF, and NF-kappaB-mediated signalling**, among others. Patients can also show Behçet-like phenotype, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, serum amyloidosis, and other clinical features.

Clinical features

- Recurrent fever
- Arthralgia
- Skin lesions (rash)
- Renal affection

Prevalence

- 1:5,000-10,000 (FMF)
- 1:1,000,000 (Majeed syndrome)
- 1:1,000 (TRAPS)
- <1:1,000,000 (FCAS)

Service benefits and management

- Monoclonal antibodies
- Antimycotics (colchicine)
- Anti-inflammatory therapy
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoinflammatory Diseases with Recurrent Fever Panel

[12 genes]

<i>ADA2</i>	<i>MEFV</i>	<i>NLRP4</i>	<i>NLRP3</i>	<i>PLCG2</i>	<i>SAA1</i>	<i>TNFAIP3</i>	<i>TNFRSF1A</i>	<i>TRNT1</i>
<i>LPIN2</i>	<i>MVK</i>	<i>NLRP12</i>						

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Aicardi-Goutières Syndrome (AGS)

Aicardi-Goutières syndrome (AGS) is an inherited heterogeneous encephalopathy with an early onset with both autosomal dominant and recessive forms. Severe manifestations include cerebral atrophy, leukodystrophy, intracranial calcifications, chronic cerebrospinal fluid lymphocytosis, increased CSF alpha-interferon, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia. This disease develops with characteristics typical of inflammatory (inflammation and tissue damage in the central nervous system) and autoimmune disorders (about 40% of AGS patients show chilblain skin lesions on the fingers, toes and ears, typical of lupus-like syndrome and recurrent fever in absence of infection). Affected genes are involved in DNA repair, innate response dysregulation, and RNA processing abnormalities.

Clinical features

- Encephalopathy
- Autoinflammation
- Autoimmunity
- IFN increased (CSF)
- Chilblain

Prevalence

- Unknown
- Few families described

Service benefits and management

- Immunosuppressive therapy
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Aicardi-Goutières Syndrome Panel

[7 genes]

ADAR IFIH1 RNASEH2A RNASEH2B RNASEH2C SAMHD1 TREX1

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Hemophagocytic Lymphohistiocytosis (HLH)

Familial hemophagocytic lymphohistiocytosis is a life-threatening inflammatory syndrome characterized by **histiocytosis**, **low or absent NK cell activity**, and an **excess** of released **cytokines**. The severity and progression of untreated disease leads to a median survival of less than two months, with the majority of deaths caused by **uncontrolled invasive infections**. There is a **predisposition** to suffer **EBV** infections, but other viral or bacterial infections can also occur. Clinical diagnostic criteria are confirmed by genetic testing, which explain approximately 45% of HLH patients, whereas 55% of the cases could be categorized as sporadic HLH with a complex origin.

Clinical features

- Histiocytosis
- Low or absent NK, cytopenia
- Lymphadenopathy
- Cytokine production dysregulation
- Prolonged fever
- Predisposition to EBV infections

Prevalence

- 1:50,000

Service benefits and management

- Immunosuppressive therapy
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Hemophagocytic Lymphohistiocytosis Panel

[29 genes]

<i>AP3B1</i>	<i>CD70</i>	<i>FAS</i>	<i>MAGT1</i>	<i>PRF1</i>	<i>RECQL4</i>	<i>STAT2</i>	<i>XIAP</i>
<i>AP3D1</i>	<i>CTPS1</i>	<i>FASLG</i>	<i>MCM4</i>	<i>PRKCD</i>	<i>SH2D1A</i>	<i>STX11</i>	
<i>CARMIL2</i>	<i>FAAP24</i>	<i>ITK</i>	<i>MYO5A</i>	<i>RAB27A</i>	<i>SLC7A7</i>	<i>STXBP2</i>	
<i>CD27</i>	<i>FADD</i>	<i>LYST</i>	<i>NLRC4</i>	<i>RASGRP1</i>	<i>STAT1</i>	<i>UNC13D</i>	

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HLH with Epstein Barr Virus Susceptibility

Inherited HLH disorders can be **triggered** by exposure to **EBV** or other viruses. Genetic disruption in the genes contained in this panel have been associated with an **inappropriate immune response** to EBV virus infection, which frequently results in a severe and often lethal (**mononucleosis**) infection, **dysgammaglobulinemia**, **lymphoproliferative disorders**, or **immunodeficiency**, where anti-EBV therapies fail. The high mortality due to these infections and the **high incidence of EBV** in the general population highlight the importance of an early genetic diagnosis in HLH patients with a strong susceptibility for those infections. Genes associated with HLH have also been linked to other immune-related disorders, including ALPs and CID.

Clinical features

- Histiocytosis
- Low or absent NK, cytopenia
- Lymphadenopathy
- Cytokine production dysregulation
- Prolonged fever
- Predisposition to EBV infections

Prevalence

- 1:50,000

Service benefits and management

- Immunosuppressive therapy
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

HLH with Epstein Barr Virus Susceptibility Panel

[13 genes]

<i>CARMIL2</i>	<i>CD70</i>	<i>FAAP24</i>	<i>MAGT1</i>	<i>PRF1</i>	<i>RASGRP1</i>	<i>XIAP</i>
<i>CD27</i>	<i>CTPS1</i>	<i>ITK</i>	<i>MCM4</i>	<i>PRKCD</i>	<i>SH2D1A</i>	

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Sample shipment



STUDY REQUISITION FORM

The sample for genetic testing must be sent together with a correctly filled requisition form.

Request at
customercare@healthincode.com

SAMPLE COLLECTION

Peripheral blood*

3 to 5 ml in
EDTA tubes



Genomic DNA*

NGS > 5-10 µg
(A260/280 = 1.8-1.9)
Sanger > 1 µg
(A260/280 = 1.8-1.9)



Saliva

Please use the indicated kit for
sample collection.

You can request it at
customercare@healthincode.com



**For delivery in over 48 h, controlled-temperature shipment (4-8 °C) is recommended*

SAMPLE PACKAGING

Each primary container (sample tube**) must be placed inside a secondary container (sealed plastic bag or Falcon tube) with enough absorbent material. Secondary recipients must be secured inside a rigid package or box with appropriate cushioning material.

*** Please make sure that the sample tube is labeled with the patient's details or reference.*

SAMPLE SHIPMENT

Schedule your shipment so that sample reception takes place Monday to Thursday between 8:00 and 17:00.

HEALTH IN CODE S. L.

Edificio O Fortín, As Xubias, s/n Campus de Oza 15006 A Coruña, Spain

Tel: +34 881 600 003

If you wish, you can request our sample pick-up service at customercare@healthincode.com


RESULTS

We will deliver our report via:


- Health in Code Client Portal
- Certified email



PRE-TEST AND POST-TEST COUNSELLING



Our studies include the possibility of pre-test and post-test counselling:



Contact information

- @ customer care@healthincode.com
immunohic@healthincode.com
- 📱 +34 881 600 003
- ✉ Ed. El Fortín As Xubias s/n
A Coruña 15006 Spain

Price list

>> Disorders of the Immune System [458 genes]	1526	1750 €
> Primary Immunodeficiencies (PID) [301 genes]	1053	1550 €
Primary Antibody Deficiencies (PAD) [41 genes]	134	1350 €
Common Variable Immunodeficiency (CVID) [25 genes]	86	1150 €
Agammaglobulinemia [10 genes]	21	950 €
Hyper-IgM Syndrome (HIGM) [8 genes]	23	950 €
Combined Immunodeficiencies (CID) [37 genes]	116	1350 €
Bare Lymphocyte Syndrome (BLS) [13 genes]	31	950 €
Severe Combined Immunodeficiency (SCID) [19 genes]	65	1150 €
Severe combined immunodeficiency [T- B+] SCID [11 genes]	27	950 €
Severe combined immunodeficiency [T- B-] SCID [8 genes]	38	950 €
Syndromes with Combined Immunodeficiency [74 genes]	318	1350 €
Dyskeratosis Congenita (DKC) [16 genes]	50	950 €
Hyper-IgE Syndrome (HIES) [14 genes]	63	1150 €
Ataxia telangiectasia (AT) [1 gene]	15	950 €
Defects in Intrinsic & Innate Immunity [67 genes]	203	1350 €
Viral Infections, Predisposition [21 genes]	63	1150 €
Mendelian Susceptibility to Mycobacterial Disease (MSMD) [17 genes]	51	1150 €
Fungal Infections, Predisposition [15 genes]	47	950 €
Invasive Bacterial Infections, Predisposition [6 genes]	11	950 €
Cystic fibrosis (CF) [1 gene]	7	750 €
Phagocytes Defects, Congenital [44 genes]	153	1350 €
Neutropenia, Syndromic [21 genes]	89	1150 €
Neutropenia, Non-Syndromic [7 genes]	17	950 €
Chronic Granulomatous Disease (CGD) [6 genes]	16	950 €
Complement System Deficiencies [38 genes]	126	1350 €
Atypical Haemolytic Uremic Syndrome (aHUS) [13 genes]	42	950 €
Disseminated Neisserial Infections [9 genes]	32	950 €
Systemic Lupus Erythematosus (SLE)-like Syndrome [8 genes]	32	950 €
Pyogenic Infections, Recurrent [6 genes]	24	950 €
Hereditary Angioedema (HAE) [2 genes]	5	750 €

TAT (turnaround time): 5 weeks

> Immune Dysregulation Diseases (IDD) [247 genes]	778	1550 €
Autoimmune Diseases (AD) [156 genes]	490	1350 €
Systemic Lupus Erythematosus (SLE) [69 genes]	111	1350 €
Autoimmune Nephropathy (AN) [52 genes]	183	1350 €
Autoimmune Lymphoproliferative Syndrome (ALPS) [21 genes]	55	1150 €
Autoimmune Enteropathy (AE) [18 genes]	70	1150 €
Autoimmune Polyendocrinopathy (AP) [13 genes]	47	950 €
Autoinflammatory Diseases (AID) [145 genes]	301	1350 €
Behçet's disease (BD) [27 genes]	88	1150 €
Inflammatory Bowel Disease (IBD) [26 genes]	72	1150 €
Autoinflammatory Diseases with Recurrent Fever [12 genes]	40	950 €
Aicardi-Goutières Syndrome (AGS) [7 genes]	19	950 €
Hemophagocytic Lymphohistiocytosis (HLH) [29 genes]	96	1150 €
HLH with Epstein Barr Virus Susceptibility [13 genes]	33	950 €

Familial study ¹

TAT: 2 weeks

	one variant	two variants	three variants	four variants
index case evaluated ²	170 €	255 €	340 €	425 €
without index case	240 €	340 €	440 €	540 €

¹ For structural variants (gross rearrangements, copy-number variation [insertions, deletions and duplications], inversions, translocations, etc.), contact clinicalteam@healthincode.com for a quote. ² Index case previously evaluated by *Health in Code*

Single gene sequencing

TAT: 2 weeks

Single gene sequencing	750 €
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For queries about specific genes, please contact customer-care@healthincode.com

Genetic variants report without sequencing

TAT: 2 weeks

Interpretation of a single variant	240 €	Additional variant (per unit)	150 €
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MLPA

TAT: 6 weeks

MLPA 1 kit	350 €	MLPA 2 kits	600 €
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Exome analysis

TAT: 2-5 weeks

Sequencing + FASTQ	950 €
Sequencing + FASTQ + variant annotation	1450 €
Sequencing + FASTQ + variant annotation + interpretation	1950 €



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