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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 Erythematous (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 Erythematous (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 Erythematous (SLE) [69 genes]	Behçet's Disease (BD) [27 genes]	HLH with Epstein Barr Virus Susceptibility [13 genes]
Autoimmune Nephropathy (AN) [52 genes]	Inflammatory Bowel Disease (IBD) [26 genes]	
Autoimmune Lymphoproliferative Syndrome (ALPS) [21 genes]	Autoinflammatory Diseases with Recurrent Fever [12 genes]	
Autoimmune Enteropathy (AE) [18 genes]	Aicardi-Goutières Syndrome (AGS) [7 genes]	
Autoimmune Polyendocrinopathy (AP) [13 genes]		

PRIMARY IMMUNODEFICIENCIES (PID) [301 GENES]

Defects of adaptive immunity				*Defects of innate immunity*		
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 Erythematous (SLE)-like Syndrome [8 genes]
				Invasive Bacterial Infections, Predisposition [6 genes]		Pyogenic Infections, Recurrent [6 genes]
				Cystic Fibrosis (CF) [1gene]		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 Inmunodeficiencias 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 Immunodefic 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
ACD
ACP5
ACTB
ADA
ADA2
ADAM17
ADAR
ADGRE2
AICDA
AIRE
AK2
ANXA11
AP3B1
AP3D1
APOL1
ARID5B
ARPC1B
ATG16L1
ATG5
ATM
ATP6AP1
B2M
BANK1
BCL10
BCL11B
BLK
BLM
BLNK
BTK
BTNL2
C1QA
C1QB
C1QC
C1QTNF4
C1R
C1S
C2
C3
C4A
C4B
C5
C6
C7
C8A
C8B
C8G
C9
CALCOCO2
CARD11
CARD14
CARD9
CARMIL2
CASP10
CASP8
CCBE1
CCDC88B
CCL2
CCL22
CCR1
CCR3
CCR5
CCR9
CD14
CD19
CD226
CD247
CD27
CD3D
CD3E
CD3G
CD40
CD40LG
CD46
CD55
CD59
CD70
CD79A
CD79B
CD81
CD8A
CDCA7
CEBPE
CFB
CFD
CFH
CFHR1
CFHR2
CFHR3
CFHR4
CFHR5
CFI
CFP
CFTR
CHD7
CIITA
CLCN7
CLEC16A
CLEC7A
CLPB
CORO1A
CR2
CSF2RA
CSF2RB
CSF3R
CSK
CTC1
CTLA4
CTPS1
CTSC
CXCL13
CXCR4
CXCR5
CYBA
CYBB
DCLRE1B
DCLRE1C
DDX58
DGAT1
DGKE
DKC1
DNAJC21
DNASE1
DNASE1L3
DNMT3A
DNMT3B
DOCK2
DOCK8
E2F1
EGFR
ELANE
EPCAM
EPG5
ERAP1
ERCC6L2
ETS1
EXTL3
F12
FAAP24
FADD
FAS
FASLG
FCGR2A
FCGR2B
FCGR3A
FCN3
FERMT3
FOXN1
FOXP3
FPR1
FUT2
G6PC3
G6PD
GATA1
GATA2
GFI1
GINS1
GUCY2C
HAS2
HAX1
HELLS
HMOX1
HNF1A
HYOU1
ICAM1
ICOS
IFIH1
IFNAR2
IFNGR1
IFNGR2
IGLL1
IKBKB
IKBKG
IKZF1
IKZF3
IL10
IL10RA
IL10RB
IL12A
IL12B
IL12RB1
IL12RB2
IL15
IL15RA
IL17F
IL17RA
IL17RC
IL18R1
IL1RN
IL21
IL21R
IL23A
IL23R
IL2RA
IL2RG
IL36RN
IL7R
INO80
IRAK1
IRAK4
IRF1
IRF2BP2
IRF3
IRF5
IRF7
IRF8
IRGM
ISG15
ITCH
ITGAM
ITGB2
ITK
JAGN1
JAK1
JAK3
KDM6A
KIRREL2
KLRC4
KMT2D
KRAS
LACC1
LAMTOR2
LAT
LCK
LIG1
LIG4
LIMK2
LPIN2
LRBA
LRRC8A
LYST
MAGT1
MALT1
MAN2B1
MAP3K14
MASP1
MASP2
MBL2
MC2R
MC3R
MCM2
MCM4
MECP2
MEFV
MICA
MICB
MKL1
MME
MOGS
MPO
MRAP
MRC1
MS4A1
MSH6
MSN
MST1
MTHFD1
MTHFR
MTMR3
MVK
MYD88
MYH9
MYO5A
MYO5B
MYSM1
NBAS
NBN
NCF1
NCF2
NCF4
NCSTN
NEIL1
NEUROG3
NFAT5
NFKB1
NFKB2
NFKBIA
NHEJ1
NHP2
NLRC4
NLRP12
NLRP3
NOD2
NOP10
NPHS1
NR0B1
NR4A2
NRAS
NSMCE3
OAS1
OAS2
ORAI1
OSTM1
OTULIN
PARN
PBX1
PDCD1
PDGFRA
PEPD
PGM3
PHF11
PIK3CD
PIK3R1
PLA2R1
PLCG2
PLEKHM1
PMS2
PNP
POLE
POLE2
PRDM1
PRF1
PRKCD
PRKDC
PRKG1
PRPS1
PSEN1
PSENEN
PSMB8
PSTPIP1
PTEN
PTGS2
PTPN2
PTPN22
PTPRC
PXK
RAB27A
RAC2
RAG1
RAG2
RANBP2
RASGRP1
RBCK1
RECQL4
REL
RELB
RFX5
RFXANK
RFXAP
RHOH
RMRP
RNASEH2A
RNASEH2B
RNASEH2C
RNF168
RNF31
RNU4ATAC
RORC
RPSA
RTEL1
SAA1
SAMD9
SAMD9L
SAMHD1
SATB1
SBDS
SEC61A1
SEMA3E
SERPING1
SH2D1A
SKIV2L
SLC11A1
SLC26A3
SLC35C1
SLC37A4
SLC46A1
SLC7A7
SLC9A3
SMARCAL1
SMARCD2
SNX10
SP110
SPATA5
SPINK5
SPINT2
STAT1
STAT2
STAT3
STAT4
STAT5B
STAT6
STIM1
STK4
STN1
STX11
STXBP2
TAGAP
TAP1
TAP2
TAPBP
TAZ
TBK1
TBX1
TBX21
TCF3
TCF7
TCIRG1
TCN2
TERC
TERT
TFRC
TGFB1
THBD
THBS1
THSD7A
TICAM1
TINF2
TIRAP
TLR1
TLR2
TLR3
TLR5
TLR7
TLR8
TLR9
TMC6
TMC8
TMEM173
TNF
TNFAIP3
TNFRSF11A
TNFRSF13B
TNFRSF13C
TNFRSF1A
TNFRSF4
TNFSF11
TNFSF12
TNFSF13
TNFSF15
TNFSF4
TNIP1
TRAF3
TRAF3IP2
TREX1
TRIM21
TRNT1
TTC37
TTC7A
TYK2
UBAC2
UBE2L3
UHRF1BP1
UNC119
UNC13D
UNC93B1
UNG
USB1
VPS13B
VPS45
WAS
WDR1
WIPF1
WRAP53
XIAP
XKR6
ZAP70
ZBTB24
ZNF341

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 Inmunodeficiencias 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
- Christine M, Warrington R. Primary immunodeficiency. *Allergy Asthma Clin Immunol.* 2011;7(S1):1-8. doi:10.1186/1710-1492-7-S1-S11
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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
ACP5
ACTB
ADA
ADA2
AICDA
AIRE
AK2
AP3B1
AP3D1
APOL1
ARPC1B
ATM
ATP6AP1
B2M
BCL10
BCL11B
BLM
BLNK
BTK
C1QA
C1QB
C1QC
C1R
C1S
C2
C3
C4A
C4B
C5
C6
C7
C8A
C8B
C8G
C9
CARD11
CARD9
CARMIL2
CASP8
CCBE1
CCL2
CD19
CD247
CD27
CD3D
CD3E
CD3G
CD40
CD40LG
CD46
CD55
CD59
CD79A
CD79B
CD81
CD8A
CDCA7
CEBPE
CFB
CFD
CFH
CFHR1
CFHR2
CFHR3
CFHR4
CFHR5
CFI
CFP
CFTR
CHD7
CIITA
CLCN7
CLEC7A
CLPB
CORO1A
CR2
CSF2RA
CSF2RB
CSF3R
CTC1
CTLA4
CTPS1
CTSC
CXCR4
CYBA
CYBB
DCLRE1B
DCLRE1C
DGKE
DKC1
DNAJC21
DNMT3B
DOCK2
DOCK8
ELANE
EPG5
ERCC6L2
EXTL3
F12
FCGR3A
FCN3
FERMT3
FOXN1
FOXP3
FPR1
G6PC3
G6PD
GATA1
GATA2
GFI1
GINS1
HAX1
HELLS
HMOX1
HYOU1
ICOS
IFIH1
IFNAR2
IFNGR1
IFNGR2
IGLL1
IKBKB
IKBKG
IKZF1
IL10
IL10RA
IL10RB
IL12B
IL12RB1
IL17F
IL17RA
IL17RC
IL21
IL21R
IL2RA
IL2RG
IL7R
INO80
IRAK1
IRAK4
IRF2BP2
IRF3
IRF7
IRF8
ISG15
ITGB2
JAGN1
JAK1
JAK3
KDM6A
KMT2D
LAMTOR2
LAT
LCK
LIG1
LIG4
LRBA
LRRC8A
LYST
MAGT1
MALT1
MAP3K14
MASP1
MASP2
MBL2
MC3R
MCM2
MCM4
MKL1
MOGS
MPO
MRC1
MS4A1
MSH6
MSN
MTHFD1
MYD88
MYSM1
NBAS
NBN
NCF1
NCF2
NCF4
NCSTN
NFAT5
NFKB1
NFKB2
NFKBIA
NHEJ1
NHP2
NOD2
NOP10
NSMCE3
ORAI1
OSTM1
PARN
PGM3
PHF11
PIK3CD
PIK3R1
PLCG2
PLEKHM1
PMS2
PNP
POLE
POLE2
PRKDC
PRPS1
PSEN1
PSENEN
PTEN
PTPRC
RAC2
RAG1
RAG2
RANBP2
RBCK1
REL
RELB
RFX5
RFXANK
RFXAP
RHOH
RMRP
RNF168
RNF31
RNU4ATAC
RORC
RPSA
RTEL1
SAMD9
SAMD9L
SBDS
SEC61A1
SEMA3E
SERPING1
SLC11A1
SLC35C1
SLC37A4
SLC46A1
SMARCAL1
SMARCD2
SNX10
SP110
SPATA5
SPINK5
STAT1
STAT2
STAT3
STAT5B
STIM1
STK4
STN1
TAP1
TAP2
TAPBP
TAZ
TBK1
TBX1
TCF3
TCIRG1
TCN2
TERC
TERT
TFRC
THBD
TICAM1
TINF2
TIRAP
TLR1
TLR2
TLR3
TMC6
TMC8
TNFRSF11A
TNFRSF13B
TNFRSF13C
TNFRSF4
TNFSF11
TNFSF12
TNFSF13
TRAF3
TRAF3IP2
TRNT1
TTC37
TTC7A
TYK2
UNC119
UNC93B1
UNG
USB1
VPS13B
VPS45
WAS
WDR1
WIPF1
WRAP53
ZAP70
ZBTB24
ZNF341

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]

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

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
- Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. *Nat Rev Immunol.* 2013;13(7):519-533. doi:10.1038/nri3466
- Fried AJ, Bonilla FA. Pathogenesis, diagnosis, and management of primary antibody deficiencies and infections. *Clin Microbiol Rev.* 2009;22(3):396-414. doi:10.1128/CMR.00001-09
- Herriot R, Sewell WAC. Antibody deficiency. *J Clin Pathol.* 2008;61(9):994-1000. doi:10.1136/jcp.2007.051177
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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]
BLNK *BTK*	*CD79A*	*CD79B*	*IGHM**	*IGKC**	*IGLL1*	*LRRC8A*	*PIK3R1*	*TCF3*

** 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]

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

Panels included:

> Bare Lymphocyte Syndrome (BLS) [13 genes]

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Inmunodeficiencias primarias. *J Clin Immunol.* 2018;38 (1):129-143. doi:10.1007/s10875-017-0465-8
- Immune deficiency foundation (IDF). Stem Cell and Gen Therapy. https://primaryimmune.org/treatment-information/stem-cell-and-gene-therapy. 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.
- Lohmann K, Klein C. Next Generation Sequencing and the Future of Genetic Diagnosis. *Neurotherapeutics.* 2014;11 (4):699-707. doi:10.1007/s13311-014-0288-8
- Paul Szabolcs M-CH of P of U. Combined Immune Deficiency (CID) Syndromes. http://www.chp.edu/our-services/rare-disease-therapy/conditions-we-treat/combined-immune-deficiency-syndromes. Accessed April 5, 2018.

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]

B2M	*CIITA*	*MAGT1*	*RFXANK*	*TAP1*	*TAPBP*	*ZAP70*
CD8A	*LCK*	*RFX5*	*RFXAP*	*TAP2*	*UNC119*	

- Blum JS. Bare Lymphocyte Syndrome. In: *Encyclopedia of Immunology*. Elsevier; 1998:329-332. doi:10.1006/rwei.1999.0085
- Genetics Home Reference. Bare lymphocyte syndrome type I. https://ghr.nlm.nih.gov/condition/bare-lymphocyte-syndrome-type-i#. Bare lymphocyte syndrome type II. https://ghr.nlm.nih.gov/condition/bare-lymphocyte-syndrome-type-ii#inheritance.Accessed April 6, 2018.
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- Kallen ME, Pullarkat ST. Type II Bare Lymphocyte Syndrome. *J Pediatr Hematol Oncol.* 2015;37(4):e245-e249. doi:10.1097/MPH.0000000000000278
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Severe Combined Immunideficiency (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*	*FOXN1*	*IL7R*	*NHEJ1*	*RAG1*	

Panels included:

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

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

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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]

CD247	*CD3E*	*CORO1A*	*IL2RA*	*IL7R*	*PTPRC*
CD3D	*CD3G*	*FOXN1*	*IL2RG*	*JAK3*	

- Bousfiha A, Jeddane L, Picard C, et al. The 2017 IUIS Phenotypic Classification for Inmunodeficiencias primarias. *J Clin Immunol.* 2018;38(1):129-143. doi:10.1007/s10875-017-0465-8
- Fischer, A. (2000). Severe combined immunodeficiencies (SCID). Clinical and Experimental Immunology, 122(2), 143–149. https://doi.org/10.1046/J.1365-2249.2000.01359.X
- 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 Inmunodeficiencias 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]

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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]

ACD	*DCLRE1B*	*NHP2*	*PARN*	*SAMD9*	*STN1*	*TERT*	*USB1*
CTC1	*DKC1*	*NOP10*	*RTEL1*	*SAMD9L*	*TERC*	*TINF2*	*WRAP53*

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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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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]

ARPC1B	*DOCK8*	*IL21R*	*PHF11*	*STAT3*	*TYK2*	*WIPF1*
DOCK2	*FOXP3*	*PGM3*	*SPINK5*	*STK4*	*WAS*	*ZNF341*

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- Sowerwine, K. J., Holland, S. M., & Freeman, A. F. (2012). Hyper-IgE syndrome update. Annals of the New York Academy of Sciences, 1250(1), 25–32. https://doi.org/10.1111/j.1749-6632.2011.06387.x

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*	*PSENEN*	*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 [21genes]

> 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. 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, oportunistic 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]

CCL2	*IFNGR1*	*IL12B*	*IRF8*	*JAK1*	*MRC1*	*SLC11A1*	*TLR1*	*TYK2*
CYBB	*IFNGR2*	*IL12RB1*	*ISG15*	*MC3R*	*RORC*	*STAT1*	*TLR2*	

- 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 diagnosiis 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 myelodisplasia, 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]

ACTB	*CSF2RA*	*CYBB*	*G6PC3*	*GINS1*	*LAMTOR2*	*NCF4*	*SLC35C1*	*VPS13B*
AP3B1	*CSF2RB*	*DNAJC21*	*G6PD*	*HAX1*	*LYST*	*NOD2*	*SLC37A4*	*VPS45*
AP3D1	*CSF3R*	*ELANE*	*GATA1*	*HYOU1*	*MKL1*	*PGM3*	*SMARCD2*	*WAS*
CEBPE	*CTSC*	*FERMT3*	*GATA2*	*ITGB2*	*NCF1*	*RAC2*	*TAZ*	*WDR1*
CLPB	*CYBA*	*FPR1*	*GFI1*	*JAGN1*	*NCF2*	*SBDS*	*USB1*	

Panels included:

> Neutropenia, Syndromic [21genes]

> 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
- 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
- Murphy K, Weaver C. *Janeway's Immunbiology.*; 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]

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

- 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, Beaupain 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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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
- 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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- 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]

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

Panels included:

> Atypical Haemolytic Uremic Syndrome (aHUS) [13 genes]

> Disseminated Neisserial Infections [9 genes]

> Hereditary Angioedema (HAE) [2 genes]

> SLE-like Syndrome [8 genes]

> Pyogenic Infections, Recurrent [6 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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- Prohászka Z, Nilsson B, Frazer-Abel A, Kirschfink M. Complement analysis 2016: Clinical indications, laboratory diagnostics and quality control. Immunobiology. 2016;221(11):1247-1258. doi:10.1016/J.IMBIO.2016.06.008
- 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	*CFB*	*CFHR1*	*CFHR3*	*CFHR5*	*G6PD*	*DGKE*	*THBD*
CD46	*CFH*	*CFHR2*	*CFHR4*	*CFI*			

- Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: Diagnosis and treatment. A consensus document. *Nefrologia.* 2015;35(5):421-447. doi:10.1016/j.nefroe.2015.11.006
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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*

- 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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Systemic Lupus Erythematous (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 Erythematous (SLE)-like Syndrome Panel							[8 genes]
C1QA	*C1QB*	*C1QC*	*C1R*	*C1S*	*C2*	*C4A*	*C4B*

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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*

- 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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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*	

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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 Lymphohistiocytosis (HLH) & EBV Susceptibility [29 genes]

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Immune Dysregulation Diseases Panel [247 genes]

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

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

Systemic Lupus Erythematous (SLE)

Monogenic forms of **lupus** are rare and frequently catalogued as **lupus-like** syndromes, which present some clinical features of systemic lupus erythematous **(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 Erythematous Panel [69 genes]

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

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Autoimmune Nephropathy (AN)

Autoimmune nephropathies include disorders that are caused by immune responses against kidney structures, producing **glomerulonephritis, membranous nephropathy o 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]

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

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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
- Immunosupressor for autoimmunity reactions
- Monoclonal Abs
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Lymphoproliferative Syndrome Panel [21 genes]

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

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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-celiac 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
- Immunosupressive agents (cyclosporin)
- Genetic counseling
- Accurate diagnosis and phenotype-genotype correlation

Autoimmune Enteropathy Panel [18 genes]

CIITA	*CD55*	*EPCAM*	*GUCY2C*	*MYO5B*	*NFAT5*	*SKIV2L*	*SLC9A3*	*STAT1*
CTLA4	*DGAT1*	*FOXP3*	*IL10*	*NEUROG3*	*NLRC4*	*SLC26A3*	*SPINT2*	*TTC37*

- 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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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]

AIRE	*CTLA4*	*FOXP3*	*ITCH*	*MRAP*	*NR0B1*	*STAT1*	*STAT3*	*STAT5B*
CIITA	*DOCK8*	*IL2RA*	*MC2R*					

- Hannibal MC, Torgerson T. IPEX Syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. SourceGeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.
- 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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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
- Arthralagia
- 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]

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

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)

Behcet 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

Behcet Disease Panel [27 genes]

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

- Berteau F, Rouviere B, Delluc A, Nau A, Le Berre R, Sarrabay G, Touitou I, de Moreuil C. Autosomic dominant familial Behçet disease and haploinsufficiency A20: A review of the literature. Autoimmun Rev. 2018 Aug;17(8):809-815. doi: 10.1016/j.autrev.2018.02.012. Epub 2018 Jun 8.
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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]

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

- Bianco AM, Girardelli M, Tommasini A. Genetics of inflammatory bowel disease from multifactorial to monogenic forms. DOI: 10.3748/wjg.v21.i43.12296
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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
- Arthralagia
- Skin lesions (rash)
- Renal afection

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]
ADA2	*MEFV*	*NLRC4*	*NLRP3*	*PLCG2*	*SAA1*	*TNFAIP3*	*TNFRSF1A*	*TRNT1*
LPIN2	*MVK*	*NLRP12*						

- Bousfiha A. et al. The 2017 IUIS Phenotypic Classification for Inmunodeficiencias primarias. J Clin Immunol. 2018 Jan;38(1):129-143. doi: 10.1007/s10875-017-0465-8. Epub 2017 Dec 11.
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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*

- Crow YJ1,2. Aicardi-Goutières Syndrome. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 2005 Jun 29 [updated 2016 Nov 22].
- Gorman JA1, Hundhausen C2, Errett JS3,4, Stone AE3,4, Allenspach EJ1,5, Ge Y6, Arkatkar T1, Clough C1, Dai X1, Khim S1, Pestal K4, Liggitt D7, Cerosaletti K2, Stetson DB4, James RG1,5, Oukka M1,4,5, Concannon P6, Gale M Jr3,4, Buckner JH2, Rawlings DJ1,4,5. The A946T variant of the RNA sensor IFIH1 mediates an interferon program that limits viral infection but increases the risk for autoimmunity. Nat Immunol. 2017 Jul;18(7):744-752. doi: 10.1038/ni.3766. Epub 2017 May 29.
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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]

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

- Cetica V1, Sieni E1, Pende D2, Danesino C3, De Fusco C4, Locatelli F5, Micalizzi C6, Putti MC7, Biondi A8, Fagioli F9, Moretta L6, Griffiths GM10, Luzzatto L11, Aricò M12. Genetic predisposition to hemophagocytic lymphohistiocytosis: Report on 500 patients from the Italian registry. J Allergy Clin Immunol. 2016 Jan;137(1):188-196.e4. doi: 10.1016/j.jaci.2015.06.048. Epub 2015 Sep 2.
- Henter JI1, Aricò M, Elinder G, Imashuku S, Janka G. Familial hemophagocytic lymphohistiocytosis. Primary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998 Apr;12(2):417-33.
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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]

CARMIL2	*CD70*	*FAAP24*	*MAGT1*	*PRF1*	*RASGRP1*	*XIAP*
CD27	*CTPS1*	*ITK*	*MCM4*	*PRKCD*	*SH2D1A*	

- Bousfiha A. et al. The 2017 IUIS Phenotypic Classification for Inmunodeficiencias primarias. J Clin Immunol. 2018 Jan;38(1):129-143. doi: 10.1007/s10875-017-0465-8. Epub 2017 Dec 11.
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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 ºC) 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

@ customercare@healthincode.com
immunohic@healthincode.com

+34 881 600 003

Ed. El Fortín As Xubias s/n
A Coruña 15006 Spain

Price list

TAT (turnaround time): 5 weeks

NGS Panels	Size (Kb)	Price
>> 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 [21genes]	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 Erythematous (SLE)-like Syndrome [8 genes]	32	950 €
Pyogenic Infections, Recurrent [6 genes]	24	950 €
Hereditary Angioedema (HAE) [2 genes]	5	750 €

	Size (Kb)	Price
> Immune Dysregulation Diseases (IDD) [247 genes]	778	1550 €
Autoimmune Diseases (AD) [156 genes]	490	1350 €
Systemic Lupus Erythematous (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 €

For queries about specific genes, please contact customercare@healthincode.com

Genetic variants report without sequencing

TAT: 2 weeks

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

MLPA

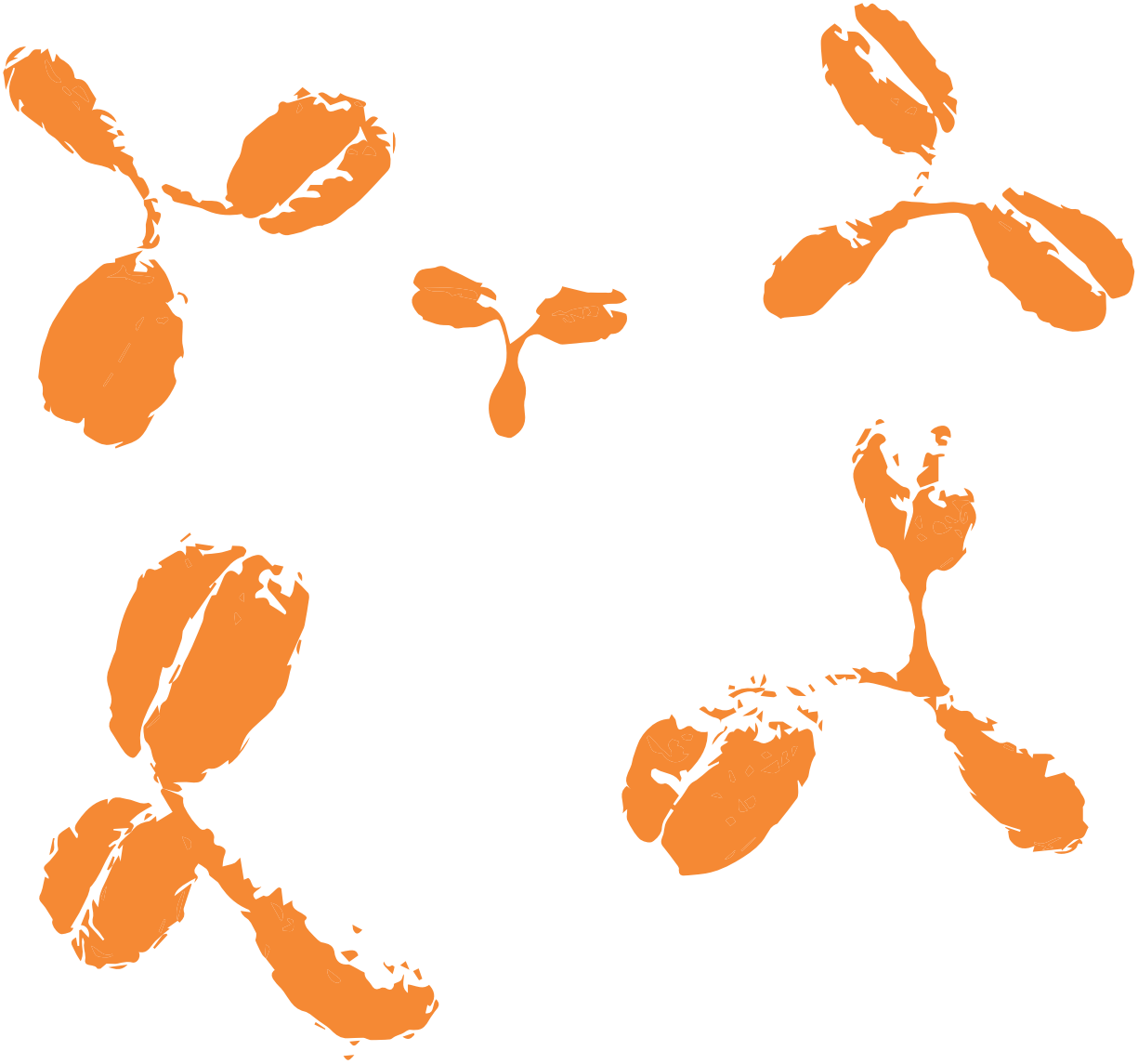
TAT: 6 weeks

MLPA 1 kit	350 €	MLPA 2 kits	600 €

Exome analysis

TAT: 2-5 weeks

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



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