Table 1 Diseases of immune dysregulation

	Disease	Circulating T cells	B cells	Serum Ig	Associated features	Inheritance	Genetic defects/presumed pathogenesis	OMIM	HGNC symbol	HGNC ID(s)	ENSEMBL ID
1.	**Immunodeficiency with hypopigmentation**										
A	**Chediak-Higashi syndrome**	Normal	Normal	Normal	Partial albinism, giant lysosomes, low NK and CTL activities, acute-phase reaction, encephalopathic accelerated phase	AR	Defects in *LYST* gene, impaired lysosomal trafficking	214500, 606897	LYST	1968	ENSG00000143669
B	**Griscelli syndrome, type 2**	Normal	Normal	Normal	Partial albinism, low NK and CTL activities, acute-phase reaction, might have encephalopathy	AR	Defects in *RAB27A* encoding a GTPase in secretory vesicles	607624, 603868	*CASP8*	1509	ENSG00000069974
C	**Hermansky-Pudlak syndrome, type 2**	Normal	Normal	Normal	Partial albinism, **neutropenia,** low NK and CTL activity, increased bleeding,	AR	Mutations of *AP3B1* gene, encoding for the β subunit of the AP-3 complex	608233, 603401	AP3B1	566	ENSG00000132842
2.	**Familial hemophagocytic lymphohistiocytosis (FHL) syndromes**										
A	**Perforin deficiency**	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *PRF1*; perforin, a major cytolytic protein	603553, 170280	*PRF1*	9360	ENSG00000180644
B	**Munc 13-D deficiency**	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *MUNC13D* required to prime vesicles for fusion	608898, 608897	*UNC13D*	23147	ENSG00000092929
C	**Syntaxin 11 deficiency**	Normal	Normal	Normal	Severe inflammation, fever, decreased NK and CTL activities	AR	Defects in *STX11*, involved in vesicle trafficking and fusion	603552, 605014	*STX11*	11429	ENSG00000135604
D	**STXBP2 (Munc 18-2) deficiency, FHL5**	Normal	Normal	Normal or low	Severe inflammation, fever, splenomegaly, hemophagocytosis possible bowel disease.Decreased NK and CTL activities with partial restoration after IL-2 stimulation	AR	Mutations in *STXBP2*, required for fusion of secretory vesicles with the cell membrane and release of contents	613101, 601717	STXBP2	11445	ENSG00000076944
3.	**X-linked lymphoproliferative syndrome**										
A	**XLP1**	Normal	Normal or reduced	Normal or low Igs	Clinical and immunologic abnormalities triggered by EBV infection, including hepatitis, aplastic anemia, lymphoma	XL	Defects in *SH2D1A* encoding adaptor protein regulating intracellular signals	308240, 300490	SH2D1A	10820	ENSG00000183918
B	**XLP2**	Normal	Normal or reduced	Normal or low Igs	Clinical and immunologic abnormalities triggered by EBV infection, including splenomegaly, hepatitis, hemophagocytic syndrome, lymphoma	XL	Defects in *XIAP* encoding an inhibitor of apoptosis	300635, 300079	XIAP	592	ENSG00000101966
4.	**Syndromes with autoimmunity**										
A	**Autoimmune lymphoproliferative syndrome (ALPS)**										
I	**CD95 (Fas) defects, type 1a**	Normal, increased double-negative ($CD4^-$ $CD8^-$) $\alpha\beta^+$T cells	Normal	Normal or increased	Defective lymphocyte apoptosis, splenomegaly, adenopathy, autoimmune blood cytopenias, increased lymphoma risk	AD rare severe ARcases	Defects in *TNFRSF6*, cell-surface apoptosis receptor	601859, 134637	FAS	11920	ENSG00000026103
II	**CD95L (Fas ligand) defects, ALPS type 1b**	Normal, increased double-negative ($CD4^-$ $CD8^-$) $\alpha\beta^+$T cells	Normal	Normal	Defective lymphocyte apoptosis, splenomegaly, adenopathy, autoimmune blood cytopenias, lupus	AD	Defects in *TNFSF6*, ligand for CD95 apoptosis receptor	134638	FASLG	11936	ENSG00000117560
III	**Caspase 10 defects, ALPS type 2a**	Normal, increased $CD4^-$ $CD8^-$ $\alpha\beta^+$T cells	Normal	Normal	Adenopathy, splenomegaly, defective lymphocyte apoptosis, autoimmune disease	AD	Defects in *CASP10*, intracellular apoptosis pathway	603909, 601762	CASP10	1500	ENSG00000003400
IV	**Caspase 8 defects, ALPS type 2b**	Normal, slightly increased $CD4^-$ $CD8^-\alpha\beta^+$T cells	Normal	Normal or decreased	Adenopathy, splenomegaly; defective lymphocyte apoptosis and activation; recurrent bacterial and viral infections	AD	Defects in *CASP8*, intracellular apoptosis, and activation pathways	607271, 601763	CASP8	1509	ENSG00000064012
V	**NRAS gain-of.function, ALPS type 3**	Normal, increased double-negative ($CD4^-$ $CD8^-$) $\alpha\beta^+$T cells	Normal, elevation of CD5 B cells	Normal	Defective lymphocyte apoptosis, splenomegaly, adenopathy, multiple autoantibodies, increased leukaemia and lymphoma risk	AD, sporadic	*NRAS* gain-of –function mutation augments RAF/MEK/ERK signaling which decreases the proapoptotic protein BIM and attenuates intrinsic, nonreceptor-mediated mitochondrial apoptosis.	164790	NRAS	7989	ENSG00000213281
	FADD deficiency	Increased DNT cells	Normal	Normal	Functional hyposplenism, recurrent bacterial, and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis	AR	Mutations in *FADD* encoding an adaptormolecule interacting with FAS, and promoting apoptosis, inflammation and innate immunity	613759, 602457	FADD	3573	ENSG00000168040
B	**APECED, autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy***	Normal, increased $CD4^+$ cells	Normal	Normal	Autoimmune disease of parathyroid, adrenal and other organs plus candidiasis, dental enamel hypoplasia and other abnormalities	AR	Defects in *AIRE*, encoding a transcription regulator needed to establish thymic self-tolerance	240300, 607358	AIRE	360	ENSG00000160224
C	**IPEX, immune dysregulation, polyendocrinopathy, enteropathy (X-linked)**	Normal, lack of $CD4^+$ $CD25^+$ $FOXP3^+$ regulatory T cells	Normal	Increased IgA, IgE	Autoimmune diarrhea, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema	XL	Defects in *FOXP3*, encoding a T-cell transcription factor	304790, 300292	*FOXP3*	6106	ENSG00000049768
D	**CD25 deficiency**	Normal to modestly decreased, impaired T cell proliferation	Normal	Normal	Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity as in IPEX syndrome.	AR	Defects in IL2Rα chain	606367, 147730	IL2RA	6008	ENSG00000134460
	ITCH deficiency*	Not assessed (Th2skewingin *Itch*-deficient mice)	Not assessed (B cells are dysfunctional in *Itch*-deficient mice)	Not assessed (elevatedin *Itch*-deficient mice)	Multi-organ autoimmunity, chronic lung disease, failure to thrive, developmental delay, macrocephaly	AR	Mutations in *ITCH*, an E3 ubiquitin ligase	613385, 606409	ITCH	13890	ENSG00000078747
E	**STAT5b**	Modestly decreased, impaired development and function of γδT cells,Treg, and NKcells, impaired T cell proliferation	Normal	Normal	Growth hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, low NK activity	AR	Defects in STAT5B gene	604260	STAT5B	11367	ENSG00000173757

NK, Natural killer; *CTL*, cytotoxic T-lymphocyte; *AR*, autosomal recessive inheritance; *XL*, X-linked inheritance; *AD*, autosomal dominant inheritance; *LYST*, lysosomal trafficking regulator; *RAB27A*, Rab protein 27A; *PRF1*, perforin 1; *SH2D1A*, SH2 domain protein 1A; *TNFRSF6*, tumor necrosis factor receptor soluble factor 6; *APECED*, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *AIRE*, autoimmune regulator; *IPEX*, immune dysregulation–polyendocrinopathy–enteropathy–X-linked; *FOXP3*, Forkhead box protein 3.

*APECED is also presented in **Error! Reference source not found.**

*STXBP2/Munc18-2deficiencyhasbeenaddedasthecauseof"FHL5,"anewformofFHL.Ofnote,"FHL1"hasnotyetreceivedagenetic/molecularidentification. FADDdeficiencyisclassifiedamongthecausesofALPS.Itshouldbestressedhowever that FADDdeficiencyisamorecomplexsyndromethatencompasses hyposplenism,hencebacterialinfections,aswellasabrainandliverprimarydysfunction.EBV-drivenlymphoproliferationisalsoobservedinITK deficiency andin MAGT1deficiency(**Table1**).*