Supplementary Table 1. Known clinical features of recognised interferonopathies according to proposed molecular mechanisms

1. Mutated proteins acting directly on nucleic acid substrates and their sensing								
	1.1 DNA sensing							
		Aicardi-Goutières syndrome (AGS)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		225750	TREX1* (3p21.31)	Deoxyribonuclease	AR or DN (AD?)	LOF leading to increased DNA sensing	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[10, 17-19]
		610333	RNASEH2A* (19p13.13)	Ribonuclease	AR	LOF leading to increased RNA/DNA hybrid sensing	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[18, 20-21]
		610326	RNASEH2B* (13q14.3)	Ribonuclease	AR	LOF leading to increased RNA/DNA hybrid sensing	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[18, 20-21]
		610329	RNASEH2C* (11q13.1)	Ribonuclease	AR	LOF leading to increased RNA/DNA hybrid sensing	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations, dysmorfisms	[18, 20-21]
		612952	SAMHD1* (20q11.23)	Control of dNTP pool	AR	LOF leading to increased DNA sensing	Mild Aicardi-Goutières Syndrome, oral ulcers, cerebral vasculopathy with early onset stroke, arthropathy arthropathy with progressive contractures	[18, 22-24
		Monogenic Systemic Lupus Erythematosus (SLE) and Chilblain Lupus						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Clinical picture***		***Ref.***
		225750	TREX1* (3p21.31)	Deoxyribonuclease	AR or DN (AD?)	LOF leading to increased DNA sensing	familial chilblain Lupus monogenic SLE	[26-29]
		610448	SAMHD1* (3p21.31)	Control of dNTP pool	AR/AD	LOF leading to increased DNA sensing	familial chilblain Lupus	[23-24, 30]
		615934	TMEM173* (5q31.2)	Cytosolic DNA signal transduction	AD	GOF leading to constitutive activation of sensitivity to cytosolic nucleic acids	familial chilblain Lupus	[31]
		STING-Associated Vasculopaty with onset in Infancy (SAVI)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		615934	TMEM173* (5q31.2)	Cytosolic DNA signal transduction	AD	GOF leading to constitutive activation of sensitivity to cytosolic nucleic acids	Systemic and peripheral vessel inflammation, cutaneous vasculopathy (fingers, toes, cheeks and ears), distal tissue damage, nasal septum perforation, telangiectasia, interstitial lung disease, pulmonary	[32]

							arterial hypertension	
		X-Linked reticulate Pigmentary Disorder (XLPDR)						
		OMIM	***Gene (locus)***	***Protein***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		301220	POLA1* (Xp22.1-p21.3)	DNA polymerase	XLR	LOF leading to increased RNA/DNA hybrid sensing	reticulate pigmentary disorder, primary immunodeficiency with autoinflammatory features	[33]
		Liver Fibrosis (LF), Glomerulonefritis (GN) and Neonatal Anemia (NA)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		126350	DNASE2* (19p13.13)	Deoxyribonuclease	AR	LOF leading	Severe neonatal anemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy and increased anti-DNA antibodies	[34]
	1.2 RNA sensing							
		Aicardi-Goutières Syndrome (AGS)						
		OMIM	***Gene (locus)***	***Protein***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		615010	ADAR1* (1q21.3)	RNA editing	AR or DN	LOF leading to impaired RNA editing and aberrant sensing of cytosolic RNA species	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[35-36]
		615846	MDA5 (or IFIH1)* (2q24.2)	dsRNA sensing	AD	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	Progressive familial encephalopathy, basal ganglia calcifications, white matter alterations	[37]
		Spastic Paraparesis (SP)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		615010	ADAR1* (1q21.3)	RNA editing	AR or DN	LOF leading to impaired RNA editing and aberrant sensing of cytosolic RNA species	Spastic paraparesis	**[**35,38]
		615846	MDA5 (or IFIH1) (2q24.2)	dsRNA sensing	AD	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	early-onset spastic paraparesis with brain calcification	[37]
		Bilateral Striatal Necrosis (BSN)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		615010	ADAR1* (1q21.3)	RNA editing	AR or DN	LOF leading to impaired RNA editing and aberrant sensing of cytosolic RNA species	Non-syndromic bilateral striatal necrosis with severe dystonia of varying evolution.	[35, 39]
		Singleton-Merten Syndrome (SMS)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***

		182250	MDA5 (or IFIH1)* (2q24.2)	dsRNA sensing	AD	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	Early aortic and valvular calcification, dental anomalies (early-onset periodontitis and root resorption, dental dysplasia), skeletal abnormalities, osteopenia, acro-osteolysis. glaucoma, psoriasis	[40-41]
		616298	RIG-I (or DX58, Atypical form)* (9p21.1)	dsRNA sensing	AD	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	Early aortic and valvular calcification, dental anomalies (early-onset periodontitis and root resorption, dental dysplasia), skeletal abnormalities, osteopenia, acro-osteolysis. glaucoma, psoriasis	[42]
		Deforming Arthropathy (DA)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		182250	MDA5 (or IFIH1)* (2q24.2)	dsRNA sensing	AD	GOF leading to constitutive activation of sensitivity to cytosolic RNA nucleic acids	Deforming arthropathy	[37, 43]
		Dyscromatosis Symmetrica Hereditaria (DSH)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		127400	ADAR1* (127400)	RNA editing	AR or DN	LOF leading to impaired RNA editing and aberrant sensing of cytosolic RNA species	hyperpigmented and hypopigmented macules on the face and dorsal aspects of the extremities that appear in infancy or early childhood	[35, 44-45]
	1.3 DNA repair							
		Ataxia Telangectasia (AT) and Immunodeficiency (ID)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		607585	ATM* (11q22.3)	dsDNA break repair	AR	LOF leading to dsDNA breaks	Ataxia Telangectasia	[46]
		Immunodeficiency (ID)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		602450	ARTEMIS (or DCLRE1C)* (10p13)	dsDNA break repair	AR	LOF leading to dsDNA breaks	Immunodeficiency	[47]
	1.4 Mitocondrial nucleic acid							
		Bilateral Striatal Necrosis (BSN) and Infantile Encefalopathy (IE)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		609060	PNPT1** (3q25.32)	Polynucleotide phosphorylase	AR	LOF targeting mitocondrial RNA	Bilateral striatal necrosis and infantile encefalopathy	[48]
		Cystic leukoencephalopathy without megaloencefphaly and AGS (unclear link)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		612951	RNASET2**	Ribonucleases	AR	Unknown	Cystic leukoencephalopathy without	**[**49-50]

			(6q27)	(RNases)			megaloencefphaly	
		616084	TRNT1** (3p26.2)	tRNA nucleotidyltransferase	AR	Unknown, likely mtd sRNA accumulation		**[**51-53]
2. Mutated protein acting indirectly on type I interferon signaling components or in an undefined manner								
	2.1 IFN-negative regulation							
		ISG-15 Deficiency						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		600555	ISG-15* (2q32.2)	ISG transcription inhibition	AR	LOF in molecules responsible for limiting IFNAR1-2 signaling, leading to uncontrolled ISG 15 production	Intracranial calcifications, seisures, Mendelian susceptibility to Mycobacterial infections	[54]
		Aicardi-Goutières syndrome (AGS)-like						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		607057	USP-18* (22q11.21)	ISG transcription inhibition	AR	LOF in molecules responsible for limiting IFNAR1/2 signaling, leading to uncontrolled ISG production	Aicardi-Goutières syndrome-like	[55]
	2.2 Post-IFN receptor cascade							
		Infection susceptibility and autoimmune diseases						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		600555	STAT1** (2q32.2)	ISG expression induction	AR	GOF leading to persistent ISG induction	hypothyroidism, alopecia, vitiligo, bronchiectasis	[56-57]
			Gene	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		600556	STAT2** (12q13.3)	ISG expression induction	AR	GOF leading to persistent ISG induction	neurodevelopmental delay, hypothyroisism, neuroinflammatory disease, progressive intracranial calcification, white matter disease, intracranial hemorrhage ,systemic inflammation and multiorgan dysfunction (recurrent fever, hepatosplenomegaly, cytopenia with marked thrombocytopenia, raised ferritin, and elevated liver enzymes. acute kidney injury with hypertension and nephrotic range proteinuria)	[58]
		Hypereosinophilia, hepatosplenomegaly and atopic dermatitis						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		147795	JAK1** (1p31.3)	IFN post-receptor signaling	AD	GOF leading to persistent ISG induction	Hypereosinophilia, hepatosplenomegaly and atopic dermatitis	[59]

		Penttinem Syndrome (overlapping PRAAS)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		601812	PDGFRB** (5q32)	tyrosine-kinase receptor	AD	GOF leading to STAT family activation, unclear mechanism	Prematurely aged appearance lipoatrophy, epidermal and dermal atrophy,hypertrophic lesions,thin hair, proptosis, underdeveloped cheekbones, marked acro-osteolysis,	**[**60]
	2.3 ER-Golgi							
		COPA Syndrome						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	*Ref.*
		601924	COPA* (1q23.2)	Vescicle transport	DN (dominant)	unclear	inflammatory arthritis, interstitial lung disease with alveolar hemorrages, pulmonary arterial hypertension, glomerulonefritis	[61]
	2.4 Complement							
		Monogenic SLE						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
			C1q*	Alternative complement pathway	AR	LOF leading to increased IFN signaling through an unknown mechanism (possibly through apoptotic DNA/RNA	Early onset Systemic Lupus Erythematosus (SLE)	[62-63]
	2.5 Unfolded Protein Response (UPR)							
		Trichohepatoenteric Syndrome (THES)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		222470	SKIV2L (5q15)*	RNA helicase	AR	LOF leading to aberrant RNA signaling via MAVS due to disruption of the UPR	Severe intractable diarrhea, hair abnormalities (trichorrhexis nodosa), facial dysmorphism, immunodeficiency	[64]
	2.6 Proteasome							
		Proteasome Associated Autoinflammatory Syndrome (PRAAS) including Cronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE), Joint contractures, Muscolar atrophy, microcytic anemia and Panniculitis-induced lipodystrophy (JMP), Japanese Autoinflammatory Syndrome with Lipodystrophy (JASL), Nakajo-Nishimura Syndrome (NNS) with nodular erythema, elongated and thickened fingers and emaciation						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		256040	PSMB8* (6p21.32)	Proteasome	AR	LOF causing proteasomal dysfunction leading to increased IFN signaling through an unknown mechanism	Recurrent fever, severe growth retardation, violaceous periorbital changes, panniculitis induced lipodystrophy, mild lymphocytic meningitis, headache, basal ganglia calcifications, ILD, non-erosive synovitis, arthralgia, myositis, recurrent infections, cytopenias, systemic hypertension, dyslipidemia,	[65-82]
		177045	PSMB9*	Proteasome	AR	LOF causing		

			(6p21.32)			proteasomal dysfunction leading to increased IFN signaling through an unknown mechanism	elevated acute phase reactants and hypergammaglobulinemia, Joint contractures, Muscolar atrophy, microcytic anemia and Panniculitis-induced lipodystrophy (JMP), Japanese Autoinflammatory Syndrome with Lipodystrophy (JASL), Nakajo-Nishimura Syndrome (NNS) with nodular erythema, elongated and thickened fingers and emaciation, orofacial and dental abnormalities	
		602177	PSMB4* (1q21.3)	Proteasome	AR	LOF causing proteasomal dysfunction leading to increased IFN signaling through an unknown mechanism		
		176843	PSMA3* (14q23.1)	Proteasome	AR	LOF causing proteasomal dysfunction leading to increased IFN signaling through an unknown mechanism		
		613386	POMP* (13q12.3)	Proteasome	DN (dominat)	LOF causing proteasomal dysfunction leading to increased IFN signaling through an unknown mechanism LOF		
	2.7 Undefined							
		Retinal Vascylopathy with Cerebral Leukodystrophy (SPENCD)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		607944	ACP5* (19p13.2)	Phosphatase	AR	LOF leading to increased IFN signaling through an unknown mechanism	Spondyloenchondrodysplasia (SPENCD), combined immundeficiency	[83-85]
		Monogenic SLE, Sjogren and Raynaud						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		607944	ACP5* (19p13.2)	Phosphatase	AR	LOF leading to increased IFN signaling through an unknown mechanism	Monogenic SLE, Sjogren and Raynaud	[86-89]
		Encefalopathy (IE) and Movement Disorders (MD)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***
		615273	NGLY1* (3p24.2)	N-deglycosylation	AR	LOF leadingto chronic IFN activation through an unknown mechanism	Infantile encefalopathy, movement disorders	[86-89]
		ADA2 deficiency (unclear)						
		OMIM	***Gene (locus)***	***Protein function***	***Inheritance***	***Mutation effect***	***Clinical picture***	***Ref.***

		615688	CECR1 (ADA2)** (22q11.1)	adenosine deaminase	AR	LOF, unknown mechanism	Early-onset stroke and vasculopathy, polyarterite nodosa, livedo reticularis	[90-92]