JEM Journal of Experimental Medicine

REVIEW

Genes and Immunity Focus

Monogenic disorders of the IRF transcription factors

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Interferon regulatory factors (IRFs) are a family of transcription factors essential for immune system development and host defense. Beyond immunity, IRF6 plays an indispensable role in craniofacial development. Inborn errors of IRFs (IE-IRFs) are a group of rare monogenic disorders caused by damaging variants in the IRF family of genes. In this review, we comprehensively discuss known IE-IRFs and how they contribute to our understanding of human biology, and provide a framework for their diagnosis and treatment. The IRF transcription factors mediate a wide range of biological functions. Accordingly, genetic defects in individual IRFs give rise to diverse human phenotypes, including increased susceptibility to infection, impaired immune development, and even congenital anatomical anomalies. Our collective understanding of IE-IRFs is a powerful example of how integration of clinical care with mechanistic translational research can transform the lives of patients while simultaneously advancing our fundamental understanding of human biology.

Introduction

Interferon regulatory factors (IRFs) were initially identified and named based on their ability to promote type I interferon (IFN) production (Miyamoto et al., 1988). Since then, nine human IRFs have been discovered: IRF1 through IRF9. In this review, we provide an overview of the structure and function of each known IRF as developed through *in vitro* experiments, mouse models, and human studies, a clinical description of known human inborn errors of IRFs (IE-IRFs), and an approach to their diagnosis and management.

Each member of the IRF family shares a highly conserved N-terminal DNA-binding domain (DBD) that interacts with DNA elements such as the IFN-stimulated response element (ISRE) (Fig. 1 A) (Escalante et al., 1998; Levy et al., 1988). The C terminus of IRFs has an IRF-associated domain (IAD), which is crucial for mediating interaction with other IRFs, transcription factors, and cofactors (Meraro et al., 1999; Sharf et al., 1997). IRF2 through IRF7 also have a C-terminal autoinhibitory domain (Bailey et al., 2005; Brass et al., 1996; Chen et al., 2008; Qin et al., 2003; Sathish et al., 2011; Yamamoto et al., 1994). The classic activation of the IRFs involves phosphorylation, homo- or heterodimerization, nuclear translocation, and DNA binding (Fig. 1 B).

Inborn errors of immunity (IEIs) are a group of disorders characterized by the absence or dysfunction of critical components of the immune system (Notarangelo et al., 2020; Turvey et al., 2024). Over 550 unique forms of IEI have been described, most resulting from damaging monogenic germline variants (Poli et al., 2025). A functioning immune system is key to human health: IEIs are therefore associated with broad manifestations spanning infection, autoimmunity, inflammation, and cancer. The majority of human IE-IRFs are IEIs, highlighting the crucial role of IRFs in immune function. The first IEI linked to an IRF variant was IRF8 deficiency, published in 2011 (Hambleton et al., 2011). This was followed by the description of IEIs caused by damaging genetic changes in *IRF7* and *IRF3* in 2015 (Andersen et al., 2015; Ciancanelli et al., 2015), *IRF4* and *IRF9* in 2018 (Guérin et al., 2018; Hernandez et al., 2018), and finally, *IRF1* in 2023 (Rosain et al., 2023). While no IEIs have been attributed to IRF2, IRF5, or IRF6, damaging variants in *IRF6* underlie developmental disorders that typically affect the orofacial region, including Van der Woude syndrome (VWS) and the more severe popliteal pterygium syndrome (PPS) (Kondo et al., 2002; Lees et al., 1999). A brief overview of key features of each human IE-IRF can be found in Table 1, with a comprehensive overview of peer-reviewed cases provided in Table 2.

Human IE-IRFs

IRF1

IRF1 was originally identified as a transcriptional regulator in IFN-induced signaling pathways, where it mediates antimicrobial responses (Harada et al., 1989; Miyamoto et al., 1988). Activation of type I IFN receptors and pattern recognition receptors (PRRs) allows IRF1 to bind to ISRE DNA elements, initiating transcription of type I IFN and a subset of IFN-stimulated genes

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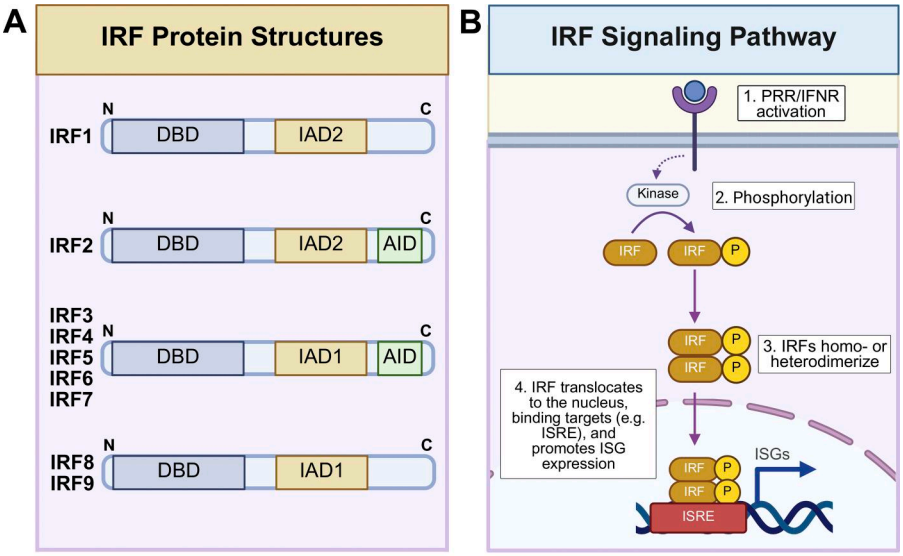

Figure 1. **Structural representations of IRF proteins and the IRF signaling pathway. (A)** IRF proteins are a family of transcription factors. The IRF DBD mediates interactions with DNA targets, the IAD mediates dimerization and interaction with other factors, and the autoinhibitory domain (AID) limits IRF activity. **(B)** Schematic overview of the IRF signaling pathway. PRR or IFN receptor activation triggers intracellular signaling leading to IRF phosphorylation, dimerization, nuclear localization, and modulation of gene expression, including ISG expression for most IRFs. Created in BioRender, https://BioRender.com/b0q00jx.

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(ISGs) (Fig. 2 A) (Harada et al., 1989; Harada et al., 1990). Mice deficient in IRF1 have impaired Th1 responses (Kamijo et al., 1994; Lohoff et al., 2000; Lohoff et al., 1997; Salkowski et al., 1999; Taki et al., 1997). Consequently, IL-12 production, IFN-γ response, natural killer (NK) cell development, and macrophage nitric oxide production are impaired. Thymocyte development is also impaired in *Irf1*-deficient mice with reduced $CD8^+$ T cells, impaired TCR-mediated signal transduction, and reduced MHC class I expression (Matsuyama et al., 1993; Penninger et al., 1997). *Irf1*$^{-/-}$ mice have elevated susceptibility to intramacrophagic pathogens, including *Mycobacterium bovis*, *Leishmania major*, and *Listeria monocytogenes* (Kamijo et al., 1994; Lohoff et al., 2000; Lohoff et al., 1997; Taki et al., 1997).

Autosomal recessive (AR) IRF1 deficiency was reported in two unrelated patients with severe forms of Mendelian susceptibility to mycobacterial disease (MSMD) (Rosain et al., 2023). MSMD is a monogenic disorder, which typically presents with early-onset life-threatening infections due to weakly virulent mycobacteria, including the bacillus Calmette–Guérin (BCG) vaccine strain, environmental mycobacteria, and related intramacrophagic pathogens (Hambleton et al., 2011; Khavandegar et al., 2024; Rosain et al., 2023). An inverse relationship between IFN-γ activity and both MSMD penetrance and severity has been recognized, emphasizing the importance of IFN-γ in antimycobacterial response (Cooper et al., 1995; Dupuis et al., 2000; Khan et al., 2016; Wenner et al., 1996). Reinforcing this relationship, MSMD is also caused by the disruption of a large number of genes crucial to IFN-γ immunity, such as *IL12B*, *IFNG*, and *IFNGR1* (Bustamante, 2020; Casanova and Abel, 2002; Shanmuganathan et al., 2022).

Both IRF1-deficient patients experienced recurrent mycobacterial disease, including disseminated BCG and *Mycobacterium avium* complex infection, without apparent susceptibility to other pathogens apart from one infection with histoplasmosis, an intramacrophagic fungus. Patients had reduced circulating dendritic cells (DCs), plasmacytoid DCs (pDCs), NK cells, innate lymphoid precursors, and type 2 innate lymphoid cells. Naïve $CD8^+$ and recent thymic emigrant $CD4^+$ T cells were dramatically reduced, while memory and terminally differentiated effector T cells were increased. The affected patients had homozygous variants in *IRF1* (p.R129* in P1 and p.Q35* in P2), resulting in complete IRF1 deficiency and abolished transcriptional activity. Despite normal blood levels, IFN-γ response was impaired in fibroblasts and myeloid and lymphoid cells, but IFN-α/β response was normal, other than impairment of a small subset of ISGs.

These findings support the importance of IFN-γ in antimycobacterial immunity and parallel impaired Th1 responses in *Irf1*$^{-/-}$ mice (Kamijo et al., 1994; Lohoff et al., 1997; Taki et al., 1997). Interestingly, IRF1 deficiency is not known to produce broad infection susceptibility, despite having a role in type I IFN response (Harada et al., 1989). This may be explained by *IRF1* primarily mediating only a small subset of ISGs and redundancy with IRF1-independent type I IFN production (Reis et al., 1994; Sato et al., 2000).

IRF2

IRF2 is typically described as a transcriptional repressor of ISGs, counteracting IRF1 by competing for the same DNA-binding sites, and limiting the harmful effects of excessive IFNs (Harada et al., 1989). IRF2 knockdown severely limits human NK cell proliferation, maturation, cytotoxic potential, and cytokine secretion (Persyn et al., 2022). Mouse models of IRF2 deficiency demonstrate impaired control of the inflammatory response with hyperactivation of $CD8^+$ T cells, further reinforcing the role of IRF2 in negative regulation of IFN signaling (Hida et al., 2000). IRF2-deficient mice also have impaired Th1 responses, immature NK cells, and poor control of *L. major* and lymphocytic choriomeningitis virus (Lohoff et al., 2000; Matsuyama et al., 1993; Salkowski et al., 1999; Taki et al., 2005). To date, no patients have been identified with monogenic IRF2 disease.

Table 1. **Common characteristics of IE-IRFs**

Gene		***IRF1***	***IRF3***		***IRF4***				***IRF6***		***IRF7***		***IRF8***		***IRF9***
Inheritance pattern		**AR**	**AD (HSE)**	**AD**	**AD (T95R)**	**AD (F359L)**	**AD (R98W)**	**AR (V405Gfs Ter127)**	**AD (VWS)**	**AD (PPS)**	**AR**	**AD**	**AR**	**AD**	**AR**
Mechanism		**LOF**	**HI**	**HI**	**MM**	**MM**	**HI**	**UPD**	**HI**	**DN**	**LOF**	**?**	**LOF**	**DN**	**LOF**
Bacterial susceptibility		✓			✓	✓	✓	?					✓	✓	
Viral susceptibility			✓	✓	✓	✓		✓			✓	✓	✓	✓	✓
Known pathogen range		Weakly virulent mycobacteria + *Histoplasma capsulatum*	HSV	Respiratory viral infections: Severe SARS-CoV-2 and influenza	*P. jirovecii*, vaccine strain BCG, *M. bovis*, CMV, EBV, … (see Table 2)	CMV, HSV, VZV, oral mycosis, *G. lamblia*, onychomycosis, … (see Table 2)	Tw	Rotavirus, *C. albicans*, HSV, respiratory infections (unknown cause)	No known infection susceptibility	No known infection susceptibility	Respiratory viral infections: severe SARS-CoV-2 and influenza + RSV, TBE virus, and adenovirus	Respiratory viral infections: severe SARS-CoV-2 and influenza	Weakly virulent mycobacteria		Respiratory viral infections: severe SARS-CoV-2 and influenza + eight other viruses (see Table 2)
													+ EBV, influenza, *C. albicans*, rhinovirus, HPV, CMV, and mycoplasma	+ EBV, HPV, recurrent *Clostridium difficile*	
Cellular abnormalities	CD4⁺ T cells	↑↓			↓	↑↓		↑↓					↓	↑	↓
	CD8⁺ T cells	↑↓				↑↓		↓					↓		
	NK cells	↓↓											↓		↓
	B cells	↑			↓↓	↓		↓					↓	↓	↓
	DCs	↓						↑↓					↓↓/↓↓↓	↓	
	Monocytes							↑↓					↓↓/↓↓↓	↑	
IFN impairment		IFN-γ	IFN-α/β	IFN-α/β	IFN-γ		IFN-γ	IFN-γ			IFN-α/β/λ1	IFN-α/β	IFN-γ	IFN-α	IFN-α
Gene expression defect		↓	↓	↓	↑↓	↑↓	↓	↓	Likely ↓		↓	↓	↓	↓	↓
Other defects		Reduced innate lymphoid precursors			Hypogammaglobulinemia	Hypogammaglobulinemia, premature hair graying		Agammaglobulinemia, hypereosinophilia, and hemophagocytosis	Lip pits and CLP	Lip pits, CLP, popliteal webbing, syndactyly, hypodontia, and deformities of the limbs and genitals	Impaired viral control in fibroblasts and pulmonary epithelia	Impaired IAV control in macrophages	Increased hypofunctional granulocytes. Intracerebral calcification and developmental delay	Mild neutrophilia	Impaired IAV control in fibroblasts, hypogammaglobulinemia

HI, haploinsufficiency; DN, dominant negative; MM, multimorphic; HSE, herpes simplex encephalitis; LOF, loss of function; TBE, tick-borne encephalitis; cellular abnormalities, abnormal count/function; IFN impairment, abnormal production/response; ↑, elevated; ↓, reduced; ↑↓, mixed effect or variable by genotype. See Table 2 for a detailed characterization of each IE-IRF.

Table 2. **Comprehensive overview of IE-IRFs**

Gene	Inheritance (mechanism)	OMIM	Known variants (# patients, # kindreds)	Effect on protein	Effect on gene expression	Cytokine defects	Major clinical features	Pathogen susceptibility	Effect on lymphoid cells	Effect on myeloid cells	Other effects	References
IRF1	AR (LOF)	620668	p.R129* (1, 1)	Elevated level but truncated	Reduced activity for ISRE5 and IRFE3. Impaired gene expression for leukocyte activation, cytokine signaling	Impaired IFN-γ response. Mild impairment of IFN-α/β response	Early-onset severe MSMD	Weakly virulent mycobacteria and *H. capsulatum*	Severe reduction of NK cells and ILC precursors. Reduced naïve $CD8^+$ T cells and RTE $CD4^+$ T cells. Elevated memory $CD8^+$, T_{FH}, effector T, and IgA+ memory B cells. Impaired Th1 response	Reduced cDC1, cDC2, and pDCs	Impaired control of mycobacteria in IRF1-deficient phagocytes	Rosain et al. (2023)
			p.Q35* (1, 1)	Produced but lacking the first 84 amino acids of the DBD								
IRF3	AD (HI)	616532	p.R285Q (1, 1)	Impaired phosphorylation and dimerization	Impaired *IFNB* promoter activity	Impaired type I/III IFN, CXCL10, and TNF-α	Healthy until HSE (ages 15 and 34). Incomplete penetrance	HSV-1	Not reported	Not reported	Reduced fibroblast IFN-β. Reduced interaction with innate adaptor proteins	Andersen et al. (2015); Mørk et al. (2015)
			p.A277T (1, 1)	Not reported								
		N/A	c.1576C>T (p.P447S) (1, 1)	Reduced in PBMCs, normal *in vitro*	Impaired ISG expression. Failed IRF7 upregulation	Impaired type I/III IFN, IL-6, and TNF-α	Severe respiratory viral infections	IAV & SARS-CoV-2	Not reported	Not reported		Thomsen et al. (2019b); Zhang et al. (2020)
			p.E49del (1, 1) p.N146K (1, 1)	Not reported								
IRF4	AR (UPD)	621097	p.V405GfsTer127 (1, 1)	Reduced level	Increased expression of genes associated with proinflammatory macrophage polarization	Impaired IFN-γ production	Intrauterine growth retardation, dermatitis, fevers, tachycardia, generalized adenopathy, hypoglycemia, and failure to thrive. HSCT at 2 years, died at day +2	Rotavirus, *C. albicans*, HSV, and respiratory infections with unknown cause	Reduced B cells, T_{FH}, Th17, Tregs, and memory T cells with a severe reduction of memory B and effector memory $CD8^+$ T cells. Elevated RTE $CD4^+$ T cells. Agammaglobulinemia. Elevated Th1:Th2 ratio	Hypereosinophilia, and hemophagocytosis. Severely reduced CD1a+ DCs and elevated pDCs	Abnormal lymph node architecture	Bravo García-Morato et al. (2018)
	AD (MM)		p.T95R (7, 6)	Normal protein level, impaired localization	Impaired expression of genes associated with plasma cell differentiation. Neomorphic upregulation of CXCL13	Impaired IL-12 and IFN-γ production. Reduced polyfunctional cells producing both IFN-γ and TNF-α	High susceptibility to opportunistic infection. Hypogammaglobulinemia. Early onset (<1 year). HSCT (2/7). Chronic diarrhea	P. jirovecii, CMV, EBV, vaccine strain BCG, *M. bovis*, *Escherichia coli*, enterovirus, *Streptococcus pneumoniae*, PIV, rhinovirus, *Streptococcus mitis*, *Aspergillus fumigatus*, and *Klebsiella pneumoniae*	Reduced $CD19^+$ B, memory B cells, Th17, and T_{FH}. Elevated naïve and transitional B cells. Impaired B cell maturation, isotype switching, plasma cell maturation, and agammaglobulinemia	None reported	Multimorphic: hypomorphic binding to canonical sites, neomorphic binding to novel targets, and hypermorphic binding to ISRE	Fornes et al. (2023)
			p.F359L (3, 1)	Normal level, and localization. DN effect on ISRE	Impaired ISRE binding but increased expression from AICE and EICE. Low expression of genes associated with plasma cell differentiation	Neomorphic binding to proteins for positive regulation of type I IFN production	High susceptibility to opportunistic infection. Hypogammaglobulinemia. Premature hair graying	CMV, *G. lamblia*, HSV, molluscum contagiosum, VZV, *C. albicans*, and onychomycosis	Childhood panhypogammaglobulinemia. Reduced plasmablasts, naïve $CD4^+$ & $CD8^+$ T cells. Elevated terminal effector $CD4^+$ and $CD8^+$ T cells	None reported	Altered binding with IRF4-associated proteins (↓ PC4, ↑ JUNB, novel binding ETV6)	Thouenon et al. (2023)
	AD (HI)		p.R98W (4, 1)	Elevated level. Normal nuclear localization	Impaired expression from ISRE and AICE. Decreased expression of STAT1 and CD80	Impaired expression of IFNG, LTA, and IL2RA	WD (2 classic WD, 2 with joint symptoms). Incomplete penetrance	Tw	None reported	None reported		Guérin et al. (2018)

Table 2. **Comprehensive overview of IE-IRFs (*Continued*)**

Gene	Inheritance (mechanism)	OMIM	Known variants (# patients, # kindreds)	Effect on protein	Effect on gene expression	Cytokine defects	Major clinical features	Pathogen susceptibility	Effect on lymphoid cells	Effect on myeloid cells	Other effects	References
IRF6	AD (VWS)	119300	Missense, nonsense, or splicing variants in the DBD and IAD	Primarily hypomorphic effect			Lip pits with or without CLP	No known infection susceptibility	None reported	None reported		Kondo et al. (2002); Peyrard-Janvid et al. (2005)
	AD (PPS)	119500	Missense, nonsense, or splicing variants in the DBD and IAD, with a high prevalence of missense variants near R84 in the DBD	Primarily dominant negative	p.S424L variant significantly reduced transcriptional activity. Loss of contact between DBD and DNA in p.R84C and p.R84H variants		CLP, lip pits, popliteal webbing, syndactyly, hypodontia, and deformities of the limbs and genitals	No known infection susceptibility	None reported	None reported	A single case of AR IRF6 variants has been linked to PPS	Kondo et al. (2002); Peyrard-Janvid et al. (2005); Matsuzawa et al. (2010); Leslie et al. (2015)
IRF7	AR (LOF)	616345	p.F410V/p.Q421* (1, 1)	Reduced level, impaired localization	Impaired expression of many ISGs, but normal upregulation of a subset of ISGs. Failed IRF7 upregulation	Impaired type I/II/III IFN. Normal IL-6 and TNF-α	Severe viral infections with one to three major episodes	Severe IAV and SARS-CoV-2. RSV, TBE virus and adenovirus	Increased memory T cells to SARS-CoV-2 infection or vaccination. Increased CD4⁺ T cells to IAV. Intact B cell responses	Normal pDC counts but impaired type I/III IFN production	Fibroblasts: impaired IFN-β and poor control of viral replication. Pulmonary epithelial cells: poor IRF7 and IFN-β production	Ciancanelli et al. (2015); Zhang et al. (2020); Campbell et al. (2022)
			p.A280GfsX12 (2, 1) p.W91* (1, 1) p.P364AfsX38 (1, 1) p.D117N/p.M371V (1, 1)	Reduced level								
			p.E28Q/A62T (1, 1)	Normal level								
	AD (likely LOF)	N/A	p.Q185* (1, 1)	Reduced level	Impaired response to IFN-β pretreatment but normal ISG (IFIT1) and TNFA expression	Impaired type I/II/III IFN	Severe SARS-CoV-2 (4/5) and influenza (1/5)	Severe IAV and SARS-CoV-2	Not reported	Not reported	Defective control of viral replication in monocyte-derived macrophages	Thomsen et al. (2019a); Zhang et al. (2020)
			p.E331V (isoform B, canonical p.E360V, 1, 1)	Normal level								
			p.R7fs (1, 1) p.P246fs (1, 1) p.R369Q (1, 1) p.F95S (1, 1)	Not reported								

Table 2. **Comprehensive overview of IE-IRFs (*Continued*)**

Gene	Inheritance (mechanism)	OMIM	Known variants (# patients, # kindreds)	Effect on protein	Effect on gene expression	Cytokine defects	Major clinical features	Pathogen susceptibility	Effect on lymphoid cells	Effect on myeloid cells	Other effects	References
IRF8	AR (LOF)	226990	p.K108E (1, 1)	Normal amount but altered structure/folding	Nearly inactive for *IL12B* and NOS2 promoters	Reduced IFN-γ, TNF-α, IL-17, IL-6, and IL-10. Impaired IL-12 response to IFN-γ pretreatment, absent at baseline	MSMD. HSCT curative	Weakly virulent mycobacteria and *C. albicans*	Reduced NK cells but elevated CD56bright population. Normal T and B cells	Severely reduced monocytes and DCs, reduced tissue macrophages. Elevated $CD34^+$ progenitors. >98% granulocytes with cultivation of stem cells		Hambleton et al. (2011); Salem et al. (2014); Mace et al. (2017)
			p.R83C/R291Q (1, 1)	Normal level but impaired nuclear localization	Reduced expression of IRF4 and IRF1. Impaired regulation of IRF1-driven ISRE activity. Failed expression from EICE. Altered gene expression pattern, including genes crucial to immune development, and function	Absent IL-12, reduced IFN-γ, IL-6, IL-10, and TNF-α levels. Elevated IL-10 in one case	Fatal in infancy (2/3). Recurrent viral infection, intracerebral calcification, disseminated BCGosis. Developmental delay, facial dysmorphism, and short stature (1/3). HSCT (1/3)	Influenza, rhinovirus, non-SARS-CoV-2 coronavirus, CMV, mycoplasma, and *Acinetobacter baumannii*	Reduced Th1, Th17, $CD3^+$, $CD8^+$ T cells, $CD8^+$ memory T cells, memory B cells. Reduced NK cell terminal differentiation with impaired B cell class switching and somatic hypermutation. One case with only mild $CD4^+$ lymphopenia with no other T cell defects	Increased dysfunctional granulocytes. Reduced or absent monocytes, pDCs, and cDC1s		Bigley et al. (2018); Dang et al. (2021); Rosain et al. (2022)
			p.R111*/p.R111* (1,1) p.R111*/c.55del (1, 1)	Reduced level of truncated protein and impaired localization								
	AD (DN)	614893	p.T80A (2, 2)	Normal level	Low activity for *IL12B* and NOS2 promoters. Impaired expression of genes vital for pDC function and development	Reduced IL-12 *in vitro* but normal in BCG-stimulated blood. Normal IFN-γ but impaired IFN-α production	MSMD (1/3), EBV viremia (1/3), and HPV-positive tumor (1/3)	Weakly virulent mycobacteria, EBV, and HPV	Elevated central and effector memory T cells. Impaired Th1 response. Decreased memory B cells, but increased IgG and normal IgA levels	Reduced pDCs, cDC1 DCs. Mild neutrophilia and monocytosis		Hambleton et al. (2011); Ham et al. (2025)
			p.*427Lext*42 (2, 1)	Impaired localization. DN effect on IRF8 and IRF1								
IRF9	AR (LOF)	618648	c.991G>A (IRF9-Δex7, p.D331N) (1, 1)	Transcripts missing exon 7, none with D331N. Formation of ISGF3 lost	Impaired ISRE activity and reduced expression of a wide range of canonical ISGs. Failed upregulation of IRF7	Impaired type I IFN production. Some IFN-α2 in blood	Repeated severe viral infections	IAV/IBV, SARS-CoV-2, adenovirus, PIV, MMR-strain virus, RSV, VZV, dengue fever, Zika virus, and enterovirus	Reduced B cells, $CD4^+$ T cells, and transient decrease in NK cells. Hypogammaglobulinemia	None reported	Fibroblasts: poor IFN-α2 response and impaired control of IAV and VSV. Prolonged IFNAR signaling and IFN-γ–like transcriptional profile	(Hernandez et al., 2018; Bravo García-Morato et al., 2019); Lévy et al. (2021b); Gothe et al. (2022)
			p. E166Lfs*80 (IRF9-Δex5) (2, 1)	No detectible protein								

HI, haploinsufficiency; DN, dominant negative; MM, multimorphic; ILC, innate lymphoid cell; RTE, recent thymic emigrant.

IRF3

IRF3 is critical for the early IFN response and, together with IRF7, amplifies the later stages of IFN signaling (Sato et al., 2000). IRF3 is phosphorylated and activated by PRRs, resulting in homodimerization, or heterodimerization with IRF7, promoting ISG expression (Fig. 2 B) (Liu et al., 2015; Osterlund et al., 2007; Sato et al., 2000). Mice deficient in IRF3 have poor production of type I IFNs and impaired control of viral infections, including influenza and HSV (Hatesuer et al., 2017; Menachery et al., 2010; Sato et al., 2000).

Autosomal dominant (AD) IRF3 deficiency predisposes to severe viral infections, including herpes simplex encephalitis (HSE), severe influenza, and SARS-CoV-2 pneumonia (Andersen et al., 2015; Mørk et al., 2015; Thomsen et al., 2019b; Zhang et al., 2020). Two cases of AD IRF3 deficiency underlying HSE have been described (Andersen et al., 2015; Mørk et al., 2015). The first patient developed HSE at age 15 years and was found to have a heterozygous *IRF3* variant (p.R285Q) inherited from a healthy father, demonstrating incomplete penetrance. This variant showed impaired phosphorylation, dimerization, and subsequent transcriptional activity for the *IFNB* promoter. The disease mechanism was attributed to haploinsufficiency as a dominant-negative effect was ruled out. The second patient (p.A277T) presented with HSE at age 34 years. Primary samples from both patients showed impaired cytokine production, namely, IFN-γ and CXCL10, in response to HSV-1.

More recently, AD IRF3 deficiency has also been linked to severe respiratory viral infections (Thomsen et al., 2019b; Zhang et al., 2020). A 55-year-old patient presented with a life-threatening infection caused by the influenza A virus (IAV) subtype H1N1. Sequencing identified a heterozygous variant in the 3′ untranslated region of *IRF3* (c.1576C>T), giving rise to p.P447S in one of eight splice variants (Thomsen et al., 2019b). IRF3 protein expression was reduced in patient PBMCs; however, it was normal in c.1576C>T overexpression systems. Patient cells infected with IAV had impaired induction of *IFNA2*, *IFNB*, and *IFNL1*. Importantly, IRF7 also failed to be upregulated, limiting the late-phase IFN response. Heterozygous missense *IRF3* variants were also found in two females with life-threatening COVID-19 at ages 23 and 60 years, respectively (Zhang et al., 2020). Patient variants were confirmed deleterious using an IFN-β reporter assay.

The impaired IFN responses observed in IRF-deficient humans mirror findings from models of IRF3 deficiency. Furthermore, mice and humans share infection susceptibility with both having an increased risk for viral pathogens, including HSV and influenza. The lack of a strong cellular phenotype in human IRF3 deficiency also aligns with mouse models. Together, these lines of data converge to confirm the crucial role of IRF3 in antiviral type I IFN responses.

IRF4

IRF4 (also know as Pip, LSIRF, ICSAT, MUM1) is not directly involved in IFN signaling but is instead expressed in T cells, B cells, and macrophages, where it is crucial to immune development and function (Eisenbeis et al., 1995; Matsuyama et al., 1995). Activation of antigen receptors, PRRs, and CD40 promotes IRF4 phosphorylation, enabling it to form homodimers or heterodimers with transcription factors such as PU.1 and BATF, thereby facilitating DNA binding and downstream gene regulation (Fig. 2 C) (Brass et al., 1996; Brass et al., 1999; De Silva et al., 2012; Li et al., 2012; Negishi et al., 2005; Ochiai et al., 2013; Remesh et al., 2015). IRF4 overexpression in human B cells stimulates plasma cell differentiation (Sciammas et al., 2006). Mouse models reinforce the importance of IRF4 in B cell function, including differentiation, receptor editing, proliferation, class switch recombination, and plasma cell formation (Klein et al., 2006; Maffei et al., 2023; Mittrücker et al., 1997; Ochiai et al., 2013; Sciammas et al., 2006). Beyond B cells, Irf4$^{-/-}$ mice also have impaired CD4^{+} and CD8α+ DC development, and T cell development, including Th1:Th2 balance and CD8^{+} T cell proliferation, function, and memory response (Aliberti et al., 2003; Harberts et al., 2021; Krishnamoorthy et al., 2017; Man et al., 2013; Mittrücker et al., 1997; Schiavoni et al., 2002). Consequently, *Irf4*-deficient mice are susceptible to a range of bacterial, viral, and parasitic infections (Honma et al., 2008; Man et al., 2013; Nayar et al., 2014; Raczkowski et al., 2013).

Damaging genetic variants in *IRF4* cause a range of immunodeficiencies, spanning combined immunodeficiency to a very specific predisposition to Whipple's disease (WD), with the nature of the immune defect determined by the impact of the genetic lesion on IRF4 function (Bravo García-Morato et al., 2018; Fornes et al., 2023; Guérin et al., 2018).

The first *IRF4*-linked IEI predisposed to WD (Guérin et al., 2018). WD is a rare complication of *Tropheryma whipplei* (Tw) infection, occurring in only 4.6 per 1 million hospitalizations in the United States (Ahmad et al., 2022). Before its association with IRF4, WD had not been linked to any IEIs. A study of a multiplex family with four WD patients and five Tw carriers suggested an AD predisposition to Tw with age-dependent incomplete penetrance (Guérin et al., 2018). All those who developed WD were previously healthy. The four WD patients and five Tw carriers were all heterozygous for the p.R98W variant in *IRF4*, although additional heterozygous family members were noncarriers of Tw, emphasizing the incomplete penetrance. The *IRF4* p.R98W variant failed to bind or activate ISRE or AICE promoters, and the disease mechanism was attributed to haploinsufficiency resulting from a lack of activity of the p.R98W IRF4 proteins present in the nucleus.

The second description of an IEI attributed to IRF4 was described in a 5-mo-old girl with intrauterine growth retardation, dermatitis, fevers, tachycardia, generalized adenopathy, hypoglycemia, and failure to thrive who was found to have a uniparental disomy of chromosome 6, resulting in the presence of a homozygous *IRF4* variant, c.1213-2A>G (p.V405GfsTer127). Infection history included rotavirus, *Candida albicans*, HSV, and respiratory infections with unknown cause. Notable immune features included agammaglobulinemia with absent memory B cells. The patient was treated with allogeneic hematopoietic stem cell transplant (HSCT) at 2 years and died at day +2. Although this patient exhibited striking phenotypic similarities to *Irf4*$^{-/-}$ mouse models, the genetic complexity introduced by uniparental isodisomy, coupled with the absence of functional validation, precludes definitive conclusions.

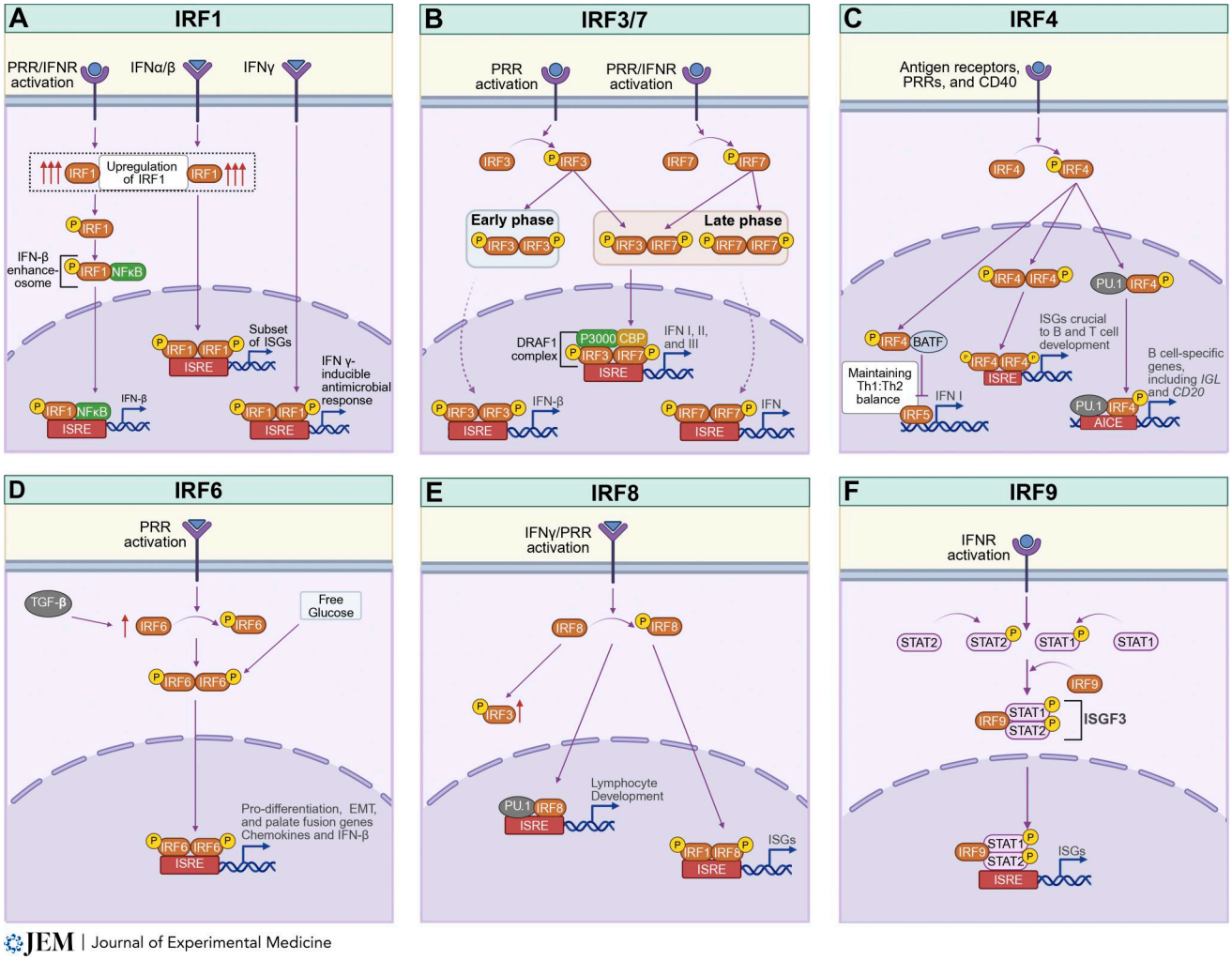

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Figure 2. **Key signaling pathways related to IE-IRFs.** IRFs primarily mediate the expression of ISGs from the ISRE in response to activation of IFNRs and PRRs. Dysregulation in these pathways leads to distinct clinical immunodeficiencies (IRF1, IRF3, IRF4, IRF7, IRF8, IRF9) or developmental syndromes (IRF6). **(A)** Upon binding the ISRE, IRF1 induces expression of a subset of ISGs. **(B)** IRF3 and IRF7 stimulate type I, II, and III interferon production. **(C)** IRF4 is crucial for lymphocyte development through interaction with the ISRE and AICE motifs. **(D)** IRF6 regulates genes required for epithelial differentiation and palate fusion. **(E)** IRF8 promotes lymphocyte development through interaction with the ISRE. **(F)** IRF9 complexes with STAT1 and STAT2 to form ISGF3, which drives ISG expression. AICE = AP-1-IRF composite element; EMT = epithelial–mesenchymal transition; and IFNRs, IFN receptors. Created in BioRender, https://BioRender.com/3h8qi1u.

In 2023, the IRF4 international consortium identified a multimorphic variant in *IRF4*, p.T95R, in seven patients from six kindreds, presenting with fully penetrant AD multimorphic IRF4 combined immunodeficiency (Fornes et al., 2023). Clinical characteristics indicated a significant combined immunodeficiency: all patients experienced severe infections within the first year of life from opportunistic pathogens such as *Pneumocystis jirovecii*, viruses (CMV and Epstein-Barr virus [EBV]), and weakly pathogenic mycobacteria (BCG and *M. bovis*). IRF4 mRNA and protein levels were normal. Patients had a notable B cell developmental arrest characterized by increased naïve and transitional B cells, reduced plasmablasts, decreased immunoglobulin isotype switching, and agammaglobulinemia. T_H17 and T_{FH} were reduced and, when stimulated, had decreased production of IL-12 and IFN-γ. This phenotype was replicated in both *Irf4* p.T95R knock-in mice and B cells transduced with *IRF4* p.T95R. The p.T95R variant had dominant-negative and hypomorphic effects, which failed to upregulate canonical IRF4 targets. Furthermore, a novel subset of genes was upregulated, demonstrating a neomorphic effect. There was also a hypermorphic effect with increased noncanonical DNA-binding activity. Together, the mechanism of this *IRF4* p.T95R disease was surprising and novel with a simultaneous multimorphic combination of dominant loss, gain, and new functions for IRF4. Thus, this discovery expanded the classic description of "Müller's morphs" (Muller, 1932).

The final IEI currently linked to IRF4 was found in a family with AD IRF4 deficiency. The three affected family members displayed recurrent infections, hypogammaglobulinemia, abnormal T cell subsets, and early hair graying (Thouenon et al., 2023). This early hair graying is intriguing given that *IRF4* polymorphisms have been linked to hair graying and skin color

(Adhikari et al., 2016; Han et al., 2008). Infections were caused by a variety of pathogens including CMV, *Giardia lamblia*, HSV, varicella-zoster virus (VZV), molluscum contagiosum, and fungi. All affected patients received intravenous immunoglobulin (IVIG) for hypogammaglobulinemia as children, with antibody levels normalizing by adulthood. Immunophenotypic analysis revealed impaired plasmablast differentiation with low plasma cells and abnormal T cell phenotypes, including low naïve and elevated terminal effector $CD4^+$ and $CD8^+$ T cells. Each patient carried *IRF4* p.F359L, with no impairment of mRNA and protein production or localization. *IRF4* p.F359L had a dominant-negative effect on the ISRE and elevated binding to AICE and EICE, with an overall shift in gene expression from ISRE to AICE sites, opposing the normal shift from AICE to ISRE sites during B cell development (Cocco et al., 2020; Ochiai et al., 2013). This resulted in low expression of genes associated with B cell differentiation, including *PRDM1*, *XBP1a201v*, and *CD38*.

When considered together, this series of IEIs caused by damaging variants in *IRF4* highlights the importance of this transcription factor in lymphocyte development, resulting in a unifying phenotype of broad immunodeficiency, altered lymphocyte development, and impaired antibody production that mirrors models of IRF4 deficiency. Moreover, this series of IRF4-related IEIs vividly emphasizes that it is essential to consider variant-specific effects in human IE-IRFs.

IRF5

IRF5 is an important mediator of cytokine production downstream of PRRs, with activation resulting in IRF5 phosphorylation, homodimerization, nuclear translocation, and stimulation of proinflammatory gene expression, including type I IFNs (Banga et al., 2020; Barnes et al., 2001; Barnes et al., 2004; Chen et al., 2008; Takaoka et al., 2005). Human leukocytes deficient in IRF5 have impaired B cell activation, plasmablast differentiation, and production of immunoglobulins, reactive oxygen, and nitrogen species, with impaired response to influenza and poor clearance of intracellular bacteria (De et al., 2017; Forbester et al., 2020; Hedl et al., 2019). Murine models reinforce the role of IRF5 in immune function, including cytokine and chemokine production and Th1 and proinflammatory M1 macrophage polarization (Feng et al., 2012; Sun et al., 2016; Takaoka et al., 2005; Weiss et al., 2015; Yanai et al., 2007). $Irf5^{-/-}$ mice are susceptible to a range of bacterial and viral pathogens (Paun et al., 2008).

No cases of monogenic human IRF5-mediated disease have been identified; however, IRF5 has been implicated as a polygenic risk locus for SLE, systemic sclerosis, Sjögren's syndrome, and inflammatory bowel disease (Dideberg et al., 2007; Graham et al., 2006; Hou et al., 2023; López-Briceño et al., 2024; Miceli-Richard et al., 2009; Saigusa et al., 2015; Sigurdsson et al., 2008; Sigurdsson et al., 2005; Wang et al., 2019; Xu et al., 2016). The link between IRF5 and SLE is further supported by IRF5-deficient mice showing resistance to murine lupus (Ban et al., 2021; Pellerin et al., 2023; Pellerin et al., 2021; Song et al., 2020).

IRF6

Expanding the biological repertoire of the IRF family, the main roles of IRF6 are outside the immune system. IRF6 is primarily expressed in epithelial cells, where it is activated by PRRs and free glucose, resulting in phosphorylation, dimerization, and nuclear translocation (Fig. 2 D) (Bailey et al., 2008; Kwa et al., 2014; Lopez-Pajares et al., 2025; Wright et al., 2024). IRF6 then binds the ISRE motif to mediate chemokine production, epidermal differentiation, epithelial–mesenchymal transition, and palate fusion (Bailey et al., 2008; Ke et al., 2019; Ke et al., 2015; Kwa et al., 2014; Lopez-Pajares et al., 2025). IRF6-deficient human keratinocytes have severe impairments of differentiation, cell–cell adhesion, and migration, with a loss of both polarization and the ability to move as a collective epithelial sheet (Ghassibe-Sabbagh et al., 2021; Girousi et al., 2021). Complete ablation of *Irf6* in murine models is lethal in early development (Ingraham et al., 2006; Richardson et al., 2006). The targeted expression of IRF6 in the basal epithelium of Irf6 knockout mice partially rescues their phenotype, with embryos surviving the perinatal period; however, orofacial clefting and palate and tongue adhesions remain (Kousa et al., 2017). *Irf6*-deficient mice have a failure of terminal epidermal differentiation, causing abnormal skin, limb, and craniofacial development (Carroll et al., 2025; Ingraham et al., 2006; Richardson et al., 2006).

In humans, damaging *IRF6* variants cause monogenic VWS and PPS, which result in cleft lip/palate (CLP) and other developmental differences (Kondo et al., 2002; Kumaran et al., 2004; Murray et al., 1990; Schutte et al., 1999; Zucchero et al., 2004). VWS is the most common syndromic form of CLP, resulting in the development of lip pits (i.e., depressions of the lower lip or blind-ended fistulae) with or without CLP (Bennun et al., 2018; Busche et al., 2016; Kondo et al., 2002; Kumaran et al., 2004). PPS extends this phenotype to also include popliteal webbing, syndactyly, hypodontia, and deformities of the limbs and genitals (Bennun et al., 2018; Kondo et al., 2002; Lees et al., 1999; Leslie et al., 2015; Soekarman et al., 1995).

Both VWS and PPS are primarily inherited through AD *IRF6* variants with variable expressivity and incomplete penetrance (Alade et al., 2020; Escobar and Weaver, 1978; Kondo et al., 2002; Leslie et al., 2015). A single case of AR *IRF6* variants has also been linked to PPS (Leslie et al., 2015). Most PPS- and VWS-associated variants are in the DBD and IAD, with a high prevalence of missense variants near R84 in the DBD in PPS (Alade et al., 2020; Busche et al., 2016; de Lima et al., 2009; Kondo et al., 2002; Leslie et al., 2013; Matsuzawa et al., 2010; Peyrard-Janvid et al., 2005).

Due to the phenotypic similarities between VWS and PPS, it is hypothesized that they are a spectrum of the same disorder (Kondo et al., 2002; Leslie et al., 2013; Soekarman et al., 1995). This concept is supported by variants shared across both diagnoses, and some families have both diagnoses across multiple generations (Busche et al., 2016; de Lima et al., 2009). Others suggest that these syndromes are allelic with IRF6 haploinsufficiency due to protein-truncating variants resulting in VWS, and dominant-negative missense variants in functional domains of IRF6 underlying PPS; however, the existence of variants shared across syndromes complicates this model framework (de Lima et al., 2009; Kondo et al., 2002). Finally, *IRF6* polymorphisms may also increase the risk and/or severity of nonsyndromic CLP (Alappat et al., 2025; Askarian et al., 2023;

Bezerra et al., 2020; Leslie and Marazita, 2013; Ludwig et al., 2012; Nasroen et al., 2023; Zhang et al., 2024).

IRF7

IRF7 is vital in the late IFN response where IFN stimulation results in homodimerization or heterodimerization with IRF3, promoting ISG expression (Fig. 2 B) (Marié et al., 1998; Marié et al., 2000; Osterlund et al., 2007; Sato et al., 1998; Sato et al., 2000). *Irf7*$^{-/-}$ mice have impaired production of type I IFNs and are susceptible to viral pathogens, including influenza (Hatesuer et al., 2017; Honda et al., 2005; Sato et al., 2000). IRF7-deficient patients reveal a predisposition to severe viral infections, including IAV, SARS-CoV-2, respiratory syncytial virus, and adenovirus (Campbell et al., 2022; Ciancanelli et al., 2015; Thomsen et al., 2019a; Zhang et al., 2020). Both AR and AD forms of IRF7 deficiency have been described.

AR IRF7 deficiency was first described in a 2.5-year-old with severe H1N1 IAV causing acute respiratory distress syndrome who carried compound-heterozygous missense variants in *IRF7* (Ciancanelli et al., 2015). Both variants disrupted IRF7 localization with loss of function for *IFNB*, *IFNA4*, and *IFNA6* promoters. Type I and III IFNs were reduced in patient PBMCs at baseline, and IFN-α, IFN-β, and IFN-λ1 responses were impaired to 11 different viruses. Interestingly, some ISGs known to inhibit IAV replication were upregulated normally, possibly through intact IFN-β signaling. Patient fibroblasts and fibroblast-derived pulmonary epithelial cells also had reduced IRF7 expression and poor IFN-γ responses. Interestingly, the patient's lack of severe influenza infections since vaccination suggests that IRF7 is likely redundant for vaccine-mediated influenza immunity.

AR IRF7 deficiency also underlies severe SARS-CoV-2 infections (Zhang et al., 2020). Two patients carrying biallelic damaging *IRF7* variants had no history of clinically significant viral infections until the ages of 49 and 50 years, when they developed severe COVID-19. IRF7 protein production was reduced, and patient pDCs were unable to produce type I or III IFNs upon exposure to SARS-CoV-2. In a follow-up study, four additional patients with AR IRF7 deficiency were described, which broadened the viral susceptibility phenotype to include SARS-CoV-2, influenza, respiratory syncytial virus, and adenovirus (Campbell et al., 2022). These patients typically had one to two episodes of pulmonary viral infections, with ages of onset ranging from 6 mo to 38 years. Transcriptional activity was reduced or absent for all variants. No IRF7 could be detected in patient PBMCs stimulated with IFN-β, and IFN-α response was impaired in PRR-stimulated pDCs. Adaptive responses to SARS-CoV-2 infection and vaccination were intact.

The first description of AD IRF7 deficiency was in an adult with severe influenza infection who was heterozygous for the p.E331V variant in the inhibitory domain of IRF7 (Thomsen et al., 2019a). Neither IRF7 mRNA nor protein levels were affected, but patient PBMCs had impaired IFN-β priming with reduced upregulation of *IFNB*, *IFNA2*, and *IFNL1*. Patient-derived macrophages had impaired control of IAV replication. This discovery was significantly expanded by the addition of five additional patients with AD IRF7 deficiency (p.R7fs, p.Q185*, p.P246fs, p.R369Q, and p.F95S) who all experienced severe COVID-19 (Zhang et al., 2020). Functional workup of these additional patients found both low IRF7 expression and low type I IFN production in vivo during SARS-CoV-2 infection.

Together, these studies confirm that both AR and AD IRF7 deficiencies present with susceptibility to a narrow range of respiratory viral infections, commonly SARS-CoV-2 and IAV. Memory responses were intact, suggesting that severe infection likely results from the disruption of both type I and III IFNs in pDCs and respiratory cells. Immunity to less virulent pathogens may stem from the small amounts of residual IFN-β, providing some level of protection. Patients with IRF7 deficiency share a similar presentation to models of IRF7 deficiency. Both have impairments of IFN production, and susceptibility to viral infections in the absence of a strong cellular phenotype.

IRF8

IRF8 (also known as ICSBP) is primarily expressed in myeloid and lymphoid cells, where, upon PRR or IFN-γ binding, IRF8 is phosphorylated, promoting heterodimer formation with PU.1, IRF1, or IRF2, and subsequent ISG expression (Fig. 2 E) (Bovolenta et al., 1994; Driggers et al., 1990; Eklund et al., 1998; Li et al., 2011; Nelson et al., 1996; Sharf et al., 1997; Tailor et al., 2007). *In vitro* models demonstrate the importance of IRF8 in the development and function of macrophages, DCs, and B cells, including in the production of IFN and specific antibodies (Gupta et al., 2015; Lee et al., 2006; Scheller et al., 1999; Schiavoni et al., 2002; Tailor et al., 2007; Tamura et al., 2000; Tsujimura et al., 2003). Similar findings are observed in *Irf8*$^{-/-}$ mice, which have a Th2 bias, elevated granulocytes, impaired development of B cells from the pre-pro-B cell stage, and poor development of CD8α^{+} and CD4^{-}CD8α^{-} DC subsets (Aliberti et al., 2003; Giese et al., 1997; Schiavoni et al., 2002; Tailor et al., 2008; Tamura et al., 2005; Wang et al., 2008). *Irf8*-deficient mice are susceptible to a range of bacterial and parasitic infections, particularly with intramacrophagic pathogens such as *M. bovis* (Alter-Koltunoff et al., 2008; Fortier et al., 2009; Marquis et al., 2009; Scharton-Kersten et al., 1997; Turcotte et al., 2007).

Genetic variants in *IRF8* cause both AR and AD forms of MSMD, with the recessive form being more severe (Hambleton et al., 2011). The phenotype of IRF8-related disease later expanded to encompass a more complex immunodeficiency syndrome as more patients were identified (Bigley et al., 2018; Mace et al., 2017; Salem and Gros, 2013).

AR IRF8 deficiency was first recognized in a 10-wk-old patient with disseminated BCG infection, oral candidiasis, and cachexia (Hambleton et al., 2011). She had absent DCs and monocytes, variable tissue macrophages, elevated neutrophils, and CD34^{+} progenitors. Monocyte development was severely impaired, with growth factor–stimulated circulating stem cells producing >98% granulocytes. Stimulated whole blood had low IFN-γ, TNF-α, IL-10, IL-6, and absent IL-12. CD4^{+} T cells had poor secretion of IFN-γ, IL-17, and IL-10, with only a partial IFN-γ response following IL-12 preincubation. Sequencing revealed a homozygous missense variant (p.K108E) located in the DBD of IRF8. This variant altered protein structure/folding and was nearly inactive for *IL12B* and *NOS2* promoters. A cord-blood HSCT was curative. Although the initial description focused on

the MSMD phenotype, the index patient did show broader susceptibility, including oral candidiasis and severe respiratory viral infection (Salem et al., 2014).

A subsequent patient who was compound-heterozygous for two damaging *IRF8* variants (p.R83C/p.R291Q) presented with recurrent viral infections, granuloproliferation, BCGosis, intracerebral calcification, and developmental delay (Bigley et al., 2018). Further assessment revealed low T cells, impaired B cell class switching, somatic hypermutation, and maturation with dysplastic and hypofunctional granulocytes. A third case of AR IRF8 deficiency was later reported in a neonate with severe neutrophilia, monocytopenia, impaired IFN-γ response, and recurrent and eventually fatal infection in infancy (Dang et al., 2021). Further testing revealed homozygous *IRF8* variants p.R111*, reduced *IRF8* mRNA, and elevated IL-4, IL-6, and IL-10. More recently, another infant was found to have AR IRF8 deficiency, carrying compound-heterozygous *IRF8* variants: c.55del and p.R111* (Rosain et al., 2022). The infant died at 10 months of refractory pulmonary alveolar proteinosis following a history that included sepsis, respiratory distress, viral pulmonary disease, disseminated BCGosis, facial dysmorphism, short stature, and intracerebral calcification. p.R111* resulted in absent IRF8 protein expression and c.55del, which was predicted to produce a truncated protein, p.D19Tfs*8, due to reinitiation of transcription at p.M22. Both p.R111* and c.55del had loss-of-function in a luciferase reporter system, with impaired repression of IRF1-mediated ISRE transcriptional activity. Further assessment revealed an accumulation of neutrophils, absent monocytes, cDC1, pDCs, mild $CD4^+$ lymphopenia, and B cell lymphopenia with low memory B cells. Platelet counts were also low, and there was impaired IFN-γ, IL-1β, IL-10, IL-12p70, IL-23, and TNF-α production, but normal IFN-α.

Four patients with AD IRF8 deficiency have been reported. The first two were heterozygous for a *de novo* IRF8 p.T80A variant (Hambleton et al., 2011). Following BCG vaccination, one had repeated chronic granulomatous tuberculoid lesions and lymphadenopathy at 1–2 years of age, and the other had recurring lymphadenopathy spanning 30 years. Both were managed successfully with antimycobacterial drugs. The T80A variant did not affect the IRF8 protein level or stability but impaired the expression of target promoters *IL12B* and *NOS2*, with a dominant-negative effect over wild-type IRF8. $CD1c^+$ DCs were reduced with poor IL-12 production *in vitro*, but normal IL-12 production in BCG-stimulated whole blood. IFN-γ production was normal, unlike recessive IRF8 deficiency. Two more patients were later identified with AD IRF8 deficiency (Ham et al., 2025). The proband presented with persistent EBV viremia, and the mother presented with an HPV-positive tumor. Both carried an *IRF8* variant c.1279dupT (p.*427Lext*42), which resulted in extension of the IRF8 protein by 42 amino acids. This elongated IRF8 protein had impaired nuclear translocation with a dominant-negative effect on wild-type IRF8 and IRF1, resulting in abnormal transcriptional and proteomic profiles, including those associated with pDC function and development and cytokine function. It is worth noting that the proband also carried a STAT3 variant (p.G743V); however, functional testing revealed no STAT3 abnormalities. Both patients had reduced pDCs, cDC1s, elevated central and effector memory T cells, mild neutrophilia, and mild monocytosis. The proband also had decreased memory B cells, but both had increased IgG and normal IgA levels. NK cell subsets and function were normal. Notably, neither had a history of mycobacterial infection; however, neither was vaccinated for BCG, and it is possible they had not been exposed.

When considered together, these phenotypes align with the known roles of IRF8 in myeloid and lymphoid development (Lee et al., 2006; Tailor et al., 2008; Tamura et al., 2005). AD IRF8 deficiency typically causes a limited MSMD phenotype, while the more severe AR IRF8 deficiency results in a broader immunodeficiency.

IRF9

IRF9 (also known as p48, ISGF3γ) is integral to IFN responses by mediating ISG expression as a part of the ISGF3 complex with STAT1 and STAT2 (Fig. 2 F) (Bluyssen et al., 1996; Fu et al., 1990; Kimura et al., 1996; Odendall and Kagan, 2015; Paul et al., 2018). IRF9 is also crucial for positive feedback in the late phase of the IFN response, by mediating the expression of IRF7 (Sato et al., 1998; Sato et al., 2000). Mouse models of IRF9 deficiency have impaired NK cell survival, B cell function, class-switched antibody production, DC response, and elevated $CD8^+$ T cell exhaustion, with susceptibility to a range of viral pathogens (Geary et al., 2018; Hofer et al., 2012; Huber et al., 2017; Thibault et al., 2008).

AR IRF9 deficiency predisposes to viral infections with a broader range of susceptibility than seen in patients with other deficiencies in IRFs crucial to type I IFN responses such as IRF3 and IRF7 (Bravo García-Morato et al., 2019; Hernandez et al., 2018). The first patient with AR IRF9 deficiency presented with severe influenza at the age of 2 years (Hernandez et al., 2018). She experienced RSV, IAV, adenovirus, parainfluenza virus infections, recurrent bronchiolitis, and recurrent fevers of unknown cause. She was repeatedly admitted to the intensive care unit, including one admission for septic shock without a detectable pathogen. Sequencing identified a homozygous variant in *IRF9*, c.991G>A, affecting the final nucleotide of exon 7. Although predicted to cause an amino acid substitution (p.D331N), the variant was also shown to disrupt splicing of exon 7, which forms a large portion of the IAD. No variant transcripts were detected. IRF9-Δex7 lost the ability to form ISGF3, and ISRE binding was impaired. Patient-derived fibroblasts and B cells had impaired ISG modulation, and fibroblasts also failed to control IAV replication, even with IFN-α2b pretreatment.

Later, a set of siblings with AR IRF9 deficiency was described (Bravo García-Morato et al., 2019). The proband had multiple severe viral infections beginning in the first year of life, including RSV and disseminated postvaccination VZV, resulting in prolonged intensive care unit stays, persistent neurological impairment, and bronchiectasis. The proband had mild $CD4^+$ T and B lymphopenia with low IgG, and the sister had transient NK and B lymphopenia. IVIG was started at the ages 9 years for the proband and 3 wk for the sister from which point neither experienced any severe disease episodes. Both carried a homozygous splicing variant causing skipping of exon 5 and a premature stop codon c.577+1G>T (p.Glu166LeufsTer80). IRF9 protein was

not produced, and stimulated patient-derived fibroblasts and PBMCs failed to induce ISGs. Notably, the upregulation of *IRF7* was also lost, which may contribute to the family's severe phenotype. Nevertheless, these findings should be interpreted with some caution, however, as consanguinity was present and only panel sequencing was performed. It is possible that other variants may contribute to the patient phenotype, given that the AR IRF9 patient reported by Hernandez et al. did not share the same cellular phenotype (Hernandez et al., 2018).

Due to its importance in the IFN response, it is unsurprising that damaging variants in IRF9 increase susceptibility to viral infections. IRF9-deficient patients also share many other similarities with models of IRF9 deficiency, including impaired IFN production, ISG expression, and cellular phenotypes of impaired NK cells, B cells, and poor class-switched antibody production.

Clinical approach to the diagnosis and management of IE-IRFs

IE-IRFs present with a broad range of clinical manifestations and span several classification categories proposed by the International Union of Immunological Societies (Poli et al., 2025). When evaluating a patient, the specific IE-IRF to consider will therefore depend on their clinical features. We recommend a baseline immunological assessment including complete blood count with differential, serum immunoglobulin levels, specific vaccine titers, and enumeration of T, B, and NK cells by flow cytometry. These studies may provide important clues to an underlying IE-IRF, such as absent monocytes in the setting of IRF8 deficiency or B cell developmental arrest in IRF4 defects. Additional specialized diagnostic immunology tests may be considered depending on the conditions under consideration and local testing availability.

In many instances, however, baseline immunology evaluation may be normal despite an underlying IE-IRF. Therefore, in combination with this baseline assessment, we advocate for a "genetics-first" approach for securing a definitive diagnosis. While gene panels are popular and cost-effective, clinicians must be aware no panel is completely comprehensive. Therefore, whole-exome (or even whole-genome) sequencing should be considered if a gene panel is negative but clinical suspicion remains high. A diagnosis can be made when a known disease-causing genetic variant is found in a patient with a compatible clinical phenotype. However, if a variant of uncertain significance is found, a current challenge for the field is that functional assessment of such candidate variants is limited to the research domain.

Treatment approaches for IE-IRFs are tailored to the patient and their underlying disease. First and foremost, it must be noted that most IE-IRFs present with pathogen susceptibility, either broad or limited to a small group of pathogens. Patients diagnosed with an IE-IRF should be monitored closely for infection, particularly for those where the patient is at high risk (e.g., HSE in some AD IRF3 cases). Treatments often combine prophylaxis to prevent infection with key pathogens (e.g., *P. jirovecii* in IRF4 defects) and immunoglobulin replacement in patients with antibody production defects (e.g., AR IRF9 deficiency). Attenuated live vaccines should be used with caution in IE-IRFs with poor control of pathogen replication, such as avoidance of BCG vaccination in cases with susceptibility to weak mycobacterial infections (AR IRF1, AD IRF4, and AD/AR IRF8 deficiencies). Treatments designed to supplement defective IFN production have also been used, such as recombinant IFN-γ in IRF1 deficiency or Peg-IFN-α2a treatment in a patient with AD IRF3 deficiency (Lévy et al., 2021a; Rosain et al., 2023). Furthermore, antiviral monoclonal antibodies, such as casirivimab and imdevimab, have been effective in one case of AR IRF9 deficiency to prevent severe COVID-19 (Lévy et al., 2021b). However, because of the severity of the broad immune defect in some IRF-deficient patients, potentially curative HSCT may be indicated (e.g., IRF4 and IRF8) (Bigley et al., 2018; Bravo García-Morato et al., 2018; Fornes et al., 2023; Hambleton et al., 2011). Finally, as IRF1, IRF3, IRF8, and IRF7 have been proposed to play a role in tumor suppression, clinicians should be aware that patients may have a risk of tumorigenesis; however, only AD IRF8 deficiency has been definitely associated with tumor development (Ham et al., 2025; Holtschke et al., 1996; Nozawa et al., 1999; Qing and Liu, 2023; Turcotte et al., 2005; van der Weyden et al., 2017; Wang et al., 2024).

As IRF6 variants are primarily linked to CLP, the approach to diagnosis and treatment differs from the other IE-IRFs. In the case of VWS or PPS, genetic testing should be performed to confirm a link to IRF6 variants. Regardless of the underlying cause, surgical reconstruction may be required for CLP, and for the correction of knee flexion contracture in some PPS patients (Bennun et al., 2018; Gardetto and Piza-Katzer, 2003). Studies support the importance of early surgical intervention for PPS patients (Dobs et al., 2021; Gardetto and Piza-Katzer, 2003).

How the characterization of human IE-IRFs has shaped our understanding of fundamental IRF biology

Our understanding of the biological roles of IRFs has been greatly enriched by the study of rare human IE-IRFs. For example, IRF1 was initially described as a transcription factor mediating IFN response to viruses; however, through reports of human IRF1 deficiency we learn that IRF1 is largely dispensable for type I IFN production and antiviral response (Miyamoto et al., 1988; Rosain et al., 2023). Instead, patients have profound susceptibility to mycobacterial infection because of impaired IFN-γ response. Furthermore, IRF1-deficient patients have impaired Th1 responses, altered dendritic, T, and NK cell development, and reduced expression of genes vital to leukocyte activation, supporting roles of IRF1-mediated signaling in leukocyte development and function, aligning with findings in mouse models (Gabriele et al., 2006; Lohoff et al., 2000; Taki et al., 1997).

Similarly, IRF3, IRF7, and IRF9 were proposed to be vital to the early and late phases of IFN response (Kimura et al., 1996; Sato et al., 2000). This is validated by the findings of impaired type I IFN responses and subsequent viral susceptibility in human IRF3, IRF7, and IRF9 deficiency (Campbell et al., 2022; Hernandez et al., 2018; Thomsen et al., 2019b). The role of IRF9 in both type I and III IFN signaling, stronger cellular phenotype, and the broad expression of IRF9 may explain its wider infectious susceptibility phenotype than that seen in IRF3 or IRF7 deficiency (Coccia et al., 2004; Paul et al., 2018).

The pleiotropic functions of the IRF family are nicely illustrated by IRF8 deficiency, which was initially described as a

cause of MSMD, but is now appreciated to cause a more complex syndrome spanning abnormal hematopoiesis, immunodeficiency, and immune dysregulation (Bigley et al., 2018; Hambleton et al., 2011). Not surprisingly, IRF8-deficient patients share some similarities to those deficient in IRF1, including predisposition to mycobacterial infections, as both have important roles in Th1 responses, by mediating IFN-γ and IL-12 signaling (Cooper et al., 1995; Schiavoni et al., 2002; Taki et al., 1997). However, compared with IRF1 deficiency, damaging genetic variants in IRF4 and IRF8 cause more profound cellular defects and a broader spectrum of immunodeficiency, reinforcing the important roles of IRF4 and IRF8 in the development and function of both lymphoid and myeloid cells (Lee et al., 2006; Matsuyama et al., 1995; Yamagata et al., 1996). Furthermore, the AD and AR IRF4-deficient patients have a broad range of clinical presentations determined by their genotype, supporting the theorized dose- and context-dependent functions of IRF4 (Himmelmann et al., 1997; Ochiai et al., 2013; Krishnamoorthy et al., 2017; Cook et al., 2020). Some features shared by all IRF4-deficient patients, including defects in B cell maturation, isotype switching, and plasma cell differentiation, support the crucial role of IRF4 in B cell development and function (Lu et al., 2003).

IRF6 is unique in that its role is primarily outside of immune function, instead being vital to orofacial development, skin, and limb development (Kondo et al., 2002). Patients deficient in IRF6 present with a broad range of phenotypes from lip pits without CLP in some VWS cases, to severe developmental deficiencies with CLP, popliteal webbing, syndactyly, hypodontia, and deformities of the limbs and genitals in PPS patients. Together, this illustrates the role of IRF6 in guiding the development and organization of tissue throughout the body by mediating terminal epidermal development, reinforcing similar findings in IRF6-deficient mice (Carroll et al., 2025; Ingraham et al., 2006; Richardson et al., 2006).

Conclusion

The IRF family of proteins is central to many biological processes, explaining the range of phenotypes experienced by patients with IE-IRFs. IRF3, IRF7, and IRF9 are crucial for mediating protective IFN responses, explaining the viral susceptibility in patients with impairments in these transcription factors. IRF1-deficient patients have reduced ability to control mycobacterial infection due to impaired type II IFN responses and myeloid development. In contrast, IRF4 and IRF8 are crucial to various immune functions, explaining why affected patients have defects in immune development and broader infection susceptibility. Our rapidly growing recognition of the human IE-IRFs is a powerful example of how the integration of clinical care with translational science can transform the lives of affected individuals. Our current ability to diagnose and treat the IE-IRFs is true precision medicine in practice!

Acknowledgments

Author contributions: Mattison P. Stojcic: conceptualization, investigation, project administration, visualization, and writing—original draft, review, and editing. Pariya Yousefi: visualization and writing—review and editing. Catherine M. Biggs: conceptualization, supervision, validation, and writing—review and editing. Stuart E. Turvey: conceptualization, funding acquisition, project administration, supervision, and writing—review and editing.

Disclosures: The authors declare no competing interests exist.

Submitted: 6 May 2025
Revised: 5 July 2025
Accepted: 16 October 2025

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