

INSIGHTS

Null *IFNAR1* and *IFNAR2* alleles are surprisingly common in the Pacific and Arctic

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In this issue of *JEM*, Bastard et al. (2022. *J. Exp. Med.* <https://doi.org/10.1084/jem.20220028>) show that a loss-of-function *IFNAR1* allele is common in western Polynesians, while Duncan et al. (2022. *J. Exp. Med.* <https://doi.org/10.1084/jem.20212427>) report that a loss-of-function *IFNAR2* allele is common in Inuits. Homozygotes lack type I IFN immunity but are selectively vulnerable to influenza, COVID-19 pneumonia, and complications of live-attenuated viral vaccines.

Upon binding of type I IFNs to IFN- α receptor 1 (IFNAR1) and IFN- α receptor 2 (IFNAR2), tyrosine kinase 2 (TYK2) and JAK2 phosphorylate STAT1 and STAT2, which associate with IFN regulatory factor 9 (IRF9) to form IFN-stimulated gene factor 3 (ISGF3), which regulates the transcription of genes. Type I IFN signaling has been shown to be essential for immunity to various viruses in the few inbred mice studied, but studies of rare human individuals with inborn errors of type I IFN immunity have challenged this view. The range of severe viral disease in patients with autosomal recessive (AR) complete IFNAR1, IFNAR2, TYK2, STAT1, STAT2, or IRF9 deficiency is narrower than predicted. AR TYK2 deficiency impairs, but does not abolish, cellular responses to type I IFN, accounting for the few viral diseases, and their mildness, in these patients (Kreins et al., 2015). By contrast, patients with AR deficiencies of STAT1, STAT2, or IRF9 suffer from life-threatening disease with live-attenuated viral vaccine (LAV) and natural viral infections. AR deficiency of STAT2 or IRF9 is clinically more severe than TYK2 deficiency, at least because ISGF3-dependent responses to type I IFNs, and possibly also to type III IFNs, are abolished. AR STAT1 deficiency is even more severe, probably because responses to STAT-dimer-dependent responses to all three types of IFN are also abolished (Table 1).

Patients with deficiencies of IFNAR1 or IFNAR2 suffer from an unexpectedly narrow range of viral infections, similar to that of patients with STAT2 or IRF9 deficiency. In the cells studied, mostly peripheral blood monocytes and fibroblasts, IFNAR1 and IFNAR2 deficiencies abolish the responses to the one or two type I IFNs tested. Assuming that the defect affects all cell types, and all 17 type I IFNs, it is remarkable that the 13 confirmed patients from 11 kindreds described to date suffered only from measles, mumps, rubella vaccine (MMR) disease (Duncan et al., 2015; Gothe et al., 2022; Hernandez et al., 2019; Passarelli et al., 2020; Zhang et al., 2020), yellow fever vaccine (YFV) disease (Bastard et al., 2021b; Hernandez et al., 2019), influenza, herpes simplex encephalitis (HSE; Bastard et al., 2021a), and more recently, critical COVID-19 (Abolhassani et al., 2022; Khanmohammadi et al., 2022; Zhang et al., 2020). Furthermore, penetrance is even incomplete for most of these viral diseases (Table 1). Two previously healthy adults suffered only from critical COVID-19 pneumonia, with this infection leading to the diagnosis of AR IFNAR1 deficiency (Zhang et al., 2020). Many viruses therefore seem to be controllable without type I IFN, but is this presumption correct? Given the small number of patients reported, there is almost certainly ascertainment bias. It remains



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possible that many more individuals have died from infection with these or other viruses or LAV than have been reported. Alternatively, these gene defects may be compensated for by other alleles or immune mechanisms.

Two papers in this issue of *JEM* provide surprising evidence for a high frequency of null alleles of *IFNAR1* in western Polynesians and *IFNAR2* in Inuits. These null alleles are common in these remote populations, in which they have an estimated allele frequency >1% (3.4 and 1.25% respectively) but are absent or extremely rare elsewhere (Bastard et al., 2022; Duncan et al., 2022). They were identified through genetic studies of five patients in the Arctic and seven

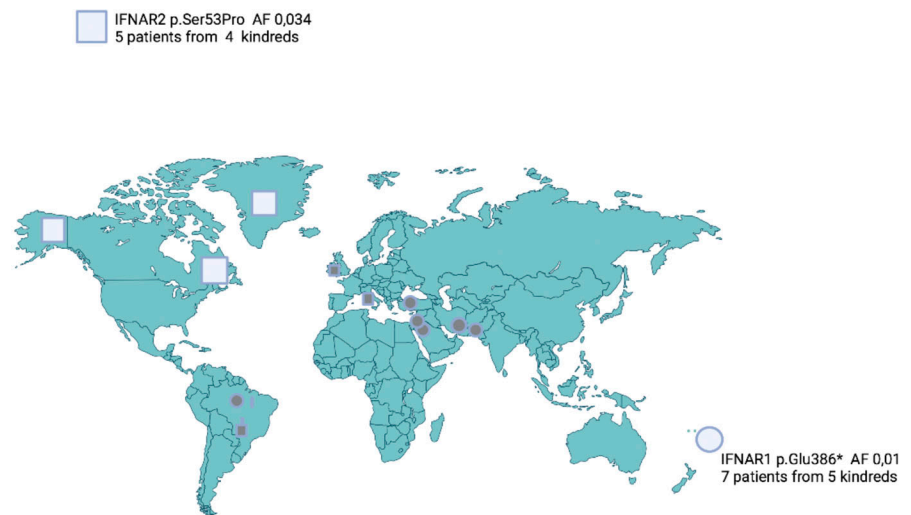
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patients in the Pacific population with life-threatening natural viral infections or post-LAV infections, with MMR or MMR-V (measles, mumps, rubella varicella vaccine) disease the most frequent presentation (observed in 10 of the 12 patients). The IFNAR1 p.Glu386* variant is not expressed at the cell surface and is loss-of-function for luciferase activity in response to IFN- α 2 when overexpressed. In patient-derived cells, the impaired IFN-stimulated gene (ISG) induction in response to IFN- α 1, IFN- ω , and IFN- β , but not IFN- γ , was rescued by introduction of the WT allele (Bastard et al., 2022). The IFNAR2 p.Ser53Pro variant is not expressed at the cell surface either, and neither patient-derived peripheral blood mononuclear cells nor fibroblasts displayed an upregulation of ISG expression in response to IFN- α . Complementation with the WT IFNAR2 allele restored both ISG induction and cell surface expression (Duncan et al., 2022). The authors point out that about 1 in 1,539 individuals in Greenland and 1 in 6,450 in Samoa are homozygous for these alleles and, therefore, are at risk for life-threatening LAV disease or natural viral infection (Bastard et al., 2022; Duncan et al., 2022).

These findings confirm the high, yet incomplete, penetrance of susceptibility to life-threatening disease due to LAV in patients with IFNAR1 and IFNAR2 deficiency, with only 10/12 patients reporting illness following MMR vaccination (Bastard et al., 2022; Duncan et al., 2022). These reports also highlight, for the first time, the role of live-attenuated varicella vaccine as a cause of disease in both IFNAR1 and IFNAR2 deficiencies (Bastard et al., 2022; Duncan et al., 2022). Moreover, the development of acute respiratory distress syndrome due to influenza A infection in one patient, and of severe COVID-19 disease in several others, points to the possibility of fatal disease following infection with these viruses. It is tempting to speculate that WT measles and VZV, just like COVID-19 and influenza, could potentially be fatal. Finally, the finding of a high HSV-1 viremia in a patient with MMR disease suggests the non-redundant role of type I IFN signaling for controlling HSV-1, as revealed by the description of a patient with HSE (Bastard et al., 2021a; Duncan et al., 2022). Interestingly, two patients received oral LAV without developing disease: a rotavirus vaccine in one patient



IFNAR1- (dots) and IFNAR2-deficient (squares) patients around the world. White symbols represent alleles with a frequency > 1%; gray symbols represent previously described rare variants.

(IFNAR2-deficient), and the oral polio vaccine in the other (IFNAR1-deficient). Neither resulted in disease. It is not possible to draw definitive conclusions from these two observations, but it is possible that the action of type III IFNs may have compensated for the type I IFN deficiency.

Despite the high frequency of these deleterious alleles in these distant and isolated populations, and despite LAV disease uncovering IFNAR1/2 deficiency, the need to continue MMR vaccination efforts cannot be overstated. Immunologically, individuals with IFNAR1 or IFNAR2 deficiency would be expected to be highly susceptible to life-threatening disease due to natural measles, mumps, rubella or VZV infection. Indeed, a recent outbreak of measles in Samoa resulted in high mortality. The findings of these papers call for a population-specific approach, in which targeted sequencing of the deleterious allele in neonates should be envisaged. A similar strategy has been employed in Manitoba to detect a common deleterious *IKBKB* allele that results in severe combined immunodeficiency in First Nation communities (Rubin et al., 2018). Nevertheless, the incomplete penetrance of the diverse clinical phenotypes of IFNAR1 and IFNAR2 deficiencies, together with the reality that homozygous IFNAR1- and IFNAR2-deficient patients are probably living normal lives in these populations, makes it harder to make any clear recommendations. Careful medical and ethics

appraisal is required, together with a judicious weighing up of the benefits and drawbacks of long-term treatment with intravenous immunoglobulin or acyclovir relative to consistent adherence to the population-wide vaccine schedule, with early anti-inflammatory and/or antiviral intervention upon disease manifestations.

Ascertainment bias notwithstanding, these findings suggest that human type I IFNs are more redundant than initially thought. Type I IFN-independent restriction factors may act against many viruses in human tissues, as reported before (RNA lariat debranching enzyme [DBR1], small nucleolar RNA H/ACA box 31 [SNORA31], epidermodysplasia verruciformis-calcium-and-integrin-binding protein 1 [EVER-CIB1]; Casanova and Abel, 2021). Nevertheless, we can also anticipate an expansion of the spectrum of viral susceptibility with the description of increasing numbers of individuals with IFNAR1 or IFNAR2 deficiency. In geographically isolated populations, such as those of the Arctic or the Pacific, genetic drift has probably been at work, with serial founder effects, isolation, or bottlenecks followed by rapid expansions of the population (Quintana-Murci, 2019). There is no reason to suspect that these loss-of-function alleles have been subject to positive selection. Moreover, in both the Inuit and western Polynesian populations, exposure to some viruses is recent, resulting in little negative selection.

Table 1. Patients with complete AR IFNAR1 and IFNAR2 deficiency reported to date

Patient (kindred)	Mutation	Origin	Age at presentation (Y/N)	MMR	MMR disease	Other LAV	COVID-19/ influenza	Other	HLH	Outcome	Reference
Mutation in IFNAR1											
1(I)	Homozygous c.674-2A>G	Iran	12 mo	Y	Disseminated, encephalitis			CMV		A	Hernandez et al. (2019)
2(I)	Not genotyped		12 mo	Y	Disseminated					Fatal	
3(II)	p.W261X and c.674-1G>A	Brazil	14 yr	Y	Uneventful	YFV: disseminated disease; BCG and oral polio, uncomplicated		Seroconversion to CMV, HSV1, HSV2	A		
4(III)	Complete homozygous deletion from intron 10 to exon 11 and 3'UTR	Palestinian territory	13 mo	Y	Prolonged fever, spontaneous recovery			Gingivostomatitis and aseptic meningitis, HSE at 19 mo, fatal at 20 mo	Fatal		Bastard et al. (2021a)
5(III)	Complete homozygous deletion of intron 10 to exon 11 and 3'UTR		6 mo	N				Meningitis with deafness age 14 yr after mumps?			
6(III)	Not genotyped		12 mo	Y	Disseminated disease					Fatal	
7 (IV)	p.Ser422Arg;p.Ser422Arg	Saudi Arabia	26 yr	?			Fatal COVID-19			Fatal	Zhang et al. (2020)
8(V)	p.Trp73Cys;p.Trp73Cys	Turkey, Pakistan	38 yr	?			Critical COVID-19				
9(VI)	p.Gln308Ter; p.Gln308Ter	?	15 mo	Y	Encephalitis, with cerebral atrophy (no vaccine strain viruses in CSF/serum)			Seroconversion to EBV, HSV, CMV	Y	Fatal	Gothe et al. (2022)
10(VII)	p.H263fs* ₁ ;H263 fs*	Iran	8 mo	Y	N	BCG, oral polio, uncomplicated	Critical COVID-19 (MIS-C + pneumonia)	8 mo chronic RTI, age 2 yr mucormycosis of nose and sinuses	Y		Abolhassani et al. (2022)
11(VIII)	Homozygous c.674-2A>G	Iran	12 mo	Y	Meningitis		Critical COVID-19; recurrent influenza			A	Khanmohammadi et al. (2022)

Table 1. Patients with complete AR IFNAR1 and IFNAR2 deficiency reported to date (Continued)

Patient (kindred)	Mutation	Origin	Age at presentation	MMR (Y/N)	MMR disease	Other LAV	COVID-19/ influenza	Other	HLH	Outcome	Reference
12(X)	p.Glu386* ^{p.Glu386*}	West Polynesia	12 mo	Y	Meningoencephalitis, disseminated	BCG, oral polio, uncomplicated			Y	Fatal	Bastard et al. (2022)
13(X)	p.Glu386* ^{p.Glu386*}	West Polynesia	12 mo	Y	Meningoencephalitis, disseminated				Y	Fatal	
14(X)	p.Glu386* ^{p.Glu386*}	West Polynesia	8 wk	Y, MMR-V	Meningoencephalitis, disseminated			Enterovirus meningoencephalitis	Y	Fatal	
15(XI)	p.Glu386* ^{p.Glu386*}	West Polynesia	13 mo	Y	Meningoencephalitis, disseminated			Neonatal CMV, recovered; reactivation CMV hepatitis during MMR disease, parainfluenzavirus 1 + during MMR disease	Y	Fatal	
16(XI)	p.Glu386* ^{p.Glu386*}	West Polynesia	16 mo	Y	Meningoencephalitis			Enteroviral meningitis, second MMR tolerated; hospitalized 4x for bronchiolitis	Y	A	
17(XII)	p.Glu386* ^{p.Glu386*}	West Polynesia	14 mo	Y	Meningoencephalitis			21 mo viral pneumonia + PCR rhinovirus, parainfluenzavirus, RSV, and bocavirus	?	A	
18(XII)	p.Glu386* ^{p.Glu386*}	West Polynesia	10 mo	Y, MMR, MMR-V	No			Hib bacteremia and meningitis, RSV + at PCR with multiple organ failure, 2x bronchiolitis <12 mo; adv and hMPV resp exacerbation	N	A	
Mutation in IFNAR2											
1(I)	p.E104fs110X; p.E104fs110X	UK	13 mo	Y	Meningoencephalitis			HHV6: uncomplicated infection, seroconversion for CMV, EBV	?	Fatal	Duncan et al. (2015)
2(I)	p.E104fs110X; p.E104fs110X	UK	Neonatal diagnosis	N	/				?	A	
3(II)	c.840+1 G>T; c.840+1 G>T	Brazil	13 yr	?	Uneventful	YFV: disease				A	Bastard et al. (2021b)
4(II)	?	Brazil	19 yr	?	/	YFV: disease, fatal at 19 yr				Fatal	
5(III)	p.Leu79Ter; p.Ile185MetfsTer12	Italy	22 mo	Y	Trigger for HLH		Influenza pneumonia	Flu, HSV + pneumonia	Y	A	Passarelli et al. (2020)
6(IV)	p.Ser53Pro;p.Ser53Pro	Greenland	22 mo	Y	Meningoencephalitis	BCG:uncomplicated		EBV reactivation, VZV, HSV1, CMV	?		Duncan et al. (2022)
7(V)	p.Ser53Pro;p.Ser53Pro	Nunavik	12 mo	Y	Meningoencephalitis	BCG: rotavirus vaccine uncomplicated	Fatal COVID-19	Uncomplicated hand foot mouth disease with herpangina, HSV1 stomatitis		Fatal	
8(V)	p.Ser53Pro;p.Ser53Pro	Nunavik	5 yr	Y	Uneventful		Self-limiting COVID-19			A	
9(VI)	p.Ser53Pro;p.Ser53Pro	Alaska	8 mo	Y	?	VZV vaccine: disseminated disease	Relapsing COVID-19			Fatal at 3 yr (neurological disease)	
10(VI)	p.Ser53Pro;p.Ser53Pro	Alaska	13 mo	Y	Disseminated disease	VZV vaccine: disseminated disease		Adv, RSV, CMV, EBV, HHV6, HSV1 (+ in BAL at the time of LAV disease)		Fatal	

A, alive; BAL, broncho-alveolar lavage; CSF, cerebrospinal fluid; BCG, bacille Calmette-Guerin; RSV, respiratory syncytial virus; RTI, respiratory tract infection; adv, adenovirus; resp, respiratory; hMPV, human metapneumovirus; HHV6, human herpes virus 6; HLH, hemophagocytic lymphohistiocytosis/inflammation; MIS-C, multisystem inflammatory syndrome in children, N, no; Y, yes.

These findings corroborate previous observations of rare patients and suggest that type I IFN is redundant for host defense against most viruses, in most humans. This is not inconsistent with the negative selection acting on the IFNAR1 and IFNAR2 loci and with complete AR IFNAR1 and IFNAR2 deficiencies being extremely rare, reported to date in only nine patients from eight unrelated kindreds for complete AR IFNAR1 deficiency and four patients from three unrelated kindreds for AR complete IFNAR2 deficiency, respectively. Indeed, vulnerability to one or a few viruses may be sufficient to exert negative selection.

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