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RESEARCH

Severe Adverse Reaction to Measles Vaccine Due to Homozygous Mutation in the IFNAR2 Gene: A Case Report and Literature Review

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Abstract
Receiving the measles vaccination is crucial for controlling the disease and preventing severe complications. However, adverse reactions can occur in individuals with inborn errors of immunity. This case report details a severe reaction to the measles vaccine in a ten-month-old female with a homozygous mutation in the IFNAR2 gene, leading to immunodeficiency-45. Following vaccination, she developed viremia, meningoencephalitis, and multi-organ failure. Genetic analysis identified a Variant of Uncertain Significance (VUS) in the IFNAR2 gene, which is essential for type I interferon (IFN-I) signaling. This case highlights the importance of incorporating genetic screening into vaccination programs for individuals at risk. It demonstrates the complex relationship between genetic mutations and the immune responses to the vaccines.

Keywords Measles · Measles vaccine · IFNAR2 · Interferon · Inborn errors of immunity

Introduction

Measles, caused by a Morbillivirus—a negative-sense, single-stranded, enveloped RNA virus within the Paramyxovirus family—, is a highly infectious disease, controlled mainly through mandatory vaccination programs [1–4]. These programs have significantly reduced morbidity and mortality [2]. The development and widespread administration of the measles vaccine have significantly contributed to the global effort to prevent this contagious disease and its severe complications, including lethal neurological diseases [2–4].

Measles can cause acute brain inflammation, such as primary measles encephalitis, which eventually causes chronic neurological sequences, such as measles inclusion body encephalitis [3–6]. Subacute sclerosing panencephalitis typically develops in children aged 8–12 after several years following initial measles infection [3]. Measles encephalitis has been observed in individuals with hereditary primary immunodeficiencies (PIDs), also known as inborn errors of immunity (IEI), particularly those caused by defects in the immune response mediated by type I interferon (IFN-I) [3, 4, 6–12]. IFN-1 plays a crucial role in the immune response to viral pathogens, releasing these cytokines, specifically IFN-α and IFN-β, that activate the IFN-α/β transmembrane receptor (IFNAR), which is a complex composed of IFNAR1 and IFNAR2 subunits [8–10, 13]. The signaling pathway triggers the Janus kinases (JAKs) and the subsequent phosphorylation of signal transducers and activation of transcription (STAT) proteins, leading to the transcription of IFN-stimulated genes (ISGs) [8–10, 13]. The complexity of immune defenses highlights the delicate balance required to maintain homeostasis while combating viruses.

Genetic mutations within the IFNAR complex lead to IEI [8–10, 12]. Specifically, mutations in the IFNAR2 gene lead to immunodeficiency-45 (IMD45), an autosomal recessive disorder that disrupts the IFN-1 signaling pathway [8–10]. This leaves affected individuals vulnerable to severe

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complications from natural infection or live-attenuated vaccines [8–10].

This report investigates a severe adverse reaction to the measles vaccine in a ten-month-old female, characterized by viremia, meningoencephalitis, and multi-organ failure, traced back to a homozygous mutation in the IFNAR2 gene. This report underscores the critical need for genetic screening in vaccination programs, especially for individuals suspected of having congenital immunodeficiencies and their relatives. It also emphasizes the importance of ongoing research into immune responses and vaccine safety.

Case Presentation

A ten-month-old female infant with no significant neonatal and past medical history was referred to a tertiary care center. She was experiencing severe symptoms that began approximately 12 days after receiving her scheduled 9-month measles vaccine. Initially, the infant's mother reported a high-grade fever and localized red swelling at the vaccination site on the left thigh, which progressively darkened and increased in size. Subsequently, a generalized purpuric rash spread all over her body. Despite receiving intravenous antibiotics at a primary care center, her condition deteriorated, and she was admitted to the emergency department.

Upon her arrival, the infant exhibited shock symptoms: lethargy, hypoactivity, cold extremities, and delayed capillary refill. She was immediately admitted to the Pediatric Intensive Care Unit (PICU) for urgent fluid resuscitation and administration of broad-spectrum antibiotics. A comprehensive physical examination showed a purpuric rash with a blackish discoloration on her left thigh, measuring 4 × 4 cm, without any discharge. Initial laboratory findings (Fig. 1) showed thrombocytopenia, elevated inflammatory markers, disseminated intravascular coagulation (DIC), elevated liver enzymes, low fibrinogen, and hypoalbuminemia, indicating multi-organ involvement with systemic inflammatory response and potential viremia. This prompted immediate interventions, including multiple transfusions of platelets and albumin to address the coagulopathy and hypoalbuminemia, which were critical to stabilizing her condition.

The patient's development of acute onset symptoms following the measles vaccination, along with a positive vaccine strain measles virus IgM and IgG, confirmed an acute measles infection. This led to treatment with Vitamin A and steroids, aimed at addressing the measles complications. Despite these measures, the patient's condition initially worsened, necessitating intensive care with mechanical ventilation due to respiratory failure, further indicating the severe impact of the infection on multiple organ systems.

During her PICU stay, her condition fluctuated, marked by continuous fever spikes and clinical deterioration, leading to respiratory failure. A chest x-ray revealed bilateral pleural effusion, necessitating chest tubes insertion (Fig. 2A). Laboratory tests (Fig. 1) returned negative results for blood and urine cultures, and there was no evidence of Hemophagocytic Lymphohistiocytosis (HLH). Despite these findings, the severity of her condition necessitated a multi-disciplinary team approach.

The team included a pediatrician, infectious diseases specialist, immunologist, and critical care specialist to manage the complex case. Diagnostic imaging for the thigh was conducted to rule out deep tissue infections, abscess formation and necrotizing fasciitis, followed by lumbar puncture to assess potential central nervous system involvement (Fig. 2E-F). Although no abscess or necrotizing fasciitis were found, the lumbar puncture showed a high white blood cell count with a predominance of lymphocytes, raising concerns about CNS involvement (Fig. 1) that may indicate meningoencephalitis.

A detailed family history revealed consanguinity between the parents (Fig. 3). The mother experienced one first-trimester miscarriage for unknown reasons. The oldest sibling contracted measles at the age of one year and developed meningitis after receiving the vaccine; he is now eleven years old and deaf. Immunological testing of the patient unveiled a homozygous Variant of Uncertain Significance (VUS) in the IFNAR2 gene (c.713 C > A,p.Ser238*,NM_001289125.1), indicating an autosomal recessive immunodeficiency type 45 [14]. During a detailed genetic analysis using next-generation sequencing (NGS), a homozygous VUS was detected in the IFNAR2 gene, which is crucial for the body's immune defense mechanisms against viruses. The genetic testing involved fragmenting the genomic DNA and enriching specific target areas, including the human coding exome and mitochondrial genome [14]. This targeted DNA was then sequenced on an advanced Illumina platform to ensure comprehensive and accurate detection of genetic variants [14]. Through an in-depth bioinformatics analysis, which included alignment to the reference GRCh37/hg19 genome, the variant c.713 C > A was identified, resulting in a premature stop codon at p.Ser238* [14]. Despite the precise detection, the impact of this specific mutation on the protein function and its clinical implications remains uncertain. Further familial immunological study disclosed the same genetic mutation in different zygosities [14]. The oldest sibling was homozygous for the IFNAR2 gene, while the parents and her other two siblings were heterozygous for the gene. The patient's parents and two siblings, who have a heterozygous IFNAR2 gene mutation, are in good clinical condition with no history of significant infection, hyperinflammatory episodes, or vaccine responses. Furthermore,

Fig. 1 Lab Results

Important Labs	Result on admission	Result follow up	Result follow up	Result on discharge	Reference range
White Blood Cells (WBCs)	13.44	28.5	21.3	11.8	> 6.00 - < 18.00 10*3/uL
Absolute Neutrophil Count (ANC)	11.17	15.1	9.8	5.3	> 1.00 - < 6.00 10*3/uL
Hemoglobin	13.5	7.9	11	10.2	11.1 - 14.1 g/dL
Platelets	35	54	730	614	100 - 450 10*3/uL
Erythrocyte Sedimentation Rate (ESR)	2	2	18	-	0 - 20 mm/H
C-Reactive Protein (CRP)	135	120	51.30	-	< = 3.00 mg/l
Lactate Dehydrogenase (LDH)	> 1,995.00				125.00 - 220.00 U/L
Ferritin	26.781	> 40.000	25.325	1.014	22.00 - 275.00 ug/l
Fibrinogen	1,03	0.6	0.7	1.2	> 1.61 - < 4.39 G/L
Triglycerides	2,37	1.98	4.1		<=1.70 mmol/L
Alanine Aminotransferase (ALT)	168	555	135	36	0.00 - 55.00 U/L
Aspartate Aminotransferase (AST)	554	1,711	210	78	5.00 - 34.00 U/L
Gamma-Glutamyl Transpeptidase (GGT)	118	196	205	153	9.00 - 36.00 U/L
Albumin	31.90	18.3	27	37	28.00 - 44.00 g/l
International Normalized Ratio (INR)	1.87	1.46	1.10		0.81 - 1.23
Prothrombin Time (PT)	22	17.3	14.2		> 9.7 - < 12.6 seconds
Activated Partial Thromboplastin Time	>180.0	41	37	26	>25.3 - < 38.3 seconds
(APTT)					
Cerebrospinal (CSF) WBCs	38				< = 5.0 cu/mm
CSF protein	0.6970				0.1500 - 0.4000 g/l
CSF glucose	2.8				> = 2.20 mmol/L
CSF culture	No growth at 72 hours				
Blood culture	No growth at 120 hours				
Urine cultures	No growth at 18 - 24 hours				
Viral panel	Rhino virus positive				Negative
Vaccine Strain Measles antibodies	IgM AB Positive	IgG AB Positive			
Lymphocytes marker	Absolute lymphocytes 5.72 x10.e9/L CD3: 43.6% CD4: 32.1 % CD8: 9.35 % CD19: 43.9 % CD16+56: 10%				
Immunoglobulin	IGG 17.8 g/l IGA 1.45 g/l IGM 1.65 g/l				IGG 2.9 - 10.7 g/l IGA 0.4 - 1.2 g/l IGM 0.3 - 1.5 g/l
HIV PCR	Negative				Negative

there was a notable case of immunodeficiency in a cousin, who had Bare lymphocyte syndrome and underwent a bone marrow transplant.

After a 10-day stay in the PICU, the patient's condition began to significantly improve. During this time, the healthcare team continuously adapted their management strategies to meet her changing clinical needs. This experience underscores the vital importance of a flexible and comprehensive approach to patient care. She received vitamin A (10,000 IU for 2 days) and methylprednisolone (2 mg/kg for 10 days, followed by a tapering schedule), spending a total of 12 days in the PICU and an additional 10 days in the ward.

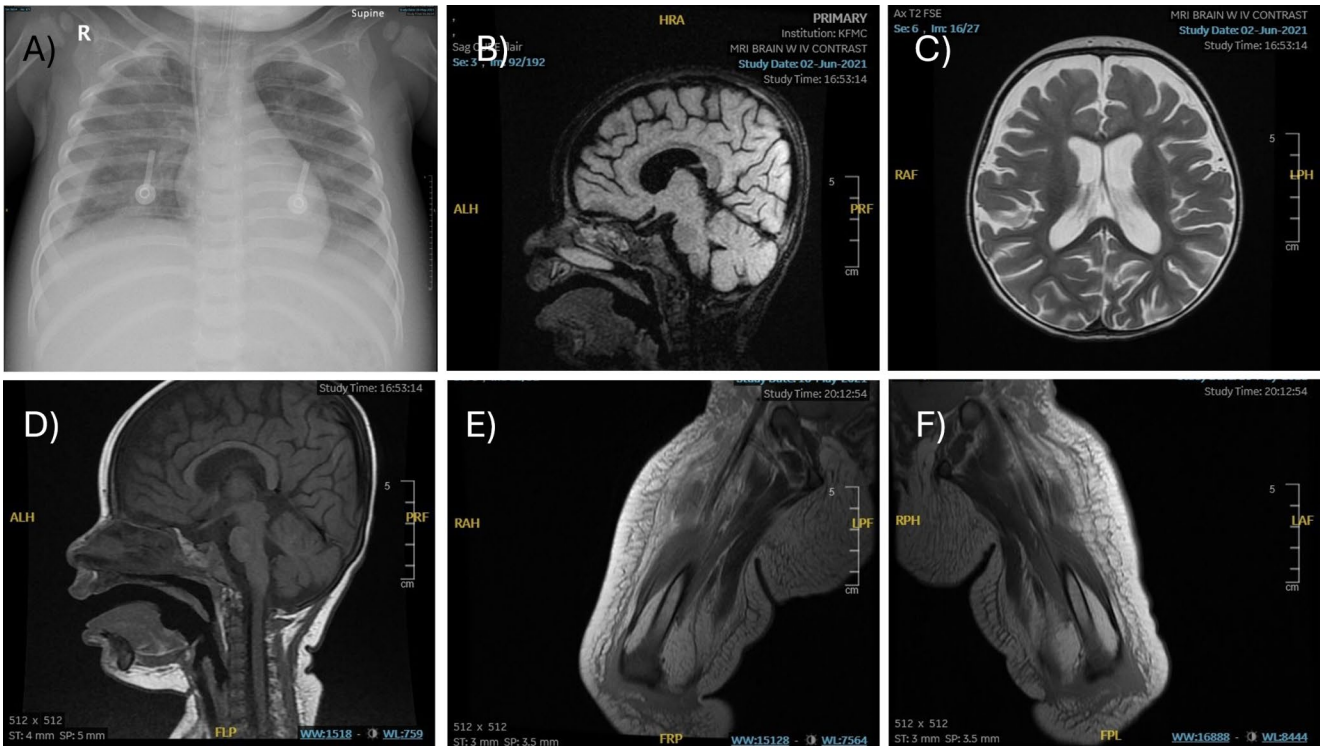

Fig. 2 **a)** Chest x-ray **b-d)** Brain MRI shows mild global brain volume loss with mild chronic hydrocephalus. No signs for active encephalitis, meningoencephalitis, or meningitis. **e-f)** Necrotic lesion of the left thigh with extensive soft tissue swelling and edema in the thigh with deep intramuscular fascia involvement. No fluid collection, abscess, gas locules, or evidence of osteomyelitis

Her condition stabilized, allowing for a gradual weaning from mechanical ventilation and a shift towards recovery. Subsequently, the mother expressed concern about her child's vision, noting that she was not tracking objects. This observation was confirmed through clinical examination. Further consultations with an ophthalmologist showed that the ocular nerve was spared, which suggested potential cortical blindness, a condition managed with ongoing neurological and supportive care. A brain MRI showed a mild global volume decrease, which was closely monitored as part of her long-term care plan (Fig. 2b-d).

The patient was eventually discharged in a stable condition, with a comprehensive follow-up plan involving multiple specialties to monitor her development, manage potential complications, and ensure the well-being of the patient and her family. At three years of age, the patient demonstrated remarkable progress, catching up on her developmental milestones with only mild speech delay and normal growth patterns, without any further hospital admissions.

Discussion

IEI are a group of genetic disorders that compromise the immune system by affecting either adaptive immunity (T cell, B cell, or combined immunodeficiencies) or innate immunity (phagocyte and complement disorders) [12, 15, 16]. These impairments hinder the body's ability to combat viral infections, making individuals vulnerable to severe infections [12, 15, 16]. IEI can become evident after environmental exposures and are often linked to malignant, allergic, or autoimmune conditions [15–17]. Examples include interferon regulatory factor 4 (IRF4) mutation, IRF8 mutation, MDA5 deficiency, RNA polymerase III haploinsufficiency, TLR3 deficiency, and CIB1 deficiency [17–20]. Inherited IFNAR1 deficiency represents a rare and critical example for IEI that impairs IFN-1 signaling, thereby increasing susceptibility to viral infections [17]. Individuals with this deficiency have exhibited life-threatening reactions to live-attenuated vaccines, including those for measles and yellow fever [21]. A proline deletion in IFNAR1 has been shown to disrupt IFN-1 signaling, resulting in increased resistance to tuberculosis but heightened susceptibility to hepatitis b virus (HBV) infection in Chinese populations [22]. The homozygous IFNAR1 nonsense variant (p.Glu386*) results in a truncated, non-functional protein, leaving fibroblasts unresponsive to IFN-1 [23]. This variant is prevalent in Samoa and several Pacific islands [23]. Another significant discovery identified a homozygous deletion in IFNAR1 (IFNAR-1557Gluext*46), which impairs IFN-α-induced signaling and increases vulnerability to cytomegalovirus infection [24]. Furthermore, IFNAR1 mutations have been associated

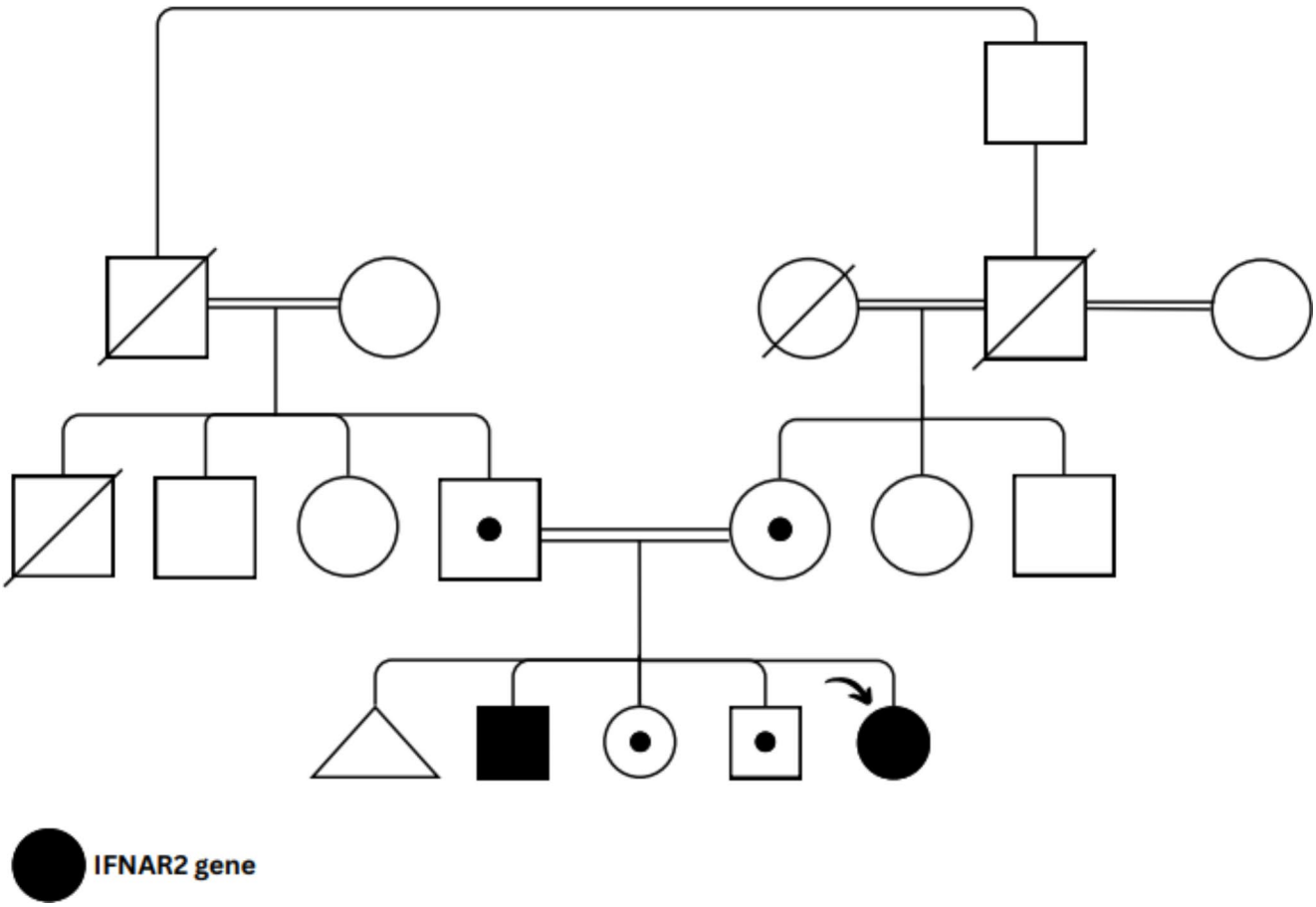

Fig. 3 Pedigree Chart

with HLH, a hyperinflammatory syndrome triggered by viral infections, and severe outcomes from COVID-19, with cases requiring intensive care due to extensive pulmonary involvement [25, 26]. IRF9 deficiency, a form of IEI, significantly impacts antiviral defense and inflammation [27, 28]. It is associated with life-threatening influenza pneumonitis due to impaired type I and III interferon responses, particularly against influenza A virus [27]. Patients with IRF9 deficiency show prolonged, inadequate regulation of interferon signaling, resulting in hyperinflammation and HLH driven by IFN-γ-like effects [28]. IRF9 is also crucial in preventing CD8 + T cell exhaustion by controlling early viral replication and modulating ISGs expression [29]. IFNAR2, an essential part of the IFN-1 signaling pathway, is crucial for antiviral immunity [30]. These findings highlight the critical role of the IFN-1 signaling pathway in antiviral defense and the significant impact of its deficiencies on disease susceptibility.

IFNAR2 is a widely expressed transmembrane receptor that features a heavily N-glycosylated extracellular region with two fibronectin domains and a cytoplasmic C-terminal domain [10]. IFNAR2 exists in three isoforms: the first isoform is a non-functional protein due to its truncated cytoplasmic domain [10, 31]. The second isoform is longer, containing the functional trans-membrane protein that works in conjunction with IFNAR1 [10, 31]. The third isoform is a soluble version known as sIFNAR2, which can act as a decoy receptor to modulate the activity of interferons [10, 31]. IFNAR2 is responsible for antiviral, anti-inflammatory and proinflammatory regulation once it's activated by binding to IFN-1 [32].

The research on IFN pathways in host immunity has practical implications, as molecular defects often indicate susceptibility to pathogens [33, 34]. Several cases demonstrate the complexity of immune responses and signaling crosstalk, which are underscored by mutations affecting the IFN pathways [33, 34]. (Fig. 4) summarize the IFN pathways that plays a pivotal role in triggering immune responses against viral infections [24, 35–37]. The innate immune system uses pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs), triggering protective responses like cytokine and IFN production [38]. Microbial product recognition by various cell-surface and intracellular PRRs, such as Toll-like receptors (TLRs)

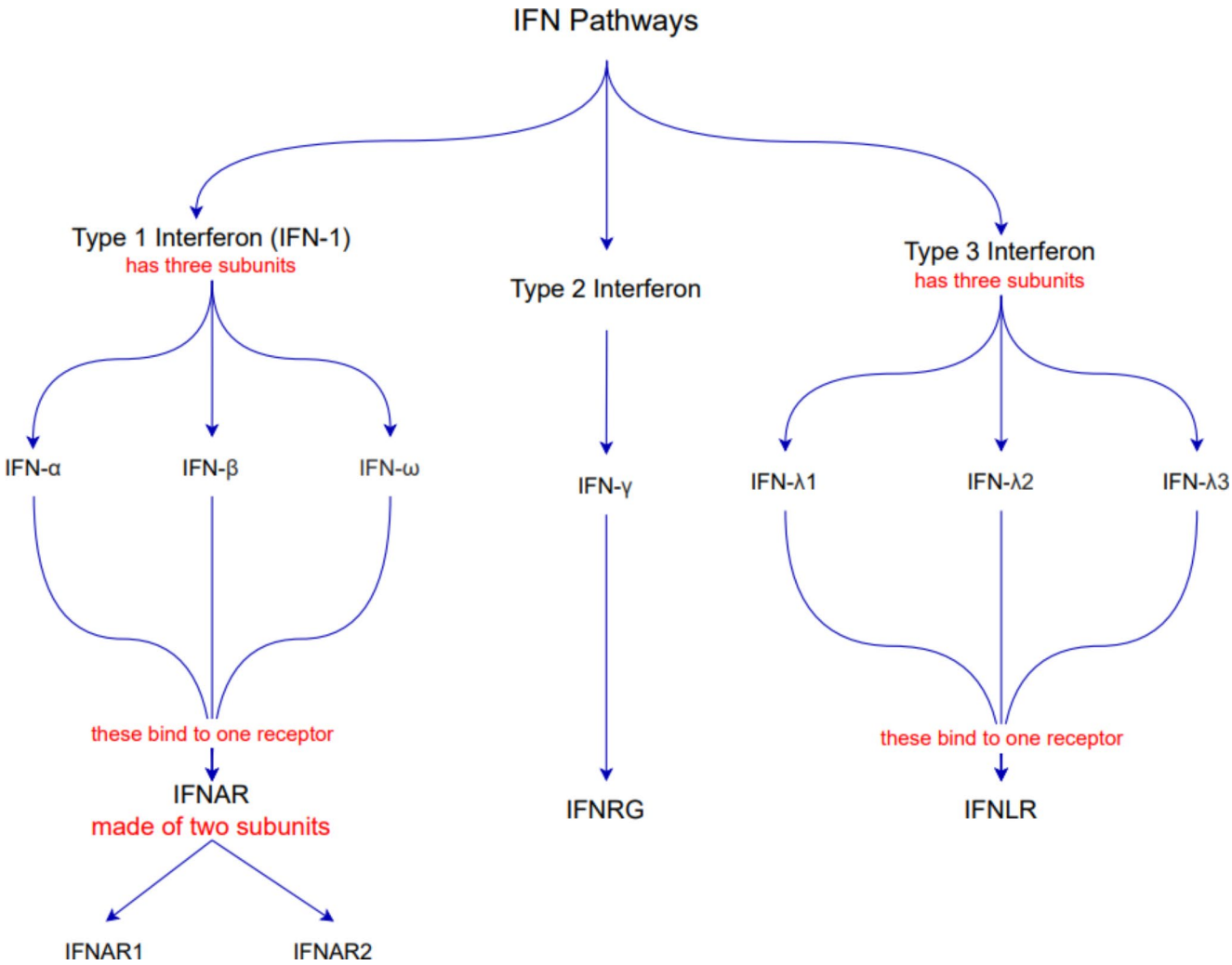

Fig. 4 INF pathways with their receptors

and (retinoic acid-inducible gene) RIG-I, produces IFN-1 through multiple signaling pathways [38]. IFNs-1 trigger immune responses by inducing MHC class I expression and stimulating NK and CD8 + T cells, through a cascade of intracellular signals [30, 32, 34, 38–40]. IFN-1 binds with IFNAR2 with higher affinity and strengthens the interaction, while IFNAR1 initiates downstream signaling [10, 31, 39, 41]. Upon binding with its ligand, IFNAR2 forms a ternary complex with IFNAR1 and IFN-I, activating the JAK-STAT pathway [10, 31, 39, 41]. This leads to the recruitment of Janus kinases (JAK1) (via IFNAR2) and tyrosine kinase 2 (TYK2) (via IFNAR1), resulting in their mutual phosphorylation and the subsequent activation of STAT1 and STAT2 by JAK1, forming a p-STAT1/p-STAT2 heterodimer that drives downstream signaling (Fig. 5) [10, 30–32, 34, 38–41]. The p-STAT1/p-STAT2 heterodimer associates with interferon regulatory factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISGF3) [10, 31, 32, 39, 41]. This complex translocates to the nucleus which binds to specific DNA sequences, termed interferon-stimulated response elements (ISRE), thereby directly initiating the transcription of ISGs (Fig. 5) [10, 31, 32, 39, 41]. The transcription of ISGs inhibits viral replication by stimulating antiviral genes, promotes apoptosis in infected cells, and recruits immune cells such as NK cells and cytotoxic T lymphocytes [10, 31, 32, 39, 41]. Furthermore, the IFNAR complex activates STAT1 homodimers and STAT3 homodimers, with STAT1 homodimers binding to gamma-activated sequences (GAS) to induce pro-inflammatory genes, while STAT3 homodimers suppress these genes, via unknown transcriptional repressors [32]. IFN-I-activated STAT3 is regulated by the SIN3A co-repressor complex, which inhibits STAT3 target genes by deacetylating STAT3 and histones [32]. Loss of SIN3A allows STAT3 to reduce ISG expression. Additionally, IFN-1 can activate STAT4, STAT5, and STAT6 activated in specific cells in certain manner [10, 32].

In one study with an IFNAR2 variant, the c.A311del mutation led to the truncation of all IFNAR2 isoforms at

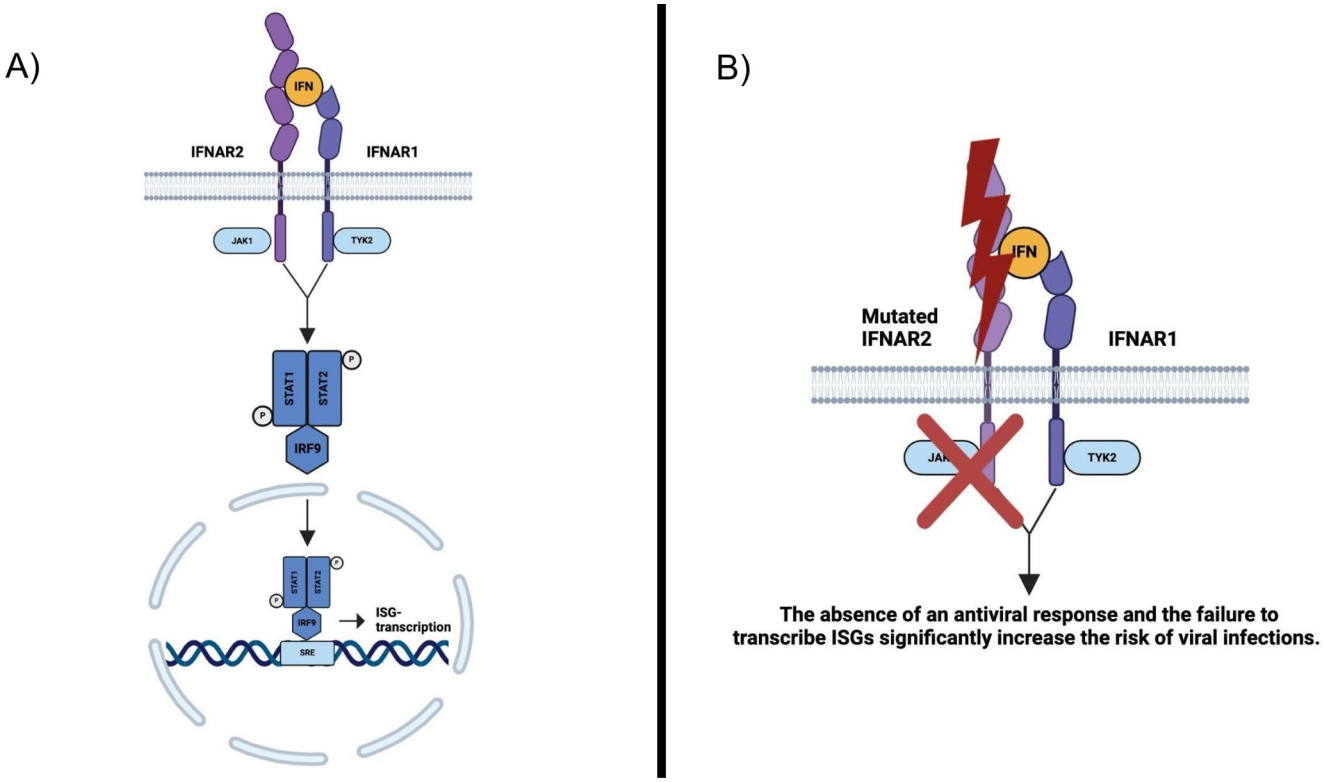

Fig. 5 (**A**) Normal, (**B**) The mutated IFNAR2

the first N-terminal fibronectin III domain, resulting in loss of detectable protein with specific C-terminal antibodies, similar to observations in IFNAR2-deficient sarcoma cells [8]. Complementation with wild-type IFNAR2 in affected fibroblasts restored IFN-α response, evidenced by normal STAT1 phosphorylation, ISG induction, and reduced viral protein expression, effectively managing the replication of IFN-sensitive viruses [8]. This finding underscores the critical role of IFNAR2 in the IFN-α/β pathway and human antiviral immunity [8]. Despite severe defects in IFN signaling and high susceptibility to viral challenges in vitro, the clinical impact of common viruses remained minimal until the onset of MMR vaccine-related complications [8]. Additionally, the ability to control cytomegalovirus despite severe immunological defects suggests compensatory mechanisms in herpesvirus surveillance, highlighting potential redundancy in IFN-mediated defenses [8].

Another IFNAR2 variant, p.Ser53Pro, has been linked to Inuit ancestry, which affects responses to wild-type and vaccine-strain viruses, such as MMR [10]. This missense mutation, consistently found across several individuals, with a homogenous substitution at serine position 53, shows a unique presence not cataloged in the gnomAD database [10]. Structural analysis suggests the mutation disrupts local hydrogen bonds in the IFNAR2 protein, impairing its function [10]. In a study of 4,630 Greenlandic individuals, the variant was mostly found in heterozygosity, indicating some population-specific prevalence [10]. Leukocytes from individuals with this variant express significantly lower IFNAR2 levels, impairing their response to IFN-I [10]. This defect is evidenced by the absence of STAT1 phosphorylation in these cells, crucial for the JAK-STAT signaling pathway activation by IFN-I [10]. Experiments confirmed defective IFNAR2 signaling in patients' cells treated with recombinant IFNβ [10]. The variant also failed to induce ISG expression, crucial for antiviral defense [10]. Functional assays showed that fibroblasts from affected patients could not mount an antiviral state against various viruses, including measles, mumps, HSV1, and VZV, emphasizing the critical role of IFNAR2 in antiviral defense [10].

Furthermore, research investigated a Caucasian boy with HLH who carried novel IFNAR2 gene mutations [9]. These mutations disrupt the IFN-I signaling pathway, crucial for NK cell function [9]. The boy's condition was triggered after receiving the live-attenuated MMR vaccine at 22 months old, presenting with high fever, lethargy, and a persistent rash [9]. Clinical symptoms and lab findings confirmed HLH, which was successfully treated with methylprednisolone and glucocorticoids [9]. Genetic analysis identified two frameshift mutations in the IFNAR2 gene (c.234delT and c.555_559delAAAAG), resulting in premature stop codons and a complete lack of IFNAR2 protein

[9]. This deficiency prevented STAT1 phosphorylation in response to IFNα, which is critical for antiviral defenses [9]. Notably, NK cells from the patient failed to degranulate or inhibit IFNγ production upon IFNα stimulation, unlike cells from his parents and healthy controls [9]. Flow cytometry confirmed the patient's NK cells lacked CD107a expression, a marker for degranulation, when pre-incubated with IFNα and exposed to target cells [9]. This impaired NK cell function is linked to HLH pathogenesis, where defective cytotoxic activity and dysregulated IFNγ production exacerbate hyperinflammatory responses [9].

Moreover, mutations in IFNAR2 have been associated with varying COVID-19 outcomes, highlighting its significance in the disease's pathogenesis [31, 42, 43]. Several studies have demonstrated that single-nucleotide variants (SNVs) in the IFNAR2 gene can significantly affect the immune response to SARS-CoV-2 [31, 42]. These variants may alter the protein's function, impacting how effectively the body can combat the virus [31]. Genome-wide association studies (GWAS) linked the A allele of rs2236757 in IFNAR2 with severe COVID-19 outcomes in United Kingdom patients, including the need for mechanical ventilation and pneumonia [31]. This association was confirmed in large cohorts and various populations, with a stronger effect observed in non-white patients in Brazil [31]. In Mexican and Vietnamese populations, IFNAR2 variants were associated with increased mortality and susceptibility to SARS-CoV-2 [31]. Additionally, whole-genome sequencing in multiethnic cohorts identified rare IFNAR2 variants linked to severe COVID-19, particularly in Asian populations [31].

Additionally, a study identified a homozygous essential splicing variant in the IFNAR2 gene (c.840 + 1G > T) in a 35-year-old Brazilian woman, confirmed through Sanger sequencing [44]. This patient, who had no previous history of severe viral infections, developed yellow fever vaccine-associated viscerotropic disease (YEL-AVD) after receiving the live-attenuated yellow fever vaccine (YFV-17D) at the age of 13 [44]. Within three days of vaccination, she exhibited fever and gastrointestinal symptoms, which rapidly escalated to include epistaxis, hepatitis, and hypotension, requiring urgent hospitalization [44]. Despite the severity of her condition, she recovered fully with supportive care [44].

The presence of genetic mutations in the IFNAR2 gene is also a significant factor influencing the immune response to HBV infections [31, 45]. Variants such as rs2229207 have been associated with an increased risk of chronic HBV infection [31, 45]. These mutations can alter the function of the interferon receptor, compromising the body's antiviral response and facilitating the virus' ability to evade immune control [31, 45].

Conclusion and Future Directions

The clinical presentation of IFNAR2 deficiency reveals several critical traits, such as increased vulnerability to life-threatening complications from live-attenuated vaccines like MMR and YFV-17D, virus-induced hyperinflammation meeting HLH criteria, and severe complications from naturally acquired infections like SARS-CoV-2 and HBV. The significant susceptibility to systemic live-attenuated viruses in individuals with IFN-α/β signaling deficiencies highlights the need for caution, as these viruses can spread extensively and become more pathogenic.

Future research should explore the IFNAR2 pathway in depth to understand the molecular mechanisms underlying its role in antiviral immunity. Developing targeted therapies to enhance IFN-α/β signaling could be crucial in reducing associated risks. Additionally, it is essential to implement early consultation with a clinical immunologist with robust genetic screening protocols in vaccination programs for individuals suspected of having IEI. Tailored vaccination strategies, such as using non-live vaccines and administering antiviral immunoglobulins, must be developed to ensure safe immunization practices and appropriate post-exposure prophylaxis. Long-term, interdisciplinary follow-up care is vital for managing complications and improving outcomes for patients with similar genetic profiles.

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Author Contributions G.A., Z.O., and F.A.A.: conceptualization. G.A., Z.O., D.H.H., and A.M.A.: writing—original draft preparation. G.A., A.A.N., H.A.S., and F.A.A.: writing—review and editing. G.A., Z.O., and F.A.A.: prepared figures. G.A. and F.A.A.: supervision. All authors have read and agreed to the published version of the manuscript.

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Data Availability Sequence data of this study have been deposited in Mendeley database https://doi.org/10.17632/zfnx5nywjz.1. Also data is provided within the manuscript and the supplementary information files.

Declarations

Ethical Approval The studies involving humans were approved by King Fahad Medical City (KFMC) IRB Committee (23–565). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by– product of routine care or industry. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Competing Interests The authors declare no competing interests.

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