Received: 1 May 2017 | Revised: 20 July 2017 | Accepted: 23 July 2017

DOI: 10.1002/humu.23302

MUTATION UPDATE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

IFN-γR1 defects: Mutation update and description of the *IFNGR1* variation database

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Communicated by Jürgen Horst

Abstract

IFN-γ signaling is essential for the innate immune defense against mycobacterial infections. IFN-γ signals through the IFN-γ receptor, which consists of a tetramer of two IFN-γR1 chains in complex with two IFN-γR2 chains, where IFN-γR1 is the ligand-binding chain of the interferon-γ receptor and IFN-γR2 is the signal-transducing chain of the IFN-γ receptor. Germline mutations in the gene *IFNGR1* encoding the IFN-γR1 cause a primary immunodeficiency that mainly leads to mycobacterial infections. Here, we review the molecular basis of this immunodeficiency in the 130 individuals described to date, and report mutations in five new individuals, bringing the total number to 135 individuals from 98 kindreds. Forty unique *IFNGR1* mutations have been reported and they exert either an autosomal dominant or an autosomal recessive effect. Mutations resulting in premature stopcodons represent the majority of *IFNGR1* mutations (60%; 24 out of 40), followed by amino acid substitutions (28%, 11 out of 40). All known mutations, as well as 287 other variations, have been deposited in the online *IFNGR1* variation database (www.LOVD.nl/IFNGR1). In this article, we review the function of IFN-γR1 and molecular genetics of human *IFNGR1*.

KEYWORDS

IFNGR1, IFN-γR1 deficiency, immunodeficiency, IMD27A, IMD27B, Mendelian susceptibility to mycobacterial disease, mutation, polymorphism, variation

1 | BACKGROUND

IFN-γR1 deficiency is caused by loss-of-function (LOF) mutations in *IFNGR1*, that are either autosomal recessive (AR), leading to immunodeficiency 27A (IMD27A; MIM# 209950), or autosomal dominant (AD), leading to immunodeficiency 27B (IMD27B; MIM# 615978) (OMIM 2017). Together with other immunodeficiencies that either affect IFN-γ signaling or IFN-γ production, it is often designated as Mendelian susceptibility to mycobacterial disease (MSMD). IFN-γR1 deficiency affects the response to IFN-γ and has as hallmark that it leads to infections with weakly virulent mycobacteria, such as non-tuberculous, environmental mycobacteria, and the live, attenuated *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) strain that is used as a vaccine against tuberculosis. Infections with other intracellular pathogens, such as Salmonellae, Listeria, Histoplasma, Toxoplasma, and viruses, are occasionally also found in these patients (van de Vosse, van Dissel, & Ottenhoff, 2009). In addition to susceptibility to infection, there also appears to be an increased tendency to develop malignancies: one patient developed Kaposi sarcoma (Camcioglu et al. 2004), one pineal germinoma (Taramasso et al. 2014), and two developed B-cell lymphomas (Bax et al. 2013; J.T. van Dissel, unpublished data).

IFN-γ signaling plays a key role in innate immunity against mycobacteria. Upon infection with mycobacteria, various mycobacterial molecules are recognized by the pattern recognition receptors on antigen presenting cells, which then start to produce IL-23 (composed of IL-12p40 and IL-23p19) and IL-18 (Verreck et al., 2004). IL-23 and IL-18 bind to their respective receptors on Natural killer-like T cells to activate production of IFN-γ (van de Wetering, de Paus, van Dissel, & van de Vosse, 2009). The IFN-γ subsequently binds to the IFN-γ receptor on macrophages and dendritic cells, which results in transcription of cytokines, such as IL-12 (composed of IL-12p40 and IL-12p35), and various molecules involved in microbicidal mechanisms. At a later stage during the infection, IFN-γ is mainly produced by Th1 cells in response to IL-12 and IL-18 released by the antigen presenting cells. This pathway is called the type 1 cytokine pathway, a defect in any of the essential molecules in this pathway results in susceptibility to mycobacterial infections (Bustamante, Boisson-Dupuis, Abel, & Casanova, 2014; van de Vosse et al., 2009; Wu & Holland, 2015).

The human *IFNGR1* gene is located on chromosome 6q23.3 and spans an area of about 22 kb. A single transcript is transcribed from its seven exons. This transcript is translated into a 489 aa long IFN-γR1 precursor protein of which the signal peptide (aa 1–17) is cleaved off

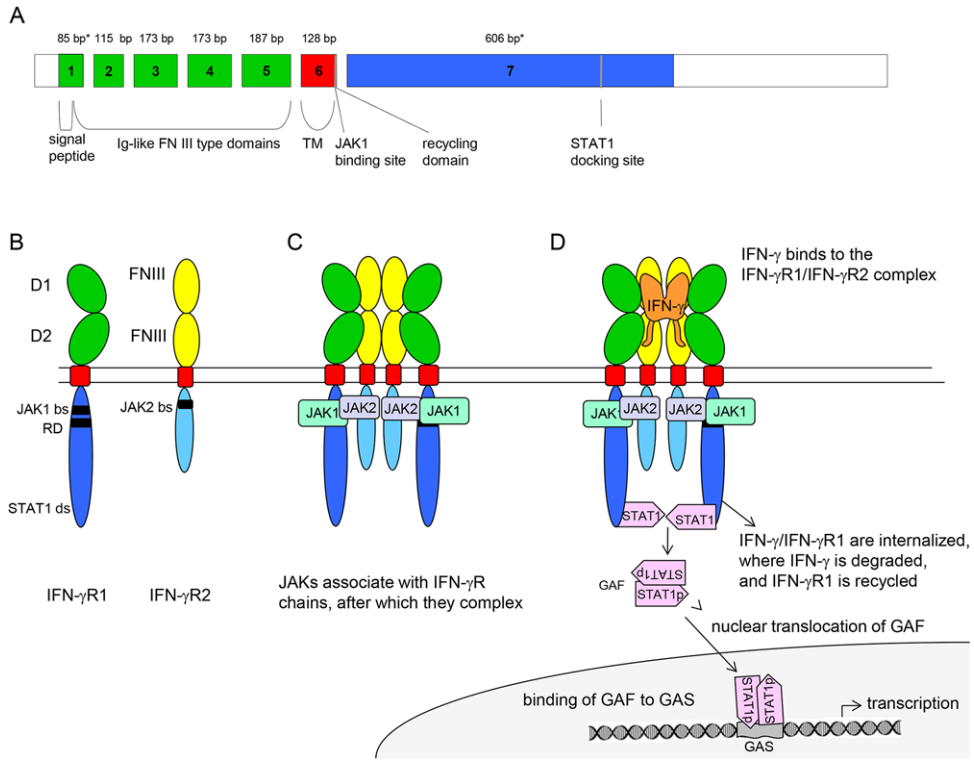

FIGURE 1 Schematic representation of *IFNGR1*, the IFN-γ receptor chains and signal transduction through the IFN-γ Receptor. **A**: The seven exons of the *IFNGR1* gene, distance between exons is not to scale. In white, the untranslated regions; in green, the regions encoding the extracellular region; in red, the region encoding the transmembrane domain; and in blue, the region encoding the intracellular domain. **B**: The mature IFN-γR1 chain, without the 17 aa signal peptide, contains an extracellular segment comprised of two Ig-like Fibronectin type III domains (D1 and D2, at aa 14–102 and aa 114–221), a single transmembrane domain (TM, aa 246–266), and an intracellular part that contains the motif required for the JAK1 binding site (JAK1 bs, aa 283–286), the recycling domain (RD, aa 304–308), and the STAT1 docking site (STAT1 ds, aa 457–461). The IFN-γR2 chain also contains two Fibronectin type III domains (FIII) and a JAK2 binding site (JAK2 bs) **C**: The IFN-γR chains bind their respective JAKs and preassemble to form the tetrameric IFN-γ receptor. **D**: Schematic representation of signal transduction via the IFN-γ receptor. After IFN-γ binds to the complex, STAT1 is phosphorylated (pSTAT1). pSTAT1 molecules form anti-parallel homodimers, known as GAF, that are released from the receptor and translocated to the nucleus where they bind to the GAS in the promoters of various genes to initiate transcription. Schematic representations are based on the crystal structure of IFN-γ/IFN-γR1 complex (Randal & Kossiakoff, 2001; Walter et al., 1995) and the UniProt database (www.uniprot.org)

to produce the 472 aa (53 kDa) mature IFN-γR1 protein (Aguet, Dembic, & Merlin, 1988). This protein consists of an extracellular domain that contains two Ig-like Fibronectin type III domains that are both involved in IFN-γ binding, a transmembrane domain (aa 248–270), and an intracellular domain that contains a JAK1 binding domain, a recycling domain, and a STAT1 docking site (Farrar, Fernandez-Luna, & Schreiber, 1991; Greenlund et al., 1995; Randal & Kossiakoff, 2001; Walter et al., 1995; Yancoski et al., 2012) (Figure 1A).

An assessment of the significance of *IFNGR1* variants is critical to accurately determine diagnoses and providing genetic counseling for affected families. Here, we provide an exhaustive description of the mutations found in this gene. The clinical findings in IFN-γR1 deficiency have been excellently reviewed previously (Bustamante et al., 2014; Dorman et al., 2004; Filipe-Santos et al. 2006; Wu & Holland, 2015) and are not part of this review.

2 | IFN-γR1 FUNCTION

The IFN-γ receptor consists of two IFN-γR1 chains and two IFN-γR2 chains (Figure 1B). IFN-γR1 is the ligand-binding chain of the IFN-γ receptor and is ubiquitously expressed on the cell surface although expression varies depending on the cell type. IFN-γR2 is known as the signal-transducing chain of the IFN-γ receptor (although in fact both chains are involved in signal transduction) and is expressed highly on myeloid cells, moderately on B cells and low on T cells (Bernabei et al., 2001). Initially it was thought that only after binding of an IFN-γ dimer to two IFN-γR1 chains do the IFN-γR1 chains form a complex with the IFN-γR2 chains (Randal & Kossiakoff, 2001). Confocal microscopy however showed that the IFN-γ receptor is pre-assembled (Figure 1C) before IFN-γ binding (Krause et al., 2002). Janus kinase 1 (JAK1) bound to IFN-γR1 is essential for this pre-assembly, whereas JAK2 bound to IFN-γR2 is not (Krause et al., 2006). Upon the binding of IFN-γ to the IFN-γ receptor, JAK1 and JAK2 are phosphorylated and activated and STAT1 is recruited to the receptor complex. As a result, the receptor complex undergoes a conformational change and induces STAT1 phosphorylation (Figure 1D). This phosphorylation of STAT1 occurs very fast (detectable within minutes) after binding of IFN-γ to its receptor. The pSTAT1 molecules form anti-parallel homodimers, known as gamma-interferon activated factor (GAF), which are released from the receptor and translocated to the nucleus where they

bind to the promoters of various genes to activate transcription. The promoter sequences the GAF bind to are called the gamma-interferon-activated sites (GAS) and contain the palindromic consensus sequence TTTCCNGGAAA (Schindler, Levy, & Decker, 2007). Some of the genes activated are *TNF*, *CXCL11*, *FCGR1A*, and various *IRFs*. After signaling, the IFN-γR1 chains complexed with IFN-γ are internalized where IFN-γ is degraded and IFN-γR1 is stored until it is recycled back to the cell surface (Celada & Schreiber, 1987) (Figure 1D).

3 | ANIMAL MODELS

Two mouse strains with complete AR *Ifngr1* mutations exist, these are the Ifngr1^0 and Ifngr1$_{WU}^-$ knock-out strains (Huang et al., 1993; Lee et al., 2013). No mouse model exists that mimics the AD defect that is present in many of the patients. Similar to patients that have complete defects in *IFNGR1*, mice completely lacking *Ifngr1* are highly susceptible to infection with the slow growing *M. bovis* BCG resulting in poor granuloma formation and death (Kamijo et al., 1993). Two rapidly growing mycobacteria on the other hand, *M. abscessus* and *M. chelonae*, had an initial higher outgrowth of bacteria in mice lacking *Ifngr1*, but were eventually contained in these mice (Rottman et al., 2007). Apparently, other defense mechanisms are available to help control rapidly growing mycobacteria. Similar to patients with IFN-γR1 deficiency, mice lacking *Ifngr1* had an inadequate response to other intracellular infections as well, such as vaccinia virus, Listeria, and Leishmania (Cantin, Tanamachi, Openshaw, Mann, & Clarke, 1999; Lee et al., 2013; Swihart et al., 1995). Mice lacking *Ifngr1* have also been reported to be more susceptible to malignancies (Bian et al., 2016; Shankaran et al., 2001).

4 | DATABASE

To provide an overview of all reported mutations, polymorphisms, and other variations that affect the *IFNGR1* gene, an *IFNGR1* variation database (www.LOVD.nl/IFNGR1) was created. With the aim of creating the most complete and up-to-date information publicly available, clinicians and researchers may submit new sequence variants and introduce their patients carrying novel or known sequence variants into the database. New variation data are checked by the Mutalyzer program (Wildeman, van Ophuizen, den Dunnen, & Taschner, 2008) to ensure a nomenclature following Human Genome Variation Society (HGVS) recommendations (den Dunnen & Antonarakis, 2000, 2001), and will be curated. All currently known *IFNGR1* variant data from on-line available publications and abstracts have been entered in the variation database, including some patients and mutations that have not yet been published. Variations affecting the coding sequence that are present in the SNP database have been entered as well. The *IFNGR1* gene has its own homepage with a summary of general information on the gene and the database, the chromosomal location of the gene, and the number of reported and unique variants in the database. Information on individual sequence variants ("view unique variants") includes exon–intron location, DNA change, RNA change, protein change, predicted effect, and the first description of the variant. Patient information extrapolated from publications includes clinical diagnosis, pathogenicity of the sequence variant, mode of inheritance, ethnic origin, and the number of patients reported per family. Hyperlinks to relevant gene and disease information as well as publications from the PubMed (https://www.ncbi.nlm.nih.gov/Pubmed) and OMIM (https://www.ncbi.nlm.nih.gov/Omim) databases are included.

5 | *IFNGR1* MUTATIONS

Pathogenic mutations in *IFNGR1* were first reported in 1996 by Newport et al. (1996) and Jouanguy (1996) and have since been found in 135 individuals, 130 of which were reported before and five are newly reported. In total, 40 unique *IFNGR1* mutations have been identified (Table 1) that are distributed across all seven exons (Figure 2). The majority of these mutations are private: 28 mutations have been found only in single families, 11 are found in two to seven families, and only one has been found in 41 families. This last mutation, c.819_822del (often referred to as c.818del4), is located in a deletion hotspot as it often arises de novo (Jouanguy et al., 1999). Another deletion hotspot has been reported as well, causing the mutation c.563_566del, although that mutation has not been found in more than three families thus far (Rosenzweig et al., 2002). Due to these deletion hotspots, the largest number of mutated alleles are found in exon 6 (Figure 2A) although this is not the exon with the largest number of unique mutations (Figure 2B) or the largest number of unique mutations per 100 nt (Figure 2C). All AD mutations are in exon 6, whereas no AR mutations have been identified in exon 6 so far (Table 1). In exon 7, only one mutation has been identified so far, p.Ser485Phe, and although it is highly likely that it is the cause of disease in the child in which it was identified, the child died before functional analyses could be performed so its deleterious effect has not been proven (Galal et al., 2012).

Of some mutations the effect is immediately obvious, of others it may not be. The premature stopcodons in the extracellular domain (encoded by exon 1–5) have an obvious effect: the truncated protein, if any is produced, cannot be expressed on the membrane and therefore results in a complete defect. The premature stopcodons in the intracellular domain that have been found so far are all in exon 6, leave the transmembrane domain intact, and affect the recycling domain, causing the protein to accumulate on the membrane. These defective proteins are able to bind IFN-γ and are able to form a receptor complex with IFN-γR2 chains but they lack the STAT1 docking site so they are unable to signal and thus exert a dominant negative effect.

Of the 11 missense mutations found (Table 1), two (p.Cys77Phe and p.Cys85Tyr) were found not to be expressed on the patients' cells, which explains how they cause complete defects (Chantrain et al., 2006; Noordzij et al., 2007). Lack of expression of these proteins may be due to the protein quality control system in the endoplasmic reticulum that prevents transport of mutant or misfolded proteins, and targets these for degradation. The choice of antibodies is very important in these experiments as for instance p.Val63Gly was found to be expressed on monocytes in tiny (four antibodies) or normal (two antibodies) amounts depending on the antibodies used (Allende et al., 2001; Sologuren et al., 2011). p.Cys77Tyr was found to be expressed on the patients' cells, these cells however failed to bind IFN-γ,

TABLE 1 Deleterious mutations in the *IFNGR1* gene

Region	DNA sequence change[a]	Protein change[b]	Protein expression on cell[c]	Effect	Remarks	First description
Exon 1	c.2T > A	p.Met1Lys	− − +	AR, partial		Kong et al. (2010)
Exon 1	c.25del	p.Val10Serfs*5	− −	AR, complete	Reported as 22delC	Holland et al. (1998)
Exon 2	c.104_107dup	p.Ile37Tyrfs*3	− −	AR, complete	Reported as 107ins4	Altare et al. (1998)
Exon 2	c.105dup	p.Thr36Tyrfs*3	− −	AR, complete	Reported ad 105insT	Dorman et al. (2004)
Exon 2	c.106_107insT	p.Thr36Ilefs*3	− −	AR, complete		Dorman et al. (2004)
Exon 2	c.110T > C	p.Ile37Thr	+ −	AR, partial		E. van de Vosse (unpublished data)
Exon 2	c.114_135del	Ser39Tyrfs*16	− −	AR, complete	Reported as Glu38fsX54	Wang et al. (2014)
Exon 2	c.131delC	p.Pro44Leufs*18	− −	AR, complete		Jouanguy et al. (1996)
Exon 2	c.166del	p.Val56Serfs*6	− −	AR, complete		Cunningham et al. (2000)
Exon 2	c.170del	p.Pro57Leufs*5	− −	AR, complete	Reported as 168delC	Dorman et al. (2004)
Exon 2	c.182T > A	p.Val61Glu	n.a./−	AR, complete	Reported as V61Q but should be: V61E	Jouanguy et al. (2000)
Exon 2	c.188T > G	p.Val63Gly	− +	AR, partial		Allende et al. (2001)
Exon 2	c.197A > G	p.Tyr66Cys	n.a./+	AR, complete		Dorman et al. (2004)
Intron 2	c.200+1G > A	affects splicing?	− −	AR, complete	RNA undetectable	Altare et al. (1998)
Intron 2	c.201-2A > G	p.Asn70_Lys103del	− −	AR, complete	r.201_302del	Holland et al. (1998)
Exon 3	c.230G > A	p.Cys77Tyr	+/−	AR, complete		Jouanguy et al. (2000)
Exon 3	c.230G > T	p.Cys77Phe	− −	AR, complete	Reported as C77F, mutation not specified	Chantrain et al. (2006)
Exon 3	c.254G > A	p.Cys85Tyr	−/− − +	AR, complete		Noordzij et al. (2007)
Exon 3	c.260T > C	p.Ile87Thr	+/− − +	AR, partial		Jouanguy et al. (1997)
Exon 3	c.295_306del	p.Trp99_Val102del	+	AR, complete	Reported as 295del12	Jouanguy et al. (2000)
Exon 3	c.339T > A	p.Tyr113*	− −	AR, complete		Prando et al. (2010)
Exon 3	c.347C > A	p.Ser116*	− −	AR, complete	Reported as 395C > A	Newport et al. (1996)

(Continues)

TABLE 1 (Continued)

Region	DNA sequence change[a]	Protein change[b]	Protein expression on cell[c]	Effect	Remarks	First description
Intron 3	c.373+1G > T	p.Val68Lysfs*6	– –	AR, complete	r.201_373del	Roesler et al. (1999)
Exon 4	c.453del	Phe151Leufs*2	– –	AR, complete		Tsolia et al. (2006)
Exon 4	c.523del	p.Tyr175Metfs*2	– –	AR, complete		Koscielniak et al. (2003)
Exon 5	c.563_566del	p.Leu188Argfs*14	– –	AR, complete	Reported as 561_564delACTC	Roesler et al. (1999)
Exon 5	c.653_655del	p.Glu218del	– +	AR, complete	Reported as 652del3	Jouanguy et al. (2000)
Exon 5	c.655G > A	p.Gly219Arg	n.a.	AR, complete[d]		Tesi et al. (2015)
Exon 5	c.672G > A	p.Trp224*	– –	AR, complete[e]		Gutierrez et al. (2016)
Exon 5	c.683delC	p.Thr228Metfs*16	– –	AR, complete	Reported as 726delC	Ward et al. (2007)
Exon 6	c.774_777del	p.Phe258Leufs*18	++	AD, partial	774del4	Okada et al. (2007)
Exon 6	c.794delT	p.Phe265Serfs*12	++	AD, partial		Storgaard et al. (2006)
Exon 6	c.805delT	p.Tyr269Ilefs*8	++	AD, partial		Rose et al. (2014)
Exon 6	c.813_816del	p.Lys272Leufs*4	++	AD, partial	Reported as 811del4	Sasaki et al. (2002)
Exon 6	c.817dup	p.Ile273Asnfs*2	++	AD, partial	Reported as 817insA	Dorman and Holland (2000)
Exon 6	c.819del	p.Asn274Ilefs*3	++	AD, partial	Reported as 818delT	Jouanguy et al. (1999)
Exon 6	c.819_822del	p.Asn274Hisfs*2	++	AD, partial	Reported as 818del4	Jouanguy et al. (1999)
Exon 6[f]	c.832G > T	p.Glu278*	++	AD, partial		Villella et al. (2001)
Exon 7	c.1454C > T	p.Ser485Phe	n.a.	AR, complete[d]	Reported as S485F	Galal et al. (2012)
Exon 1–7	Large genomic deletion	no protein produced	– –	AR, complete	No transcript produced	de Vor et al. (2016)

[a] Mutations are numbered in accordance with GenBank entry NM_000416.2, where +1 corresponds to the A of the ATG translation initiation codon.
[b] Amino-acid changes are numbered in accordance with UniProt entry P15260.
[c] +, normal expression; ++, increased expression; + –, expression on patient's monocytes, absent on patient's T cells; – –, no expression; – +, reduced expression or expression not detectable with all antibodies used; – – +, only residual expression and not on all cell types; +/ –, expression detectable on patient cells but not in retroviral system; –/– –+, not expressed on patient cell but residual expression in retroviral system; +/ ––+, expressed on patient cells but only residual expression in retroviral system; n.a./– , not analyzed in patient cells but absent in retroviral system; n.a. , not analyzed.
[d] The IFN-γ response of the patient could not be analyzed, high plasma IFN-γ however suggests a complete defect.
[e] Predicted effect, although not analyzed.
[f] *Note*: the mutation p.Glu278* is mistakenly placed in exon 7 in Figure 1 of the review by (Bustamante et al., 2014). AR, autosomal recessive; AD, autosomal dominant.

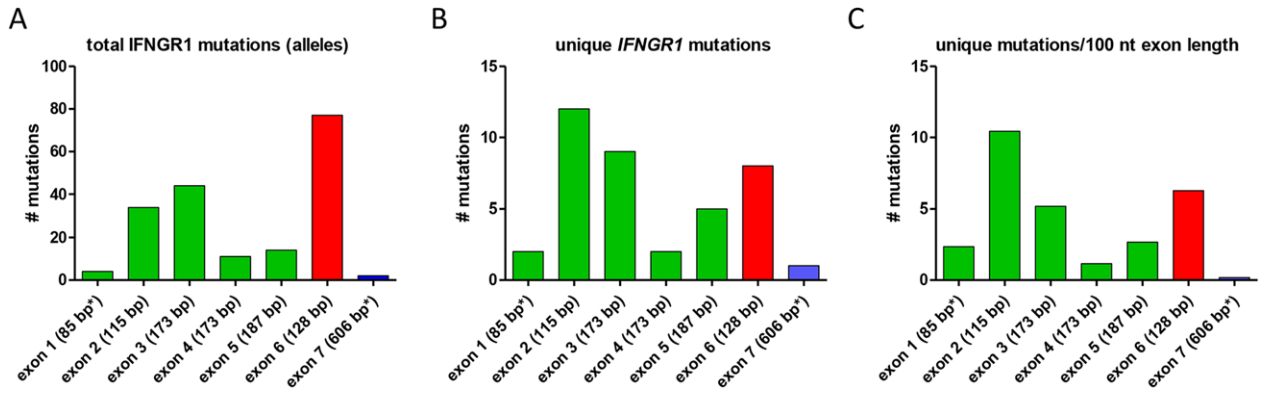

FIGURE 2 Genomic structure, encoded protein domains, and mutation distribution in the *IFNGR1* gene. Numbers of total (**A**) and unique (**B**) variants are shown, as well as mutation distribution ratio as determined by dividing the number of unique mutations per exon by the exon length (**C**). *Indicated lengths of exon 1 and 7 in graph are the lengths of the ORFs. Note: mutations in splice sites are grouped under affected exon. The large genomic deletion encompassing the entire *IFNGR1* gene is not taken into account

explaining its detrimental effect (Jouanguy et al., 2000). p.Ile87Thr is also expressed on the cell surface, the cells showed an impaired response of which the mechanism is unclear, but that could be complemented by expression of wild-type IFN-γR1 (Jouanguy et al., 1997; Sologuren et al., 2011). That also the cell type may affect expression is illustrated by the mutation p.Ile37Thr, that was absent on patient's T cell blasts but expressed on the patient's monocytes (E. van de Vosse, unpublished data).

It is unknown whether the mutation p.Val61Glu affects cell surface expression in patient' cells since this mutation has been found in a patient that did show IFN-γR1 expression but that was compound heterozygous for two mutations thus prohibiting assignment of the expression to either or both alleles (Jouanguy et al., 2000). Of the mutation, p.Tyr66Cys cell surface expression was not analyzed in the patient's cells (Dorman et al., 2004). In a retroviral expression system, it appeared to be expressed in normal amounts on the cell surface (van de Wetering, de Paus, van Dissel, & van de Vosse, 2010). The affected amino acid is one of the amino acids that are directly involved in IFN-γ binding (Lys64, Tyr66, Val68, Ala70, Ser95, Asn96, Trp99, Trp224) (Randal & Kossiakoff, 2001), which explains its detrimental effect.

The effect of the missense mutation p.Met1Lys is clear as it removes the start codon. Indeed on the patient's fibroblasts, no IFN-γR1 was detectable. Residual amounts of the protein were however detected on the membrane of the patient's B cells in which an alternative start codon (Met19) is used (Kong et al., 2010). Although no expression or functional analyses are available of the missense mutations p.Gly219Arg and p.Ser485Phe, prediction programs indicate these amino acid substitutions are damaging and the high amount of IFN-γ in the patients' serum samples strongly suggest severe IFN-γR1 defects (Galal et al., 2012; Tesi et al., 2015).

Expression of seven of the 11 missense mutations was analyzed in a retroviral expression system. Six of these were found not to be expressed on the cell surface (p.Val61Glu, p.Cys77Phe, p.Cys77Tyr) or only in very tiny amounts (p.Val63Gly, p.Cys85Tyr, p.Ile87Thr) (van de Wetering et al., 2010). Only one, p.Tyr66Cys, was found to be expressed on the cell surface (van de Wetering et al., 2010). Of the variants that were not expressed in the retroviral system, p.Cys77Phe and p.Cys85Tyr were also not expressed on patients' cells, of Val61Glu surface expression could not be determined in patient' cells. p.Cys77Tyr was found not to be expressed in the retroviral expression system (van de Wetering et al., 2010); however, it was found to be expressed on patient' monocytes (Jouanguy et al., 2000). p.Val63Gly and p.Ile87Thr were only detected in tiny amounts in the retroviral expression system, whereas in monocytes from various patients, expression was normal ((Allende et al., 2001) and (Jouanguy et al., 1997; Sologuren et al., 2011)). Expression of p.Val63Gly and p.Ile87Thr was low on EBV cells of various patients although the difference with controls was not significant for most antibodies tested (Sologuren et al., 2011). Since in most studies, including the retroviral expression study, a variety of antibodies was used, the difference in cell surface expression appears to vary depending on the cell type analyzed. Care should be taken as these results indicate that cell surface expression of IFN-γR1 in a retroviral expression system may not always reflect cell surface expression on patient cells.

To determine the effect of missense mutations that are expressed on the cell surface, the capacity of the cells to bind IFN-γ can be analyzed. IFN-γ binding capacity was found to be low in cells from multiple patients with the p.Val63Gly mutation, IFN-γ binding capacity was not tested in cells with the p.Ile87Thr mutation. The deleterious effect of the p.Val63Gly and p.Ile87Thr mutations may be caused by low expression, low IFN-γ binding capacity, or a combination of both (Sologuren et al., 2011).

Regardless of whether or not expressed on the cell surface, both partial and complete *recessive* mutations can lead to high IFN-γ levels in the serum (Allende et al., 2001; Fieschi et al. 2001), whereas in the serum of healthy individuals, IFN-γ is usually undetectable. Particularly during the acute phase of infection, serum IFN-γ can rise to extremely high levels in these patients (de Vor et al., 2016; Sologuren et al., 2011).

5.1 | Genotype–phenotype correlation

Although both the AR and AD mutations in *IFNGR1* affect IFN-γ responses, there is a marked difference in the effect. The AR mutations lead mostly to complete deficiency, with the exception

of four missense mutations that lead to partial deficiency (Table 1). Among the partial AR mutations, the p.Met1Lys mutation is more severe than the p.Val63Gly and p.Ile87Thr mutations (Kong et al., 2010). The severity of the p.Ile37Thr mutation compared with the other three is not clear yet. The AD mutations are all due to premature stopcodons in the intracellular domain of the protein well before the recycling domain. This blocks the internalization of the IFN-γ/IFN-γR1 complex after signaling and causes the truncated IFN-γR1 to accumulate on the membrane. The accumulated truncated proteins can still bind IFN-γ and probably complex with IFN-γR2 chains but are unable to signal as they are lacking the JAK1 binding site and the STAT1 docking site, thus severely affecting signaling. IFN-γ signaling is however not completely abolished because from the healthy allele normal IFN-γR1 is produced. Due to the accumulation of the truncated IFN-γR1, the normal IFN-γR1 is only a small proportion of the total IFN-γR1 on the cell membrane, thus allowing only a fraction of the IFN-γ receptors to contain two functional IFN-γR1 chains and respond normally to IFN-γ.

The clinical phenotype of individuals with *complete* AR mutations is primarily determined by the pathogens encountered, as they are all highly susceptible to severe mycobacterial infections. The mycobacterial infections in individuals with either *partial* AR or *partial* AD mutations are naturally less severe than those with complete deficiency; there is however also a feature that is very specific for the individuals with partial mutations, as more than half of them develop multifocal osteomyelitis with either *Mycobacterium avium* or *M. bovis* BCG. Multifocal osteomyelitis is also found in other patients with partial defects in IFN-γ signaling, namely those with partial LOF mutations in *STAT1* (Boudjemaa et al., 2017; Hirata et al., 2013; Shamriz et al. 2013; Tsumura et al., 2012). The mechanism behind the occurrence of multifocal osteomyelitis in individuals with partial defects in IFN-γ signaling is a puzzling feature. Recently it was reported that IFN-γ plays a role in inhibiting osteoclastogenesis in human cells and that this inhibition is reduced in osteoclasts from patients with partial *IFNGR1* or *STAT1* defects (Nishimura et al. 2015). This suggests that increased osteoclastogenesis is somehow involved in the occurrence of osteomyelitis; how this works and why patients with complete defects do not develop osteomyelitis is however still unclear.

5.2 | Disease penetrance and age at onset

The clinical presentation varies between patients with the same mutation; this may be partly due to differences in exposure to the various pathogens and may also be due to differences in genetic background of the individuals. Penetrance of complete AR mutations appears to be full with an early onset (mean 3.1 years; Dorman et al., 2004), whereas among the individuals with AD mutations, several were reported not to be affected. These may however still develop infections at a later age as mean disease onset in patients with AD mutations was 13.4 years, with a range of 1.5–57 years (Dorman et al., 2004). Adult onset, at the age of 20 years, has also been reported for one patient with the partial AR mutation p.Ile87Thr (Remiszewski et al., 2006).

5.3 | Variations of unknown significance identified in patients

Several variations have been identified of which the significance is unknown because they were identified only heterozygously, in individuals that do not have typical symptoms of IFN-γR1 deficiency, and/or were not analyzed for functional effect. One variation, p.Ile183Val, that was found heterozygously in a patient with an osteosclerotic metatarsal bone tumor and that was reported to be a mutation (Bińczak-Kuleta et al., 2016), has an unknown significance since no immunological assays were performed to determine its functional effect, and prediction programs suggest that it is most likely a neutral variant (Supp. Table S1). The variation has been entered in the database as polymorphism with "probably no pathogenicity." Another variation, p.Gln190Arg, found heterozygously in twins with *M. bovis* BCG lymphadenitis, was determined not to be the cause of the lymphadenitis as functional analyses showed the IFN-γ response was normal (Kong et al., 2013). Prediction programs indicate it is a neutral variant (Condel score 0.417). The last variation, p.Glu487*, was found heterozygously in a patient with common variable immunodeficiency and respiratory tract infections. It results in an IFN-γR1 protein lacking only the last three amino acids. Functional analysis showed a mildly reduced IFN-γ response (Dr Frank van de Veerdonk, personal communication). Whether the variation causes the reduced IFN-γ response and the clinical presentation is unknown. Analysis of these variations of unknown significance in a retroviral expression model will be able to determine their functional effect.

5.4 | Diagnosis of IFN-γR1 defects

The diagnosis of defects in IFN-γR1 is initially aimed at determining whether any form of MSMD is present. This is done by determining the IFN-γ response in whole blood or PBMCs. To subsequently focus on IFN-γ signaling STAT1 phosphorylation or CD64 upregulation in response to IFN-γ can be measured in monocytes. High amounts of IFN-γ in plasma are a strong indication for an AR defect in either IFN-γR1 or IFN-γR2. Determining expression of IFN-γR1 is valuable to identify the greatly increased expression that indicates AD mutations, as well as greatly reduced or absent expression of most AR mutations (see Table 1). Ultimately the causative mutation(s) needs to be identified in the *IFNGR1* gene to verify the diagnosis.

5.5 | Treatment of patients with IFN-γR1 defects

The only curative treatment for patients with complete defects is hemopoietic stem cell transplantation (Roesler et al., 2004). Patients with partial defects require (prophylactic) treatment with antibiotics and may benefit from recombinant human IFN-γ (Sologuren et al., 2011).

6 | *IFNGR1* POLYMORPHISMS

Although *IFNGR1* displays low nucleotide diversity compared with other genes involved in inflammatory responses (Manry et al., 2011),

TABLE 2 *IFNGR1* missense variations that are either common and/or were determined to have little or no effect on function

SNPid	Region	DNA sequence change[a]	Protein change	Minor allele frequency[b]	Functional analysis
rs11575936	Exon 1	c.40G > A	p.Val 14Met	0.003	Gao et al. (2015); van de Wetering et al. (2010)
rs17175322	Exon 2	c.181G > A	p.Val61Ile	0.002	van de Wetering et al. (2010)
n.a.	Exon 4	c.446C > T	p.Ser149Leu	n.a.	van de Wetering et al. (2010)
rs137853274	Exon 4	c.538G > A	p.Gly180Arg	0.003	n.a.
rs55666220	Exon 5	c.589G > A	p.Glu197Lys	0.001	n.a.
rs17175350	Exon 7	c.1004A > C	p.His335Pro	0.004	van de Wetering et al. (2010)
rs199641966	Exon 7	c.1056A > G	p.Ile352Met	n.a.	van de Wetering et al. (2010)
rs374787981	Exon 7	c.1190A > G	p.Tyr397Cys	n.a.	Gao et al. (2015)
rs1887415	Exon 7	c.1400T > C	p.Leu467Pro	0.084	van de Wetering et al. (2010)

[a]Variations are numbered in accordance with GenBank entry NM_000416.2, where +1 corresponds to the A of the ATG translation initiation codon.
[b]Data from the SNP database (dbSNP 2017). n.a., not available.

a large number of SNPs in *IFNGR1* are known, including missense variations that affect the amino acid sequence (dbSNP 2017). Very few of the missense variations in *IFNGR1* are present at an overall minor allele frequency of ≥0.001; these are p.Val14Met, p.Val61Ile, p.Gly180Arg, p.Glu197Lys, p.His335Pro, and p.Leu467Pro (Table 2). van de Wetering et al. (2010) showed using expression constructs that p.Val14Met, p.Val61Ile, p.His335Pro, p.Leu467Pro and the less common p.Ser149Leu and p.Ile352Met variants are indeed polymorphisms that have little (p.Val14Met, p.His335Pro, p.Ile352Met) or no (p.Val61Ile, p.Ser149Leu, p.Leu467Pro) effect on IFN-γR1 function. The variation p.Val14Met and the less common p.Tyr397Cys were also shown with expression constructs to have only a small effect on IFN-γR1 function (Gao et al., 2015). The variations p.Gly180Arg and p.Glu197Lys were not analyzed.

In addition to the polymorphisms described above, many variations are present in the SNP database with low frequencies: 81 synonymous SNPs and 194 variations that affect the amino acid sequence of the protein. All have been included in the *IFNGR1* variation database. The variations that affect the amino acid sequence and their predicted effect on IFN-γR1 function are listed in Supp. Table S1. No conclusions or clinical diagnosis can be based on the predicted effects, the actual functional effects can only be determined experimentally.

6.1 | Associations of polymorphisms with disease

Many common SNPs in the *IFNGR1* gene region were analyzed for association with various aspects (a.o. susceptibility, severity, and laboratory parameters) of immune-mediated and infectious diseases. The SNPs analyzed in those studies are located in exons, introns, or in the vicinity of the *IFNGR1* gene. A summary of the literature on these association studies is beyond the scope of this report. In general however small effects were found, if any, and these have not yet been replicated in independent cohorts.

7 | FUTURE PROSPECTS

The *IFNGR1* variation database will help investigators and clinicians to quickly determine whether a variation is a known mutation, a known polymorphism, or a variation with unknown effect requiring further analysis. Future submissions are encouraged to keep the database up-to-date and complete, and the database will also be updated regularly by the curator by searching for published sequence variants in *IFNGR1*. The database will provide a complete and up-to-date overview of all reported variants in *IFNGR1*.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

ETHICAL COMPLIANCE

The patient clinical data in the database www.LOVD.nl/IFNGR1 have either been obtained from publications or have been obtained in a manner conforming with the hospital's medical ethical committee.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: van de Vosse E, van Dissel JT. IFN-γR1 defects: Mutation update and description of the *IFNGR1* variation database. *Human Mutation*. 2017;00:1–11. https://doi.org/10.1002/humu.23302