The Role of Interferon-λ Locus Polymorphisms in Hepatitis C and Other Infectious Diseases

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Key Words
Interferon-λ · IL28B · Polymorphism · Single-nucleotide polymorphism · Hepatitis C virus · Autoimmunity · Cytokines · Epithelium · Host defence · Immune response · Virology

Abstract
Since its discovery in 2003, the type III interferon-λ (IFN-λ) family has been found to contribute significantly to the host response to infection. Whilst IFN-λ shares many features with type I IFN induction and signalling pathways, the tissue-specific restricted expression of its receptor, IL28RA, makes IFN-λ a major mediator of host innate immunity in tissues and organs with a high epithelial cell content. Host susceptibility and responses to infection are known to be heterogeneous, and the identification of common genetic variants linked to disease outcome by genome-wide association studies (GWAS) has underscored the significance of host polymorphisms in responses to infection. Several GWAS have highlighted the IFN-λ locus on chromosome 19q13 as an area of genetic variation significantly associated with hepatitis C virus (HCV) infection, and the rs12979860 genotype can be used in clinical practice as a biomarker for predicting a successful response to treatment with pegylated IFN and ribavarin. Here, we discuss IFN-λ genetic polymorphisms and their role in HCV and other infectious diseases as well as their potential impact on clinical diagnostics, patient stratification and therapy. Finally, the broader role of IFN-λ in the immunopathogenesis of non-infectious inflammatory diseases is considered.

Introduction
The host response to infection is complex, and whilst the virulence of the infecting pathogen plays a major role in the establishment and severity of disease, the contribution of host genetic variations to disease susceptibility and the outcome of infection are significant. Several diseases and disorders are known to be caused by genetic variation within components of the immune system, for example in interferon (IFN)-mediated host immunity pathways [1, 2]. Genome-wide association studies (GWAS) provide a powerful tool to link genetic polymorphisms to specific diseases and have enabled the identification of markers associated with pathogens including the human immunodeficiency virus (HIV), hepatitis C virus (HCV), dengue virus, malaria, and Mycobacterium tuberculosis [3].
In 2009, three independent GWAS found a single-nucleotide polymorphism (SNP), rs12979860, in the promoter region of IFN-λ3 (IL28B) to be significantly associated with spontaneous virus clearance and a sustained virological response (SVR) to HCV infection following treatment [4–6]. The identification of this SNP has led to considerable efforts to understand the IFN-λ locus and how its polymorphisms influence HCV infection, as well as other diseases, with the number of publications increasing from around 40 in 2010 to almost 300 in 2012 and up to 200 to date in 2014 (search terms ‘IL28B polymorphism’, ‘rs12979860’ and ‘rs8099917’).

This review provides a brief overview of the IFN-λ family, the numerous genetic polymorphisms found at this locus and the relationship between these variants and clinical infection medicine. The importance of ethnic and genetic considerations when studying disease association of SNPs will be discussed. Finally, we will explore the genetic considerations when studying disease association of SNPs.

Anti-Viral Effects of IFN-λ

The IFN-λ family exerts anti-viral activity against a range of RNA and DNA viruses responsible for diverse infections, including hepatitis B (HBV) and C viruses (HCV) [21], herpes simplex virus types 1 and 2 (HSV-1/2) [20, 22], cytomegalovirus [23], human herpesvirus 6B [24] and HIV [25]. As the predominant IFN induced in response to respiratory viruses [26], IFN-λ contributes considerably to the control of viral infections of the respiratory tract, including influenza A virus [27–29], human metapneumovirus and the severe acute respiratory syndrome (SARS) coronavirus [30]. Although only expressed in a minority of individuals, IFN-λ4 exerts antiviral activities against HCV and 2 human coronaviruses, HCoV-229E and the Middle East respiratory syndrome (MERS)-CoV, despite its relatively low level of expression [9, 31]. The capacity of cells to respond to IFN-λ is determined by the expression of the IL28RA receptor subunit which is predominantly expressed on hepatocytes and cells of epithelial origin [8, 10, 32, 33]. This restricted receptor expression and the consequent tissue-specific anti-viral effects suggest a major role for IFN-λ in the protection of the epithelium from viral infection [34–36].

Anti-Tumorigenic Effects of IFN-λ

Type I IFNs are used therapeutically in the treatment of some cancers [37], and due to the overlap in their downstream signalling pathways there is mounting evidence that the IFN-λ family shares these anti-tumorigenic properties [15, 38]. IFN-λs have been demonstrated to possess pro-apoptotic and anti-metastatic effects in mouse models [39, 40] as well as in human lung cancer cell lines in vitro [41]. These findings highlight the significance of IFN-λ in the cellular defence against both invading viral pathogens and malignant host cells.
IFN-λ Polymorphisms and Viral Hepatitis

In 2009, GWAS aiming to identify genetic determinants of therapy response in HCV patients identified multiple SNPs within the IFN-λ locus on chromosome 19q13 that were linked to disease and treatment outcome [4–6]. Since then, numerous studies have verified these associations, discovered correlations with other diseases and identified more SNPs within this locus (table 1). The rs12979860 SNP is located 3 kb upstream of IFN-λ3 (fig. 1), and a CC genotype at this location is associated with both SVR to pegylated IFN-α and ribavirin treatment, and spontaneous viral clearance in chronic HCV infection [4, 42]. A similar study found a haplotype with 6 polymorphisms [rs12980275, rs8105790, rs8103142, rs10853727, rs8109886 and rs8099917 (GCCTAG)] to be overrepresented in patients who failed to respond to treatment, and in particular the minor G allele at both rs12980275 and rs8099917 was found to be strongly linked to a failure to clear infection (null virological response; NVR) [5, 6].

Following the identification of rs12979860 as a strong predictor of therapy outcome in HCV patients, studies in other cohorts found alternative SNPs to be better predictors of treatment success. rs8099917 is the strongest predictor of disease outcome in the Japanese population, and an increased number of TA dinucleotide repeats was associated with a lower rate of viral clearance [5, 6].

Table 1. Interferon-λ polymorphisms and disease association

| SNP          | Gene           | Minor/major allele | Effects of the minor allele                                                                 | Ethnicities implicated | References |
|--------------|----------------|--------------------|----------------------------------------------------------------------------------------------|------------------------|------------|
| rs12979860   | IFN-λ3 (3 kb upstream) | T/C                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | AA, C, H, LA           | 4, 103     |
|              |                 |                    | Decreased rates of SVC                                                                       | A, Eu                  | 42         |
|              |                 |                    | HSV: higher rates of recurrent/more severe herpes labialis                                    | I                      | 20         |
|              |                 |                    | Allergic disease: greater chance of being affected by allergies                              | C                      | 87         |
| rs8099917    | IFN-λ3 (8.9 kb upstream) | G/T                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | Au (Eu), LA            | 5, 103     |
|              |                 |                    | Decreased rates of SVC in HCV                                                                 | Eu, Ch                 | 61, 104    |
|              |                 |                    | HTLV-1: development of HAM/TSP                                                                  | B                      | 81         |
|              |                 |                    | CMV: lower viral replication in transplant recipients                                           | Na                     | 67         |
| rs28416813   | IFN-λ3 (distal promoter region) | G/C                | HCV: decreased effectiveness of PegIFN-α and ribavirin treatment                               | J                      | 6          |
| rs8103142    | IFN-λ3 (third exon) | C/T                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | J, Au                  | 5, 6       |
| rs4803217    | IFN-λ3 (5' UTR)  | A/C                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | Eu                     | 105        |
| rs368234815  | Frame shift expresses IFN-λ4 | ΔG/TT            | HCV: poor response to PegIFN-α/ribavirin treatment (associated with lower rates of viral clearance) | AA, S                  | 9, 45      |
| rs11881222   | IFN-λ3 (7.5 kb upstream) | G/A                | HCV: decreased effectiveness of PegIFN-α and ribavirin treatment                               | J                      | 6          |
| rs4803219    | IFN-λ3 (5' UTR)  | T/C                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | J                      | 6          |
| rs72258881   | IFN-λ3 (promoter region) | TA repeat        | Number of repeats correlated with gene expression                                              | J                      | 70         |
| rs8105790    | IFN-λ3 (promoter region) | T/C                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | J, Au                  | 5, 6       |
|              |                 |                    | Decreased rates of SVC                                                                       | Ch                     | 104        |
| rs7248668    | Upstream of IFN-λ3 | G/A                | HCV: decreased effectiveness of PegIFN-α/ribavirin treatment                                    | J                      | 6          |
| rs12980275   | Downstream of IFN-λ3 | G/A                | HCV: associated with NVR with PegIFN-α/ribavirin treatment                                     | J, L                   | 6, 103     |
|              |                 |                    | Decreased rates of SVC                                                                       | Ch                     | 104        |
| rs10853727   | IFN-λ3 (promoter region) | G/A                | HCV: associated with NVR with PegIFN-α/ribavirin treatment                                     | Au                     | 5          |
| rs8109886    | IFN-λ3 (promoter region) | A/C                | HCV: associated with NVR with PegIFN-α/ribavirin treatment                                     | Au                     | 5          |

PegIFN-α = Pegylated interferon-α; AA = African American; C = Caucasian; H = Hispanic; LA = Latin American; Eu = European; Ch = Chinese; J = Japanese; Au = Australian; I = Italian; B = Brazilian; NA = North American; A = African; S = Swiss.

a Originally identified in the IFN-λ3 promoter.
peats at rs72258881, in the promoter region of IFN-λ3, is also strongly linked to a successful viral response in Japanese individuals [43, 44]. The dinucleotide variant (TT/ΔG) rs368234815 (or ss469415590) has recently been identified, and the ΔG frame shift allele, which leads to expression of IFN-λ4, is the major variant in Africans and the strongest known host factor for predicting failure to clear HCV in this population [9]. The homozygous TT genotype at this locus also has a strong positive correlation with HCV clearance and treatment outcome [45–47].

Linkage disequilibrium (LD) between SNPs found within the IFN-λ region is a prominent feature and makes it difficult to assign a causative role to individual SNPs, particularly if they are far apart. In sickle cell anaemia, for example, a functional SNP has been found in high LD with SNPs up to 2.5 Mbp away [48]. In the context of IFN-λ3 polymorphisms, the high LD observed between rs12979860 and rs368234815 ($r^2 = 0.988$) gives the latter SNP limited use as a marker in this population (fig. 2) [49]. However, the evidence that the rs368234815 genotype actually provides a better prediction of therapy outcome in Caucasians co-infected with HIV-1 and HCV highlights the difficulties in forming reliable associations between disease and SNPs [50].

The ability of cells to respond to IFN-λ is dependent on the expression of the receptor IL28RA, and there is some evidence that SNPs on this gene are linked to chronic HCV infection. Whilst the major allele at rs10903035 (AA) was found to be overrepresented in a persistently infected, albeit untreated, at-risk group in the Chinese population, the minor G allele has been linked to PEG-IFN-α treatment failure in chronic HCV [51, 52]. Cui et al. [51] also found the rs11249006 GG allele to be linked to a reduced susceptibility to persistent HCV; however, a later study in the Chinese Han population found no such link [53]. Further investigation in much larger sample groups is required to fully understand the role of IL28RA polymorphisms, if any, in disease.

Whilst the impact of IFN-λ and its SNPs on HCV is clear, its role in HBV infection remains controversial despite increasing global interest [reviewed in 54]. Several SNPs have been studied in HBV patient cohorts. The CG rs12979860/rs8099917 haplotype block was found to be associated with HBV seroclearance [55], and both rs12979860 and rs1298025 have been positively linked to response to pegylated IFN-α therapy [56, 57]. In addition, the rs10853728 SNP [in low LD with rs8105790 (68%), rs12979860 (70%) and rs8099917 (68%)] has been linked to chronic hepatitis in HBeAg-negative patients (p =

![Fig. 1. Location of SNPs in the IFN-λ gene locus. Schematic representation of the IFNL locus in chromosome 19q13, with key SNPs within non-coding and coding regions highlighted. SNPs discussed throughout this review are highlighted.](image-url)
0.032), suggesting a potential role for IFN-λ in hepatic inflammation in HBV patients [58]. However, as many other reports have found no links between IFN-λ and chronic HBV infection, a consensus on its role is yet to be reached [59, 60].

**Mechanisms of Action**

In the area of HCV, significant associations have been made between SNPs at the IFN-λ locus, disease susceptibility and treatment outcome; however, the mechanisms via which these polymorphisms functionally influence innate immunity remain ill defined. Of the numerous SNPs within the IFN-λ locus (fig. 1), many are located in the promoter region and could directly influence protein expression by altering the transcription factor binding affinity or chromatin accessibility [61, 62]. For example, SNPs rs12978960, rs4803221 and rs368234815 are proposed to be located within a CpG island [17, 45, 62, 63]. Methylation and deamination at CpG islands cause epigenetic changes promoting the recruitment of proteins associated with less transcriptionally active heterochromatic DNA and thus may alter IFN-λ3 expression. Whilst a recent investigation into the transcriptional regulation of IFN-λ suggested that the majority of the control occurs within the first kilo base pair upstream of IL28B, excluding both rs12979860 and rs8099917, it is well established that the risk alleles at these SNPs (T and G, respectively) alter the mRNA and protein expression in peripheral blood mononuclear cells, sera and the liver in HCV patients as well as healthy individuals [5, 6, 64–69].

In addition to being located within a CpG island, the ΔG allele at rs368234815 is associated with expression of IFN-λ4 and a reduced expression of IFN-λ3 mRNA. The high LD between this and SNP rs12979860, and the combined physiological effects of reduced IFN-λ3, increased IFN-λ4 expression and the associated feedback mechanisms remains unclear. The promoter polymorphism rs72258881 consists of a TA nucleotide repeat, and whilst evidence suggests that the increasing length of TA repeats results in a higher level of transcriptional activity of the IFN-λ3, the mechanism is undefined [70].

Recently, host polymorphism-dependent expression of IFN-λ has been linked to the HCV-induced microRNA (miRNA) miR-122, which is highly expressed in the liver. High levels of miR-122 are linked to a protective CC genotype in rs12979860 and SVR in chronic
IFN-λ Polymorphisms and HCV Treatment

Following the original GWAS studies, and numerous subsequent independent re-validations, a patient’s IL28B genotype is known to be associated with their likelihood of achieving an SVR to pegylated IFN and ribavirin therapy. Current guidelines recommend IL28B genotype testing if the results would influence management plans [74]. Considering the substantial side effect burden of IFN therapy, patients may be reluctant to start treatment, but knowledge of their IL28B genotype and likely response to treatment can facilitate a more informed decision. However, the truly remarkable efficacy of new direct-acting anti-viral agents for the treatment of genotype 1, 2 and 3 HCV infections means that the pegylated IFN and ribavirin therapy regime is now all but obsolete [75]. It remains to be seen whether IL28B genotype will also be predictive of the responsiveness to these new direct-acting anti-viral agents.

IFN-λ Polymorphisms and Other Infectious Diseases

In addition to their role in HCV infection, IFN-λ SNPs have been investigated in the context of other infectious diseases. Following the identification of Med23 as an anti-viral host factor in HSV-1 infection in vitro, the IL28B genotype was explored in patients suffering recurrent orofacial herpes. The minor T allele at rs12979860 was found to be associated with the severity and frequency of oral herpes labialis recurrence [20]. A more recent study in HIV-infected patients found that individuals homozygous for the ΔG mutation at SNP rs368234815 had a higher incidence of developing CMV retinitis [77]. Infection of retinal epithelial cells by CMV causes retinal damage resulting in blindness, and the reduced IFN-λ3 expression as a result of this ΔG mutation may contribute to higher replication levels of CMV and an increased likelihood of developing retinitis. IFN-λ SNPs have also been investigated in the context of HIV ‘controllers’ who suppress the HIV viral load in the absence of therapy. One such study found the protective rs12979860 CC genotype to be associated with spontaneous HIV control; however, in addition to having very low numbers in comparison to non-controllers (53 vs. 389), this group also had a high rate of HCV co-infection, making firm conclusions difficult [78].

Genetic variation in IFN-λs has also been linked to infection with 2 potentially oncogenic viruses: human papilloma virus and human T-lymphotropic leukaemia virus (HTLV) type I. A genetic association study found SNPs in IFN-λ2 and IFN-λ3 to be linked to human papilloma virus persistence and cervical cancer, albeit with a low significance [79]. The risk alleles at rs12979860 (CT) and rs8099917 (GG) have been linked to the incidence of HTLV-1-associated myelopathy/tropical spastic paraparesis [80, 81]. However, another study failed to link the rs8099917 genotype and disease, even though the protective allele (TT) was associated with higher IL28B levels in HTLV-1 mono-infected patients in comparison to HTLV-1/HCV co-infected patients [82]. As a virus predominantly infecting CD4+ T-lymphocytes, the relevance of IFN-λ polymorphisms and generally a type III IFN response in HTLV-1 infection and associated inflammatory diseases is not clear, and further studies in larger cohorts are required to fully understand this and the role of IFN-λ in the development of virus-induced cancers.

Despite being the major IFN expressed in airway cells in response to infection [26–28], surprisingly little is known about the effect of IFN-λ SNPs on respiratory infectious diseases. One study exploring the SNPs rs12979860 and rs8099917 in infants hospitalised with RSV-associated bronchiolitis found no link to the course of clinical infection or viral load even though a significant association between raised IFN-λ1 levels in airway secretions and the severity of disease in infants hospitalised due to RSV bronchiolitis has been observed [83, 84]. This apparent negative link between IFN-λ and disease prognosis raises the possibility that overexpression of IFN-λ may actually be detrimental to patient health, particularly in the context of respiratory infections. In such infections, the predominant induction of IFN-λ may contribute significantly to the phenomenon of hypercytokinaemia, acute respiratory distress syndrome and respiratory failure, necessitating mechanical ventilation in life-threatening disease [85].

IFN-λ Polymorphisms, Inflammation and Allergic Disease

IFN-λs contribute to inflammatory responses, and thus polymorphisms which alter IFN-λ expression may...
have a role in the immunopathogenesis of inflammatory diseases [86]. IFN-λ suppresses allergic asthma in mouse models as a result of promoting Th1 and suppressing Th2 responses [88, 89], and bronchial epithelial cells from asthmatic patients are impaired in their ability to express IFN-λ in response to infection [90]. It is possible, therefore, that polymorphisms that reduce IFN-λ levels are responsible for a dominance of Th2 cells and the resultant inflammatory and allergic diseases, and one study found the risk T allele at rs12979860 to be overrepresented in a cohort of allergy sufferers [87]. However, contradictory reports of elevated IFN-λ levels in asthma patients [91, 92] indicate the need for further studies to elucidate the role of IFN-λ and its polymorphisms in inflammatory disease.

IFN-λ expression and signalling are also linked to the autoimmune disease systemic lupus erythematosus (SLE), with higher levels of IFN-λ (mRNA and protein), and its subsequent stimulation of cytokine expression, in SLE patients thought to contribute to the observed inflammation and associated organ damage in SLE disease [93, 94]. Interestingly, the IL28RA SNP rs4649203 minor allele is linked to an increased risk of SLE in the Chinese Han population [96] and, whilst the effect of this polymorphism is not known, its location in the 3′ UTR suggests that it may influence receptor expression. Whilst the underlying cause of SLE remains undefined, an infectious agent has long been suspected [reviewed in 96]. It is unsurprising, therefore, to find links between host polymorphisms influencing IFN-λ pathways and SLE, and the role of IFN-λ in inflammatory and autoimmune diseases warrants further investigation.

**IFN-λ Polymorphisms and Disease Association: Ethnicity and Gender Considerations**

The most studied SNP in the IFN-λ locus, rs12979860, shows extensive geographical variation in allele frequencies, with the C allele, associated with clearance of HCV, present at very high (>90%) rates in East-Asian populations and at low rates (<40%) in African populations (fig. 3a). This disparity in C allele frequency correlates with the observed clinical differences between these populations, where East Asians have a more than 3 times greater rate of HCV clearance [42, 97]. The ethnicity-dependent distribution of the protective CC genotype also partially explains the differences in SVR between African Americans and European Americans, where chronic infection occurs more often in people of African descent (76.4%) compared to Caucasian populations (44%) [4]. Such variation in allele frequencies is
also likely to contribute to the global variations in ‘predictor’ genotypes, such as the SNPs rs8099917 and rs368134815 being the strongest predictors of HCV therapy outcome in Japanese and African populations, respectively [9, 43]. Intra-regional variation in SNP allele frequencies is also noted, with CC frequencies ranging from 80% in Asian Australians to 19% in Mediterranean Australians (fig. 3b) [98], and this high level of variation even within the relatively small population of Australians (~23 million) should be considered when utilising genotypes for patient stratification.

The observed correlation between geographically distinct genotypes and chronic disease prevalence provides evolutionary evidence for maintenance of the protective alleles in the IFN-λ SNPs, i.e. maintenance of a CC at rs12989760 in areas endemic for chronic HCV. However, this does not explain the high prevalence of the so-called ‘risk’ T allele at this SNP in populations such as the Australian Aboriginal and Mediterranean populations. In some well-known genetic disorders, such as sickle cell anaemia, individuals homozygous for the mutation in question suffer severe disease, whilst the heterozygosity actually confers a level of protection against malaria. It is possible, therefore, that the risk allele at rs12979860 may confer some as yet unidentified genetic advantage to some populations whilst simultaneously rendering others susceptible to chronic diseases such as HCV.

Interestingly, there is also evidence for a gender bias with respect to the association between IL28B SNPs and HCV. The rs12979860 genotype has been found to be a more reliable predictor of a favourable outcome of HCV infection in the female gender [42]. This gender bias was supported by a later study showing a similar rate of spontaneous viral clearance in women with TT/CT alleles and spontaneous viral clearance in women with TT/CT alleles and this high level of variation even within the relatively small population of Australians (~23 million) should be considered when utilising genotypes for patient stratification.

Concluding Remarks

Since its discovery in 2003, there has been an explosion of data describing the possible roles type III IFN in infectious and non-infectious human disease. Whilst the assessment of host genetics contributes to diagnostic and therapy options in oncology, this is surprisingly underexploited in other fields of medicine. The IL28B polymorphism rs12979860 is the only host SNP to be used as a genetic biomarker for infectious diseases, and genotyping at this locus is incorporated into patient stratification for the clinical management of HCV infection [100]. Whilst the link between IFN-λ polymorphisms and HCV infection is the most robust and well described, this review has highlighted a number of other infectious and inflammatory diseases in which polymorphisms affecting IFN-λ expression or signalling have been implicated. The data for many of these diseases, however, remain unconvincing. Many studies have been limited by often very small sample sizes and small effect sizes, and variations in patient characteristics make inter-study comparisons difficult. Given the levels of intra-regional genotype variation within some populations, caution should be used when interpreting the population stratification in such association studies, particularly in those with relatively high p values. Finally, the existence of LD between SNPs within the IFN-λ locus makes it difficult to assign causality to an individual polymorphism. However, it seems likely that host polymorphisms affecting the IFN-λ signalling axis will play a key role in the advancing field of novel host biomarkers for patient management and differential therapy.

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