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Human Genetic Determinants of Viral Diseases

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Abstract

Much progress has been made in the identification of specific human gene variants that contribute to enhanced susceptibility or resistance to viral diseases. Herein we review multiple discoveries made with genome-wide or candidate gene approaches that have revealed significant insights into virus–host interactions. Genetic factors that have been identified include genes encoding virus receptors, receptor-modifying enzymes, and a wide variety of innate and adaptive immunity-related proteins. We discuss a range of

pathogenic viruses, including influenza virus, respiratory syncytial virus, human immunodeficiency virus, human T cell leukemia virus, human papilloma virus, hepatitis B and C viruses, herpes simplex virus, norovirus, rotavirus, parvovirus, and Epstein-Barr virus. Understanding the genetic underpinnings that affect infectious disease outcomes should allow tailored treatment and prevention approaches in the future.

INTRODUCTION

Viruses co-opt numerous cellular pathways to complete their replication cycles, providing myriad points of contact between virus components and cellular proteins. Viruses also often encode proteins that subvert human immune mechanisms. Thus, pathogenic viruses can provide selective pressures for evolutionary adaptation of multiple features of human biology (101). Virus–human interactions have driven as much as 30% of human genome evolution since divergence from chimpanzees (38), and genetic variation among humans produces a wide variety of responses to viral infections. One of the earliest demonstrations of this genetic effect was provided by the examination of poliovirus infection in twins, in which at least one twin was diagnosed with paralytic poliomyelitis (52). Paralytic polio disease in the second twin was significantly more likely among identical versus fraternal twins, indicating a genetic influence on this infection outcome. Further, a landmark study comparing causes of premature death among adoptees with the causes of death of their biological and adoptive parents provided strong evidence for heritable factors in infectious disease mortality (135). In this review, we summarize a variety of notable examples of specific genes and genetic variants linked to particular outcomes of viral infections (**Table 1**).

Genes discussed herein that increase or decrease susceptibility to viral diseases may be grouped into several broad functional classifications (**Table 1** and **Figure 1**). For example, gene variations associated with resistance to particular infections often involve virus entry receptors, coreceptors, or receptor-modifying enzymes. Likewise, polymorphisms leading to over- or under-production of specific cytokines can also influence viral disease severity. Genetic defects in other aspects of cellular innate and adaptive immune responses to viral infections, such as virus sensing, signaling in response to viruses, activity of antiviral restriction factors, or proper initiation of T cell responses, have also been associated with enhanced severity of numerous viral infections. Recognition of such classifications can provide a framework for identifying new biologically plausible susceptibility or resistance loci, though additional classifications are likely to be added as new genetic determinants of viral diseases continue to be discovered.

Several approaches have been applied to identify genetic factors linked to virus infection susceptibility or disease outcome. These studies typically require the identification of individuals with unusual responses to infections, such as an abnormal severity of illness, rare complications, or an unusually rapid or slow progression of disease. The study of candidate genes is one strategy that has proven successful for identifying disease susceptibility loci among such individuals. Candidate genes are usually chosen based on biological plausibility established by in vitro assays or larger genetic screens. Many studies have focused on immunity-related genes, such as human leukocyte antigen (HLA) genes or genes associated with induction or effector functions of antiviral interferons (IFNs). Indeed, such studies are duly warranted given the prominent role of immunity genes in defending against viruses, and that many immunity-related genes are, in humans, highly polymorphic (101). Alternatively, extensive use of unbiased whole-genome approaches, such as genome-wide association studies (GWASs), has identified potential susceptibility genes among

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Table 1 List of genes in which variants have been associated with particular disease outcomes in specific virus infections

Human gene	Variant-associated disease manifestation	Gene functional category	Reference(s)
Influenza virus			
IFITM3	Severe influenza	Antiviral restriction factor	39, 162, 177
IRF7	Severe influenza	Transcription factor	27
CPTII	Influenza-associated encephalopathy	Cell homeostasis	21, 94, 171
SFPA/B	Severe influenza	Cell homeostasis	53, 155
RSV			
SFPA/D	Bronchiolitis	Cell homeostasis	83, 92, 153
VDR	Bronchiolitis	Transcription factor	68, 80, 102, 141
IL8	Bronchiolitis	Cytokine	61
IL4	Bronchiolitis	Cytokine	26, 56, 173
IL4RA	Bronchiolitis	Cytokine	56, 149
IL13	Need for mechanical ventilation	Cytokine	124
IL10	Need for mechanical ventilation	Cytokine	44, 168
HIV			
CCR5	Resistance to infection, slow disease progression	Virus entry coreceptor	33, 90, 129
HLAB57	Low viral load and slow T cell decline	Antigen presentation	2, 40, 74, 103
KIR3DS1	Slow disease progression	Adaptive immune cell development	98, 151
TRIM5A	Accelerated disease progression	Antiviral restriction factor	136
APOBEC3G	Accelerated disease progression	Antiviral restriction factor	3
IFITM3	Accelerated disease progression	Antiviral restriction factor	176
HTLV-1			
EPC1	Aggressive type adult T cell lymphoma	Cell homeostasis; transcription factor	106
TNF	Adult T cell lymphoma	Cytokine	157
IL13	Adult T cell lymphoma	Cytokine	161
VCAM1	Adult T cell lymphoma	Adaptive immune cell development	161
MMP9	HTLV-1-associated myelopathy/tropical spastic paraparesis	Cell homeostasis	78
IL18	High viral load	Cytokine	127
IFNG	High viral load	Cytokine	127
IL28B (*IFNL3*)	High viral load	Cytokine	5
IL10	High viral load	Cytokine	128
HPV			
TNF	Increased cervical cancer risk	Cytokine	7, 34, 35, 77, 79
P53	Increased HPV-associated cancer risk	Cell homeostasis	142
EVER1/2	Epidermodysplasia verruciformis in beta-HPV infections	Cell homeostasis	113, 125, 150

(*Continued*)

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Table 1 (*Continued*)

Human gene	Variant-associated disease manifestation	Gene functional category	Reference(s)
HCV			
IL28B (*IFNL3*)	Spontaneous clearance and improved IFN treatment response	Cytokine	8, 43, 57, 58, 100, 108, 126, 145, 148, 152, 159
IFNL4	Spontaneous clearance and improved IFN treatment response	Cytokine	75, 108, 109, 121, 151
HBV			
INTS10	Chronic infection	Cell homeostasis	87
STAT4	Hepatocellular carcinoma	Transcription factor	69, 70, 71, 76
NTCP	Resistance to chronic infection	Virus entry receptor	111, 116
HSV			
STAT1	Multiple infections including herpes simplex encephalitis	Transcription factor	20, 37
NEMO	Multiple infections including herpes simplex encephalitis	Signaling molecule	122
UNC93B	Herpes simplex encephalitis	Virus sensor	18, 147
TLR3	Herpes simplex encephalitis	Virus sensor	175
TRAF3	Herpes simplex encephalitis	Signaling molecule	118
TRIF	Herpes simplex encephalitis	Signaling molecule	130
TBK1	Herpes simplex encephalitis	Signaling molecule	51
IRF3	Herpes simplex encephalitis	Transcription factor	4
TBX21	HSV-2 susceptibility	Transcription factor; adaptive immune cell development	146
CSSG1	Frequent cold sore outbreaks	Unknown function	55, 81
Norovirus			
FUT2	Resistance to infection	Virus entry receptor-modifying enzyme	31, 41, 88, 89, 93, 96, 158
Rotavirus			
FUT2	Resistance to infection	Virus entry receptor-modifying enzyme	114
Parvovirus			
B3GALNT1	Resistance to infection	Virus entry receptor-modifying enzyme	48
A4GALT	Resistance to infection	Virus entry receptor-modifying enzyme	138
EBV			
IL10	Resistance to infection	Cytokine	49, 50
IL1B	Resistance to infection	Cytokine	62
MAGT1	Chronic infection	Cell homeostasis	19, 86
SH2D1A	Extreme sensitivity to EBV, fatal mononucleosis	Adaptive immune cell development	143
ITK	Extreme sensitivity to EBV, fatal lymphoproliferation	Adaptive immune cell development	60, 95, 140

Abbreviations: EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papilloma virus; HSV, herpes simplex virus; HTLV-1, human T cell leukemia virus type 1; IFN, interferon; RSV, respiratory syncytial virus.

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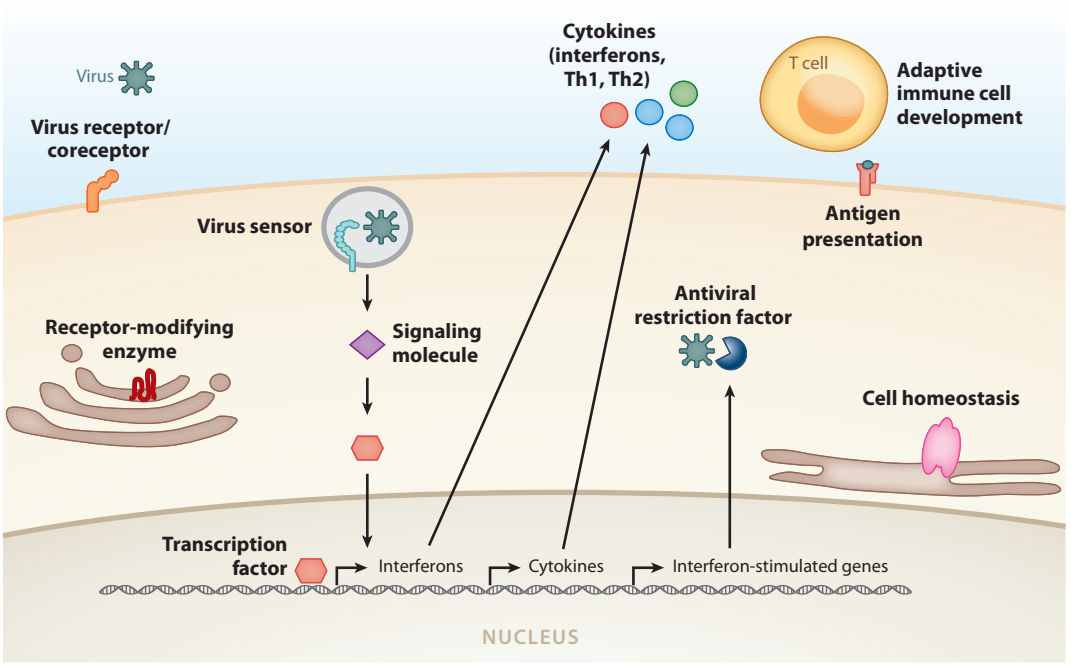

Figure 1

General categories of genes in which variants have been associated with susceptibility or resistance to specific viral diseases. Human genetic determinants of viral diseases can be broadly categorized based on the distinct cellular functions of their associated proteins (*labeled in bold text*). Abbreviation: Th, T helper.

patient cohorts afflicted with specific disease manifestations of viral infections. GWASs typically require large groups of correctly diagnosed study participants in order for rare disease-associated polymorphisms to be identified with statistical significance. Similarly, a more recently adopted approach utilizes whole exome sequencing (WES) to pinpoint gene polymorphisms that underlie specific viral disease phenotypes. Application of WES to individual patients can identify polymorphisms previously implicated in an observed infection phenotype while also allowing for variant discovery studies when performed in aggregate (179), although WES does not allow for discovery of noncoding DNA variants. We discuss multiple examples in which important information has been gained from both candidate gene studies and genomic approaches.

For nearly all of the viral infections we consider below, specific HLA alleles have been implicated in susceptibility to, or protection from, severe infection, likely owing to the ability of distinct HLA variants to present unique peptide repertoires to T cells. Because the role of HLA variation in infectious diseases has been reviewed previously (9, 156), we have opted to discuss specific HLAs only when the link to a viral infection outcome is exceptionally well-supported or significant. Likewise, some of the most important infections in human history, such as poliovirus and smallpox virus, are absent from our discussion of specific genetic susceptibility factors because these viruses were largely eliminated from the human population by vaccines prior to the modern genomic era. Nonetheless, our knowledge of human genetic factors involved in viral infections continues to grow, and may provide the information necessary to treat or eradicate additional infectious diseases in the human population in the future.

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INFLUENZA VIRUS

Influenza virus circulates in a seasonal pattern, and as much as 20% of the human population is infected in any given year (104). Although most people experience moderate respiratory symptoms and recover within one week, a small percentage is afflicted with severe respiratory distress or other rare complications.

The emergence of novel influenza viruses in recent years has allowed the identification of specific genetic deficiencies of the innate immune system that were perhaps previously masked in these patients by a functional adaptive immune response against seasonal strains. IFN-induced transmembrane protein 3 (*IFITM3*) arose as a candidate gene for control of influenza virus infection based on previous studies indicating that IFITM3 mediates a majority of the antiviral action of IFNs against influenza virus in cells (13), and that *Ifitm3* is essential for limiting infection severity in mice (39). In two independent studies performed on British and Chinese subjects, respectively, *IFITM3* was sequenced in individuals hospitalized for severe infection with the newly emergent 2009 pandemic H1N1 influenza A virus (39, 177). Both studies found a significant increase in homozygosity of an *IFITM3* single-nucleotide polymorphism (SNP), rs12252-C, in severely ill patients versus matched control populations (39, 177). A similar study that examined Chinese patients infected with an emergent H7N9 virus of avian origin also correlated homozygosity of rs12252-C with faster disease progression and fatality (162). This *IFITM3* polymorphism is predicted to cause alternative splicing of the transcript, resulting in truncation and altered localization of IFITM3, though the existence of a shortened form of IFITM3 remains to be conclusively demonstrated (39). Recent work in vitro suggests that although this alteration of IFITM3 decreases antiviral activity against influenza virus, its activity against retroviruses is increased (29), thus revealing a potential selective advantage for the SNP that may explain its high prevalence in certain human populations (177). Additionally, given that IFITM3 antiviral activity is highly regulated by at least four posttranslational modifications, polymorphisms in factors that install or remove these modifications and impact influenza virus susceptibility may be uncovered in the future (22–24, 117, 172).

Although the *IFITM3* SNP is the most reproducibly identified genetic factor associated with severe influenza, it accounts for only a fraction of severe infections (39). Importantly, polymorphisms in other IFN-related genes also affect influenza virus infection outcomes. Indeed, a study of a French child with a near-fatal infection by the 2009 pandemic H1N1 virus utilized WES to identify distinct rare mutations in each copy of the patient's IFN regulatory factor 7 (*IRF7*) gene, which encodes a critical transcription factor involved in type I IFN production (27). Remarkably, both mutations decreased IRF7 protein function, and cells from this patient supported aberrantly high virus replication that was rescued by complementation with wild-type IRF7 or by treatment with IFN (27). Thus, inactivation of IFN responsiveness by a variety of mechanisms can result in negative influenza virus infection outcomes.

Influenza-associated encephalopathy (IAE) is a rare neurological complication of infection that does not usually involve direct infection of neural tissues (139). IAE patients often display abnormal acylcarnitine fatty acid chain lengths, which suggest a potential aberration in lipid metabolism (21). A candidate gene approach in Japanese and Chinese cohorts demonstrated that IAE is reproducibly associated with several specific polymorphisms in the carnitine palmitoyltransferase II (*CPTII*) gene (21, 94, 171). The amino acid changes within CPTII result in decreased enzymatic activity at 41°C, consistent with a buildup of long chain fatty acids in the serum of affected patients upon onset of fever (171). Thus, it appears that some cases of IAE result from an underlying metabolic abnormality that is exacerbated by infection.

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In addition to the genes discussed above, many other potential influenza virus susceptibility genes have been identified using SNP arrays, though, in general, results have not been reproducible between studies. One notable finding from these studies is that SNPs in genes encoding lung surfactant proteins (SFTPs), including *SFTPA* and *SFTPB*, have been associated with severe influenza virus infections (53, 155), as well as other respiratory infections as discussed below. SFTPs are secreted into the lung alveolar space, and may have direct antiviral or immunomodulatory activities (47), although additional studies are needed to fully validate the importance of SFTP variations in human influenza virus infections.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) infection leads to a wide spectrum of clinical outcomes, from a mild cold to severe bronchiolitis, pneumonia, or even asthma. Nearly all children have been infected with RSV at least once by two years of age. Approximately 1–2% of infected children develop disease that requires hospitalization (105, 144). Genetic studies of otherwise healthy infants and children have identified SNPs in genes involved in immune defense that are overrepresented in patients hospitalized with RSV compared to either healthy controls or patients with milder RSV disease. At present, genetic susceptibility to RSV is best characterized as a complex trait in which multiple loci across the genome likely contribute to disease severity (25).

Similar to influenza virus, lung SFTPs can impact RSV infections by directly limiting the infection of lung epithelia by RSV and by regulating the immune response against the virus (47). Polymorphisms in *SFTPA2* (G223L) and *SFTPD* (M11T) were shown to be associated with severity of RSV infection in cohorts of patients from Finland and the United States (83, 92, 153). Several studies have also demonstrated a significant association between the *FokI* start codon polymorphism of the vitamin D receptor gene (*VDR*) (which codes for an intracellular receptor and transcription factor) and severity of RSV bronchiolitis (68, 80, 102). The *FokI* polymorphism exacerbates RSV pathogenesis by coding for a VDR that fails to restrain STAT1-mediated antiviral cytokine responses, leading to increased immunopathology (141). Similarly, a promoter polymorphism in the *IL8* gene (−251A), encoding the neutrophil-recruiting chemoattractant IL-8, leads to increased IL-8 production and is associated with RSV bronchiolitis, particularly in infants without other known risk factors (61). TLR4 and CD14 are involved in the innate immune sensing of RSV infection and induction of inflammatory mediators and were thus among the first proteins to be predicted to be associated with disease severity. Although some investigations observed correlations between *CD14* and *TLR4* polymorphisms and RSV bronchiolitis, recent meta-analysis of multiple studies indicates a lack of association (64, 91, 123, 178).

In adaptive immunity to RSV, the balance between T helper 1 (Th1) and Th2 immune responses plays a critical role in pathology during infection, as Th2-dominated responses associate with disease progression. Multiple studies have shown that the RSV G protein triggers the expression of the Th2 cytokines IL-13, IL-5, and IL-4 in mice and human cells, promoting eosinophilia and Th2 immunopathology (10, 67, 73). Genetic association studies in cohorts of children from China, Korea, Chile, and the Netherlands showed that gain of function variants in the *IL4* promoter (−590T and −589T) (26, 56, 173) or in the IL-4 receptor alpha chain gene (Q551R) (56, 149) were associated with higher susceptibility to RSV. Likewise, a large study in a German cohort found an association between the IL-13 promoter variant −1112T and severity of RSV disease (124). In two additional studies, variants that impact the production of the Th2-promoting cytokine IL-10 (−1117G and −3585A) were found to increase the risk of needing mechanical ventilation during RSV infection (44, 168). Overall, susceptibility to severe RSV infections

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appears to involve multifactorial immunity gene networks operating at multiple levels within the host.

HUMAN IMMUNODEFICIENCY VIRUS

More than 30 years after the discovery of the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS), research clearly indicates that individuals have significant variability in their susceptibility to HIV type 1 (HIV-1) infection, in their viral control, and in their progression to AIDS. A small subset of HIV-1-infected individuals, termed HIV-1 controllers, do not exhibit viremia even in the absence of antiretroviral therapy and do not progress to AIDS. Multiple genetic studies of HIV-1 controllers have identified a homozygous 32-bp deletion in the *CCR5* gene, encoding a nonfunctional HIV-1 coreceptor (33, 90, 129). This genetic variant, termed *CCR5Δ32*, is the only genetic factor that has been consistently associated with initial resistance to HIV-1, highlighting the important role of CCR5 in HIV-1 infection in vivo. Though additional human gene polymorphisms have been linked with initial HIV-1 infection susceptibility, including genes encoding CCR5 ligands, they occur at very low frequencies, they occur only in specific ethnicities, and their functional contributions to HIV-1 infection in patient populations are largely unconfirmed (134).

Host genetic determinants also affect the rate at which viremia is controlled, and the severity of disease progression. An early study of the role of HLAs in HIV-1 infection found that homozygosity of any HLA class I allele was associated with more rapid progression to AIDS and death and also that specific HLAs could be particularly detrimental (17). Conversely, several GWASs and additional candidate gene studies examining HLAs have converged on a strong and consistent protective link between *HLA-B*57*, decreased HIV-1 viral load, and reduced CD4 T cell decline; carriers of the allele also appear asymptomatic of acute infection (2, 40, 74, 103). Mechanistically, these protective effects are elicited through HLA-B*57 presentation of immune epitopes from HIV-1 Gag to cytotoxic T cells (65).

Certain haplotypes and copy number variants of the killer cell immunoglobulin-like receptor (*KIR*) genes, which are expressed on natural killer cells and some CD8 T cells, affect HIV-1 disease progression. Despite an incomplete understanding of the mechanisms involved, the effect is multifaceted and there seems to be significant interplay with HLA ligands to mount effective viral control (1, 11, 115). For example, *KIR3DS1* helps prevent progression to AIDS, but this occurs only in those who also have a particular *HLA-B* allele (98). The ongoing work to dissect these interactions highlights the challenges in identifying and understanding functional networks involved in viral disease outcomes.

Polymorphisms in a variety of host restriction factors thwart HIV-1 replication and affect disease progression in HIV-1-infected individuals. Examples include variations in genes encoding the IFN-inducible proteins TRIM5α (136), APOBEC3G (3), and IFITM3 (176). SAMHD1 is a newly discovered HIV-1 restriction factor that can be counteracted by Vpx protein from HIV-2 and certain simian immunodeficiency viruses (59, 82, 137). Although polymorphisms in *SAMHD1* are not associated with natural control of HIV-1 infection in European and African-American cohorts (30), it remains unknown whether *SAMHD1* polymorphisms are associated with HIV-2 infection in humans.

HUMAN T CELL LEUKEMIA VIRUS TYPE 1

Human T cell leukemia virus type 1 (HTLV-1) is an oncogenic retrovirus that infects and transforms CD4 T cells. Although this viral infection is widespread across the world with as many as

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20 million infected individuals, only 5–10% will develop any HTLV-1-related disease (66). The two most prominent diseases associated with HTLV-1 are adult T cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a slow, progressive, chronic disease of the spinal cord (45, 120). A long clinical latency period of several decades and relatively low disease penetrance in infected individuals indicate that host genetic variation plays an important role in HTLV-1 disease.

ATL typically occurs in individuals who acquire HTLV-1 early in life, often as the result of breastfeeding (16). A genome-wide linkage analysis mapped a major susceptibility locus for predisposition to HTLV-1 infection in African breastfed children to chromosome 6q27 (119), though the causative locus has not been determined. Recently, spectral karyotyping in patients with aggressive type ATL—characterized by less than 10 months survival—identified a common breakpoint cluster region on chromosome 10 (106). The chromosomal breakpoints clustered within the *EPC1* gene locus, which codes for a protein involved in histone acetylation and gene transcriptional regulation. Overexpression of *EPC1* accelerated leukemia cell growth in vitro, suggesting that altered levels of EPC1 may contribute to leukemogenesis in patients with aggressive-type ATL (106).

Specific polymorphisms that influence ATL and HAM/TSP development have also been identified, primarily using candidate-based gene approaches. A study from Japan identified a SNP in the *TNF* promoter region (−857T) that was enriched in ATL patients compared to healthy HTLV-1 carriers (157). Conversely, a Caribbean study that examined SNPs in 38 gene candidates found that SNPs in the coding regions of *IL13* (A98G) and *VCAM1* (G149A)—both of which are known to be upregulated in HTLV-1-infected T cells—were associated with decreased risk for ATL development (161). In HAM/TSP patients, expansions of a CA repeat polymorphism in the *MMP9* gene correlate with development of disease (78), and individual SNPs in the immunity-related cytokine genes *IL18*, *IFNG*, *IL28B*, and *IL10* have each been associated with higher proviral load (5, 127, 128). Such findings further highlight the genetic complexity underlying HTLV-1-mediated disease.

HUMAN PAPILLOMA VIRUS

Human papilloma virus (HPV) is the most common sexually transmitted virus in the United States (36). HPV has been detected in as much as 40% of the sexually active population, and most individuals will become infected at some point in their lifetime (36). Although most infected persons show no symptoms, HPV can cause warts and a variety of cancers. The virus is the leading cause of cervical cancer, with nearly 100% of cases being linked to persistent HPV infection (160). Although the vast majority of the population is exposed to HPV, symptoms are rare and cervical cancer rarer still. Thus, it is likely that host genetic factors contribute significantly to the variation seen in outcomes following HPV infection.

Several studies suggest that polymorphisms in the *TNF* gene can alter the course of HPV infections. TNF is released in abundance following infection and plays an integral role in the immune response to HPV (34). A deficient response allows persistence of HPV, whereas excess TNF promotes expression of HPV oncoproteins E6 and E7 that constitutively progress the cell cycle in cervical keratinocytes (34, 42). As such, rs1800629-A, a polymorphism in the *TNF* promoter region that increases TNF production, has been reproducibly observed to confer an increased risk of cervical cancer development (7, 35, 77, 79).

One of the best-established links between HPV infection and cervical cancer is the interaction of the tumor suppressor p53 with the oncogenic E6 protein of HPV. E6 binds to p53 and initiates its degradation, leading to unchecked cellular proliferation (132, 164). Interestingly, a P72R variant of p53 is more susceptible to E6-mediated degradation (142). Homozygosity for

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p53-P72R is correlated with significantly increased risk of HPV-associated cancer compared to heterozygosity or homozygosity of the reference allele (72P) (142).

Host genetic variation also plays a role in the rarest outcome of HPV infection, epidermodysplasia verruciformis, a disease characterized by massive wart growth primarily on the head and extremities, caused by beta-HPV infection (85, 113). Beta-HPV is considered harmless in the general population because, unlike other HPV genera, viruses in this genus are unable to disrupt cellular zinc homeostasis in order to replicate (85). Zinc homeostasis is regulated by epidermodysplasia verruciformis endoplasmic reticulum (EVER) proteins, and mutations in *EVER1* and *EVER2* have been consistently linked to epidermodysplasia verruciformis and progression to cancer (113, 125, 150). Defective EVER proteins fail to complex with other zinc transporter proteins, disrupting the intracellular distribution of Zn^{2+} ions, thus creating an environment favorable to beta-HPV replication (85).

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HEPATITIS C VIRUS

Hepatitis C virus (HCV) is a global health problem that affects more than 184 million people worldwide (154). HCV infection has two main outcomes. Following viral exposure, approximately 25% of people spontaneously clear the virus. The remaining 75% of those infected progress to chronic infection, which can result in cirrhosis, hepatocellular carcinoma (HCC), and extrahepatic complications (154). Spontaneous viral clearance is mediated in part by antiviral IFN responses. Indeed, exogenous IFN-α was the mainstay of chronic HCV treatment until the recent introduction of highly effective direct-acting antiviral medications. Although IFN therapies can be effective in achieving a sustained antiviral response, they fail to eliminate HCV in a significant proportion of patients (154).

In attempts to identify genetic factors that contribute to differential infection and therapeutic outcomes, several large independent GWAS efforts revealed an association between SNPs proximal to the *IL28B* locus (rs8099917 and rs12979860) and response to pegylated IFN plus ribavirin treatment (43, 145, 148). Of note, these SNPs are in strong linkage disequilibrium. In subsequent studies, they were found to be associated with spontaneous clearance of HCV (126, 152), and rs12979860 was associated with the control of viremia that often occurs following pregnancy (58). The *IL28B* gene, recently renamed *IFNL3*, encodes a type III IFN that elicits the expression of antiviral genes. Although SNPs proximal to a gene with clear antiviral function suggest a potential mechanistic connection to HCV clearance, both rs8099917 and rs12979860 SNPs lie outside of the *IFNL3* coding sequence.

Hepatocyte RNA sequencing studies identified an additional genetic variant, rs368234815 (originally designated ss469415590), adjacent to the *IFNL3* locus. This variant is in strong linkage disequilibrium with rs12979860 and has similar associated effects on HCV infection and treatment outcomes (121). The rs368234815 variant resides within a previously unidentified type III IFN gene, which was designated *IFNL4*. This polymorphic site has two variant alleles: ΔG [encoding an intact *IFNL4* open reading frame (ORF)] and TT (an insertion frameshift variant that disrupts the *IFNL4* ORF). Unexpectedly, the ΔG variant, predicted to encode full-length IFNL4, is associated with unfavorable clinical outcomes, including decreased viral clearance and decreased response to IFN therapy (109). Furthermore, patients with an intact *IFNL4* ORF encoding a functionally impaired IFNL4 S70 variant (rs117648444) exhibit better clinical outcomes than patients with a proline at position 70 encoding fully active IFNL4 (151).

A mechanistic understanding of how *IFNL3/4* variants affect HCV pathogenesis and clearance remains unclear. Paradoxically, clinically unfavorable genotypes are associated with higher IFN-stimulated gene expression in the liver during chronic HCV infection (57, 159). However,

this expression profile, perhaps established by IFNL3 or IFNL4 signaling, could render cells refractory to subsequent IFN-α stimulation (131). Although data support *IFNL4* rs368234815 as the strongest predictor of spontaneous clearance and positive treatment outcomes (8, 108, 121), evidence for regulatory effects of additional *IFNL3* noncoding variants (100) presents challenges in ascribing a phenotype to a single site. Further mechanistic clarification of these effects remains an area of active research.

Characterization of the *IFNL4* locus has raised additional questions regarding its evolutionary history. The ΔG variant (intact ORF) has been selected against in non-African human populations (75). It is possible that intact *IFNL4* emerged as a host defense factor to combat other ancient viral pathogens, but was later negatively selected in shifting host–pathogen relationships. At present, many unresolved questions are driving research on this intriguing example of virus–host coevolution.

HEPATITIS B VIRUS

It is estimated that hepatitis B virus (HBV) has infected two billion people worldwide, and although most infections are effectively controlled and cleared by the immune response, as many as 250 million people remain chronically infected (84, 133). HBV persistence can lead to immune-mediated damage to the liver, a major risk factor for cirrhosis and HCC (170). Efforts to identify host susceptibility factors for chronic HBV infection and HCC have been focused on areas with the highest infection rates, such as Southeast Asia or the East Pacific (32).

GWASs and candidate gene studies aimed at identifying HBV susceptibility loci have most frequently identified genetic variants in the HLA class I and II genes (reviewed in 99), although GWASs have also uncovered unexpected genes that influence HBV infections. A study comparing individuals who have experienced spontaneous recovery versus chronic infection identified a novel susceptibility locus for persistent HBV at chromosome 8p21.3 (87). Expression quantitative trait loci associations from liver tissues of patients with persistent infection suggested a functional role for the *INTS10* gene from this region. Researchers found a two-fold decrease of INTS10 in the plasma of patients with persistent HBV and also demonstrated that INTS10 is capable of suppressing HBV replication in vitro. This antiviral function was dependent on IRF3, suggesting that INTS10 augments the type I IFN response.

Another noteworthy GWAS effort associated increased risk of HBV-related HCC with a variant in the third intron of *STAT4* (70). Further, carriers of the high-risk allele had lower levels of *STAT4* in HCC and nontumor tissues compared to other genotypes, and lower STAT4 expression in tumor compared to adjacent normal tissue. This link between *STAT4* variation and HBV infection severity has been verified in additional cohorts (69, 71, 76), although the mechanistic role of STAT4 in controlling infection remains under investigation.

In 2012, identification of the putative receptor for HBV, the sodium taurocholate cotransporting polypeptide (NTCP), revealed a new gene candidate with a potential role in modulating human responses to infection (169). Indeed, an *NTCP* variant (S267F) that is primarily found in Asian populations (111) was associated with resistance to chronic HBV infection (116). Structural modeling suggested that this switch from a hydrophilic to hydrophobic residue is positioned to affect NTCP-ligand interactions and therefore, potentially, HBV entry into the cell.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) types 1 and 2 are double-stranded DNA viruses in the α-herpes virus family and are widespread throughout the world (12, 167). These viruses cause lifelong infection in the sensory nerve ganglia, producing oral or genital lesions as the primary symptom of infection

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(167). Although infection is currently incurable, balance is generally attained between the virus and host, with lesions occurring only as a result of local triggers. However, severe disease can occur in immunocompromised individuals, and some individuals are more susceptible to frequent HSV lesion outbreaks. Studies have now linked genetic susceptibility loci to recurrent HSV lesions, or to the rare HSV-1 infection complication known as herpes simplex encephalitis (HSE).

HSE affects a small number of HSV-1 patients but is the most common form of viral encephalitis in Western countries. Identification of gene mutations in IFN-related pathways has revealed a critical role for these cytokines in controlling HSV and limiting its subsequent pathology in humans. STAT1, a molecule essential for IFN signaling, was first correlated with HSE pathology in 2003 when the *STAT1* genes were sequenced in two unrelated infants exhibiting severe viral and bacterial disease (37). Both died from viral disease, one specifically from HSE, and both were identified as having distinct homozygous mutations in *STAT1* (L600P and 1757–1758delAG) that made cells unresponsive to stimulation by IFN-α/β or -γ (37). This work provided an initial link between a defective IFN response and HSE. A follow-up report examined two siblings with severe and recurrent intracellular bacterial and viral infections, including recurrent HSV infections in one of the siblings. Again, examination of *STAT1* as a candidate gene revealed a homozygous mutation (P696S) that caused impaired splicing of *STAT1* mRNA and reduced expression, thus diminishing IFN responsiveness in the patients' cells (20). Another study identified a child with HSE who possessed a frameshift insertion creating a premature stop codon in *NEMO* (exon 2, 110_111insC), a gene which has been shown to be essential for NF-κB activation and for subsequent IFN-β production (6, 122). Fibroblasts and blood cells from the child exhibited impaired production of IFNs in response to both TLR3 ligation and direct viral infection, and this likely contributed to the patient's death by HSE (6, 122). Together, these studies indicate that complete or partial loss of the IFN response leads to increased susceptibility to viral diseases including HSV infections and HSE.

Although *STAT1* and *NEMO* impairments result in multiple severe infectious diseases, including HSE, sporadic HSE can also occur in otherwise healthy individuals who are not afflicted with increased susceptibility to other infections. The first genetic link to HSE in otherwise immunocompetent children was identified in 2006 (18). Stimulation of HSE patient blood cells with HSV-1 or endosomal TLR ligands showed impairments in IFN production, and this finding suggested defects in the patients' TLR responses. Through candidate gene sequencing, it was determined that the two children in this study inherited autosomal recessive mutations resulting in a loss of expression of the protein UNC-93B (exon 8, del1034–1037; exon 6, 781G>A) (18). UNC-93B is required for signaling of TLRs 3, 7, and 9 (147), and has been implicated in the control of HSV-1 through promoting production of IFN-α/β in a TLR3-dependent manner (18). Indeed a dominant negative form of TLR3 (P554S) has now also been linked to HSE in otherwise healthy children (175), as have mutations in the TLR3-associated signaling molecules TRAF3 (R118W) (118), TRIF (R141X; S186L) (130) and TBK1 (D50A; G159A) (51), as well as the transcription factor IRF3 (R285Q) (4). These genetic studies revealed that although TLR3 is expressed on multiple cell types and recognizes a common virus product, double-stranded RNA, surprisingly, it appears to be essential only for control of neurotropic virus infections in humans.

Additional gene polymorphisms likely serve as risk factors for HSV infection and pathology, and these continue to be explored. One study investigated SNPs in the human *TBX21* gene, which encodes a transcription factor known to influence HSV-2 adaptive immune responses (146). Investigators observed that a SNP (rs17244587-A) in the 3′ untranslated region of *TBX21* was a risk factor for susceptibility to HSV-2, and that a homozygous genotype was found only in HSV-2-positive individuals. Other groups have attempted to address the frequency of oral lesions and what causes certain individuals to have repeated outbreaks. A genetic linkage analysis of over

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350 HSV-1 infected individuals identified a region on chromosome 21 associated with increased frequency of cold sore outbreaks (55). This team then further mapped the susceptibility locus to an uncharacterized gene, which they subsequently named cold sore susceptibility gene-1 (*CSSG1*) (81). Follow-up studies on the role of this gene have not yet been published.

NOROVIRUS AND ROTAVIRUS

Norovirus, also referred to as Norwalk virus, is one of the most common causes of acute gastroenteritis, yet studies in human subjects have shown that a significant portion of the population is innately resistant to infection, independent of the presence of anti-norovirus serum antibodies (72, 112). Norovirus binds to carbohydrates of the histo-blood group family on intestinal epithelial cells (97). Indeed, cellular binding is dependent upon the presence of α1,2-linked fucose on the surface of cells. This requires a functional α1,2-fucosyltransferase gene (*FUT2*), which encodes a Golgi enzyme that transfers a terminal fucose onto glycoproteins and glycolipids (97). Approximately 20% of Europeans are homozygous for an inactivating missense mutation in *FUT2* (428G>A), and a nonsense mutation (385A>T) is also present in Asian populations (41). In a seminal study, human volunteers were infected with norovirus and assessed for mutation of *FUT2*. Even at high doses of the virus, none of the individuals with defective *FUT2* genes showed clinical signs of infection, developed a norovirus antibody response, or had detectable virus in stool samples, thus decisively demonstrating the role of *FUT2* in controlling susceptibility to norovirus infection (88). The requirement for active FUT2 in norovirus infections has been confirmed by several subsequent studies on additional cohorts (31, 89, 93, 158). However, the protective effects of altered *FUT2* alleles may be norovirus strain specific (46), and additional related factors, such as ABO blood type, also influence susceptibility (63, 96, 107). In addition, FUT2 functionality has been linked to infection with rotavirus, another enteric pathogen that causes diarrheal disease in children, and that utilizes cell surface carbohydrates for attachment (114). These results provide a basis for identifying individuals resistant to infection by these viruses and suggest that the development of purified fucose-containing oligosaccharides may be effective as anti-infectives (163).

PARVOVIRUS

Although parvoviruses generally do not cause disease in humans, the B19 strain typically causes a mild skin rash in children, and can cause more serious anemia in those who are immunocompromised or in those already genetically predisposed to hemolytic disorders. Infection is largely restricted to erythroid cells, and the virus uses the blood group P antigen, a glycosphingolipid globoside, as an entry receptor (14). In one of the earliest mechanistic examples of specific resistance to infection, it was shown that rare individuals lacking P antigen displayed no serological evidence of previous infections with B19, whereas a high percentage of the controls were positive for anti-B19 antibodies (15). Likewise, cells from P-negative donors could not be infected, even at extreme doses (15). To date, P-negative phenotypes have been attributed to several rare polymorphisms in two genes, *B3GALNT1* and *A4GALT*, which encode glycosyltransferases involved in distinct steps of P antigen biosynthesis (48, 138, 165, 166).

EPSTEIN-BARR VIRUS

Epstein-Barr virus (EBV) infects over 90% of the global population and establishes a lifelong latent infection in B cells (28). Although disease manifestation is often mild or asymptomatic,

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EBV can cause acute infectious mononucleosis, chronic infections, and a variety of cancers, namely lymphomas (28). Host genetic polymorphisms influence the initial immune response to the virus as well as viral reactivation and latency. Indeed, these factors account for much of the observed variation in EBV-related disease outcomes.

Cytokine genes that affect the inflammatory response have been implicated in controlling EBV infections. High levels of IL-10 production, for example, are protective against primary and chronic EBV infection despite IL-10 being an immunosuppressive anti-inflammatory cytokine (50). Three polymorphic sites in the *IL10* promoter region (rs1800871, rs1800872, and rs1800896) cause varying levels of IL-10 production. The high production allele, in which all three SNPs are present, is significantly linked to EBV resistance (49, 50). In a group of adults, EBV-seronegative individuals were nearly twice as likely to have the high production allele compared to seropositive individuals (50). Moreover, in a cohort of children, high IL-10 production was significantly correlated with seronegativity and effectively postponed, but did not prevent, primary EBV infection (49). A polymorphism in *IL1B* (rs16944), which results in a weaker inflammatory response, is also associated with EBV resistance (62). These studies collectively suggest that a reduced inflammatory response may be beneficial in controlling EBV.

There are also several rare genetic abnormalities affecting lymphocyte function that lead to increased susceptibility to EBV. Mutations observed in the magnesium transporter gene *MAGT1* (10-bp deletion at the exon 7 splicing site; nonsense mutation in exon 3) lead to impaired lymphocyte responses following infection (86). Under normal conditions, there is a rapid influx of Mg^{2+} ions following antigen stimulation, which promotes expression of the natural killer activating receptor NKG2D in natural killer and CD8 T cells (19, 86). However, *MAGT1* mutations reduce the level of free Mg^{2+}, markedly reducing ion influx and causing reduced NK and T cell responses (86). Dysfunctional MAGT1 is a hallmark of X-linked immunodeficiency with Mg^{2+} defect, Epstein-Barr virus infection, and neoplasia (XMEN) disease (19). Individuals with XMEN disease suffer from rampant EBV infections and often develop lymphomas at young ages due to their inadequate immune responses against the virus (19). Likewise, individuals with X-linked lymphoproliferative disease type 1 (XLP1) suffer from extreme sensitivity to EBV and often develop fatal mononucleosis (54, 110). XLP1 is characterized by mutations in *SH2D1A*, which encodes the signaling lymphocytic activation molecule-associated protein (143). This protein is crucial for directing CD8 T cells to virus-infected B cells, making it especially important in EBV infections (54, 110). IL-2-inducible T cell kinase (ITK) deficiency manifests very similarly to XMEN and XLP1 but is distinguished from these diseases because of its inheritance pattern (60). ITK is essential for the development of natural killer T cells (NKTs), and both nonsense mutations and deletions in the *ITK* gene effectively inhibit NKT development (60, 95, 140). NKTs may prevent viral reactivation following latent EBV infection (140). Overall, there are various mutations underlying EBV susceptibility that each lead to defects in cytotoxic immune cell killing mechanisms, underscoring the important role of this adaptive immune function in controlling EBV.

CONCLUDING REMARKS

Genetic studies of virus susceptibility in humans have contributed to a better understanding of the essential elements necessary for virus resistance and control, although in many instances causative mechanisms for effects of specific gene variants are lacking. Studies focused on HIV, HBV, norovirus, rotavirus, and parvovirus have shown that variations in genes encoding virus receptors or receptor-modifying enzymes render humans highly resistant to infection (15, 33, 88, 90, 114, 116, 129), and suggest that blockade of receptor binding or inhibition of virus entry pathways may represent an effective antiviral paradigm for prevention or treatment of infection.

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In other instances, genetic studies have provided unanticipated results. One notable example is the apparent lack of increased susceptibility to infectious diseases other than HSE in individuals lacking functional UNC-93B and TLR3 (18, 175). Unlike the role of TLR3 in detecting numerous pathogens in cell lines and in mice, it appears that human TLR3 and its signaling pathways play a unique role in neuronal defense against HSV-1, but are not essential for defense against other commonly encountered viruses (174). Other innate immune factors, such as IRF7 and IFITM3, appear to be essential for virus control primarily upon encountering a new virus for which individuals lack adaptive immune memory. Thus, immune defects caused by variation in these genes were unmasked in seemingly healthy individuals upon infection with emergent influenza viruses (27, 39, 162, 177).

Still other factors identified by genetic methods are the subjects of ongoing research to clarify their roles in viral pathogenesis. IFNL4, as an inducer of antiviral gene expression, might be expected to contribute to antiviral defense, yet an inactivating variant of the *IFNL4* gene is associated with better clearance of HCV infection, and this paradox remains to be fully explained mechanistically (8, 108, 121). Nonetheless, this link between HCV and *IFNL* genes represents a unique example of a genetic association that was rapidly translated for use in the clinic in designing HCV treatment regimens. We anticipate that the ongoing accumulation of knowledge on the genetics of infectious diseases (**Table 1** and **Figure 1**) will increasingly be used to identify individuals who are particularly susceptible or resistant to specific viral diseases and to enable informed and personalized vaccination and treatment approaches in the years ahead.

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