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Host genetic determinants of influenza pathogenicity

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Abstract

Despite effective vaccines, influenza remains a major global health threat due to the morbidity and mortality caused by seasonal epidemics, as well as the 2009 pandemic. Also of profound concern are the rare but potentially catastrophic transmissions of avian influenza to humans, highlighted by a recent H7N9 influenza outbreak. Murine and human studies reveal that the clinical course of influenza is the result of a combination of both host and viral genetic determinants. While viral pathogenicity has long been the subject of intensive efforts, research to elucidate host genetic determinants, particularly human, is now in the ascendant, and the goal of this review is to highlight these recent insights.

Influenza virus is a member of the *Orthomyxoviridae* family, and possesses a negative-sense RNA genome consisting of eight distinct segments encoding for 11 proteins [1]. Among the three types of influenza viruses (A, B, and C), the influenza A and B viruses produce seasonal epidemics in humans, with influenza A virus (IAV) being the major etiological agent. In addition to humans, IAV can infect swine and avian populations, which contributes to the emergence of pandemics as a result of cross species transmission.

Based on the antigenicity of their surface hemagglutinin (HA) and neuraminidase (NA) glycoproteins, IAV is currently categorized into seventeen HA (H1-H17) and ten NA (N1-N10) subtypes [2], with the majority of these subtypes isolated from wild aquatic birds. Of these subtypes, H1-H3 and N1-N2 have caused widespread human infections, with the most common illness produced by H1N1 and H3N2. Although avian influenza viruses rarely infect humans, sporadic cases of infection by H5, H7, and H9 have occurred [3–6]. While cases of human-to-human transmission of these avian viruses are limited, they are still of considerable concern because human populations are immunologically naïve to these virulent HA subtypes, raising the risk of a catastrophic pandemic.

The clinical course of influenza is dictated by the struggle between viral virulence factors and the host's protective strategies. For example, in many instances the host's neutralizing antibodies can bind to invading viruses and prevent cell entry, in turn viruses have evolved

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hypervariability within their surface antigens [7]. IAV virulence factors such as the NS1 protein that antagonize the host interferon (IFN) responses have been discussed previously [8]. In this review, we will touch briefly on the murine literature then primarily focus on human genetic determinants implicated in modulating IAV pathogenicity.

Murine genetic determinants that modulate IAV infection

Murine models are the mainstay for studying IAV infections *in vivo*. However, mice are not infected by IAV or IBV in the wild and so may not fully recapitulate the interactions occurring between these viruses and their natural hosts. Furthermore, mice are not susceptible to infection by human-derived IAV because they express avian-like sialic acid linkages (SAα-2, 3-Gal) on their cell surface proteins as opposed to those encountered by the virus on human cells (SAα-2, 6-Gal) [9–10]. Indeed, SA linkage affinity remains a key component of host susceptibility to IAV infection. [11–15]. However, repeated passaging of human-derived IAV in mice can select for HA variants with affinity for SAα-2, 3-Gal receptor thereby permitting the use of mice to characterize immune responses and pathogenicity during IAV infection [16–17].

In addition to surface receptors that determine host susceptibility to virus infection, restriction factors contribute to the host's ability to control viral replication. The *Mx1* gene (orthomyxovirus resistance gene 1) was discovered as a restriction factor that inhibits IAV infection in mice [18–20]. The murine *Mx1* gene is encoded on chromosome 16 and is one of several IFN stimulated genes (ISGs) that block IAV infection, in this instance via the inhibition of viral RNA transcription [21–24]. Mouse Mx1 protein localizes to both the nucleus and cytoplasm after IFN-induction, whereas Mx1 proteins from other vertebrates are expressed predominantly in the cytosol. Most laboratory mouse strains carry inactive *Mx1* alleles and are therefore susceptible to mouseadapted IAV infection [25–26]. In kind, hypomorphic polymorphisms of *Mx1* genes in pigs and birds are reported to be associated with enhanced host susceptibility to IAV infection [27–29].

Many studies have been conducted using mouse models to study the relationship between host genetics and IAV pathogenicity (reviewed in [30–31]). However, the conclusions drawn from these efforts must be interpreted in light of the identical genetic backgrounds of inbred mouse populations. To address potential caveats arising from genetic homogeneity, Ferris *et. al*. recently used the highly genetically diverse incipient lines of the Collaborative Cross (CC) octo-parental recombinant inbred mouse panel (pre-CC population) to study the relationship between host genetic variation and IAV infection [32]. The pre-CC population contains up to eight functionally variant alleles at any given locus with about forty million single nucleotide polymorphisms (SNPs) evenly distributed across the genome [33–36]. The authors conducted quantitative trait loci (QTL) mapping [33], and identified four QTL regions that associate with IAV infection outcomes. Among the four QTL regions, *HrI* (*H*ost *R*esponse to *I*nfluenza)-1 was mapped to a 0.71 Mb region on chromosome 16 where the *Mx1* gene is encoded and is the key host responsive QTL to IAV infection. Sequencing of the respective *Mx1* coding regions of the eight CC founder mouse strains revealed a novel *Mx1* allele that is attenuated in inhibiting IAV replication. After careful investigation, *Hrl2Hrl3*, and *Hrl4* were mapped to chromosomes 7, 1, and 15 respectively. Several

candidate genes were noted to reside within these QTL regions; the *Nox4* gene lies within *Hrl2* and plays a role in the innate immune system's Toll like receptor 4 (TLR4) pathway [37], and *Grap2* resides within *Hrl4* and is involved with leukocyte specific signaling [38].

Human genetic determinants that modulate IAV infection

An epidemiological study using genealogic databases of families in the state of Utah spanning 100 years was conducted to investigate heritable susceptibility to severe IAV infection [39]. The authors compared the influenza-associated mortality rate for consanguineal relatives of persons who died of influenza, with the mortality rates of spouses for such individuals. The results showed that consanguineal relatives of persons who died of influenza had a significantly higher risk of dying from IAV infection than matched spouses, suggesting that genetic similarities may underlie this susceptibility.

Although the vast majority of cases of avian influenza arising in humans involve bird-to-human transmission [3–6], clusters of such infections occur within families, suggesting that human-to-human transmission occurs [40–44] and that host genetic determinants may therefore play a contributory role. Alternatively, such familial clustering of infection may simply occur because of increased exposure in the absence of genetic susceptibility [45]. Of course these two possibilities are not mutually exclusive. However, the allele(s) underlying any possible human susceptibility to avian influenza infection remain(s) unknown (reviewed in [30–31, 46]). One possibility is the MxA protein, which is the human homolog of mouse Mx1 and is encoded on chromosome 21 [47]. Although the MxA protein has been shown to be an antiviral factor [24, 48], the mechanism underlying allelic phenotypic variation within the *MxA* gene and a connection to human susceptibility to IAV infection and pathogenicity remains an evolving area of investigation. Recently, the MxA protein has been shown to restrict IAV infection in a viral strain-specific manner, with avian influenza viruses exhibiting enhanced susceptibility to MxA-mediated restriction because of molecular determinants residing within their nucleoprotein genes (NP) [49] [50], [51]. Therefore, in addition to SA linkages contributing to avian influenza transmission, allelic variation within the *MxA* locus may also play a role in avian influenza infections occurring in humans.

A case-control association study was conducted to genotype 91 patients with confirmed severe pneumonia from H1N1 infection, leading to the identification of four single nucleotide polymorphisms (SNPs) that were associated with severe pneumonia [52]. Two of the SNPs were located within genes on chromosome 17, *RPAIN* – gene of RPA interacting protein, and *C1QBP* – gene of complement component 1q binding protein. The remaining two SNPs were found within *FCGR2A* – an Fc receptor gene on chromosome 1, and within a potentially intergenic region of chromosome 3. Two of these SNPs are associated with genes whose products take part in either the clearing of immune complexes (*FCGR2A*) or complement activation (*C1QBP*), suggesting that the severe disease outcome of H1N1 infection may result from variations in the host's immune response. However, it was noted that the four SNPs possessed false discovery rates of 22–56% which was attributed to the small sample size of the study [31].

The above noted genetic determinants implicated in influenza pathogenicity, as well as several additional human genes reported to affect host susceptibility to IAV infection and virus pathogenicity, are presented in Table 1. A missense mutation (F303S) of the toll-like receptor 3 (*TLR3*) gene has been associated with influenza-associated encephalopathy (IAE), a neurological sequelae of severe viral infection [53]. TLR3 recognizes double-stranded RNA (dsRNA), one of the intermediate products of IAV replication, and in turn triggers IFN production leading to an anti-IAV response. *In vitro* assays showed that a TLR3 receptor containing the F303S mutation was less effective in activating the transcription factor, NF-κB, as well as triggering downstream signaling via the IFNβ receptor, suggesting that this variant may allow enhanced IAV replication [53]. An additional *TLR3* SNP (rs5743313, genotype C/T) was identified in a study of 51 children with confirmed H1N1 infection [54]; this *TLR3* SNP was found in all of the children with IAV-associated pneumonia (18 cases), but in significantly less children with milder disease ($p < 0.0001$), further demonstrating the association between TLR3 and IAV pathogenicity.

Polymorphisms within the *carnitine palmitoyltransferase II* (*CPT2*) gene, which encodes for a mitochondrial protein that oxidizes long chain fatty acids, were also found to be enriched in patients suffering from IAE [55]. *In vitro*, these CPT2 variants demonstrated reductions in both enzymatic activity and thermal stability when compared to the wildtype allele. Cells which were transiently transfected with these CPT2 variants also showed reduced fatty acid β-oxidation (30–59% of controls) and diminished intracellular ATP levels (48–79% of controls) in comparison to controls. Moreover, cells expressing *CPT2* variants possessed decreased mitochondrial potential at both 37°C and 41°C when compared to the controls. Two additional CPT2 variants (F352C, V368I) were also isolated from two Chinese patients who were among individuals infected with IAV who demonstrated IAE [56]. Although likely not specific to IAV infection, these results suggest that such *CPT2* variants are unstable during febrile periods and thus individuals expressing these variants may be at increased risk for IAE.

CD55 is a complement pathway regulatory protein which inhibits the formation of C3 and C5 convertase, two proteases involved in complement activation and inflammation [57]. A recent study identified SNPs in the *CD55* genes of Chinese patients with severe influenza disease outcomes [58]. The *CD55* SNP (rs2564978, genotype T/T) showed significant association with severe IAV infection (p=0.011). The rs2564978 SNP of *CD55* resides in the minimal promoter region [59], and individuals with this genotype showed significantly lower levels of CD55 expression compared to those with the more common allele. Therefore, patients who carry the T/T genotype may have more robust complement activation during IAV infection, resulting in worse outcomes secondary to enhanced inflammation.

IFITM3 was identified as a host restriction factor that inhibits multiple viruses, including IAV, using several orthologous genetic approaches [60–63]. Although the mechanism of IFITM3 inhibition against virus infection is under active investigation, it has been reported that IFITM3 blocks IAV infection at the early stage of virus life cycle, and likely at the late endosomes where virus and endosomal membranes fuse [60, 64–65]. As an ISG, IFITM3 is induced by IFN and has been shown to be essential in restricting IAV infection in a mouse

model [66–67]. When examining the role of IFITM3 in human IAV infection, a minor allele, SNP rs12252-C, was found to be enriched in patients hospitalized due to H1N1/09 infection [66]. Although the exact mechanism underlying these events remains to be determined, the rs12252-genotype C/C SNP affects a splice acceptor site suggesting several possibilities [66]. Furthermore, although the rs12252-genotype C/C SNP is a minor allele in Caucasians it is more prevalent in Han Chinese populations, where it was independently found to be present in 69% of patients with severe IAV infection, as compared to only 25% of patients with mild disease [68]. When compared with patients carrying the C/T or T/T genotypes, subjects with the C/C genotype were estimated to have six-fold higher risk of developing severe disease after IAV infection [68]. Therefore, host IFITM3 genetic heterogeneity may play an important role in IAV pathogenicity and the establishment of pandemics [66, 69], especially in populations expressing higher percentages of the rs12252 allele as seen in many regions of China and Japan [68]. These data suggest that risk assessment based on IFITM3 genotyping may aid clinical management in the appropriate populations. Moreover, these results suggest that modulation of IFITM3 levels and/or actions may also have therapeutic utility in disease prevention and treatment.

Conclusion

Despite the advances of modern medicine and the availability of effective vaccines, influenza remains a major global health concern because of the morbidity and mortality caused by seasonal epidemics, as well as the emergence of pandemics and the transmission of avian influenza viruses to humans. Currently, reports of an H7N9 avian influenza virus outbreak in China have again focused global attention on this pathogen [70–71]. As noted, murine and human susceptibility to severe disease outcome is the result of a combination of both viral and host genetic determinants. Researchers have successfully focused on elucidating the viral determinants of IAV pathogenicity such as HA variability and the immune-evasive actions of IAV's NS1 protein [11–15]. On the other hand, human genetic determinants are comparatively unknown, with the above noted studies shedding light on this area of active investigation (Table 1). With the availability of greatly enhanced genome sequencing technology and super-computing capability, the tools for determining host genetic determinants that modulate influenza infection have greatly improved. The recent 2009 H1N1 pandemic also has provided an excellent opportunity to elucidate the contribution of host alleles in altering disease outcome in the absence of naturally acquired or vaccine-induced humoral immunity [66, 68]. Therefore given the continual threat posed by IAV, and the recent advances in technology, a compelling case can now be made for the creation and funding of a large-scale research initiative to fully delineate the role of host genetic determinants in IAV pathogenicity.

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Highlights

- Influenza's clinical course is dictated by the struggle between viral and host genetic determinants.
- This review primarily covers studies investigating human genetic determinants of influenza infection.
- The roles of the human genes, *MxA*, *CPT2*, *CD55*, *TLR3* and *IFITM3*, in influenza pathogenicity are discussed.

Table 1

Host genetic determinants of influenza pathogenicity

Gene	Functions	Authors	Major findings
TLR3	Toll-like receptor 3; recognizes dsRNA and triggers IFN production	Hidaka F, et. al. (2006) [53]	The F303S mutation of TLR-3 was found to be associated with IAE, and caused decreased NF-κB and IFNβ receptor functions *in vitro*.
		Esposito S, et. al. (2012) [54].	SNP (rs5743313, genotype C/T) was found in all patients with pneumonia (18 cases) but in a significantly lower number of those with milder H1N1-induced disease ($p < 0.0001$).
RPAIN	Replication Protein A (RPA) interacting protein; supplements RPA for DNA metabolism	Zuniga J, et. al. (2012) [52]	Four disease outcome-associated SNPs were identified on chromosome 17 (RPAIN and C1QBP), chromosome 1 (FCGR2A), and chromosome 3 (unknown gene). C1QBP and GCGR2A play roles in the formation of immune complexes and complement activation, suggesting that the severe disease outcome of H1N1 infection may result from an enhanced host immune response.
C1QBP	Complement component 1, q subcomponent binding protein; inhibits complement activation		
FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32); plays a role in phagocytosis and clearance of immune complexes		
CPT2	Carnitine palmitoyl-transferase II; oxidizes long chain fatty acids in mitochondria	Yao D, et. al. (2008) [55]	Polymorphisms of CPT2 were found in patients suffering from IAE; results of overexpression of CPT2 variants *in vitro* suggested that the variants were heat-labile and failed to perform optimally
		Mak CM, et. al. (2011) [56]	CPT2 variants (F352C/V368I) were found in two Chinese patients who were among individuals infected with IAV who demonstrated IAE. The F352C mutation has not been reported in Caucasian populations, suggesting an Asian-specific phenotype of heat-labile CPT2-associated IAE.
CD55	CD55 molecule; decay accelerating factor for complement	Zhou J, et. al. (2012) [58].	The *CD55* SNP (rs2564978, genotype T/T) showed significant association with severe IAV infection ($p=0.011$). Patients who carry the T/T genotype may not control complement activation as well during IAV infection, resulting in worse disease outcomes.
IFITM3	Interferon-induced transmembrane protein-3; restricts mutiple viral infections	Everitt AR, et. al. (2012) [66]	A minor allele, SNP rs12252-C, was significantly enriched for in patients hospitalized due to H1N1/09 infection.
		Zhang YH, et. al. (2013) [68].	Although the rs12252-genotype C/C SNP is a minor allele in Caucasians it is more prevalent in Han Chinese populations, where it was independently found to be present in 69% of patients with severe IAV infection, as compared to only 25% of patients with mild disease [68]. When compared with patients carrying the C/T or T/T genotypes, subjects with the C/C genotype were estimated to have six-fold higher risk of developing severe disease after IAV infection [68].