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# Host genetic susceptibility to viral infections: the role of type I interferon induction

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1           **Title: Host genetic susceptibility to viral infections: the role of type I**  
2   **interferon induction**

3   Running title: Type I interferon induction in viral infections

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9

## 10 **Abstract**

11 The innate immune response is the major front line of defense against viral infections. It  
12 involves hundreds of genes with antiviral properties which expression is induced by type I  
13 interferons (IFNs) and are therefore called interferon stimulated genes (ISGs). Type I IFNs  
14 are produced after viral recognition by pathogen recognition receptors which trigger a cascade  
15 of activation events. Human and mouse studies have shown that defective type I IFNs  
16 induction may hamper the ability to control viral infections. In humans, moderate to high-  
17 effect variants have been identified in individuals with particularly severe complications  
18 following viral infection. In mice, functional studies using knock-out alleles have revealed the  
19 specific role of most genes of the IFN pathway. Here, we review the role of the molecular  
20 partners of the type I IFNs induction pathway and their implication in the control of viral  
21 infections and of their complications.

22

## 23 **Introduction**

24 Interferons (IFNs) are cytokines that represent one of the first innate immune barriers  
25 against viruses. They were discovered in 1957 and were named after their capacity to  
26 "interfere" with virus replication. Recognition of non-specific viral molecules such as viral  
27 proteins, DNA and RNA leads to their expression. After recognition of virus components by  
28 pathogen recognition receptors (PRR), an induction cascade leads to the activation of  
29 interferon regulatory factors (IRFs), the transcriptional factors responsible for IFN genes  
30 expression<sup>1</sup>. IFNs are glycoproteins that are secreted into the extracellular medium and act as  
31 autocrine and paracrine factors. The binding to their receptors induces the expression of  
32 interferon stimulated genes (ISGs) with antiviral properties. Non exhaustively, ISGs can  
33 inhibit nuclear import of nucleic acids, synthesis of RNA and proteins, or can enhance virus

34 degradation<sup>1</sup>. Several proteins involved in IFN production and response are inhibited by non-  
35 structural proteins of various viruses which therefore escape host innate defense<sup>2</sup>.

36 IFNs are grouped in three types depending on their sequence, structure and function.  
37 IFN $\gamma$  is the only type II IFN. It is produced by natural killer cells and binds the IFN $\gamma$  receptor  
38 (IFNGR) composed of two subunits (IFNGR1/IFNGR2). This receptor recruits the Janus  
39 kinases 1 (JAK1) and 2 (JAK2), which activate the signal transducer and activator of  
40 transcription 1 (STAT1). STAT1 acts as homodimers<sup>3</sup> and binds gamma-activated sites  
41 present in the target ISGs promoters<sup>1</sup>. Type III IFNs include four IFN lambda numbered  
42 IFN $\lambda$ 1 to IFN $\lambda$ 4. The receptor to type III IFNs is composed of interleukin 28 receptor subunit  
43 alpha (IL-28Ra) and interleukin 10 receptor subunit 2 (IL-10R2). It induces the activation of  
44 the interferon-stimulated gene factor 3 (ISGF3), composed of STAT1, STAT2 and IRF9, that  
45 binds to IFN-stimulated response elements on the promoter of target ISGs<sup>4</sup>. This review  
46 focuses on type I IFNs (IFN-I) which are among the first cytokines produced after viral  
47 infection<sup>3</sup>. IFN-I usually refer to IFN $\alpha$  and IFN $\beta$ , but also include other cell- and species-  
48 specific molecules. All IFN-I signal through the IFN $\alpha$  receptor composed of two subunits  
49 (IFNAR1 and IFNAR2), which recruit JAK1 and non-receptor tyrosine-protein kinase  
50 (TYK2). These kinases activate ISGF3 which binds to IFN-stimulated response elements<sup>3</sup>.

51 Considering the crucial role of IFN-I in host responses to invading viruses, the  
52 inability to induce their expression often leads to severe symptoms. The variable outcome of  
53 viral infections has triggered genetic studies in humans and in mice<sup>5, 6</sup>. Unsurprisingly,  
54 genetic variants or deficiencies in IFN-I induction pathway genes were associated with  
55 susceptibility to diverse viruses. Here we provide a general presentation of the partners of this  
56 pathway, and we review the genetic susceptibilities to viral infections associated with these  
57 genes.

58

## 59 **Molecular mechanisms of type I IFN induction**

### 60 ***Type I interferons***

61 IFN-I is the largest family of IFN proteins. They have a common helical structure  
62 composed of 5  $\alpha$ -helices and are encoded by genes clustered on chromosome 9 in humans and  
63 on chromosome 4 in mice<sup>7</sup>.

64 The two main IFN-I are IFN $\alpha$  and IFN $\beta$ . These proteins are not constitutively  
65 expressed but are up-regulated during viral infection following the activation of the  
66 transcription factors IRF3 and IRF7<sup>8</sup>. Most animal species have multiple IFN $\alpha$  genes, 13  
67 genes with 80% nucleotide identity in human and 14 genes in mice. IFN $\alpha$ s are produced by  
68 plasmacytoid dendritic cells and hematopoietic cells (mostly leucocytes). Each type of IFN $\alpha$   
69 has a different affinity for its receptor, and thus may trigger type-specific responses<sup>9</sup>. IFN $\beta$  is  
70 encoded by a single gene, *IFNB1*, and is also present in most animal species. It is produced by  
71 fibroblasts, dendritic cells and epithelial cells<sup>9</sup>.

72 Other IFNs-I have been described in animal species or in humans. Each of them is  
73 encoded by a single gene<sup>9</sup>. IFN $\epsilon$  is constitutively expressed in the brain, lungs, small intestine  
74 and reproductive tissues. It is regulated by hormones and not during infections. IFN $\kappa$  is  
75 present in a few species including humans and mice. It is constitutively expressed in  
76 keratinocytes and can be up-regulated after exposure to double-stranded RNA (dsRNA).  
77 IFN $\omega$  is present in humans but not in mice. It is expressed mainly in leukocytes. IFN $\zeta$ , also  
78 called limitin, is an IFN-like molecule present only in mice. It is expressed in mature T  
79 lymphocytes, bronchial, epithelial and salivary duct cells. IFN $\tau$  and IFN $\delta$  have been described  
80 but are not expressed in humans or in mice.

81

### 82 ***Virus recognition by PRR***

83           The production of IFN $\beta$  and IFN $\alpha$  is induced by PRRs that recognize molecules  
84 present in pathogens called pathogen-associated molecular patterns. PRRs include Toll-like  
85 receptors (TLRs) and RIG-I-like receptors (RLRs). PRRs recognize components from  
86 bacteria, viruses and fungi and have specific ligands. During viral infections, TLR3  
87 recognizes dsRNA while TLR7 and TLR8 recognize single-stranded RNA (ssRNA) and  
88 TLR9 recognizes DNA molecules. These TLRs are produced in the endoplasmic reticulum  
89 and sense their ligands in endosomes after virus entry into host cells<sup>10</sup>. TLR2 and TLR4 are  
90 present at the cell surface and recognize viral proteins<sup>11, 12</sup>. Replication of viruses with  
91 positive ssRNA genome produces dsRNA which is recognized by TLR3 and RLRs<sup>10</sup>.

92           Three RLRs recognize viral RNA. While DDX58 (also known as RIG-I) senses 5'-  
93 phosphorylated RNA, IFIH1 (MDA5) recognizes long dsRNA. DHX58 (LGP2) facilitates  
94 viral RNA recognition by DDX58 and IFIH1<sup>13</sup> and enhances RLR-dependent IFN induction<sup>14</sup>.

95           Viral recognition by TLRs and RLRs triggers a cascade of molecular activations  
96 which results in the production of IFN-I. This pathway is summarized in Figure 1.

97

### 98 ***TLR pathway***

99           TLR3 recognition of viral RNA induces its own phosphorylation which allows the  
100 recruitment of the adaptor protein Toll-interleukin receptor (TIR) domain-containing adapter  
101 molecule 1 (TICAM1, also called TRIF)<sup>15</sup>. Interaction between TLR3 and TICAM1 is  
102 enabled by the phosphorylation of two TLR3 tyrosine residues<sup>15</sup>. TLR4 also can induce the  
103 expression of IFN-I by recognizing viral proteins present in the extracellular medium and  
104 signalling through the adaptors myeloid differentiation primary response protein (MYD88)  
105 and myelin and lymphocyte protein (MAL). Once activated, TLR4 is endocytosed and  
106 recruits TICAM1 and TIR domain-containing adapter molecule 2 (TICAM2, also called  
107 TRAM) in the endosomes<sup>16</sup>. TICAM1 recruits the TNF receptor associated factor 3

108 (TRAF3)<sup>15</sup>, which then activates the kinases responsible for the activation of the IRFs.  
109 TICAM1 is targeted by the viral 3C protease of hepatitis A virus and coxsackievirus B3  
110 (CVB3) which allows these viruses to escape the host immune response<sup>10</sup>.

111 TLR2 also activates the expression of IFN-I, but the mechanisms are incompletely  
112 understood. Signalling by TLR2 requires MAL, TICAM2 and MYD88 which, once activated,  
113 relocate to the endosomes and induce a signalling cascade resulting in IRF7 activation and  
114 IFN-I expression. Therefore TLR2 and TLR4 likely use similar mechanisms to induce IFN-I  
115 production<sup>12</sup>.

116 TLR7, TLR8 and TLR9 also induce IFN-I expression, but only in plasmacytoid  
117 dendritic cells which are known to produce high levels of IFN after viral infection. These  
118 TLRs use the MYD88 adaptor which, in plasmacytoid dendritic cells, forms a complex with  
119 IRF7. This complex allows the phosphorylation and activation of IRF7 by interleukin 1  
120 receptor associated kinase 1 (IRAK1) and triggers the expression of IFNs<sup>17</sup>.

121

## 122 ***RLR pathway***

123 Viral RNA binding on RLRs DDX58 and IFIH1 induces a conformational change of  
124 these receptors which exposes their caspase activation and recruitment domains (CARD).  
125 These domains interact with the CARD of the mitochondrial antiviral signalling protein  
126 (MAVS, also called IPS-1). Subsequently, DDX58 and IFIH1 promote the formation of  
127 prion-like MAVS aggregates, which induce TRAF3 recruitment<sup>18</sup>. Several proteins of the  
128 RLR pathway are targeted by viruses. Influenza A virus (IAV) NS1 protein and respiratory  
129 syncytial virus NS1 protein bind DDX58 and MAVS, respectively, and block their signalling.  
130 IFIH1 is degraded following poliovirus infection, and encephalomyocarditis virus (EMCV)  
131 3C protease can degrade DDX58<sup>10</sup>.

132

### 133 **Activation of IRFs**

134 TRAF3 recruits two kinases, TANK binding kinase 1 (TBK1) and inhibitor of nuclear  
135 factor kappa-B kinase subunit epsilon (IKK $\epsilon$ ), to phosphorylate and activate IRF3 and IRF7.  
136 Once phosphorylated, IRF3 and IRF7 form homodimers or heterodimers, translocate to the  
137 nucleus and promote IFN-I transcription<sup>15, 19</sup>. Viral proteins also target these factors. Ebola  
138 virus VP35 protein binds and blocks TBK1 and IKK $\epsilon$ . The hepatitis C virus NS3/4A protease  
139 degrades IRF3 while viral homologues of IRFs, such as Kaposi's sarcoma-associated  
140 herpesvirus vIRFs, bind host IRFs and inhibit IFN-I transcription<sup>10</sup>.

141 IFN $\beta$  expression is regulated by four positive regulatory domains (PRD). NF $\kappa$ B and  
142 AP1 bind PRDII and PRDIV, respectively, and promote basal expression of *IFNBI*. After  
143 viral infection, IRF3 and IRF7 are activated and bind PRDI and PRDIII to induce *IFNBI*  
144 overexpression<sup>20</sup>. IFN $\alpha$  genes have only PRDI- and PRDIII-like elements and their  
145 expression is therefore controlled exclusively by IRF3 and IRF7. IRF3 has more affinity for  
146 *IFNBI* while IRF7 has more affinity for IFN $\alpha$  genes. IRF3 is constitutively abundant but  
147 inactive while *IRF7* is an ISG present at low levels before infection and up-regulated by IFN-I  
148 signalling. Therefore, in the early phase after infection, IFN-I expression is induced by IRF3,  
149 resulting in predominant IFN $\beta$  production. IFN $\beta$  signalling induces *IRF7* expression resulting  
150 in IFN $\alpha$  production in a later phase<sup>8</sup>. IRF1 and IRF5 can also induce IFN-I expression,  
151 however both are dispensable and their role remains unclear<sup>8</sup>. Furthermore, TLRs and RLRs  
152 also activate the NF $\kappa$ B pathway after infection through TICAM1, MYD88 and MAVS to  
153 induce the production of inflammatory cytokines<sup>15</sup>.

154

### 155 **Genetic susceptibility to viral infections**

156 Several of the genes described above have been associated with susceptibilities to viral  
157 infections. These studies are summarized in Table 1 and Table 2 for human and mouse genes,



158 respectively. Human studies split into case studies and association studies. Case studies aim to  
159 identify mutations which strongly impact the severity of viral infection but are rare in the  
160 population. Association studies generally identify common variants with a moderate impact  
161 and require the analysis of large cohorts. Due to limited statistical power, they often focus on  
162 a small number of candidate genes.

163 In mice, forward and reverse genetics are used to analyze resistance to viral  
164 infections<sup>21</sup>. Reverse genetics aims at characterizing the function of a given gene by altering  
165 its sequence. Many studies have reported modified susceptibility to viral infections in mice  
166 carrying loss-of-function mutations (gene knock-outs, KO) in IFN-I pathway. Forward  
167 genetics starts with a difference of susceptibility between two strains and aims at identifying  
168 the causal genetic variants. Differences may result from random chemical mutagenesis<sup>22</sup> or  
169 from natural variants between genetically diverse mouse strains such as the Collaborative  
170 Cross<sup>6</sup>. Interestingly, studies performed on the same virus can be compared to assess the  
171 specific or overlapping roles of the genes of the IFN-I cascade in the severity of a viral  
172 infection and in its complications.

173

#### 174 ***TLR-TICAM1 pathway***

175 As *TLR3* is the primary TLR involved in IFN-I expression after virus recognition, the  
176 effects of its variants on the susceptibility to viral infections were extensively studied. In  
177 humans, association studies and case studies identified *TLR3* variants linked to increased  
178 susceptibility to IAV<sup>23-26</sup>, hepatitis B virus<sup>27</sup>, herpes simplex virus 1 (HSV-1)<sup>28-30</sup> and  
179 measles virus<sup>31</sup>. Two SNPs associated with susceptibility to IAV are in intronic regions  
180 upstream exon 4<sup>23, 24</sup>. Since this exon contains the signal induction transmembrane protein  
181 domain, these SNPs might alter TLR3 signalling. Other variants are in the luminal leucine-  
182 rich repeats of TLR3<sup>25, 26, 28, 30, 31</sup>. This region forms a solenoid critical for RNA binding<sup>30</sup> and

183 virus recognition. Lastly, mutations were identified in the TIR domain of TLR3<sup>28, 29</sup>. In  
184 particular, a non-sense mutation was identified in a case of herpes simplex encephalitis  
185 (HSE), a complication of HSV-1 infection. This mutation removes the TIR domain which is  
186 required for the recruitment of TICAM1 and downstream signalling<sup>28</sup>.

187 In contrast, a common variant in *TLR3* was associated with increased resistance to  
188 human immunodeficiency virus (HIV). The L412F allele, present in approximately 30% of  
189 Europeans and over-represented in a cohort of HIV-exposed seronegative individuals, leads to  
190 reduced viral replication and overexpression of inflammatory cytokines *in vitro*<sup>32</sup>, likely by  
191 increasing TLR3 signalling. However, the same variant showed positive association with  
192 subacute sclerosing panencephalitis, a severe complication of measles virus infection<sup>31</sup>. The  
193 increased inflammatory response due to this mutation may be advantageous in the case of  
194 HIV infection, but deleterious in the case of measles virus infection. Variants in the TLR  
195 adaptor *TICAM1* can also alter susceptibility to viruses. In humans, four mutations were  
196 identified in patients suffering from HSE, leading to decreased IFN-I expression in immune  
197 cells<sup>33, 34</sup>.

198 The TLR-TICAM1 pathway has been also extensively studied in mouse viral  
199 infections. Compared to wild-type (WT) mice, *Tlr3*-deficient mice showed a decreased  
200 survival rate with higher viral loads in coxsackievirus B3<sup>35</sup> and EMCV<sup>36</sup> infections and, while  
201 they showed an increased serum viral load but unchanged mortality after murine  
202 cytomegalovirus (MCMV) infection<sup>37</sup>. In contrast, *Tlr3*-deficient mice displayed a decreased  
203 mortality following IAV infection<sup>38</sup>. Mice carrying a frameshift-induced deletion in the  
204 *Ticam1* gene showed enhanced susceptibility to MCMV with increased viral load in the  
205 spleen and higher mortality<sup>39</sup>. Another study found that *Ticam1*-deficient mice were more  
206 susceptible to CVB3. Interestingly, these mice presented a decreased IFN-I expression 72  
207 hours post-infection, but an increased expression 7 days after infection<sup>40</sup>, which may result

208 from an uncontrolled inflammatory response. *Tlr3*-deficient mice also developed cardiac  
209 anomalies, a complication of CVB3 infection, with large myocarditic lesions and increased  
210 heart viral load<sup>35</sup>. Similarly, *Ticam1*-deficient mice presented left ventricular dysfunction and  
211 severe myocardial damage including cardiac fibrosis. These mice also showed increased heart  
212 viral load<sup>40</sup>. The overlapping phenotypes observed in these two studies are consistent with the  
213 direct interactions between *Tlr3* and *Ticam1* in the IFN-I induction cascade.

214 *Tlr3*-deficient mice were also less susceptible to vaccinia virus (VV) infection than  
215 WT mice with higher viral load, while *Ticam1*- and *Tlr4*-deficient mice were more  
216 susceptible (Hutchens et al., 2008a, 2008b). It was hypothesized that abrogating *Tlr3*  
217 signaling decreases the inflammatory response and thus the complications resulting from VV  
218 infection. In contrast, since *Tlr4* signaling activates IRFs and NFκB, *Tlr4* and *Ticam1* KOs  
219 block both pathways and lead to increased susceptibility to VV infection<sup>41,42</sup>.

220 The outcome of West Nile virus (WNV) infection in *Tlr3*-deficient mice was  
221 investigated in two studies which used the same mouse strain and two closely related virus  
222 strains with contrasted results. Wang *et al.* reported that *Tlr3*-deficient mice presented a  
223 decreased mortality after infection with WNV isolate 2741, but an increased viral load.  
224 Moreover, these mice showed decreased neuronal inflammation and blood-brain barrier  
225 permeability, suggesting that *Tlr3* is involved in the virus brain entry<sup>43</sup>. Daffis *et al.* who used  
226 the WNV strain 3000.0259 reported that *Tlr3*-deficient mice also presented a higher brain  
227 viral load but with susceptibility to WNV infection and mortality than WT mice. Unlike the  
228 previous study, blood-brain barrier permeability and neuroinflammation were not affected,  
229 compared with WT mice<sup>44</sup>. These contrasted results were attributed to the infection route, the  
230 viral dose and the cells used to produce the virus which differed between the two studies<sup>44</sup>.  
231 Interestingly, *Tlr3*-deficient mice produced normal amount of IFN-I in the first study, while  
232 they were decreased in the second study, leading to the hypothesis that IFN-I expression

233 could also have a detrimental effect in WNV infection<sup>43</sup>. These results illustrate the dual role  
234 of *Tlr3* signalling which may lead to an excessive inflammatory response, while decreased  
235 inflammation in *Tlr3* KO mice may reduce the risk of severe complication.

236

### 237 ***TLR-MYD88 pathway***

238 In mice, deficiency in *Tlr2*, *Tlr4*, *Tlr7* or *Tlr9* was associated with increased or  
239 decreased susceptibility to viral infections. However, since these receptors signal through the  
240 MYD88 adaptor which also activates the NFκB pathway, their role in the susceptibility to  
241 viruses may not be solely associated with the IFN-I pathway.

242 *Tlr7*-deficient mice were more susceptible to WNV infection<sup>45</sup>. However, they  
243 presented an increased IFN-I expression which could result from the signaling through other  
244 receptors such as *Tlr3* and RLRs. *Tlr9* and *Myd88*-deficient mice were more susceptible to  
245 MCMV with decreased IFN-I production<sup>37</sup>. *Myd88* KO mice had a reduced number of splenic  
246 plasmacytoid dendritic cells which could explain reduced levels of IFN-I. By contrast, *Tlr2*  
247 KO mice were less susceptible to HSV-1 with reduced mortality compared to WT mice. They  
248 also showed decreased NFκB-induced cytokine production which may explain a milder  
249 inflammatory state and the absence of severe complications<sup>46</sup>. IFN-I expression was not  
250 investigated although it could contribute to the pathology.

251 *Myd88* deficiency in mice also resulted in increased susceptibility to chikungunya  
252 virus (CHIKV) and severe acute respiratory syndrome coronavirus (SARS-CoV). Indeed,  
253 *Myd88* KO mice presented higher viral loads following CHIKV infection<sup>47</sup>, and higher  
254 mortality and increased viral load following SARS-CoV infection<sup>48</sup>. Two studies with WNV  
255 led to similar results<sup>45, 49</sup>. Interestingly, in one study, *Myd88* KO mice had higher levels of  
256 IFN-I after infection than WT mice due to an increased expression in bone marrow-derived  
257 macrophages. This might result from high viral replication in these cells and from the

258 signaling of other pathways, such as RLR- or *Tlr3*-dependent pathways<sup>49</sup>. The role of *Ticam2*  
259 in the susceptibility to SARS-CoV was suspected in an association study using the  
260 Collaborative Cross and was confirmed with a *Ticam2*-deficient strain which showed higher  
261 lung viral loads than WT mice<sup>50</sup>.

262

### 263 ***RLR pathway***

264 In humans, two variants were identified in *DDX58* in a patient who suffered from  
265 severe IAV infection. The R71H variant is in the CARD protein domain, while the P885  
266 variant is in the regulatory domain involved in viral RNA recognition. These variants lead to  
267 impaired IFN-I expression following IAV infection when expressed in *DDX58* deficient  
268 human embryonic kidney cells 293, but not in the patient's peripheral blood mononuclear  
269 cells where other pathways, such as *TLR7*-dependant signalling might ensure a correct  
270 expression<sup>51</sup>. Variants were identified in *IFIH1* in patients suffering from bronchiolitis  
271 following rhinovirus or respiratory syncytial virus infection and led to decreased expression  
272 of IFN $\beta$ <sup>52</sup>. Moreover, the K365E mutation was identified in a 5-year-old child suffering from  
273 numerous recurrent respiratory virus infections. This mutation prevents *IFIH1* from  
274 interacting with viral RNA, thus inhibiting IFN-I induction<sup>53</sup>. The H843A mutation in *IFIH1*  
275 was also associated with susceptibility to HCV by comparing patients with spontaneously  
276 resolved hepatitis or chronic hepatitis<sup>54</sup>. In two studies, *Ddx58*-deficient mice showed similar  
277 mortality after IAV infection compared with WT individuals<sup>55, 56</sup>. Notably, one study showed  
278 that *Ddx58* deficiency also led to defects in adaptive immunity affecting antigen presentation  
279 by dendritic cells and activation of T cell responses<sup>55</sup>. *Ifih1*-deficient mice were more  
280 susceptible to mouse hepatitis virus. Interestingly, they showed decreased expression of IFN-I  
281 but normal induction of ISGs<sup>57</sup>. Moreover, they were found to be more susceptible to human

282 metapneumovirus<sup>58</sup>, to hepatitis B virus<sup>59</sup>, to murine norovirus 1<sup>60</sup>, and more prone to develop  
283 demyelinating disease following Theiler's murine encephalomyelitis virus infection<sup>61</sup>.

284 In mice, RLRs and MAVS have often been studied together, which has unraveled their  
285 specificity. Using *Ddx58*- and *Ifih1*-deficient mouse embryonic fibroblasts (MEFs) infected  
286 with several viruses, Kato *et al.* found that these two receptors recognize different viruses.  
287 Moreover, they showed that *Ddx58*- and *Ifih1*-deficient mice were more susceptible to  
288 Japanese encephalitis virus than WT mice, and that *Ifih1*- but not *Ddx58*-deficient mice were  
289 more susceptible to EMCV<sup>62</sup>. Susceptibility of *Ifih1*-deficient mice to EMCV infection was  
290 also reported in another study<sup>63</sup>. Furthermore, *Ddx58*-deficient mice showed increased serum  
291 viral load following CHIKV infection, which was not the case for *Ifih1*-deficient mice<sup>47</sup>.  
292 These results show that *Ddx58* and *Ifih1* have complementary roles in the recognition of viral  
293 RNA, consistently with their known differences in molecular pattern recognition.

294 By contrast, both *Ddx58*- and *Ifih1*-deficient mice showed increased susceptibility to  
295 WNV. Double-deficient mice were even more susceptible and invariably died within 8 days  
296 after infection, showing that both receptors are involved in the recognition of WNV. The  
297 phenotype of double-deficient mice was very similar to that of *Mavs*-deficient mice through  
298 which both RLRs signal<sup>64</sup>. Indeed, *Mavs* deficiency resulted in increased susceptibility to  
299 WNV with higher mortality and viral load, and deficient activation of IFN $\beta$ <sup>65</sup>. *Mavs* and *Ifih1*  
300 deficiencies resulted also in increased mortality following CVB3 infection and decreased  
301 expression of IFN-I although viral titers were identical to WT mice<sup>66</sup>. *Mavs* deficiency also  
302 resulted in increased susceptibility to EMCV<sup>67</sup>, to vesicular stomatitis virus<sup>67, 68</sup> and to dengue  
303 virus (DENV)<sup>69</sup>, and in increased serum viral load following CHIKV infection<sup>47</sup>.

304 Mice deficient for the auxiliary RLR *Dhx58* gene also showed increased susceptibility  
305 to EMCV<sup>13</sup> and to WNV<sup>14</sup>. WNV-infected, *Dhx58*-deficient mice showed increased mortality  
306 but similar kinetics of IFN $\beta$  production and tissue viral loads compared with WT mice. In the

307 brain they displayed increased neuronal damage, elevated viral load in a late phase of  
308 infection, low neuroinflammation and decreased recruitment of CD8+ T cells<sup>14</sup>. *Dhx58* is  
309 therefore required for protection against WNV infection. Furthermore, mice overexpressing  
310 *Dhx58* were more resistant to IAV infection<sup>70</sup>. *In vitro*, *Dhx58*-deficient cells exposed to  
311 several RNA viruses produced less IFN-I than WT cells suggesting that *Dhx58* is required for  
312 *Ddx58*- and *Ifih1*-mediated antiviral responses<sup>13</sup>.

313

#### 314 ***Activation of IRFs and IFNs***

315 Sequencing of candidate genes in HSE patients identified a heterozygous missense  
316 mutation in *TRAF3* associated with decreased IFN-I expression<sup>71</sup> and two missense mutations  
317 in *TBK1* affecting the kinase domain and thus preventing the phosphorylation of target  
318 proteins<sup>72</sup>. These mutations resulted in reduced IFN-I expression in cells stimulated with  
319 synthetic RNA.

320 In mice, no genetic variants in *Traf3* or in *Tbk1* have been associated with altered  
321 susceptibility to viral infections. However, mice deficient for the *Ikkε* gene (encoding IKKε,  
322 a kinase involved in IRFs activation) showed extreme susceptibility to IAV despite normal  
323 expression of IFN-I. Mechanistic studies revealed that IKKε indirectly controls the expression  
324 of a subset of ISGs<sup>73</sup>.

325 Mutations in IRFs have been repeatedly associated with susceptibility to viral  
326 infections in humans and in mice. In humans, two missense mutations were found in *IRF3* in  
327 patients suffering from HSE<sup>33, 74</sup>. These mutations are located in the IRF association domain  
328 and might therefore prevent IRF3 dimerization<sup>75</sup>. A non-coding variant in *IRF3* was also  
329 associated with susceptibility to WNV by comparing asymptomatic and symptomatic infected  
330 individuals<sup>76</sup>. Moreover, a compound heterozygosity was found in *IRF7* in a patient suffering  
331 from life-threatening infection following IAV infection<sup>77</sup>.

332 In mice, *Irf3* and *Irf7* deficiencies have been studied in isolation or in combination.  
333 Both single deficiencies increased mortality following IAV infection and susceptibility was  
334 further enhanced in double deficient mice<sup>78, 79</sup>. Viral load in lungs was not significantly  
335 altered in *Irf7*-deficient mice but was increased in *Irf3*-deficient mice and even more in  
336 double-deficient mice, suggesting that *Irf7* also contributes to controlling viral replication. On  
337 day 2 after infection, IFN $\alpha$  expression was reduced in *Irf3*- but not in *Irf7*-deficient mice  
338 while IFN $\beta$  expression was reduced in *Irf7* but not in *Irf3*-deficient mice<sup>78</sup>. This result is  
339 consistent with the distinct affinities of the two IRFs for the IFN-I genes. Mice deficient for  
340 *Irf3* and *Irf7* were also susceptible to WNV with increased mortality rate and viral load,  
341 decreased expression of IFN-I and increased viral load in the brain<sup>80, 81</sup>.

342 However, the consequences of *Irf3* and *Irf7* deficiencies are variable between viruses.  
343 *Irf7*- but not *Irf3*-deficient mice were susceptible to HSV-1 and they were more susceptible to  
344 EMCV than *Irf3*-deficient mice<sup>82</sup>. In the case of CHIKV infection, *Irf3-Irf7* double KO mice  
345 were highly susceptible with increased viremia and mortality, while *Irf3*- and *Irf7*-deficient  
346 mice survived and had normal viremia<sup>83</sup>. Following DENV infection, *Irf3-Irf7* double KO  
347 mice and *Irf7*-deficient mice showed increased viral load and decreased IFN-I expression but  
348 survived the infection<sup>84</sup>. In the case of Zika virus infection, *Irf3-Irf5-Irf7* triple KO mice died  
349 with neurological disease signs, while *Irf3*-deficient mice survived<sup>85</sup>. Interestingly, *Irf3-Irf5*-  
350 *Irf7* triple KO mice survived to DENV infection through robust induction of type II IFNs, but  
351 showed increased viremia. This resistance to DENV was abolished when *Irf1* was also  
352 inactivated, which led to the identification of a protective *Irf1*-dependent pathway<sup>86</sup>.

353 Lastly, variants in IFN-I genes themselves were associated with susceptibility to viral  
354 diseases in mice. The role of IFN-I in viral infections has been extensively investigated using  
355 mice deficient for their receptor. *Ifnar1*-deficient mice showed increased susceptibility to a  
356 number of viruses including CHIKV<sup>47</sup>, Zika virus<sup>85</sup>, DENV<sup>69</sup> and Ebola virus<sup>87</sup>. Transient



357 blockade of IFN $\alpha$  and IFN $\beta$  with monoclonal antibodies resulted in increased mortality after  
358 WNV infection<sup>88</sup>. WNV susceptibility was also studied in *Ifnb1*<sup>-/-</sup> mice and led to similar  
359 results<sup>89</sup>. IFN $\beta$ -deficient mice were also found more susceptible to VV than WT mice<sup>90</sup>.  
360 These two studies led to opposite results regarding IFN $\alpha$  expression. The absence of IFN $\beta$  is  
361 expected to abrogate *Irf7* induction and thus to decrease IFN $\alpha$  expression. This was indeed  
362 observed after VV infection. However, after WNV infection, IFN $\alpha$  was upregulated, which  
363 was hypothesized to result from the high viral load<sup>89</sup>. IFN $\beta$ -deficient mice also showed  
364 increased susceptibility to IAV<sup>91</sup> and CVB3<sup>92</sup>, and increased spleen viral load following  
365 Friend virus infection<sup>93</sup>.

366

367

## 368 **Discussion**

369 Type I IFNs are critical components of the immediate response against invading viruses.  
370 Indeed, their induction allows the expression of many ISGs which can control viral infection.  
371 The pathway leading to IFN-I production is complex as many genes are involved, and viral  
372 proteins target this pathway at multiple levels. Moreover, some of these genes, such as *IRF7*,  
373 are also ISGs, which further complicates the kinetics of IFN-I activation. Despite the vast  
374 number of studies carried out on the induction of IFN-I, not all mechanisms are yet fully  
375 understood.

376 In accordance with the functions of IFN-I, mutations in most genes of the induction  
377 pathway have been associated with increased susceptibility to viral infections in human and  
378 mice. In humans, whole exome or candidate gene sequencing has identified coding and non-  
379 coding variants, primarily in patients with severe forms of infections. It is likely that other  
380 variants are present in the human population but the power to detect them in association  
381 studies depends on their frequency, on their impact on host response to infections and on

382 cohort size. In mice, most studies have used reverse genetics approaches and have  
383 investigated the consequences of complete loss-of-function mutations in infected mice which,  
384 in most cases, led to higher susceptibility, with mortality and elevated viral load in tissues.  
385 While all mutants reported here were constitutively deficient, tissue-specific conditional  
386 alleles allow investigating the pathway in specific cell lineages. For example, myeloid-  
387 conditional *Tbk1*-deficient mice showed increased survival to IAV infection with reduced  
388 inflammation in the respiratory tract, demonstrating the role of myeloid cells in disease  
389 pathophysiology<sup>94</sup>.

390 Notably, a few genes of the pathways were not tested by reverse genetics. *Tlr2* and  
391 *Tlr4* have been investigated mostly for their role in bacterial infections<sup>11</sup>. For other genes, like  
392 *Tbk1* and *Traf3*, deficiency was only studied *in vitro* on MEFs or macrophages since  
393 homozygous mice die either *in utero* (*Tkb1*) or a few days after birth (*Traf3*)<sup>95</sup>. Interestingly,  
394 Marchlik *et al.* produced a *Tbk1* mutation which resulted in a catalytically inactive protein  
395 and they could obtain homozygous deficient mice with complete ablation of IFN $\beta$   
396 production<sup>96</sup>. This difference in survival of *Tbk1*-deficient mice is likely due to the 129S5  
397 genetic background on which this allele was created, compared with the C57BL/6 background  
398 used for most KO alleles. This case highlights the importance of mouse genetic background  
399 when evaluating the phenotype resulting from gene inactivation<sup>97</sup>.

400 The formal description of the IFN-I activation cascade incompletely reflects the  
401 complexity of the mechanisms from viral components recognition to IFN-I-induced effectors.  
402 As exemplified by *Irf3* and *Irf7*, the effect of a host gene variant may be different between  
403 viruses. Moreover, while deficiency of most pathway genes resulted in increased  
404 susceptibility to viral infections due to impaired IFN $\beta$  production, it could also be associated  
405 with reduced susceptibility as in the case of *Tlr3*. This observation underlines the complexity  
406 of immune mechanisms, and the importance of balanced and well-controlled IFN response.

407 While rapid activation of ISGs is critical to the control of viral replication, excessive or  
408 persistent IFN-I production can be detrimental by triggering inflammatory processes  
409 responsible for tissue damage and organ failure. Notably, dysregulation of immune responses  
410 with delayed expression of IFN-I and robust cytokine response could be at the origin of the  
411 clinical manifestations observed in severe SARS-CoV<sup>98</sup> and SARS-CoV-2 infections<sup>99</sup>.  
412 Investigating the role of every gene of the IFN-I induction cascade by gene inactivation has  
413 contributed to dissecting the mechanisms of the pathway. However, a non-functional step may  
414 result from defective interactions between functional but incompatible partner proteins. Such  
415 interactions could occur for example if the two partners were inherited from genetically  
416 distant parents. In mice, investigating strains produced by crosses between founders of  
417 different subspecific origins, like the Collaborative Cross, may identify such situations and  
418 provide new variants for functional analysis<sup>6</sup>. With the growing evidence that microbiota can  
419 also modify the IFN-I response and therefore the susceptibility to infectious diseases<sup>100</sup>, it is  
420 clear that we are still far from understanding the subtle regulations of an essential pathway.

421

## 422 **Conflict of interest**

423 The authors declare no conflict of interest.

424

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807 **Legends**

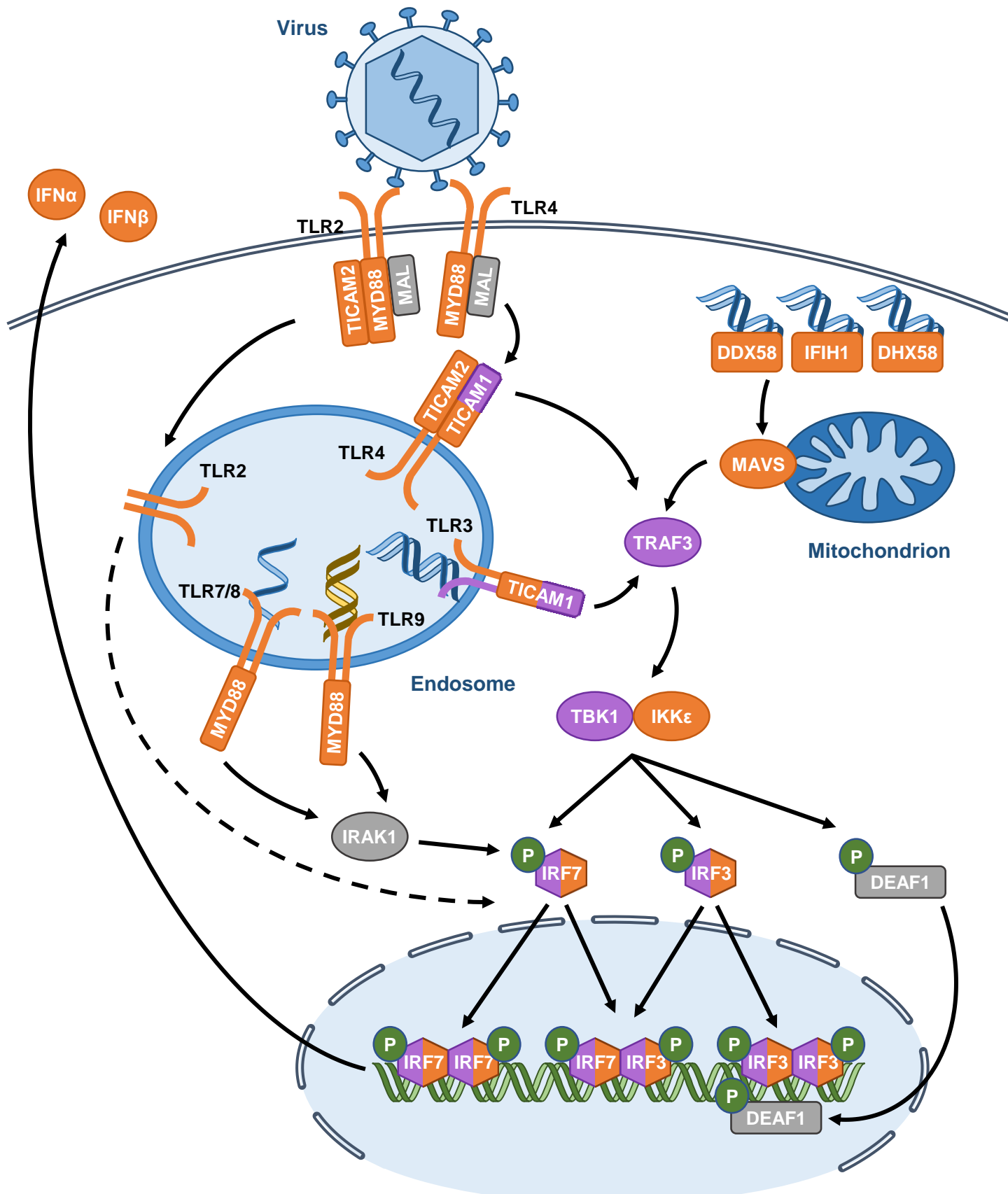
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809 **Figure 1: Induction of IFN $\alpha$  and IFN $\beta$**

810 Viral molecules (DNA, RNA and proteins) induce the expression of IFN-I after their  
811 recognition by TLRs and RLRs. Signalization leads the activation of kinases, TBK1 and  
812 IKK $\epsilon$  responsible for the activation of the transcription factors IRF3 and IRF7 which induce  
813 the expression of IFN $\alpha$  and IFN $\beta$ . Proteins for which the corresponding gene was associated  
814 with susceptibility to virus infection are indicated in orange for mouse studies and in purple  
815 for human studies. Blue, yellow and green helices depict viral RNA, viral DNA and cellular  
816 DNA molecules, respectively. Gene names are spelled according to the nomenclature rules for  
817 human genes.

818

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**Table 1: Genes with variants associated with susceptibility to viral infections in humans**

Virus	Type of study	Method	Polymorphism	Impact on gene function	Phenotype	Reference
<b><i>TLR3</i></b>						
HIV	Association study	Genotyping of a candidate gene	L412F [missense]	Increased cytokine production following stimulation of TLR3 and lower viral load	Decreased risk of infection	32
IAV	Association study	Genotyping of candidate genes	rs5743313 [intronic]	ND	Increased risk of pneumonia	23
IAV	Association study	Sequencing of candidate genes	rs5743313 [intronic]	ND	Increased risk of fatal infection	24
IAV	Case study	Sequencing of candidate genes	F303S [missense]	No induction of IFN $\beta$ and no activation of NF $\kappa$ B	Influenza-associated encephalopathy	25
IAV	Case study	WES	P554S [missense], P680L [missense]	Decreased expression of IFN $\beta$ and IFN $\lambda$	Acute respiratory distress syndrome	26
HBV	Association study	Genotyping of a candidate gene	rs1879026 [intronic]	ND	Increased risk of being infected	27
HSV-1	Case study	Sequencing of a candidate gene	P554S [missense], E746X [nonsense], G743D [missense], R811I [missense], L360P [missense]	Decreased induction of cytokines and higher viral replication rate	Herpes simplex encephalitis	28-30
MV	Association study	Genotyping of candidate genes	L412F [missense]	ND	Increased risk of subacute sclerosing panencephalitis	31
<b><i>TICAM1</i></b>						
HSV-1	Case study	WES	A568T, S160F [missense]	Decreased induction of cytokines	Herpes simplex encephalitis	33
HSV-1	Case study	Sequencing of candidate genes	R141X [nonsense], S186L [missense]	Impaired activation of IRF3 and NF $\kappa$ B, decreased induction of cytokines	Herpes simplex encephalitis	34
<b><i>DDX58</i></b>						
IAV	Case study	WES	R71H + P885S [missense]	Decreased response to ligand and expression of IFN $\beta$	Severe influenza infection	51
<b><i>IFIH1</i></b>						
HCV	Association study	Genotyping of candidate genes	H843A [missense]	Decreased expression of IFN $\beta$ and other cytokines	Chronic hepatitis C	54
HRV	Case study	WES	rs35732034 [intronic]	Lack of exon 14, decreased expression of IFN $\beta$	Bronchiolitis	52
HRV	Case study	WES	E627X [nonsense]	Lack of CTD, decreased expression of IFN $\beta$	Bronchiolitis, pneumonia	52
RSV	Case study	WES	rs35732034 [intronic]	Lack of exon 14, decreased expression of IFN $\beta$	Bronchiolitis, pneumonia	52
RSV	Case study	WES	rs35337543 [intronic]	Lack of exon 8, decreased expression of IFN $\beta$	Bronchiolitis	52
<b><i>TRAF3</i></b>						
HSV-1	Case study	Sequencing of a candidate gene	R118W [missense]	Decreased TRAF3 production	Herpes simplex encephalitis	71
<b><i>TBK1</i></b>						
HSV-1	Case study	Sequencing of a candidate gene	D50A [missense]	Decreased amount of TBK1 mRNA and protein, decreased cytokine production	Herpes simplex encephalitis	72
HSV-1	Case study	Sequencing of a candidate gene	D159A [missense]	No enzyme activity, decreased cytokine production	Herpes simplex encephalitis	72
<b><i>IRF3</i></b>						
HSV-1	Case study	WES	R285Q [missense]	No phosphorylation and dimerization of IRF3, decreased cytokine production	Herpes simplex encephalitis	33, 74
HSV-1	Case study	WES	A277T [missense]	Decreased cytokine production	Herpes simplex encephalitis	33
WNV	Association study	Genotyping of candidate genes	rs2304207 [intronic]	ND	Increased risk to have a symptomatic infection	76
<b><i>IRF7</i></b>						
IAV	Case study	WES	Q421X [nonsense]	Absence of phosphorylation and nuclear localization in absence of infection, impaired IFN $\alpha$ production (in the case of compound heterozygosity with F410V)	Life-threatening infection	77
IAV	Case study	WES	F410V [missense]	Inability to translocate to the nucleus, impaired IFN $\alpha$ production (in the case of compound heterozygosity with Q421X)	Life-threatening infection	77

For exonic variants, the effect is indicated [missense/nonsense]

Abbreviations: HBV: hepatitis B virus; HRV: human rhinovirus; HSV-1: herpes simplex virus type 1; IAV: influenza A virus; MV: measles virus; RSV: respiratory syncytial virus; WNV: West Nile virus WES: whole exome sequencing, ND: not

**Table 2: Genes with variants associated with susceptibility to viral infections in mice**

Virus	Variant*	Mortality**	Viral titer [tissue]**	Type I IFN expression [tissue]**	Reference
<i>Tlr3</i>					
CVB3	KO	+	+ [heart, serum, splenocytes]	= [heart]	35
EMCV	KO	+	+ [heart, liver]	+ [heart]	36
IAV	KO	-	+ [lung]	ND	38
MCMV	KO	=	+ [spleen]	- [serum]	37
VV	KO	-	- [abdomen, lung, chest]	= [lung]	41
WNV	KO	+	+ [brain, spinal cord, spleen]	= [lymph node, serum]	44
WNV	KO	-	+ [blood] - [brain]	- [blood, brain]	43
<i>Ticam1</i>					
CVB3	KO	+	+ [heart]	- 72h + 7 days [heart]	40
MCMV	Point mutation	+	+ [spleen]	- [serum]	39
VV	KO	ND	+ [chest]	ND	42
<i>Tlr2</i>					
HSV-1	KO	-	= [brain]	ND	46
<i>Tlr4</i>					
VV	Point mutation	+	+ [abdomen, chest, head, lung]	= [lung]	42
<i>Tlr7</i>					
WNV	KO	+	+ [blood, brain, spleen]	+ [blood]	45
<i>Tlr9</i>					
MCMV	Point mutation	+	+ [spleen]	- [serum]	37
<i>Myd88</i>					
CHIKV	KO	ND	+ [joint, serum, spleen]	ND	47
MCMV	KO	+	+ [spleen]	- [serum]	37
SARS-CoV	KO	+	+ [lung]	= [lung]	48
WNV	KO	+	+ [blood, brain, spleen]	ND	45
WNV	KO	+	+ [brain, lymph node, spleen]	+ [serum]	49
<i>Ticam2</i>					
SARS-CoV	KO	ND	+ [lung]	ND	50
<i>Ddx58</i>					
IAV	KO	=	+ [lung]	ND	55
CHIKV	KO	ND	+ [serum]	ND	47
JEV	KO	+ §	ND	- [serum] §	62
WNV	KO	+	+ [MEF]	- [MEF]	64
<i>Ifih1</i>					
CVB3	KO	+	= [liver, pancreas, serum]	- [pancreas, serum]	66
EMCV	KO	+ §	+ [heart] §	- [serum] §	62
EMCV	KO	+	ND	- [DC, MP]	63
HBV	KO	ND	+ [liver, serum]	ND	59
hMPV	KO	ND	+ [lung]	- [lung]	58
MHV	KO	+	+ [brain, heart, kidney, lung, spinal cord, spleen]	- [liver]	57
MNV-1	KO	ND	+ [intestine, spleen, lymph node]	- [DC]	60
TMEV	KO	ND	+ [brain, spinal cord]	- [brain, spinal cord]	61
WNV	KO	+	+ [DC, MP]	- [DC, MEF, MP]	64
<i>Dhx58</i>					
EMCV	KO + point mutation	+	+ [heart]	- [serum]	13
IAV	TG	-	= [lung]	- [lung]	70
WNV	KO	+	+ [brain, DC, MP]	- [DC, MP]	14
<i>Mavs</i>					
CHIKV	KO	ND	+ [serum]	ND	47
CVB3	KO	+	= [liver, pancreas, serum]	- [pancreas, serum]	66
DENV	KO	=	+ [bone marrow, lymph node, serum, spleen]	- [bone marrow, lymph node, serum, spleen]	69
EMCV	KO	+	+ [heart] §	- [serum]	67
VSV	KO	+	+ [brain, liver]	ND	67
VSV	KO	+	+ [serum]	= [serum]	68
WNV	KO	+	+ [brain, DC, kidney, MP, serum, spinal cord, spleen]	- [DC, MP]	65
WNV	KO	+	+ [DC]	- [DC]	64
<i>Ikbke</i>					
IAV	KO	+	+ [lung, MEF]	= [lung, MEF]	73
<i>Irf3</i>					
IAV	KO	+	+ [lung]	- [lung]	78
WNV	KO	+	+ [brain, kidney, lymph node, serum, spinal cord, spleen]	- [lymph node]	80
<i>Irf7</i>					
DENV	KO	ND	+ [spleen]	- [serum]	84
IAV	KO	+	ND	- [serum]	79
IAV	KO	+	= [lung]	- [lung]	78

EMCV	KO	+	ND	- [serum]	82
HSV	KO	+	ND	- [serum]	82
WNV	KO	+	+ [brain, kidney, lymph node, serum, spinal cord, spleen]	- [brain, DC, MEF, MP, serum]	82
WNV	KO	+	+ [brain, cortical neurons, DC, kidney, lymph node, MEF, MP, serum, spleen, spinal cord]	- [brain, cortical neurons, DC, MEF, MP]	81
<i>Irf3-Irf7</i>					
CHIKV	KO	+	+ [blood, brain, liver, muscle, spleen]	- [blood, feet]	83
<i>Irf3-Irf5-Irf7</i>					
ZIKV	KO	+	ND	ND	85
<i>Irf1-Irf3-Irf5-Irf7</i>					
DENV	KO	+	+ [MP]	- [MP, serum]	86
<i>Ifna</i>					
WNV	mAb treated	+	ND	ND	88
<i>Ifnb1</i>					
CVB3	KO	+	+ [liver, spleen]	ND	92
FV	KO	ND	+ [spleen]	= [plasma]	93
IAV	KO	+	+ [lung, MEF]	ND	91
VV	KO	+	+ [lung]	- [MEF]	90
WNV	KO	+	+ [brain, granule cell neurons, kidney, lymph node, myeloid cells, MEF, serum, spinal cord]	+ [serum]	89
WNV	mAb treated	+	ND	ND	88

\* Genetic variant except for 'mAb treated' in which case gene product was transiently inhibited using a monoclonal antibody. The phenotype was compared with wild type mice, except for § (compared with heterozygous mice).

\*\* + : increased; - : decreased; = : unchanged; ND: not determined.

Abbreviations: CVB3: coxsackievirus B3; CHIKV: chikungunya virus; DENV: dengue virus; EMCV: encephalomyocarditis virus; FV: friend virus; hMPV: human metapneumovirus; HSV-1: herpes simplex virus type 1; IAV: influenza A virus; JEV: Japanese encephalitis virus; MCMV: murine cytomegalovirus; MNV-1: murine norovirus 1; SARS-CoV: severe acute respiratory syndrome coronavirus; TMEV: Theiler's murine encephalomyelitis virus; VSV: vesicular stomatitis virus; VV: vaccinia virus; WNV: West Nile virus; KO: knocked-out mice, TG: transgenic mice; MEF: mouse embryonic fibroblasts, DC: dendritic cells, MP: macrophages.