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REVIEW ARTICLE

# Genetic diseases conferring resistance to infectious diseases

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**Abstract** This review considers available evidence for mechanisms of conferred adaptive advantages in the face of specific infectious diseases. In short, we explore a number of genetic conditions, which carry some benefits in adverse circumstances including exposure to infectious agents. The examples discussed are conditions known to result in resistance to a specific infectious disease, or have been proposed as being associated with resistance to various infectious diseases. These infectious disease—genetic disorder pairings include malaria and hemoglobinopathies, cholera and cystic fibrosis, tuberculosis and Tay-Sachs disease, mycotic abortions and phenylketonuria, infection by enveloped viruses and disorders of glycosylation, infection by filoviruses and Niemann–Pick C1 disease, as well as rabies and myasthenia gravis.

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We also discuss two genetic conditions that lead to infectious disease hypersusceptibility, although we did not cover the large number of immunologic defects leading to infectious disease hypersusceptibilities. Four of the resistance-associated pairings (malaria/hemogloginopathies, cholera/cystic fibrosis, tuberculosis/Tay-Sachs, and mycotic abortions/phenylketonuria) appear to be a result of selection pressures in geographic regions in which the specific infectious agent is endemic. The other pairings do not appear to be based on selection pressure and instead may be serendipitous. Nonetheless, research investigating these relationships may lead to treatment options for the aforementioned diseases by exploiting established mechanisms between genetically affected cells and infectious organisms. This may prove invaluable as a starting point for research in the case of diseases that currently have no reliably curative treatments, *e.g.*, HIV, rabies, and Ebola.


## Introduction

Some genetic conditions can confer resistance to specific infectious diseases. It is theorized that these genotypes are preferentially maintained in populations regularly exposed to certain infectious agents, especially those with high virulence. The protection afforded by these conditions has provided the impetus for understanding these genetic mechanisms of resistance that can potentially be exploited for developing novel therapies or improving current therapies. This review describes a number of these resistances, the molecular bases for each resistance, and therapeutic implications from the resistance. We also discuss two relationships that lead to infectious disease hypersusceptiblity, which also provides valuable information that has been used or will be used to develop therapies.

This review is organized based on a description of four genetic conditions/infectious resistance pairings in which there appears to be a selection pressure. The first of which is sickle cell anemia (and other hemoglobinopathies) and malaria in geographic regions in which the malaria-causing parasite and vector is endemic.[1] Interestingly, this disease complex leads to increased susceptibility to respiratory infections through a mechanism independent of hemoglobin.

The second pair involving a putative selection pressure is cystic fibrosis, which involves a mutation encoding a defective chloride channel. In unaffected individuals, this channel can be exploited by diarrhea-producing enteropathogens. The derangement of this channel may result in resistance to the enteric effects of cholera, and the cystic fibrosis genotype has a higher prevalence in regions in which cholera is or was endemic.[2]

The third selection pressure-associated pair involves Tay-Sachs disease, a lysosomal storage disease characterized by deficiency of hexosaminidase A. Historically, Ashkenazi Jews had a high prevalence of the Tay-Sachs allele and a low prevalence of tuberculosis caused by *Mycobacterium tuberculosis*, a relationship that may be related to crowded environments associated with this ethnic population and concentration of *Mycobacterium tuberculosis*.[3]

Yet another relationship with a putative selection pressure is phenylketonuria, a metabolic genetic disorder in which phenylalanine accumulates to toxic levels in the affected individual. Women who are heterozygotes for the disorder are significantly less sensitive to the abortifacient activities of the mycotoxin designated as ochratoxin A. This relationship appears to be relevant in moist regions in which pathogenic fungi are endemic.[4]

Three other relationships do not appear to have a selection pressure, one of which is congenital disorder of glycosylation 2b (CDG-IIb) which leads to impaired glycosylation of proteins and thus confers resistance to viruses that have glycosylated capsids.[5] The second "spurious" relationship involves myasthenia gravis in which autoantibodies attack the acetylcholine receptor that is coincidentally exploited as a docking site for the rabies virus; this competition may lead to resistance to rabies.[6] Finally, Niemann—Pick C1 disease is a lysosomal storage disorder in which a faulty cholesterol transporter leads to abnormal accumulation of cholesterol within lysosomes. The Ebola virus apparently uses this transporter and thus its dysfunction impairs viral pathogenicity in patients with Niemann—Pick C1 disease.[7]

It is of note that a particular genetic disorder leads to infectious disease hypersusceptibility, and this relationship has provided the basis for a preventative. Specifically, the relationship between hemosiderosis and typhoid fever has led to the development of a vaccine that intervenes in this relationship.

This literature review discusses the potential benefits garnered from further study of the pathways associated with these genetic conditions and infectious disease resistance (or hypersusceptibility). A summary of the current state of research is presented in Table 1. The more we understand about the link between these genetic conditions and the infectious disease resistances, the easier it will be to exploit the mechanism for therapeutic uses. When trying to develop therapies, the most difficult part is often finding a starting point for research. The nature of the human condition provides us with these starting points.

## Resistance to malaria and the sickle trait

Resistance to malaria has been linked to a number of conditions including hemoglobinopathies, enzymopathies, and the absence of an erythrocyte surface protein. Other