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Human genetics of infectious diseases: a unified theory

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Since the early 1950s, the dominant paradigm in the human genetics of infectious diseases postulates that rare monogenic immunodeficiencies confer vulnerability to multiple infectious diseases (one gene, multiple infections), whereas common infections are associated with the polygenic inheritance of multiple susceptibility genes (one infection, multiple genes). Recent studies, since 1996 in particular, have challenged this view. A newly recognised group of primary immunodeficiencies predisposing the individual to a principal or single type of infection is emerging. In parallel, several common infections have been shown to reflect the inheritance of one major susceptibility gene, at least in some populations. This novel causal relationship (one gene, one infection) blurs the distinction between patient-based Mendelian genetics and population-based complex genetics, and provides a unified conceptual frame for exploring the molecular genetic basis of infectious diseases in humans.

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Introduction

Although sufficient to ensure reproduction at the species level, the human immune system is weak at the individual level. Indeed, life expectancy at birth did not exceed 20–25 years of age until the advent of Pasteur's microbial theory of disease and the ensuing control of infections by hygiene, vaccines, and antibiotics (Casanova and Abel, 2005). Nevertheless, a striking feature of most infections in human populations world-wide and throughout history is their considerable inter-individual phenotypic variability, ranging from asymptomatic to lethal infections. The field of human genetics of infectious diseases aims to define the genetic variations accounting for inter-individual variability in the course of human infections. From a clinical standpoint, this human genetic view of infectious diseases provides new means of diagnosis, improves the definition of patient prognosis, and paves the way for innovative preventive and curative approaches (Casanova and Abel, 2005). The human model is also important for biological purposes, as infections and immunity occur in natural, as opposed to experimental conditions in this model (Casanova and Abel, 2004). Under the theory of natural selection of living species, the ecologically relevant functions of immune system genes are subject to natural selective pressure (Allison, 1954, 1968, 2002; Lederberg, 1999). It is therefore essential to define the function of immune genes within the setting of their natural ecosystem, within which the organisms and populations concerned live and are selected (Casanova and Abel, 2004).

According to the dominant paradigm, monogenic immunodeficiencies (also known as primary immunodeficiencies, PIDs) are rare and confer vulnerability to multiple infectious diseases (one gene, multiple infections)—that vary in nature and number with the gene affected—(Notarangelo *et al*, 2006; Ochs *et al*, 2006), whereas common infections are favoured by the polygenic inheritance of multiple susceptibility genes, most of which if not all making an individually modest contribution to the phenotype (one infection, multiple genes) (Figure 1) (Lander and Schork, 1994; Hill, 2001, 2006). For Galtonian biostatisticians, infectious diseases are seen in populations and reflect polygenic predisposition. In contrast, for Mendelian physician-scientists, severe infections do occur in individuals and result from monogenic PIDs. X-linked recessive agammaglobulinaemia, probably the first PID to be described as such in the English literature, was discovered in 1952 by Ogden Bruton in a few American children with multiple infections (Bruton, 1952, 1962). At about the same period, in 1954, Anthony Allison discovered that the sickle cell trait protects against severe forms of *Plasmodium falciparum* malaria in African populations (Allison, 1954, 2002), paving the way for acceptance of the notion of multiple-gene involvement in disease susceptibility (Min-Oo and Gros, 2005). Population-based complex genetics and patient-based Mendelian genetics have evolved in parallel for almost 50 years, even though they study the same phenomenon from two ends of a spectrum: the patient and population viewpoints. We argue here that the recent discovery of human genes conferring vulnerability or resistance to a specific infection at the individual or population level (one gene, one infection) bridges the two fields, providing experimental support for a unified theory of the human genetics of infectious diseases (Figure 1, Table I).

Monogenic traits conferring predisposition to specific infections

From idiopathic infectious diseases to novel primary immunodeficiencies

A few idiopathic infections in otherwise healthy patients have been shown to be familial, suggesting a Mendelian mode of

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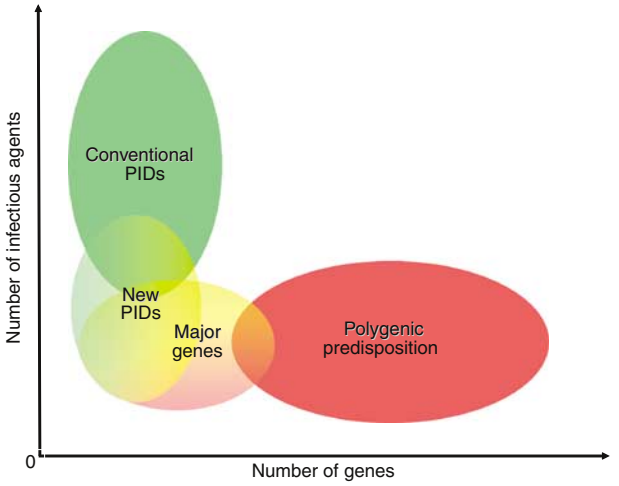

Figure 1 Human genetics of infectious diseases. The spectrum of genetic predisposition to infectious diseases in human patients is represented, according to the number of genes involved (*x*-axis) and the number of infections (*y*-axis). The dominant view in human genetics of infectious diseases postulates that rare, 'conventional', monogenic primary immunodeficiencies (PIDs, in green) predispose the individual to numerous infections (one gene, multiple infections), whereas common infectious diseases are associated with polygenic inheritance (in red) of numerous susceptibility genes (one infection, multiple genes). Novel monogenic PIDs (in yellow/green) predispose the individual to a principal or single type of infection. Major genes (in yellow/red) exert a nearly Mendelian impact at the population level and largely account for common infectious diseases in some individuals. The recent discovery of such human genes conferring vulnerability or resistance to a specific infection at the individual level (one gene, one infection) bridges the gap between the two classical fields of conventional PIDs and polygenic inheritance, as defined in the 50 s. As an example, genetic predisposition to tuberculosis, which was considered to be purely polygenic, was recently shown to reflect both new PID and major gene effects, at least in some patients (see text for details). Overall, these observations provide experimental support for a continuous spectrum of predisposition and a unified theory of the human genetics of infectious diseases.

inheritance (reviewed by Casanova *et al*, 2002, 2005; Picard *et al*, 2006). Defects of the complement membrane attack complex (1974) and properdin (1982) were found to result in selective predisposition to invasive *Neisseria* disease (reviewed by Mathew and Overturf, 2006). The corresponding germline mutations were identified from 1993 and 1995 onwards. X-linked lymphoproliferative disease (XLP), described clinically in 1975 and predisposing to lethal Epstein-Barr virus (EBV) disease, was found to be heterogeneous at the molecular level, with a first pathogenic gene identified in 1998 and a second in 2006 (Rigaud *et al*, 2006 and references therein). *Neisseria* and EBV can also affect children with conventional PIDs, unlike skin-tropic oncogenic papillomaviruses (HPVs), which almost exclusively affect patients with epidermodysplasia verruciformis (EV) (reviewed by Orth, 2006). EV was first described clinically in 1922 as a congenital dermatosis (Lewandowsky and Lutz, 1922). A recessive mode of inheritance for this disease was proposed in 1933 (Cockayne, 1933) and the role of papillomaviruses was established in 1946 (Lutz, 1946). Causal mutations in *EVER1* or *EVER2* were described in 2002 (Ramoz *et al*, 1999, 2002). The *EVER* genes belong to the transmembrane channel-like (TMC) family and may exert their anti-HPV function within keratinocytes. Retrospectively, EV was probably the first PID to be described, although the lack of a detectable immunological phenotype and the narrow range of infections precluded the use of this term at the time.

Mendelian susceptibility to mycobaterial disease

Mendelian susceptibility to mycobacterial disease (MSMD) was probably first clinically described in 1951 and has been thoroughly characterised since 1996 (Mimouni, 1951; Casanova *et al*, 1996). Patients with MSMD are highly susceptible to weakly virulent mycobacteria, but are apparently resistant to most other infectious agents, with the exception of *Salmonella* (Casanova *et al*, 1995, 1996; Levin *et al*, 1995). Since 1996, disease-causing mutations have been found in five autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B* and *IL12RB1*) and one X-linked (*NEMO*) gene. These genes are physiologically related because their products are involved in IL-12/IL-23-dependent, IFN-γ-mediated immunity (Casanova and Abel, 2002; Filipe-Santos *et al*, 2006a). Extensive allelic heterogeneity at the five autosomal loci accounts for the existence of twelve distinct genetic disorders (Jouanguy *et al*, 1996, 1997, 1999, 2000; Newport *et al*, 1996; Altare *et al*, 1998a, b; Dorman and Holland, 1998; de Jong *et al*, 1998; Döffinger *et al*, 2000; Dupuis *et al*, 2001, 2003; Fieschi *et al*, 2004; Rosenzweig *et al*, 2004; Vogt *et al*, 2005; Chapgier *et al*, 2006). X-linked MSMD is caused by *NEMO* mutations impairing the CD40-triggered induction of IL-12 production by monocyte-derived cells upon stimulation by CD40L-expressing T cells (Filipe-Santos *et al*, 2006b). Incidentally, the study of *IFNGR2* revealed that gain-of-glycosylation mutations represent up to 1.4% of disease-causing missense mutations in humans (Vogt *et al*, 2005). Altogether, studies of MSMD have shown that the IL-12/23-IFN-γ circuit is crucial for host defence against mycobacteria and *Salmonella* but redundant against most other microorganisms.

Mendelian predisposition to Streptococcus pneumoniae

Patients with PIDs affecting the splenic phagocytosis of opsonised bacteria suffer from multiple pyogenic infections, including invasive pneumococcal disease in particular (Picard *et al*, 2003b). Patients with inherited interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency are more specifically vulnerable to pneumococcus infections (Picard *et al*, 2003a, b). The first patient with IRAK-4 deficiency was described clinically in 1997 (Kuhns *et al*, 1997), the diagnosis of IRAK-4 deficiency being made in 2003 (Medvedev *et al*, 2003). Almost 30 other patients have since been identified (Currie *et al*, 2004; Enders *et al*, 2004; Chapel *et al*, 2005; Ku *et al*, 2005, 2007; Yang *et al*, 2005; Cardenes *et al*, 2006; Takada *et al*, 2006). Clinically, IRAK-4-deficient patients present recurrent infections caused by pyogenic bacteria, such as *S. pneumoniae* and *S. aureus* in particular. Only three of the identified patients had invasive disease caused by Gram-negative bacteria. IRAK-4 deficiency is a life-threatening disease in childhood, but the global trend shows a clinical improvement with age. The patients' blood cells fail to produce cytokines upon stimulation with Toll-like receptor (TLR) agonists, IL-1β and IL-18. So far, the only known exception is the induction of IFN-α/β and IFN-λ in response to TLR3 and TLR4 stimulation (Yang *et al*, 2005). Overall, the TLR and IL-1R signalling pathways that depend on IRAK-4 are critical for protective immunity to a relatively narrow group

of pathogens, including pneumococci, but redundant for protective immunity to many other pathogens.

Mendelian predisposition to herpes simplex encephalitis

Herpes simplex encephalitis (HSE) provides the best illustration that susceptibility to a single infectious disease may be associated with single-gene lesions (Casrouge *et al*, 2006). HSE, which was first described in 1941 (Smith *et al*, 1941), is the most common form of sporadic encephalitis in Western countries. Its occurrence in only a small fraction of individuals infected with the almost ubiquitous HSV-1 and in otherwise healthy individuals remained unexplained until the identification of two children with HSE who produced only low levels of IFN-α/β and -λ in response to viruses and TLR3, TLR7, TLR8, and TLR9 agonists (Casrouge *et al*, 2006). These children carry homozygous null mutations in *UNC93B1*. HSV-1 did not trigger the production of optimal amounts of IFN-β and -λ in fibroblasts from these patients, increasing levels of viral replication and cell death. Based on our previous finding that IRAK-4-deficient children did not suffer from severe viral diseases, we concluded that the induction of IFN production via TLR7, TLR8, and TLR9 is redundant for protective immunity to viruses (Yang *et al*, 2005). The results obtained for these UNC-93B-deficient patients indicate that HSE is caused by the impairment of TLR3-dependent pathways, TLR-independent pathways, or both. The UNC-93B-IFN pathway is critical for primary immunity to HSV-1 in the central nervous system. HSE thus provides the first example of a devastating and sporadic infectious disease, hitherto idiopathic, that is now known to result from a monogenic PID (Casanova *et al*, 2005).

Major genes predisposing populations to infectious diseases

The concept of major genes in human genetics

Between 1910 and 1930, the studies of Fisher, Haldane, and Wright founded population genetics by developing a mathematical framework that modelled the behaviour of genes in populations (Khoury *et al*, 1993). Bridging the gap between the Galtonian and the Mendelian approaches, Fisher developed a polygenic model in which familial correlations for quantitative traits resulted from the combined and independent action of a large number of genes, each exerting a small effect (Fisher, 1918). With the development of statistical genetics in the 1960s, models that could explicitly specify the effect of single genes in the expression of common diseases were developed (Edwards, 1969; Lalouel *et al*, 1983). This led to the concept of 'major genes/loci', the phenotypic expression of which is influenced by other genes and by the environment, and which was first formalised in the context of complex segregation analysis (Khoury *et al*, 1993). Several major genes identified by segregation analyses have been reported since the 1970s, for a number of infectious disease-related phenotypes (Abel and Demenais, 1988; Abel *et al*, 1991, 1992, 1995; Alcais *et al*, 1997; Plancoulaine *et al*, 2000, 2003). In the 1990s, with the development of highly polymorphic genetic markers (Dib *et al*, 1996), the concept of 'major genes' was applied to loci detected in genome-wide linkage studies. Such loci, including those detected in affected sib-pairs studies, are predicted to have a considerable influence on the phenotype studied (Risch, 1990; Risch and Merikangas, 1996). The first major susceptibility locus for infectious diseases was mapped in 1996, for schistosomiasis (Marquet *et al*, 1996).

Major genes for parasitic diseases

Schistosomiasis is the second most important parasitic disease world-wide after malaria (Campino *et al*, 2006). Segregation analysis (Abel *et al*, 1991) led to the mapping of a major locus controlling levels of gastro-intestinal infection with the nematode *Schistosoma mansoni* (*SM1*) to chromosome 5q31–q33 in a Brazilian population (Marquet *et al*, 1996). This mapping was replicated in a Senegalese population (Muller-Myhsok *et al*, 1997). In another study combining segregation and linkage analysis, a second major locus predisposing subjects infected with *S. mansoni* to severe hepatic fibrosis (the *SM2* locus) was mapped to chromosome 6q23 in a Sudanese population (Dessein *et al*, 1999a). This result was subsequently replicated in an Egyptian population (Blanton *et al*, 2005). Gene variants at these two major loci have yet to be discovered. These studies provide proof-of-principle that major loci may control common infectious phenotypes. They also demonstrate that levels of infection and hepatic disease owing to *S. mansoni* are under distinct genetic control (Dessein *et al*, 1999b). A major gene associated with visceral leishamiasis (or kala azar), caused by the protozoa *Leishmania donovani*, has also recently been identified (Campino *et al*, 2006). A genome-wide scan conducted in a Sudanese village led to the mapping of a major susceptibility locus to chromosome 22q12 (Bucheton *et al*, 2003). Interestingly, the effect of this locus was stronger in subjects affected at the start of the outbreak. This suggests that, for a given disease, major genes are more commonly expressed in patients with an early onset of disease.

Major genes for leprosy

Leprosy is a chronic infectious disease that still affects more than 300 000 subjects per year (WHO, 2006). In an effort to combat social stigma, the belief that leprosy was inherited was discredited when Armauer Hansen demonstrated that leprosy was caused by *Mycobacterium leprae* (Pallamary, 1955). Ironically, we know today that both the development of the disease upon exposure to *M. leprae* and the pattern of clinical manifestations displayed by leprosy patients (paucibacillary versus multibacillary) are highly dependent on human genes (Casanova and Abel, 2002; Alcais *et al*, 2005b). Twin studies in the 1960s indicated that leprosy was largely genetic (Beiguelman, 1968), and segregation studies in the 1980s provided strong evidence for the presence of a major gene, particularly in the study carried out on Desirade Island (Abel and Demenais, 1988). Two major regions were recently mapped by genome-wide linkage studies. A major locus was found on chromosome 10p13 in Indians with paucibacillary leprosy (Siddiqui *et al*, 2001). Another major locus for susceptibility to leprosy *per se* (i.e. leprosy regardless of its clinical subtype) was mapped to chromosome 6q25 in Vietnamese patients (Mira *et al*, 2003). Linkage disequilibrium studies in this region identified leprosy susceptibility variants of the regulatory region shared by *PARK2*, which encodes an E3-ubiquitin ligase called Parkin, and *PACRG* (Parkin coregulated gene) (Mira *et al*,

Table I Genetic predisposition or resistance to specific infections

Infectious agent	Clinical phenotype	Immunological phenotype	Gene/locus	References
Mendelian predisposition				
Neisseria	Invasive disease	MAC deficiency	*C5*, *C6*, *C7*, *C8A*, *C8B*, *C8G*, *C9*	Reviewed in (Mathew and Overturf, 2006)
	Invasive disease	Properdin deficiency	*PFC*	Reviewed in (Mathew and Overturf, 2006)
Mycobacteria	MSMD	IL-12/23-IFN-γ deficiency	*IFNGR1*, *IFNGR2*, *STAT1*, *NEMO*, *IL12B*, *IL12RB1*	Reviewed in (Filipe-Santos *et al*, 2006a, b)
	Disseminated tuberculosis			Reviewed in (Alcais *et al*, 2005a, b)
Streptococcus pneumoniae	Invasive disease	IRAK-4 deficiency	*IRAK4*	(Picard *et al*, 2003)
Epstein-Barr virus	X-linked lympho-proliferative disease	SAP deficiency	*SH2D1A*	Reviewed in (Picard *et al*, 2006)
		XIAP deficiency	*XIAP*	(Rigaud *et al*, 2006)
Human papillomavirus	*Epidermodysplasia verruciformis*	EVER1/EVER2 deficiency	*EVER1*, *EVER2*	(Ramoz *et al*, 1999, 2002)
Mendelian resistance				
Plasmodium vivax	Natural resistance	Lack of receptor for pathogen	*DARC*	(Miller *et al*, 1975, 1976; Tournamille *et al*, 1995)
Human immunodeficiency virus-1	Natural resistance	Lack of receptor for pathogen	*CCR5*	Reviewed in (Picard *et al*, 2006)
Norovirus	Natural resistance	Lack of receptor for pathogen	*FUT2*	Reviewed in (Picard *et al*, 2006)
Major gene[a]				
Mycobacterium tuberculosis	Pulmonary tuberculosis	To be determined	To be identified (8q12–q13)	(Baghdadi *et al*, 2006)
Mycobacterium leprae	Leprosy *per se*	To be determined	*PARK2/PACRG*	(Mira *et al*, 2003, 2004)
	Paucibacillary leprosy		To be identified (10p13)	(Siddiqui *et al*, 2001)
Schistosoma mansoni	Infection levels	To be determined	To be identified (5q31–q33)	(Marquet *et al*, 1996; Muller-Myhsok *et al*, 1997)
	Hepatic fibrosis		To be identified (6q22–q23)	(Dessein *et al*, 1999; Blanton *et al*, 2005)
Leishmania donovani	Kala-azar	To be determined	To be identified (22q12)	(Bucheton *et al*, 2003)

[a]Major genes presented in this table are those that have been identified by means of a genome-wide linkage analysis.

2004). These studies resulted in the first successful positional cloning of a major gene in a common infectious disease, and identified a new pathway of immunity to *M. leprae* (Schurr *et al*, 2006).

Major gene for tuberculosis

Tuberculosis, another common mycobacterial disease, is a leading public health problem world-wide (WHO, 2004). It was not until the 1930s that rigorous twin studies provided strong evidence for the contribution of human genetics to tuberculosis (Puffer, 1944; Dubos and Dubos, 1952). No complex segregation studies have been conducted in tuberculosis and, until the late 1990s, all investigations of host genes were based on association studies with candidate genes (Casanova and Abel, 2002; Alcais *et al*, 2005a). The most consistent results were obtained with some HLA class II and natural resistance-associated macrophage protein 1 (*NRAMP1*, alias *SLC11A1*) alleles (Alcais *et al*, 2005a). The first major locus identified by genome-wide screening was recently mapped to chromosome 8q12–q13 in adult patients with pulmonary tuberculosis from Morocco (Baghdadi *et al*, 2006). The predisposing allele is dominant, possibly accounting for the rapid decline in tuberculosis mortality rates in Europe during the 19th century, before any specific measures against the disease were taken. Efforts to identify this major gene more precisely are continuing. The other major discovery of recent years has been the demonstration that tuberculosis in children, a distinct disease, may reflect a Mendelian predisposition (Altare *et al*, 2001; Caragol *et al*, 2003; Alcais *et al*, 2005a; Casanova and Abel, 2005; Özbek *et al*, 2005). The proportion of children with disseminated tuberculosis owing to Mendelian predisposition remains to be experimentally determined, but has been estimated at 3–30% by Bayesian statistics (Alcais *et al*, 2005a). Overall, these recent studies provide the proof-of-concept that human genetics of common infectious diseases involves both Mendelian and major gene determinism.

Concluding remarks

The two related forms of genetic predisposition to infectious diseases reviewed here (one gene, one infection) bridge the gap between PIDs in individuals (one gene, multiple infections) and complex genetics in populations (one infection, multiple genes). Clearly, the concept of pathogen-specific genes applies to some, but not all individuals and populations, as the same gene may be associated with other infections in other individuals or populations. Moreover, pathogen specificity is unlikely to be strict, and degeneracy is almost inevitable, as best illustrated by the occurrence of *Salmonella* and staphylococcal infections in patients with IL-12Rβ1 and IRAK-4 deficiencies, respectively. One of the major goals of

the human genetics of infectious diseases is now to define the relative contributions of conventional PIDs, pathogen-specific monogenic traits, major genes, and purely multigenic inheritance, at both individual and population levels. An important factor to be considered is the virulence of the pathogen. A substantial proportion of predisposing Mendelian defects is expected in infectious diseases that affect only a small proportion of infected individuals (e.g. HSE). Conversely, more common polygenic predisposition is probably involved in diseases caused by more virulent microbes (e.g. HIV). The age of infection may also be a crucial factor to take in consideration, with more Mendelian traits being involved before puberty, when most primary infections do occur and when the impact of infection death on population genetics is expected to be greater (Wright *et al*, 2003). Future studies in the field should tackle these important questions.

It is often assumed that the contribution of PIDs and Mendelian traits in general, is modest at the population level. However, the emergence of pathogen-specific monogenic susceptibility traits (reviewed here) and pathogen-specific monogenic resistance traits, including defects in genes encoding chemokine receptors such as DARC and CCR5 (reviewed elsewhere (Picard *et al*, 2006) (Table I)), suggests that there may be more Mendelian disorders than initially thought (Pritchard, 2001; Pritchard and Cox, 2002; Antonarakis and Beckmann, 2006). In recent years, forward genetic studies in the mouse model have revealed a number of pathogen-specific genes, including *Mx*, *Nramp1*, *Ly49h*, and *Tlr4* (reviewed in Casanova *et al*, 2002; Buer and Balling, 2003; Haller and Kochs, 2003; Lam-Yuk-Tseung and Gros, 2003; Papathanasiou and Goodnow, 2005; Yokoyama, 2005; Beutler *et al*, 2006). These seminal studies paved the way for studies of the utmost importance in immunology. They also provided candidate genes for human infectious diseases and patients bearing mutations in their orthologs are expected to be discovered. Conversely, the impact of polygenic inheritance is often thought to be modest at the individual level. In fact, the demonstration that polygenic inheritance in individuals does confer actual predisposition to infectious diseases has not yet been shown in humans. Its demonstration in mice nonetheless suggests that this may occur in humans too (Buer and Balling, 2003; Lam-Yuk-Tseung and Gros, 2003; Papathanasiou and Goodnow, 2005; Beutler *et al*, 2006). The ongoing identification of human major genes raises hopes that a simpler, more potent form of causal determinism can be deciphered.

The clinical implications of novel PIDs are already considerable, and prospects for patient care are as promising as for conventional PIDs. Patients with impaired IFN-γ production are susceptible to severe tuberculosis and should be treated with recombinant IFN-γ (Alcais *et al*, 2005a). Similarly, patients with impaired IFN-α/β production are prone to herpes simplex encephalitis and should be treated with IFN-α (Casrouge *et al*, 2006). Major genes also hold great promise in terms of public health. The human genetics of infectious diseases also has important biological implications in the fields of immunity to infection and evolutionary immunology. The spread of the deleterious haemoglobin S (Allison, 1954; Lederberg, 1999; Allison, 2002) and DARC (Miller *et al*, 1975, 1976; Tournamille *et al*, 1995) alleles within human populations in regions endemic for *P. falciparum* and *Plasmodium vivax,* respectively, indicated that microbe-driven natural selection operates on the human genome. Major genes are expected to have important evolutionary implications, as illustrated by the dominant predisposition to tuberculosis, which might account for the rapid selection of resistant individuals (Baghdadi *et al*, 2006). Finally, studies of the novel PIDs have indicated that certain human genes exert an almost pathogen-specific effect in protective immunity, raising the exciting possibility of coevolution between animal and microbial species, as previously shown between plants and pathogens (Woolhouse *et al*, 2002; Chisholm *et al*, 2006).

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