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Genetics of Susceptibility to Infection with Enteric Pathogens

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Abstract

Purpose of review—To examine recent developments in human genetic susceptibility to enteropathogens that cause infectious diarrhea.

Recent findings—The affinity of specific Norovirus genogroups to different histo-blood group antigens (HBGA) secretor cells has been studied in different epidemiologic studies. HBGA are also used as receptors by *V. cholerae* with different degrees of affinity between biotypes. Polymorphisms in the CD14, lactoferrin and osteoprotegerin promoter genes were associated to diarrhea in travelers. SNPs in the IL-8 genes are also associated to increased risk for enteroaggregative *E. coli* and *C. difficile* infection. IL-10 haplotypes were associated to enterotoxigenic *E. coli* associated diarrhea in exposed individuals. A family-based study showed a significant association of the LPLUNC1 gene and cholera. The major histocompatibility complex class II antigens are associated to different degrees of susceptibility and resistance to *Salmonella*, *Cryptosporidium* and *Entamoeba* infection.

Summary—Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, innate and acquired immunity are being identified as determinants of host genetic susceptibility to infectious diarrhea.

Keywords

Genetic susceptibility; diarrhea; enteric infections; SNPs

Introduction

The evolutionary pressure that infectious diseases have placed on the human genome is substantial and has undoubtedly contributed over time to the functional variation of the genome. Small variations in the genome can determine the susceptibility to a particular pathogen or influence disease severity. This has been well demonstrated for numerous infectious diseases. For example, a deletion in the chemokine receptor CCR5 gene influences susceptibility to HIV infection and the progression of disease. However, the contribution that variations in a single gene have on disease susceptibility or severity is at most modest. It is thus likely that the contribution that host genetics has on susceptibility, disease severity and long term complications of infectious diarrhea are likely to be associated with variants in multiple genes involving multiple pathways. This paper summarizes recent findings on the contribution that human genetics has on the susceptibility to enteric pathogens.

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Infectious diarrhea is a major health problem worldwide. It is estimated that in developing regions of the world infectious diarrhea causes as much as 18% of deaths in children under the age of 5. Bouts of diarrhea in children under the age of 2 can result in long term developmental disabilities including growth shortfalls and impairment in cognition and schooling. Infectious diarrhea also affects 30-60% of adult travelers from developed countries visiting endemic regions of the world resulting in the syndrome of Travelers' diarrhea (TD).

The Phases of Enteric Infection, a Conceptual Framework

Enteric infections can be conceptualized as requiring of the overlapping phases of colonization, injury, control and healing. After ingestion of the enteropathogen through contaminated water or food, colonization is determined by the presence of bacterial factors (i.e. colonization factor antigens, adhesins, fimbriae) and host specific factors including pathogen receptors and the innate immunity. The innate immune response is of particular relevance since intestinal homeostasis is achieved by tolerating and controlling commensal flora and at the same time interfering with the colonization by pathogenic organisms [1○○]. During the phase of injury, bacterial products such as toxins and proteases among others induce fluid and electrolyte loss, and can damage the mucosa directly. The mucosa initially responds with the production of prostaglandins, chemokines and cytokines that recruit and activate immune effectors in an effort to contain the infection but may further damage the mucosa in the attempt. Once the infection is controlled and the process of specific humoral and cellular immunity has begun, the mucosa heals and the balance between the commensal flora and the intestine is re established. Functional polymorphisms in genes that mediate these stages may influence infection with agents of infectious diarrhea.

Genetic Bases for Enteric Infection Susceptibility, Host-Pathogen Relation

Several studies using a candidate-gene approach with preconceived hypothesis have identified specific single nucleotide polymorphisms (SNPs) in the host genome that are associated with different degrees of susceptibility to specific enteric infections.

1. Specific host receptors used by enteric pathogens and their role in susceptibility

Enteric pathogens frequently use host molecules as their specific receptors. Such is the case of histo-blood group antigens (HBGAs) which are carbohydrates that contain structurally related saccharide molecules. The O-type blood antigen is generated by a fucose transfer to a galactose residue with a α1-2 linkage, while the A-type blood group antigen and the B-blood group antigen of HBGAs are generated by a transfer of GalNAc and Gal, respectively to an H structure irrespective of the carbohydrate core structure. The fucose transfer of ABH antigens in erythrocytes is catalyzed by FUT1, a member of the fucosyltransferase family, whereas FUT2 catalyzes a different fucosyltransferase in saliva and mucosal secretions. Individuals who have null FUT2 alleles cannot synthesize ABH antigens in secretions and are called nonsecretors, although ABH antigens can be expressed in erythrocytes via FUT1. FUT2 alleles of Caucasian nonsecretors are completely inactivated by nonsense mutations, whereas those of Asian nonsecretors are incompletely inactivated by missense mutations. Thus, Asian nonsecretors are incomplete nonsecretors and produce a small amount of ABH HBGAs in their secretions.

The FUT2 gene is contained in a single 999-bp exon; several inactivating mutations responsible for the non-secretor phenotype (Se-) have been identified, including the nonsense G428A SNP that represents >95% of the inactivating mutations found in populations of European and African descent. Human HBGAs may serve as receptors for

numerous pathogens, including *Campylobacter jejuni*, *Helicobcter pylori* and Norovirus that bind to Se+ cells and *Escherichia coli* and *Staphylococcus aureus* that bind to Se- cells.

Noroviruses co-opt human HGBAs as their host receptors. This recognition is strain specific and different receptor-binding patterns have been identified. Norovirus GI-1 (Norwalk virus) binds preferably to O Se+ cells, while G-II-3 and GII-4, the worldwide predominant epidemic strains, binds preferably to A Se+ cells [2○], Se- individuals are genetically immune to those individual Norovirus infection [3]. However, some Norovirus strains in the genogroup II, are capable to bind to Se- cells regardless of their ABO type [4○].

E. coli heat-labile (hLT) and cholera (CT) toxins are also able to use the HBGAs as receptors. hLT binds to both A and B antigens. Analysis of blood group antigen binding sites showed that the GalNAcα3 residue, which defines the blood group A activity, engages in hydrogen bonds mainly with the hLT hydroxyl group on the 3-position and the nitrogen atom of the acetamido group. The terminal sugar residue of the B-antigen, differs from the A-antigen only at the 2-position where the acetamido group is replaced by a hydroxyl group. This hydroxyl preserves the hydrogen bonds provided by the acetamido nitrogen, which explains why the toxin does not discriminate notably between the A and B epitopes. Since the H antigen (O group) lacks this terminal sugar residue, the toxin is unable to bind the unmodified H antigen (O group) at all [5]. The toxins hLT and CT demonstrate distinct differences in affinity for the HBG, and interestingly among *V. cholerae*, there are also biotype and serogroup specific differences; *V. cholerae* O1 demonstrating the highest affinity

Individuals with blood group O are 50% less likely to become infected with *V. cholerae* than non-blood group O individuals, however, when infected, have twice the odds of developing symptomatic and severe infection [6○]. Notably, individuals with blood group O are preferably protected from infection with *V. cholerae* O1 rather than *V. cholerae* O139 [7].

2. Recognition of enteric pathogens by innate immunity

The innate immune system depends on the accurate recognition of pathogenic organisms via specific receptors. There are four well recognized innate immune receptors in humans; the Toll-like receptors (TLRs), nucleotide-binding and oligomerization domain like receptors (NLRs), retinoic acid-inducible gene-like receptors (RLRs), and C-type lectin receptors (CLRs) that can recognize specific components of pathogenic organisms (Table 1) and act as molecular switches to trigger the immune activation [8○○].

TLRs are localized at the plasma membrane and are type I transmembrane proteins characterized by an external domain that contains varying numbers of leucine-rich-repeat (LRR) motifs and a cytoplasmatic signaling domain homologous to that of the interleukin 1 receptor (IL-1R), named the Toll/I-1R homology domain (TIR). TLR4 acts as the pattern recognition receptor to enteric bacteria lipopolysaccharide (LPS) and appears to be under expressed by intestinal epithelial cells. There are several identified gene mutations that affect the TLR4 function; including the missense mutations at nucleotides +896 and +1196 that affect the extracellular domain (Asp299Gly and T399I) and show phenotypic differences in LPS responsiveness in humans [9].

There is data suggesting that mutations in the TLR4 play a significant role in murine model of necrotizing enterocolitis [10]; however, these finding have not been translated in humans with enterocolitis [11].

3. Innate immune activation genes associated with increased susceptibility to enteric infections

The nucleotide binding oligomerization domain-2 (NOD2) modulates the signaling induced by TLR4. Polymorphisms in TLR4 and NOD2 have been associated with Crohn's disease, a cause of inflammatory bowel disease for which an infectious cause has long been hypothesized [12].

The function of some TLRs, especially TLR4, may also depend on other associated cell surface co-receptors, such as the cluster of differentiation 14 (CD14) and lymphocyte antigen 96 (LY96, also known as MD-2).

CD14 is protein exists as two distinct forms: a glycosylphosphatidylinositol-anchored membrane molecule (mCD14) expressed mainly on the surface of monocytes/macrophages and neutrophils, and a soluble form (sCD14), which lacks the glycosylphosphatidylinositol anchor. sCD14 can also transfer LPS to plasma lipoproteins, and in excess levels can limit the amount of free LPS able to bind to the cells, substantially reducing the subsequent cytokine response. Genetic variations in the CD14 promoter gene affect the CD14 transcriptional activity and circulating sCD14 levels. There is clinical evidence demonstrate that, adults from developed countries possessing the CC genotype at the -4191 position of the CD14 promoter gene, associated with lower sCD14 expression, have a 36% higher risk of developing infectious diarrhea when traveling to a developing country. This observation is more significant for individuals developing diarrhea due to invasive organisms [13○].

Following the TLR ectodomain detection of a microbe-associated molecule, the cytoplasmic domain propagates the signal using four adapter proteins. The myeloid differentiation factor 88 (MyD88), the TIR domain-containing adapter (TIRAP, also known as MAL), the TIR domain-containing adapter inducing interferon (TRIF) and the TRIF-related adaptor molecule (TRAM) activate the phosphorilation of the inhibitor of nuclear factor-κB (NF-κB), which frees the transcription factor NF-κB to enter the nucleus. NF-κB promotes de transcription of many inflammatory response genes, including interleukins and tumoral necrosis factor (TNF).

4. Innate immune response, cellular injury modulation

The activated epithelial cells can synthesize and release interleukin-8 (IL-8) when exposed to enteropathogens. IL-8 stimulates the recruitment and transmigration of neutrophils into the intestinal lumen. The production of IL-8 in the intestine is genetically determined by at least one functional polymorphism. Individuals homozygous for the AA genotype at the -251 position of the IL-8 gene promoter produce significantly greater concentrations of IL-8 when stimulated and are at an increased risk of diarrhea due to EAEC [14] and *C. difficile* [15] associated disease (CDAD). Symptomatic CDAD subjects have a 3.3 increase in odds of having the -251 AA SNP when compared with matched controls. Moreover, individuals possessing the -251 AA SNP have a 6-times higher odds of failing to elicit an anti-toxin A IgG antibody response by an still unknown explanation, which in turn, may also influence their increased susceptibility [16].

Neutrophils that migrate to the apical side of epithelial cells release 5′-AMP, which is converted to adenosine in the lumen. The stimulation of A2b receptors by adenosine results in cAMP-dependent Cl- secretion through the cystic fibrosis transmembrane receptor (CFTR). A CFTR null allele (S489X) in mice was found to confer resistance to CT; however, this particular mutation is very rare in humans. In vitro experiments suggest that *Salmonella typhi* uses CFTR to attach to the intestinal mucosal cells. Of interest, there is a low frequency for CFTR gene mutations in populations of the world where *Salmonella* is endemic. A study conducted in Indonesia found that the 181 or 183 base pair alleles in the

highly polymorphic microsatellite IVS8CA, in the intronic region of the CFTR gene have a protective effect against the development of typhoid feve. Individuals suffering from typhoid fever are two times less likely to carry these alleles compared to matched controls [17].

TNF is produced and released by macrophages and epithelial cells in response to several bacterial products, including lipopolysaccharide, and interleukin-1 (IL-1). The TNF receptors are up regulated during bacterial infection. The binding of TNF causes a conformational change in the receptor, leading to the dissociation on the inhibitory protein silencer of death domains (SODD) from the intracellular domain. This dissociation enables the adaptor protein to bind the death domain and three pathways can be initiated; a) activation of the NF-κB pathway, b)activation of cell differentiation and proliferation by the mitogen-activated protein kinases (MAPK) pathway, or c) induction of death signaling by the caspases pathway. TNF-α has an important role in the intracellular infections. The genomic region surrounding the TNF locus on chromosome 6 has a large number of genes related to immunity and inflammation, including the major histocompatibility complex (MHC). Case control studies evaluation isolated SNPs in the TNF gene and susceptibility to *Salmonella* infection have showed conflicting results [18]. A specific haplotype (*12122*1111) constructed with independent SNPs in the BAT1, LTA and TNF genes have been associated with a decreased LPS-induced cellular TNF-α response. The frequency of this low TNF production associated haplotype is three times lower in typhoid fever patients compared with control matched controls [19].

Microarray studies done on *C. parvum* infected epithelial cells demonstrated upregulation of osteoprotegerin (OPG), a member of the TNF receptor superfamily. OPG functions as a soluble receptor activator of NK-κB ligand (RANKL) and TNF-related apoptosis-inducing ligand (TRAIL). The RANKL/OPG system also up regulates monocyte function, B-cell maturation and development of antibodies. Human intestinal epithelial cells constitutively express and secrete OPG when the NFκ-B signal is activated. OPG may, in turn, blunt the inflammatory effects of RANKL and TRAIL. OPG may function as an anti-inflammatory mediator in the gut that increases in response to intestinal infection. Low production of OPG may lead to more severe clinical manifestations in subjects infected with invasive organisms. A study was done in US travelers to Mexico at risk for TD. In this study individuals possessing the missense mutation at the +1181 position of the OPG gene, which results in a transition from a lysine to asparagines in the CC genotype, have lower levels of OPG in the stool and have a 85% increased risk of diarrhea due to inflammatory pathogens; including *Salmonella*, *Shigella*, Shiga-toxin producing *E. coli*, Enteropathogenic *E. coli*, and Enteroinvasive *E. coli* [20○○].

5. Polymorphism in innate immune proteins associated to increased susceptibility to enteric infections

Lactoferrin is an iron binding protein that is a member of the transferrin family, it is found in human secretions including milk in high concentrations. Lactoferrin is also released by activated polymorphonuclear neutrophils and posseses immunoregulatory and antibacterial properties. In animal models, lactoferrin can prevent E. coli associated endotoxic shock and interferes with the adhesion of pathogenic bacteria to epithelial cells. Lactoferrin inactivates the type III secretory system of Enteropathogenic *Escherichia coli* (EPEC). The synonymous substitution at the nucleotide +632 in the exon 15 of the lactoferrin gene (Leu632Leu) has been associated with higher lactoferrin levels in response to infection. Individuals from developed countries with the high production associated TT SNP have a forty percent higher risk of developing diarrhea when traveling to developing nations after adjusting for other known important risk factors [21]. This synonymous mutation may alter the biological

function of lactoferrin at the mRNA or protein level or be in linkage disequilibrium with another region of the genome yet to be identified.

The long palate, lung and nasal epithelium clone 1 (LPLUNC1) is an innate immunity secretory protein; it has been hypothesized to inhibit growth of gram negative bacteria by binding to the lipopolysaccharide. LPLUNC1 is highly expressed in humans during the active phase of cholera. A family-based study in Bangladesh showed a significant association of a transmitted gene in the promoter region of the LPLUNC1 gene and *V. cholerae* infection; the rs11906665 LPLUNC1 gene was transmitted up to 16 times more frequently to affected offspring. Moreover, a haplotype block containing rs17124508, rs11906665, rs1884884, rs17307318, and rs8115852 was significantly associated with cholera after permutation testing [22○○].

6. Innate immune response, tolerance

It is hypothesized that the tolerance of intestinal commensal pathogens requires of a hyporesponsive mucosa and that interleukin 10 (IL-10) may be necessary to keep this balance. IL-10 is produced by dendritic cells and macrophages, as well as T-helper lymphocytes and down regulates the production of inflammatory mediators. IL-10 favors a TH2 type of response and promotes the production of specific antibody. In IL-10 (-/-) murine models, the absence of IL-10 leads to colitis in response to commensal flora. In humans, gene promoter region polymorphisms in positions -1082, -819 and -592 determine IL-10 production. In a study conducted in US travelers to Mexico, individuals who possess the high IL-10 production associated SNPs demonstrated a fifty percent higher risk of developing diarrhea when naturally exposed to Enterotoxigenic *Escherichia coli* (ETEC) [23○]. This observation seems to be contradicting the findings in murine models of infection. The effect is probably related to the unique immunomodulatory properties of the heat-labile toxin (LT) and may represent an over reacting effect of the toxin on the host immune system since the IL-10 -/- mice have demonstrated variable phenotypes of necrotizing enterocolitis when exposed to different gram negative bacteria.

Acquired Immunity

The cellular immune activation depends on the antigen processing and presentation to the CD4+ T cells via the human leukocyte antigens (HLA), specifically major histocompatibility complex (MHC) class II. Once a T-cell recognizes a peptide within an MHC class II molecule it can stimulate B-cells. Different MHC class II alleles can affect the presentation of specific antigens and alter the resistance to different enteric infections.

A study in two Vietnamese populations reported a genetic association between typhoid fever and genes in the MHC class II. The HLA-DRB1 *0301/6/8 and HLA-DQB1 *0201-3 antigens were found more frequently in individuals with typhoid fever compared with healthy controls, whereas the HLA-DRB1 *04, *1001, and HLA-DQB1 *0401/2 antigens were significantly more frequently found in healthy subjects [24].

A cohort study in Bangladesh found a protective association of the HLA class II allele DQB1 *0601 and the heterozygous haplotype DQB1 *0601 / DRB1 *1501 with *E. histolytica* infection [25]. Another cohort study done in Bangladeshi children found an association between HLA-DQB1 *0301 and asymptomatic infection with *Cryptosporidium* spp. Of notice, the authors also found an association with the HLA class I B*15 allele, suggesting that in addition to traditional helper T cells, other components of the cellular immune response are involved with parasite eradication [26○].

Conclusion

Determining the contribution of human genetics to gastrointestinal infection is of importance. The identification of gene polymorphisms in diarrheal disease susceptibility is resulting in a better understanding of enteric infection pathogenesis in adults and children (Table 2). Genetic testing will detect populations that are at a higher risk of experiencing short term and long-term complications from infectious diarrhea. It could also be of use in determining which populations are more likely to benefit from specific therapeutic interventions or vaccination strategies that result in enhanced protective responses with less reactogenicity.

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○ of special interest

○○ of outstanding interest

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Table 1
Mammalian Toll-like receptors and their specific recognized ligands and adapters

Receptor	Ligand	Adapter
TLR 1	Bacterial triacyl lipopeptides	MyD88 / TIRAP
TLR 2	Bacterial glycolipids Bacterial lipopeptides Bacteriallipoproteins Bacterial lipoteichoic acid Fungal zymosan	MyD88 / TIRAP
TLR 3	Viral doble-stranded RNA Viral polyinosinic-polycytidylic acid	TRIF
TLR 4	Bacterial lipopolysaccharide Heat shock proteins Fibrinogen Heparan sulfate Hyaluronic acid	MyD88 / TIRAP / TRIF / TRAM
TLR 5	Bacterial flagellin	MyD88
TLR 6	Mycoplasma diacyl lipopeptides	MyD88 / TIRAP
TLR 7	Imidazoquinoline Loxoribine Bropirimine Viral single-stranded RNA	MyD88
TLR 8	Viral single-stranded RNA	MyD88
TLR 9	Bacterial CpG DNA	MyD88
TLR 10	Unknown	MyD88
TLR 11	*Toxoplasma gondii* profilin	MyD88
TLR 12	Unknown	Unknown
TLR 13	Unknown	Unknown

TLR (Toll like receptor), MyD88 (myeloid differentiation factor 88), TIRAP (TIR domain-containing adapter), TRIF (TIR domain-containing adapter inducing interferon), TRAM (TRIF-related adaptor molecule), RNA (ribonucleic acid), DNA (deoxyribonucleic acid), CpG (cytosine nucleotide next to guanine nucleotide).

Table 2
Recent specific genetic associations to different enteric infections in humans

Pathogen	Genetic associations
Norovirus	HBGAs,
Clostridium difficile	-251 in the IL-8 promoter gene.
Enterotoxigenic *E. coli*	-1082, -819 and -592 in the IL-10 promoter gene.
Enteroaggregative *E. coli*	-251 in the IL-8 promoter gene.
Vibrio cholerae	HBGAs, rs17124508, rs11906665, rs1884884, rs17307318 and rs8115852 in the LPLUNC1 gene.
Salmonella spp	HBGAs, Microsatellite IVS8CA in the CFTR intronic region, TNF gene polymorphisms, HLA-DRB1 *0301/6/8, *04 and *1001, HLA-DQB1 *0201-3 and *0401/2.
Inflammatory enteropathogens	-4191 in the CD14 promoter gene, +1181 in the OPG gene, +632 lactoferrin exon 15 gene.
Entamoeba histolytica	HLA-DQB1 *0601 and *1501.
Cryptosporidium spp	HLA-DQB1 *0301, HLA-B*15.

HBGAs (Histo-blood group antigens), IL (Interleukin), LPLUNC1 (long palate, lung and nasal epithelium clone 1), CFTR (Cystic fibrosis transmembrane conductance regulator), TNF (Tumor necrosis factor), HLA (Human leukocyte antigen), CD14 (Cluster of differentiation 14), OPG (Osteoprotegerin).