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Genetic Susceptibility to Infectious Diseases

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Abstract: *Infectious diseases are major public health problem globally in terms of mortality andmorbidity. Human genetic variation exerts a major influence on the course of disease caused by many infectious micro-organisms. However, host immunity and susceptibility is affected by many environmental factors such as nutritional status,intercurrent disease, pregnancy, immunosuppressive drugs and malignancy. Advanced DNA technology has mapped human genome and identified genes that are involved and related to resistance and susceptibility to most common microbial infections. Genome-wide association studies have identified various strong association between genetic polymorphisms and susceptibility to infectious disease phenotypes. Thisresulting the development of new branch in medicine and therapy, the personalized medicine. Understanding the human genome individual variations and specific polymorphism enabling potential selective therapy with best response and highest safety margin to ensure better patient care and treatment .Paper discuss the susceptibility and resistance to some of common pathogenic microbial infection related to the genome variation..*

Keywords: *Genetic, Humaninfection, Disease and genetic link, Genetic disease axis.*

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I. Introduction

Genetic play an important role in the sensitivity or resistance to infection. Family linkage approaches have been used to map and identify genes that cause rare monogenic susceptibility phenotypes. For example mutations in the gene for interferon –ɣ IFN-ɣ) receptor chain 1 were found to underline some rare cases of susceptibility to weakly pathogenic mycobacteria[1].Population studies and racial differences in susceptibility have also been noted.[2].Particularly striking is the apparently increased susceptibility to viral infection and tuberculosis(TB) in some previously unexposed populations [3].The use of malaria therapy for syphilis in non-immune individuals and accidental vaccination of some children with *Mycobacterium tuberculosis* rather than Calmette-Gurin bacillus in Lubeck, Germany, provided direct evidence of variable susceptibility to these pathogens [4.Frequently studied pathogenic infections include malaria,tuberculosis,HIV,chronic hepatitis,ABO blood groups, erythrocyte G6PD deficiency and others [5]. .Commonly usage of gene technology include genome sequence from individuals of different origins, understanding of pathways used in host resistance to infection, and the identification of molecules and pathways a targets for pharmacological intervention [6,7,8,]

II. Genetic And Host Relationship

There are various types of evidence that demonstrate a significant role for host genetics in variable susceptibility to infectious disease. For some infections, such as leprosy, disease has long been known to cluster in families [9], but it is often difficult to assess the relative importance to an index case and shared genes. Nonetheless, the increased risk of disease in a sibling compared with the general population is a useful measure of extent of the genetic component in a multifactorial disease [10],and appeared to be of the order of 1,5 to 5 for several infectious diseases [11].Apparent interpolation and racial differences in susceptibility have been noted [2].Particularly striking is the apparently increased susceptibility to viral infections and tuberculosis(TB) in previously unexposed populations [3In the ‘Qu’ Appelle Indians of Saskatchewan,after some decades of exposure to TB,the incidence of disease dropped 50-fold [12].The use of malaria therapy for syphilis in non-immune individuals and the incidental vaccination of some children with *Mycobacterium tuberculosis* rather than Calmette-Gurein bacillus in Lubeck,Germany provided direct evidence of variable susceptibility to these pathogens [4].

In addition to these observational data, studies of the adoptees and of twins have provided more direct quantification of the importance of host genetics in susceptibility to infectious diseases. In a study of more than 900 Scandinavian adoptees, the early death of a biologic, but not an adoptive, parents form an infectious disease was associated with an almost six fold increase in the risk of an infectious cause of death in the adoptee, consistent with a substantial role for host genetics [13].The diseases studied include TB, poliomyelitis ,leprosy, persistent hepatitis B virus (HBV) infection, *Helicobacter pylori* infection and malaria [5].In general ,it has been

easier to demonstrate a significant role for host genetic factors in infections in which only a proportion of those infected develop disease, in chronic rather than in acute infections, and in the severity of infectious disease rather than susceptibility to infection per se.

III. Genetic Disease Connection

Frequently used strategy in human studies has been the assessment of candidate genes in case control studies. Here, the frequencies of variants of a gene with a possible role in resistance (resistance to infection) are compared in individuals with and without the disease. Large sample size isnecessary, particularly for rare alleles or multiallelic genes, but such candidate genes have come from a variety of sources. A particular geographic distribution of certain hemoglobin variants suggested that they might play a role in malaria resistance. A few genes were identified as affecting susceptibility to infection in different strains of mice, leading to assessment of their human homologues. Other candidate genes were suggested by studies of the susceptibility of gene knockout mice to infectious pathogens. Expression analyses of various issues using microarrays and genome-wide screens are now providing a new source of candidate genes. Finally, variants of genes known to play role in immune or innate resistance to infection, such as human leukocyte antigen (HIA) and mannose biding lectin(MBL),have been evaluated on the basis of their known functions.

A different approach has been to search for genetic linkage to, rather than association with,an infectious disease in family studies. Identification of a chromosomal region genetically linked to susceptibility indicates that there is a susceptibility gene(or genes)somewhere in that region [10].A similar approach in mice led to the mapping of numerous susceptibility genes, and a few of these, such as the macrophage gene,Nrap1,have been identified [14].The human homologue in this case.NRAMPI (now called SLC11A1,for solute carrier family 11,member 1),was found to affect susceptibility to TB in some population [15],but human homologue of other marine susceptibility genes, such as the Mx influenza resistance gene [16], are not known to display any functional variation in humans. Morerecently, the availability of millions of SNPs mapped onto the human genome sequence has allowed the development of microarrays of typically 0.5 to 1 million SNPs that allows maskers across the entire human genome to be studied for possible disease association in a singleexperiment. Thisapproach, known as genome wide association analysis, uses tagging SNPs to identify markers that may be casually associated with susceptibility. Although this ability is still incomplete,SNP arrays are being improved by use of data from extensive analysis of patterns of association of neighboring SNPs,so-called haplotypes, in various human populations. The use of genome-wide association studies in many diseases, has successfully identified new susceptibility genes, and this approach id being actively extended to infectious diseases [8,17].

Family linkage approaches have been used to map and identify genes that cause monogenic susceptibility phenotypes. Forexample, mutations in the gene for the interferon- ɣ(IFN-ɣ) receptor chain 1 were found to underlie some rare cases of susceptibility to weakly pathogenic mycobacteria [1].Extensive sequencing of candidate susceptibility has been used to identify the molecular basis of a large number of rare monogenic syndromes that increase susceptibility to particular infections. These rare syndromes include variants of the UNC93B1 gene conferring susceptibility to herpes simplex encephalitis, mutationsin the IFN-ɣ and interleukin-12(IL-12) receptors conferring susceptibility to mycobacteria and salmonella,and mutations affecting interleukin-1 receptor-associated kinase-4 (IRK-4) increasing susceptibility to pyogenic bacteria. Todate, these are rare mutations have been of limited value in identifying common gene variants that affect susceptibility to pyogenic infectious diseases. Mutations in genes producing more generalized immunodeficiency are also found at non-polymorphic frequencies (i.e,an allele frequency of 1%).[18].

IV. Genetic Disease Axis In Common Diseasesg

The common diseases extensively studied include tuberculosis,poliomyelitis,leprosy,chronic hepatitis B virus(HBV),*Helicobacter pylori* infection and malaria [5].

4(1).Tuberculosis and TB related diseases: The genetic susceptibility studies of mycobacterial diseases have been relatively common for several reasons. Familial clustering of leprosy and TB has long been recognized and leprosy was regarded by some as a genetic disorder before *Mycobacterium leprae* was identified [9].An accident in Lubeck,Germany,in which children were immunized with *M.tuberculossi* rather than Calmette-Gurin bacillus,provided early evidence for variable susceptibility to TB.This was substantiated by many large twin studies that found higher concordance rates among monozygotic compared with dizygotic twin pairs [5].although a re-analysis of the most recent of these studies found less clear evidence of a genetic effects [15].A large twin study of leprosy in India also reported higher concordance rates in monozygotic twins but was inconclusive on the question of genetic susceptibility to leprosy type [19].Observations on the introduction of TB to some populations previously free of the infection suggested that decline in frequency of the disease over time in part reflect some natural selection for resistance genes [12].

In contrast to malaria, there is evidence that blacks are more susceptible to infection with *Tuberculosis* than whites. The clearest data were obtained in comparison of rates of skin test conversion among socioeconomically matched nursing home residents in the United States [19].Studies of large pedigree with multiple cases of leprosy or TB using complex segregation analysis techniques suggested that just one or two major genes might account for much of the genetic component of susceptibility to these diseases [20].Analysis of *M.tuberculosis* genome revealed remarkable sequence conservation among isolates, with a lack of single – nucleotide changes, suggesting that host genetic polymorphism might be relatively more important [21].Finally the chronicity of these diseases and existence of control program in many countries have facilitated to recruitment of families as well as unrelated cases.

Several genes have now been associated with susceptibility to particular mycobacterialdiseases. Early studies of HLA variation established its relevance in susceptibility to TB and leprosy, at least in Asian Populations [22].HLA-DR2 was associated with susceptibility to tuberculosis leprosy in India and more recent data support an association of this HLA type with susceptibility to tuberculosis and lepromatous forms of leprosy,as well as TB,in several Asian populations[23].Outside of Asia, no clear HLA association has been identified, and HLA-DR2 appears not to be associated with susceptibility. Variation in the promoter of tumor necrosis factor gene (TNF) has been associated with susceptibility to lepromatous but not tuberculoid leprosy in Bengal, India, and with altered susceptibility to leprosy per se in Brazil [24].

The natural resistance-associated macrophage protein-1 gene(SLC11A1) was suggested as a candidate gene for human mycobacterial disease by identification of its homologue as a susceptibility gene for some intracellular pathogens in mice [14].Variations in both the 3'-untranslated region and the promoter region of SLC11A1 have been associated with susceptibility to pulmonary TB in West Africa [15], and several other populations, but not in all of those studied [25].However, the magnitude of the effect observed in human TB is relatively modest compared with that suggested by studies of susceptibility to Calmette-Guerin bacillus in mice.There is increasing evidence that a variety of other candidate genes, such as the vitamin D receptor [26],the signaling adopter protein Mal/TIRAR [27],the c-type protein CD209[28],and the chemokine macrophage chemoattractrant protein-1 (MCP-1/CCL2] [29].may associate with TB various populations, but these require confirmation. Genes with larger effects have been sought by genome-wide linkage studies of multicase TB families without clear identification of any major loci [30].Similar family studies in leprosy found evidence of linkage to the co-regulated genes PARK2 and PACRG on chromosome 6 and to a region encoding the mannose receptor gene on chromosome 10 [31].Leprosy association studies in particular populations have implicated functions variation in the Toll-like receptor-1 gene (TLR!) and the gene encoding the cytokine lymphotoxin-cx (LTA),[32].

Rare genetic disorders have frequently been informative indicators of disease mechanisms, and this also applies to mycobacterial disease. Children who are homozygous for mutations in the IFN- ɣ receptor gene have been found to be remarkably susceptible to weeakly pathogenic mycobacteria, including the Calmette-Gurin bacillus vaccine, and have a poor prognosis [1].These children appear to have a limited increase in susceptibility to TB and marked susceptibility to Salmonellosis.Similarly rare gene "knockout "mutations in 11-12 and IL-12 receptor gene produce the phenotype of marked susceptibility to atypical mycobacterial disease and salmonella, directly implicating this cytokine and pathway in resistance to these pathogens [33].An intrinsic variant of IFN-ɣ gene that appears to affect binding of the transcription factor nuclear factor kB(INF-kB),as well as other variants of this cytokine gene and the IFN-ɣ receptor, may also affect risk of TB [34].

4(2).Chronic hepatitis B virus infection: Hepatitis B virus(HBV) was discovered during population genetic studies, and evidence that carriage of hepatitis B surface antigen tended to run in families was soon reported [35].Some population and family studies suggested the presence of a major autosomal recessive gene. The ability or inability to clear HBV is one of the most striking immunogenic dichotomies in medicine, with 1% to 12% of infected individuals becoming chronic carriers. One relatively twin study in Taiwan provided evidence that susceptibility to HBV chronic carriage, but not to HBV infection itself, isgenetically determined [36].There have been many studies of HLA class I and Class I genes in HBV of Qatari patients found HLA-DR2 to be associated with viral clearance and HDR7 with viral persistence [37].A larger study of persistently infected Gambians found a protective association with the *HLA-DRBI*1302* allele as well as a protective effect of heterozygosity in the class II regions [38].The same HLA-DR13 allele may be associated with protection in Europeans [39].HLA class II antigens have also been associated with the outcome of hepatitis C virus(HVC) infection. In contrast to HBV infection, most individuals fail toclear HCV.HLA DRB!*1101 and linked HLA-DOB!*0301 allele have been associated with higher rates of clearance in Europeans [40].

In single studies, some non HLA genes,TNH,MBL [41,42].,and the vitamin D receptor have been associated with susceptibility to HBV persistence and haptoglobin genotype may influence clearance of HCV infection [43],.Other genes, such as IL10 [44],may influence antiviral treatment in HBV and HVC infection and definition of these genetic factors could in future help identify those most likely to respond to expensive demanding therapies. The high prevalence of HBV in some populations has encountered attempts to identify

major non MNC genes using family linkage studies. In West Africans from the Gambia, linkage was identify on chromosome 21, and amino acid changes in genes encoding components of IFN-α and IFB-ɣreceptors associated with susceptibility [45].There is increasing interest in susceptibility genes for various manifestations of HCV infection and disease, and several loci have been implicated. There is strong evidence regarding HLA class II association especially for association of the DQBI *0301 allele with self-limiting disease and there is some support for other susceptibility loci,such as CCR5,various cytokines, interferon response genes, and the coagulation factor V Leiden (review by Yee and associates),[46].

4(3).HIV infection: Studies of cohorts exposed to human immunodeficiency virus(HIV) infection have identified a small proportion of individuals who,despite repeated exposure from infected sexual partners, remain HIV sero-negative [47].Some of these resistant sex workers have immunologic evidence of exposure to the virus. There also is clear evidence that individuals vary in the rate of disease progression to acquired immunodeficiency syndrome (AIDS) once infected and several genes have now been found to influence the rate. A large number of studies of HLA type in relation to rate of disease progression have been reported. Although there are marked differences among studies, some alleles have now been associated with susceptibility or resistance in more than one population. LA class I variations is consistently more important than diversity in HLA class II genes, and HLA-B is the most important class I focus [48].HLA-B35 and the HLA-AI-B8-DR3 haplotype have been associated with more rapid disease progression in several studies [49].Similarly,HLA-B27 and HLA-B57 are associated with lower rate of progression [50].Particular combinations of HLA class I,and class II alleles and variants of the transporter associated with antigen processing (TAP) genes have also been implicate [51].Evidence of linkage of the major histo compatibility complex (MHC) to the rate of decline of CD4-positive T cells in patients with AIDS provides support for the relevance of polymorphism in this region [52].

It is possible to cluster HLA class I types into so-called super types based on the types of peptides based on the type of peptides bound by particular molecules analysis of super types also shows convincing association with rate of disease progression [53].The HLA type of host appears to influences the pattern of diversity of HIV sequences that emerges during infection indicating that HLA variation can directly influence virus evolution [54].A genome-wide association study found evidence that loci other than HLA genes in the histocompatibility complex may affect the rate of disease progression [55].Also genes encoding the killer cell immunoglobulin like receptors {KIR),which modulate natural killer cell activity and interact physically with HLA class I molecules, may also interact genetically or spastically so that KIR gene variants modulate the risk association with an HLA type [56].

The discovery of the role of cytokine receptors (CCRs) as co-receptors with CD4, for viral enter into macrophages and lymphocytes has given rise to numerous studies of genetic variants of these receptors and their ligands. The CCR5 gene associations with resistance to infection and slower disease progression and now well established, [57]and variants in the CCR2 gene have also been associated with altered disease progression [58].More limited data support a role for other such as regulated on activation, normal T expressed and secreted (RANTES) [59], the sector polymorphism [60], and MCP1 [61].insusceptibility to infection or disease progression. Copy number variation in the region pf the CCL3 (MIP α) gene, leading to variable numbers of copies of CCL3L1 gene, has also been found to associate with HIV disease progression [62] perhaps providing a further example, in addition to α– globin copy number variants, of the impact structural variation in genome on infectious disease risk. However, ,most of the available information in genetic susceptibility comes from studies of susceptibility to code B virus in North Americans or Europeans, andlittle is known about genes determining susceptibility in high prevalence African and Asianpopulations, where other clade types prevalent.

V. Miscellaneous Diseases And Genetic Linkage

Limited studies of the FcɣRII immunoglobulin receptor,CD32(GCGR2A),have been undertaken in recurrent bacterial respiratory infection and in systematic meningococcal infection[63,].The results suggest that allele encoding histamine at amino acid position 132, which are associated with greater opsonic activity, may be less frequent in disease group.Studies of pneumococcal invasive disease revealed an almost threefold frequency of individuals homozaygous for codon changes inMBL[64].A study of children with a variety of infections also found increased frequencies of MBL-deficiency allele [65].

The study on *Schistosoma mansoni* worm burden and family linkage in Brazil found the evidence of linkage to a region of the long arm chromosome 5 [66].This region may also be relevant in senegalese families and encodes genes for numerouscytokines, including IL-4,IL-9,andIl-13.The same region has been genetically linked to various manifestations of atopy and asthma, consistent with speculation that a gene selected for resistance to helminthic infection might predispose for asthma with mucocutaneous leishmaniasis [67].

The researchers on cystic fibrosis {CF) advocate that CF transmembrane regulator(CFTR), mutations of which produce cystic fibrosis, is the receptor for *Salmonella typhi*,raising the possibility that heterozygotes for this disease may be resistant to typhoid [68], although studies in humans are lacking. Little is known of the

genetic basis of variable to various fungal infections, but polymorphism in the MBL.gene and the blood group secretor may be relevant.Studies of new variant Creutzfield Jakob disease (CJD) attributed to bovine spongiform encephalopathyagent[69].,sporadic CJD [70],iatrogenic CJD [71],and kuru [72],have all shown strong association with variation in the human prion protein (PRNP) gene the main tenance of this genetic variant over long periods of human evolution has been interpreted as evidence for wide spread cannibalism in some human populations.

VI. Conclusion

The association of pathogen and host genetic variations plays and essential role in determining the susceptibility and resistance to a particular microbe and the course of infection. Understanding human genome individual variations and specific polymorphism making easy potential selected medication against different infections(personalized medicine).

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