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Cytokine Polymorphisms and Relationship to Disease

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SUMMARY

Cytokines are polypeptide mediators produced by a variety of cell types that play crucial roles in immune and inflammatory responses. Genes that code for cytokines are highly polymorphic, and some of these polymorphisms directly or indirectly influence cytokine expression. The most frequent types of mutations are characterized by a change in a single nucleotide base pair and are called single nucleotide polymorphisms (SNPs). Many SNPs that affect cytokine expression represent disease modifiers and influence the severity or progression of immune-mediated and chronic inflammatory diseases. SNPs in cytokine genes have been associated with common diseases, including cardiovascular diseases, cancer, neurodegenerative diseases, allergy, and asthma, and data are now accumulating on their role in occupational/environmental diseases. All these diseases are multigenic and multifactorial in nature and involve interactions between genetic, physiological, and environmental factors. Currently, there exist inconsistencies in association studies examining relationships between cytokine SNPs and disease because of known limitations in population-based studies. Recent advances in genotyping platforms for large-scale genetic studies, more robust study designs, and haplotype analysis should help reduce the amount of spurious and inconsistent associations in the literature and allow for incorporating genetic information into the risk assessment process although challenges still remain.

Key Words: Cytokine; polymorphism; SNP; common diseases; autoimmune diseases; occupational diseases; epidemiology.

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1. INTRODUCTION

Although many rare genetic variants exist in the human genome, most of the heterozygosity can be attributed to common alleles. The rare mutations usually are the cause of rare monogenetic diseases, such as Huntington's disease. These diseases are of recent origin and highly penetrant. In contrast, the common allelic variants are present in high frequencies (>1%) in the general population. Among these, the most represented type of mutations is single nucleotide substitutions, referred to as single nucleotide polymorphisms (SNPs). Other polymorphisms, such as repeat sequences or insertion/deletions, are found less frequently in the genome. The widespread availability of human DNA sequence data has suggested that literally millions of SNPs exist but that the vast majority do not alter gene structure or function and therefore are unlikely to be associated with phenotypic changes *(1)*. Those that do affect phenotype can be referred to as "functional" polymorphisms or variants. Many of these functional variants are believed to contribute to the risk of common diseases that are polygenic in nature, and this has led to the common disease–common variant hypothesis. Several examples of important associations between common variants and common diseases include APOE*E4 and Alzheimer's disease *(2)*, CCR5Δ32 and resistance to HIV infection *(3)*, and α1-antitrypsin deficiency and chronic obstructive pulmonary disease *(4,5)*.

The potential applications for SNP studies include gene discovery and mapping, association-based candidate polymorphism testing, pharmacogenetics, diagnostics and risk profiling, homogeneity testing, and the prediction of response to environmental stimuli *(6)*. In toxicology, the focus of SNP studies has been in their role in chemical detoxification/drug metabolism, including pharmacogenetics and, to a lesser extent, receptor binding or expression of biological mediators *(7,8)*. Efforts to incorporate SNP studies into environmental epidemiology investigations have been undertaken sparingly and, when examined, have focused primarily on examining hypothesis-driven associations between environmental/occupational diseases and specific polymorphisms such as silicosis and tumor necrosis factor (TNF)-α-238, -308 *(9)*, chronic beryllium disease and HLA-DPB1 Glu69 *(10)*, and pesticide-related cancers and CYP1A1 mutations *(11)*. Although most of the major diseases of interest are polygenic, there have been limited efforts to examine the effect of multiple polymorphisms on disease modification (i.e., gene–gene–environmental interactions; Fig. 1). Furthermore, there has been little effort in incorporating genetic information into the risk-assessment process, although the advantage of such data in improving accuracy has been discussed *(12,13)*. Foremost among these would be an opportunity to pro-

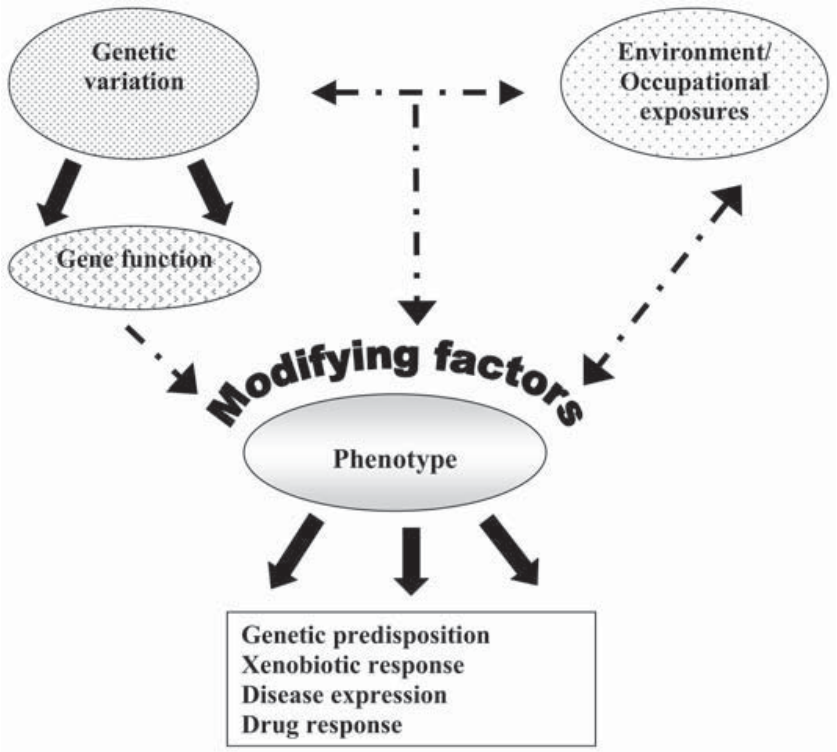

Fig. 1. A model showing genetic variants–environment interactions.

vide more accurate quantitative information on the interindividual variability likely to occur in the population.

Cytokines are not only important mediators of the immune response, but also of inflammatory responses and, thus, play a central role in the pathogenesis of chronic inflammatory diseases. The genes that control cytokine expression are highly polymorphic, and their role as modifiers of common diseases is receiving considerable attention. In this respect, epidemiological studies have identified associations between specific cytokine polymorphisms and cardiovascular diseases, cancer, neurodegenerative diseases, periodontal disease, and immune-mediated diseases such as allergic asthma and autoimmunity. Although the majority of studies published so far have focused on polymorphisms in the interleukin (IL)-1 and TNF-α gene families, most cytokines and chemokines have been examined to some extent. Population studies demonstrate, for the most part, odds ratio (OR) values for any single variant only approx 2. The relatively low ORs are probably the result of the polygenic nature of the disease under study. Accordingly, well-designed and relatively large population studies are necessary to obtain meaningful data. With respect to environmental or occupational diseases, several factors need to be considered. First, if the disease is a result of

a chemical agent, consideration must be given to polymorphisms associated with chemical metabolism in addition to those associated with disease. Second, exposure characteristics (dose, duration, etc.) are of primary consideration and, in some cases, may overwhelm differences associated with the polymorphism. Third, since genetic polymorphisms act primarily as disease modifiers, it would be important to consider disease severity in the analyses.

2. CYTOKINE POLYMORPHISMS AND THEIR ASSOCIATION WITH DISEASE

Genes that code for cytokines have been identified as candidates for many common polygenic diseases. Perturbations of the balance among cytokines, with both diverse and overlapping functions, have been implicated in the clinical course of many common disorders. One of the striking observations that has been recognized since the human genome has been sequenced is that cytokine genotypes often are associated with the course of immune or inflammatory diseases. However, with only a few exceptions, such as the association of TNF-α receptor polymorphisms with periodic fevers and the IL-2-type cytokine-receptor γ-chain family variants with severe combined immunodeficiency diseases *(14–17)*, cytokine or cytokine receptor polymorphisms have not been directly linked to disease causation. Rather, genetic polymorphisms in cytokine genes act as disease modifiers by influencing disease condition, such as severity or response to specific treatment regimens. With this in mind, examples presented here represent cytokine polymorphisms which modify inflammatory, allergic, autoimmune or immunodeficiency diseases with specific attention to those that affect environmental/occupational diseases.

3. COMMON INFLAMMATORY AND AUTOIMMUNE DISEASES

Although sometimes conflicting results have been reported, numerous investigations have suggested that polymorphisms in cytokine genes may predispose individuals to chronic inflammatory or immune-mediated diseases and affect their clinical outcomes (Table 1 *[18–48]*). For example, allergic asthma is representative of complex disorders resulting from the interaction of genetic and environmental factors in which cytokine polymorphisms influence disease susceptibility and severity. Numerous loci and candidate genes, including cytokines, have been reported to be associated with asthma, atopy, increased immunoglobulin E (IgE) levels, and bronchial hyperresponsiveness. For asthma, the studies have focused primarily on chromosomes 5, 6, 12, and 13 *(49)*. Although major histocompatability

Table 1
Examples of Associations Between Cytokine Polymorphisms and Common Complex Diseases

Disease	Cytokine SNPs	References
Asthma	TNF-α -308	*18*
	IL-10 -627	*19*
	IL-13 -1055	*20*
	TGF-β -509	*21*
Allergic and irritant contact dermatitis	TNF-α -308	*22–24*
	IL-16 -295	
Alzheimer's disease	TGF-β -509	*25*
	IL-1-α -889	*26*
	IL-6 -174	*27*
Cancer	IL-1RN VNTR	*28*
	TNF-α -308	*29*
	IL-6 -174	*30*
Coronary artery disease	IL-1RN VNTR	*31*
	IL-6 -174	*32*
	TNF-α -308	*33*
Diabetes	IL-1β +3953	*34*
	IL-6 -174	*35*
	IL-18 -137	*36*
Inflammatory bowel disease	IL-1β -511	*37*,*38*
Periodontitis	IL-1β +3953, -511	*39*
	IL-6 -174	*40*
	IL-10 -819, -592	*41*
Rheumatoid arthritis	IL-6 -174	*42*
	TNF-α -308	*43*
	IL-4 VNTR	*44*
	TGF-β1 codon 10	*45*
Systemic lupus erythematosus	IL-10 -1082, -592, -819	*46*
	TNF-α -308	*47*
Ulcerative colitis	IL-1RN VNTR	*48*

(MHC) variants are strongly associated with asthma, other inflammatory and allergic components also are involved. For example, TNF-α plays a role in the initiation of allergic asthmatic airway inflammation and in the generation of airway hyperreactivity *(50)*. A number of reports indicated an association between the TNF-α-308 variant and asthma *(18,51,52)*. Regulatory cytokines also are determining/modifying factors in immunological responses related to asthma. In this respect, IL-4 -589, -33, IL-13 -1055, IL-10 -627, and transforming growth factor (TGF)-β1-509 polymorphisms are associated with

asthma phenotypes and severity *(19–21,53–58)*. There is also evidence that susceptibility to irritant and allergic contact dermatitis may be influenced by cytokine gene polymorphisms. An association between TNF-α -308 variant and irritant contact dermatitis was reported *(22)*. Recently, associations between IL-16 -295 and TNF-α -308 polymorphisms and allergic contact dermatitis were found *(23,24)*.

Association studies have shown that the IL-1α -889, IL-1β +3953, and IL-1β-511 variants are differentially associated with an increased risk of developing progressive neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), and are associated with the age of disease onset *(26,59–63)*. Other cytokine SNPs, including TNF-α -308, IL-10 -1082, TGF-β1 -509, and IL-6 -174, also have been reported to be additive and independent risk factors for AD *(25,27,64,65)*.

Although contradictory findings have been reported, severe chronic periodontitis appears to be associated with the presence of composite IL-1β +3953 and IL-1α -889 genotypes *(39,66,67)*. Likewise, TNF-α -1031, -863 and -857, IL-2 -330 and IL-10 -1082 SNPs were reported to be disease modifiers in inflammatory periodontal diseases *(68–70)*.

Cytokines that regulate either adaptive or innate immunity influence autoimmune disease processes at multiple levels. In addition to MHC alleles, SNPs within genes that regulate proinflammatory cytokines have been extensively studied. For example, TNF-α -308, -857 and micro-satellite a6 alleles have been associated with rheumatoid arthritis *(43,71)*, systemic lupus erythematosus (SLE *[47]*), and type 2 diabetes *(72,73)*. IL-1 gene family (i.e., IL-1β and IL-receptor agonist [RN] 1) polymorphisms also have been associated with autoimmune diseases *(74–76)*. Increased levels of IL-1β are reported to play a role in the maintenance of autoimmune damage of pancreatic β cells, and the high producer IL-1β +3953 genotype is associated with increased risk of type-1 diabetes *(77)*. IL-1RN VNTR variations have been associated with a variety of autoimmune diseases, including diabetes and SLE *(78–80)*. High levels of IL-6 are observed in several autoimmune diseases, and the IL-6 –174 polymorphism has been implicated in systemic juvenile chronic arthritis, SLE and diabetes *(42,81–83)*. Table 1 provides further examples of associations between cytokine polymorphisms and chronic inflammatory and immune-mediated diseases.

4. OCCUPATIONAL AND ENVIRONMENTAL DISEASES

Occupational or environmental diseases also are multifactorial in nature, being under the influence of polygenic, physiological, and environmental factors. Assessing interactions between genes and exposure variables, such

Table 2
Examples of Associations Between Cytokine Polymorphisms and Occupational/Environmental Diseases

Disease	Cytokine SNPs	References
Alcohol and chemical-induced Hepatitis	TNF-α -308, -238	*84*
	IL-1β +3953, -511	*85*
Chemical-induced neurotoxicity	IL-1α -889	*86*
	TNF-α -308	*87*
Chronic beryllium disease	TNF-α -308	*88*
Chronic obstructive pulmonary disease	TNF-α -308, +489	*89,90*
	TGF-β codon 10	*91*
Coal workers' pneumoconiosis	TNF-α -308	*92*
Farmer's lung disease	TNF-α -308	*93*
Sarcoidosis	TNF-α -308	*94*
Silicosis	IL-1RN +2018	*95*
	TNF-α -238, -308	*9*

as duration and dose, are particularly important for understanding these diseases. Table 2 *(9,84–95)* provides examples of the associations reported between cytokine polymorphisms and various diseases with occupational/environmental origin. Representative examples are discussed herein.

Allergic occupational asthma, which is a result of workplace exposure to high- (flour, grain dust) and low-molecular weight substances (diisocyanates, metals, dyes), requires a latency period for acquiring sensitization and manifests pathologies similar to allergic asthma *(96)*. Isocyanates are common causes of occupational asthma, and HLA class II genes have been found to be involved in the risk of developing disease *(97)*. TNF-α also plays a major role in the immune and inflammatory responses of isocyanate-induced asthma. High levels of TNF-α were observed in the peripheral blood mononuclear cells of subjects exposed to isocyanates *(98)*. However, in contrast to the reports indicating an association between TNF-α -308 SNP and allergic asthma *(52,99)*, no association was found in the case of toluene diisocyanate-induced asthma *(100)*.

Silicosis, an interstitial lung disease resulting from inhalation of crystalline silica, is characterized by chronic inflammation leading to severe pulmonary fibrotic changes that are prevalent among miners, sand blasters and quarry workers. Proinflammatory cytokines, such as TNF-α and IL-1, have been implicated in the formation of these lesions. A strong association was found between disease severity and the TNF-α -238 variant *(9,95)*. Irrespec-

tive of disease severity, the TNF-α (-308) and IL-1RN(+2018) variants conferred an increased risk for the presence of disease. In studies of South African miners, TNF-α promoter polymorphisms (-308, -238, -376) were found to be associated with severe silicosis helping to confirm these associations *(101)*.

Chronic beryllium disease (CBD) is caused by hypersensitivity to beryllium in a variety of industrial processes, including computer, automotive, and ceramics. It has pathological and clinical features similar to sarcoidosis *(102)*. Recent studies investigating the contribution of HLA alleles to disease processes revealed an association between HLA-DPB1 (Glu69) variation and CBD *(103–105)*. The TNF-α -308 allele was also reported to be associated with a high level of beryllium-stimulated TNF-α, and appears to be linked to disease severity *(106)*.

5. IMMUNOMODULATION

Cytokines, like growth factors, play a central role in vascular repair and allograft survival. Cytokines, including interferon (IFN)-γ and TNF-α, are intimately involved in allograft rejection, whereas the Th2 type cytokines, IL-4, -5, and -10 are involved in allograft tolerance *(107)*. Cytokine polymorphisms have been shown to affect the survival of kidney, heart, and lung in transplant patients. TNF-α variants have been studied most extensively, and TNF-α -308 SNP is associated with acute heart, kidney, and liver rejection *(108)*. The IL-10 -1082, -819, and -592 haplotype GCC, which confers increased IL-10 levels, is protective against early acute heart graft rejection *(109)*. The IFN-γ +874 polymorphism and CA repeat in the first intron are associated with acute kidney rejection, the occurrence of kidney infections after transplant, and the development of fibrosis after lung transplantation *(110–112)*. A strong association has also been found between the TGF-β codon 25 variant and tissue rejection. Development of fibrosis after lung transplantation is associated with the TGF-β1 homozygous high producer genotype *(113)*. Cytokine polymorphisms also play a role in vaccination efficacy and are thought to be a factor responsible from inadequate responses. In this respect, the immune responses after hepatitis B vaccination are influenced by the IL-1β +3953 polymorphism *(114)*. UVB-induced immunomodulation also involves cytokines in regulatory capacity, and the IL-1β +3953 polymorphism was found to suppress antibody responses to hepatitis B in individuals exposed to UVB radiation *(115)*.

6. EPIDEMIOLOGICAL AND STATISTICAL ISSUES

The ability to accurately detect associations between genetic variants in cytokine genes and common disease in current scientific practice is faced

with multiple challenges that probably account for a large number of nonreplicable associations in the published literature *(13,116)*. Although several experimental designs are available for assessing potential associations between cytokine SNPs and disease, the case-control association study, because of its relative simplicity, is the most widely used design for detecting common disease alleles with modest risk. Depending upon factors such as the true effect size, the extent of linkage disequilibrium, the frequency of the disease in question, and the frequency of markers associated with the disease, the sample size required to detect true associations often becomes intractable *(117)*. When interactions between genes and the environment, as well as between multiple genes, are included in the research question, the challenges become even greater. There are statistical challenges as well with the problem of multiple testing being foremost. As high-throughput genetic screening of multiple SNPs becomes commonplace, the multiple testing of various SNPs on a single population often requires that *p* values for significance be adjusted so low that only the largest effect sizes are detected. Conversely, failing to adjust the significance level reduces the confidence that significant associations, when found, are actually real and meaningful. Recent reviews have provided excellent discussions of the issues and challenges involved in association studies and provide relevant guidelines for carrying out these types of studies *(118–120)*.

Recently, meta-analysis techniques have been implemented to combine genetic association data from multiple populations in both case–control *(13)* and linkage studies *(121)*. Although this technique has some limitations imposed by the heterogeneous populations examined, publication bias, and sampling biases, it may prove to be a useful analytic technique particularly when sufficient raw data are available for examining cytokine polymorphisms. Other statistical techniques are becoming available for enhancing case–control genetic association studies, including sample pooling *(122)*, genetic control *(123)*, the use of haplotypes *(124)*, and whole-genome association studies *(120)*. An overview of the various testing methods for genetic association studies, including family-based methods is presented by Schulze and McMahon *(125)*. In all situations, it is important that sound epidemiological and statistical principles be incorporated in the design and sampling of individuals from the population to maximize the power of the study and reduce the number of spurious associations.

7. GENOTYPING TECHNIQUES

Traditionally, genotyping technologies used for allelic discrimination included direct sequencing analysis and polymerase chain reaction-restriction

fragment length polymorphism (PCR-RFLP). These techniques are robust and sensitive and represent the mainstay technologies for genotyping cytokine SNPs. However, because of the laborious and low-throughput nature of these technologies, they are only amenable to analyses of small numbers of SNPs in relatively small populations. The completion of the human genome sequencing project has been accompanied by an exponential increase in genotyping demands. A comprehensive review of all genotyping platforms is beyond the scope of this discussion and has been presented elsewhere *(126,127)*. Instead, selected non-gel-based technologies that display potential for increased throughput currently being used in our laboratory will be discussed. Homogeneous solution hybridization using fluorescence resonance energy transfer is one of the most used and validated methodologies and is typified by the Taqman allelic discrimination assay *(128)*. Being homogeneous, all aspects, including amplification, detection, and identification of genotypes, are performed in a single tube. We have recently validated this assay for several important functional cytokine SNPs, and the results showed high concordance with PCR-RFLP and reduced error rates *(129)*.

Allele-specific fluorescent nucleotide incorporation techniques also have to be used to determine genotypes. Single-base extension is the most common technique used and is based on the extension of a primer by a single dideoxy (terminator) nucleotide (ddNTP) with a distinct label, fluorescence being the most common. The primer anneals immediately adjacent to the SNP site, making the incorporated ddNTP specific for one allele. Fluorescence polarization can then be used to determine genotypes *(130,131)*.

Recently, solid-phase detection platforms have been identified that are amenable to high-throughput genotyping. Two such platforms are microarray and matrix-assisted laser desorption ionization (MALDI)-mass spectrometry. Microarray detection involves the fixation of allele specific probes to a solid support and then applying samples amplified by PCR for the arrayed SNPs *(132)*. Several commercial platforms are currently available that can be used to genotype a genome-wide panel of SNPs for a single individual, some having more than 500,00 features. Therefore, this technique is applicable to projects involving genotyping of a limited number of individuals for thousands of SNPs. Recently, a microarray-based approach has been developed that is capable of genotyping very large populations for a small number of SNPs *(133)*. Genotyping using mass spectrometry has the advantage of accurately determining molecular mass. As such, the end products of allele-specific single base extension reactions can be discriminated by mass using MALDI-MS *(134)*.

8. CONCLUSION

In recent years, there has been increased attention on the effects of polymorphisms in cytokine genes and their role as modifiers of common diseases. These alleles have been implicated in influencing the clinical course of common multifactorial diseases, including cardiovascular and neurodegenerative diseases, cancer, asthma, and immune-mediated diseases. Despite some contradictory findings in SNP-disease association studies, the use of high-throughput genotyping technology and statistically robust association study designs will lead to a better understanding of disease mechanisms and identify novel therapeutic strategies as well as provide opportunities to improve the risk assessment process.

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