Cytokine Polymorphisms in Chronic Inflammatory Diseases with Reference to Occupational Diseases

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Abstract: Genes which encode inflammatory cytokines are subject to polymorphisms in their regulatory regions that may effect both the level and ratio of cytokines produced in response to exogenous stimuli. These variant alleles are observed in a large percent of the population and are often associated with increased or decreased susceptibility or severity (modifiers) to infectious, immune or inflammatory diseases. Environmental factors can also play either a direct (i.e., causative factor) or indirect (modifying factor) role in these diseases. Thus, it would follow that gene-environment interactions would effect the expression and/or progression of the disease. In the present review, the concept that some of the common allelic variants found in cytokine genes represent modifying factors in chronic inflammatory diseases associated with occupational exposure is discussed.

Key Words: single nucleotide polymorphisms; cytokine network; chronic inflammatory diseases

INTRODUCTION

Cytokines are polypeptide mediators produced by a variety of cell types that exert their biological functions through specific cell surface receptors that transmit intracellular signals [1]. Although originally thought to be specific in their actions, they demonstrate a large amount of pleiotropism and redundancy. Their multiple, overlapping and sometimes, contradictory functions depend on their local concentration, the type and maturational stage of the responding cell, and the presence of other cytokines and mediators. Cytokines play a major role in inflammatory processes as well as tissue homeostasis. With respect to inflammation, proinflammatory cytokines are classified into those involved in Th1 responses, such as interleukin IL-1, IL-6, IL-12 and TNFα, and those involved in Th2 responses including IL-4, IL-5, IL-10, IL-13 and TGFβ. Several of these cytokines are also involved in down-regulation of inflammatory pathway such as IL-6, IL-10 and the IL-1 receptor antagonist (RA). The complex interactions of cytokines is referred to as the cytokine network, and are only now being defined as it relates to disease processes.

Inflammatory reactions are an essential component of the bodies defense mechanisms that under normal circumstances are tightly regulated and of limited duration. However, when the stimulus is persistent or non-limiting, excessive or chronic production of inflammatory mediators, including cytokines, occurs resulting in disease. This chronic inflammation is characterized temporally by a slower onset and more protracted course than acute inflammation, and morphologically by abundant lymphocyte and monocyte infiltration. Subsequently, fibroblast proliferation, fibrosis and frequent microvascular proliferation may ensue. Chronic inflammation may initiate disease or exacerbate pre-existing ones including asthma, diabetes, atherosclerosis and Alzheimer's disease [2-6]. Specific examples of occupational or environmental diseases where chronic inflammation has been shown to contribute to pathogenesis include chronic obstructive pulmonary diseae (COPD), hypersensitivity pneumonitis, silicosis (black lung), sarcoidosis, chronic berryllium disease (CBD), occupational asthma, alcohol- and chemical-induced hepatitis, allergic and irritant contact dermatitis and chemical-induced neurotoxicity (Table 1) [7-26].

GENETIC POLYMORPHISMS AND DISEASE

Polymorphisms are stable, interindividual allelic variants that, relative to mutations, are present in high frequencies in the population, (i.e., >1%). These common variants usually result from the substitution of a single base pair and, hence, are referred to as single nucleotide polymorphisms, (SNPs). This introduces another element of

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Table 1. Examples of associations between cytokine polymorphisms and occupational diseases.

Disease	Cytokine polymorphism	References
Alcohol and chemical-induced hepatitis	TNFα (-308), (-238); IL-1β (+3953), (-511)	[20,21]
Allergic and irritant contact dermatitis	TNFα (-308)	[26]
Asthma	IL-4 intron 2,IL-4RA, IL-13 (-1111); TGFβ(-509); TNFα (-308)	[9-11,15,16,19]
Chemical-induced neurotoxicity	IL-1α (-889), TNFα (-308)	[22,23]
Chronic beryllium disease (CBD)	TNFα (-308)	[17]
Chronic obstructive pulmonary disease (COPD)	TNFα (-308)	[24]
Coal workers' pneumoconiosis (CWP)	TNFα (-308)	[13]
Farmer's lung disease	TNFα (-308)	[25]
Sarcoidosis	TNFα (-308)	[14]
Silicosis	TNFα (-238); IL-1RA (+2018)	[12,18]

complexity into the cytokine network as numerous SNPs have been identified in regulatory elements of genes which encode for cytokines and affect their rate of synthesis or degradation. Some examples of cytokines and their allelic variants that influence the level of expression and are associated with disease are shown in Table 2. Whether altered cytokine levels contribute to disease pathogenesis or simply are a sequela of the disease is difficult to dissect when examing cytokine levels in the disease state. An approach which attempts to overcome this problem has been to determine if cytokine gene polymorphisms are associated with disease susceptibility. Using molecular epidemiological approaches, a number of cytokine SNPs have been shown to be associated with chronic inflammatory or immune-mediated disease (Table 3). This implies that SNPs contribute to susceptibility or severity of these diseases and lends support to the 'common disease-common variant (CD-CV)' theory [27,28] as initially exemplified by the APOE*E4 allele in Alzheimers' disease. As such, studies on gene associations and disease are a complementary and necessary addition to studies using the whole genome approach to understand the underlying genetics, provide useful prognostic markers and help identify novel therapies for the disorders. Foremost, disease-associated genetic polymorphisms may reveal elements or proteins within a complex network that are critical in determining the risk and severity of disease [29,30].

Table 2. Example of cytokine SNPs found to affect expression levels and modify disease.

Cytokine	Polymorphic locus	References
IL-1α	-889, +4845	[30,95,96]
IL-1β	-511, +3953	[5,87-93]
IL-1RA	VNTR, +2018	[18,76,88,102,103,106]
IL-4	-590, +33	[9,11,109]
IL-6	-174, -572	[125-128]
IL-10	-627, -1082, -819, -592	[75,116-121,140,141]
IL-13	-1055, -1111	[10,111]
TNFα	-308, -238	[4,12-17,61,63,66-76,81,141]
TGFβ1	-509, codon 10, 25	[19,134-136,141]

STUDY METHODOLOGY

Candidate SNPs may be assessed for associations with specific disease states by utilizing a number of epidemiologic study designs including cohort, case-control, case-only and family based designs. The statistical power and sample size required to detect potential associations can vary widely depending upon the particular design which is chosen. Power and sample size issues are particularly relevant when investigation into gene-gene or gene-environment interactions are desired, as these complex associations often require a vastly greater number of subjects to obtain sufficient statistical power. Specific designs are also more or less sensitive to the violation of certain assumptions regarding the data such as linkage (the independent transmission from parent to offspring), and disequilibrium (the independent distribution of specific loci within the population). Several publications detail the calculation of power and sample size for case-control and family designs and expand upon the assumptions underlying each design [31-35].

Both cohort and case-control studies can be utilized to investigate associations between SNPs and disease, between occupational or environmental exposures and disease, and the joint interaction between exposure, genotype and disease. However, cohort studies generally require a larger sample size

Table 3. Examples of associations between cytokine polymorphisms and chronic inflammatory and immune-mediated diseases.

Disease	Cytokine polymorphism	References
Alopecia areata	IL-1RA(VNTR)	[50]
Alzheimer's disease (AD)	IL-6 (-174); TGFβ (-509)	[127,134]
Chronic bronchitis (CB)	TNFα (-308)	[71]
Coronary artery disease (CAD)	IL-1RA(VNTR) ; IL-6 (-174)	[102,128]
Fibrosing alveolitis (FA)	IL-1RA (+2018); TNFα (-308)	[76]
Inflammatory bowel disease (IBD)	IL-1β (-511)	[90,91]
Periodontitis	IL-1β (+3953); IL-1α (-889)	[5,30,92,94]
Psoriasis	TNFα (-238)	[72]
Primary sclerosing cholangitis (PSC)	TNFα (-308)	[75]
Rheumatoid arthritis (RA)	IL-1α (-889); IL-6 (-174)	[95,125]
Systemic lupus erythematosus (SLE)	IL-1RA(VNTR); TNFα (-308)	[51,70]
Ulcerative colitis (UC)	IL-1RA(VNTR)	[104]

to detect interactions than do case-control studies. Case-control studies, when carefully designed and the disease incidence is low, can provide essentially all the information that is obtained with respect to cohort designs with fewer subjects [36].

All of the designs utilized are subject to errors of classification, whether it be classifying exposures, genotypes, or disease states. These misclassification errors bias the study results toward the null hypothesis and, thus, reduce the ability to detect true associations, if they exist [33]. Moreover, the interpretation of such studies is complicated due to genetic heterogeneity among cohorts of different ethnic origin and the naturally redundant and self-compensating interplay between coexisting cytokines [37-42]. Further, specific polymorphisms may display linkage disequilibrium, and the extent and heterogenous nature of this phenomenon across the genome can lead to genotype misclassification and affect the efficiency of association studies [43-45].

The most common human diseases are thought to be multigenic and multifactorial. Thus, in assessing the role of allelic variants in disease susceptibility and progression, the effects of gene-gene as well as gene-environment interactions in disease etiology should be taken into consideration. Information regarding the interaction between genotypes and exposure variables are particularly important for occupational and environmental diseases. For these diseases, the genetic components are not, by themselves, thought to be the cause of the disease. Rather, environmental/occupation agents may interact with genetic and/or epigenetic triggers to initiate the disease process or influence the clinical outcomes.

The concept of interaction is context dependent. Interactions can be viewed in the context of statistical interaction, biological interaction, and even in a public health context [46]. A statistical interaction is precisely defined as a departure from a null model which assumes that the effects of multiple exposures/genotypes on the risk of disease are independent of one another. Thus, given that there are multiple ways which one can statistically model data regarding the risk of disease, the presence of a statistical interaction will always be dependent upon the chosen statistical model. Consequently, there is no statistical method for assessing the presence of interaction that is correct in all situations. Further, a statistical interaction is dependent upon the measure of association used to evaluate risk, therefore interaction does not necessarily have the same meaning in cohort studies as it does in case-control studies [47].

In biological terms, interactions can be defined as the joint operation of multiple factors to produce disease [46]. This is a much broader definition than the specific, model dependent criteria, used for statistical interaction. Gene-environment interactions may be measured by the different effects of an exposure on disease risk among individuals with different genotypes, or by the different effects of a genotype on disease risk among individuals with different exposures [48,49]. The ways in which genetic and environmental factors act as disease modifiers is further illustrated in Figure 1. The importance of disease-modifying genes has been demonstrated in a number of diseases such as alopecia areata, systemic lupus erythematosus, lichen sclerosus, periodontitis, asthma and silicosis, in which polymorphic loci for cytokine genes were associated with the clinical course [5,11,12,50-52].

Based on the simple gene-environment interaction model, the effects of six biologically plausible patterns of interaction on the relative risk of disease have been proposed [48]. In the first type of interaction, increased risk of disease is observed only when both genetic and environmental factors co-participate in the same pathogenetic mechanism. In type 2 interactions, environmental exposure increases risk in individuals without the corresponding genotype. In type 3 interactions, the genotype is associated with increased disease risk, whereas environmental exposure alone is not. The fourth alternative occurs when both the genotype and the environmental exposure influence risk of disease. Type 5 or 6 interactions occur when there is a reversal of the presence or absence of environmental factors. In these latter cases, the genotype is protective in the absence of environmental factors but is deleterious in the presence of the environmental factors.

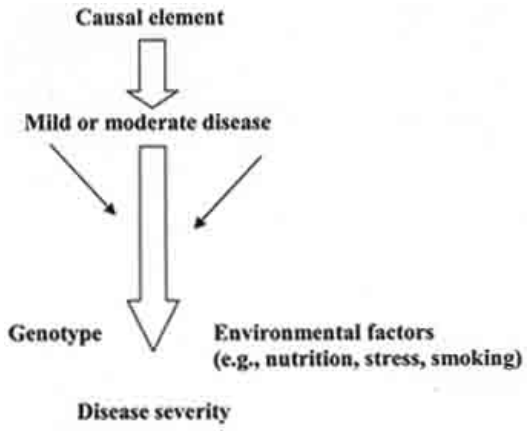

Figure 1. In the gene-environment interaction theory, the causal elements produce disease, but specific allelic variants (genetic) as well as environmental factors modify the clinical expression of disease after it has been initiated. Gene and environmental factors may have positive or negative influence on disease progression and severity.

The effects of gene-environment interactions on disease are further complicated by both the number of genetic loci that are involved, exposure variables (dose, length of exposure), other environmental exposures and the presence of etiologic heterogeneity [48,53]. The issue of confounders is also a major problem in the assessment of gene-environment interactions. Unmeasured genetic determinants and environmental exposures can each act as confounders. Race and ethnic origin are an important source of confounding in studies of gene-environment interaction and may lead to population stratification and spurious associations [54,55]. These all highlight the fact that gene-gene and gene-environment interactions are too complex for an oversimplified classification to be applicable in all diseases.

CYTOKINE POLYMORPHISMS AND THEIR ASSOCIATION WITH DISEASE

Genes which encode for cytokines have clearly been established as candidates for many diseases. As studies regarding associations between allelic variants of candidate genes and disease are sometimes conflicting, it is important to be aware of the potential limitations and interpretations of these studies. For example, it is possible that cytokines may contribute to the pathogenesis of a disease in a genetically controlled fashion but the population may not be of sufficient size or the gene products may act indirectly to influence disease. Also, improper handling of the genetic or statistical data, unclear definition of the clinical categories, elevated heterozygosity or linkage disequilibrium might effect the statistical power of the study. If the allelic variant effects only disease severity, as is the case with silicosis, the ability to detect a significant association would be directly dependent upon the ability to quantify disease severity, which is difficult for many inflammatory diseases. Nonetheless, association studies still have the advantage over linkage studies of a greater sensitivity in multifactorial diseases. With this in mind, examples are presented of established cytokine polymorphisms which have been implicated to modify chronic inflammatory diseases, often associated with environmental and occupational exposures.

TNFα

TNFα is one of the most studied inflammatory proinflammatory cytokines, being implicated in the pathogenesis of a large number of pathological processes. TNFα exhibits approximately 50% amino acid sequence homology with TNFβ. In humans the gene encoding for TNFα is located on chromosome 6 between HLA-B and DR, within the class III region of the major histocompatibility complex (MHC) [56-58]. This region contains a number of polymorphisms including 5 microsatellites and several SNPs. Two polymorphisms have been identified at positions –308 and –238 in the TNFα gene promoter containing A to G substitutions at each site [59,60]. The SNP at position –308 is associated with higher constitutive and inducible levels of TNFα [61,62] while the polymorphism at –238 is associated with an increased rate of TNFα transcription [13,63]. The SNP in intron 2/exon 3 of the TNFβ gene, with two polymorphic alleles, has been variably associated with either high or low levels of TNFβ secretion by mononuclear cells, depending upon the population under investigation [64,65]. TNF variants have been associated with inflammatory, infectious or autoimmune diseases such as malaria, psoriasis, leishmaniasis, celiac disease, systemic lupus erythematosus (SLE), chronic bronchitis, psoriasis, sepsis, chronic sinusitis, fibrosing alveolitis, primary sclerosing cholangitis (PSC) and sarcoidosis, as well as occupationally related diseases such as silicosis,

asthma, coal workers' pneumoconiosis, chronic beryllium disease (CBD) and farmer's lung disease [12,13,15,16,25,66-76]. In the case of silicosis, a strong association occurs between silicosis severity and the TNFα -238 variant, as the frequency of this variant is predictive of severe disease (adjusted odds ratio 4.0). This implies that individuals with the variant are predisposed to more rapid development of severe disease, which would account for the apparently protective effect in individuals with the wild-type allele. Regardless of disease severity, the TNFα (-308) variant showed an increased risk for both moderate and severe disease (adjusted odds ratios of 3.6 and 1.6, respectively) [12]. In a recent study, TNFα promoter polymorphisms (-308, -238, -376) were found to be associated with severe, but not less severe silicosis in black South African miners helping to confirm these associations [77]. In chronic beryllium disease, the TNFα -308 allele was reported to be associated with a high level of beryllium-stimulated TNFα an indicator of disease severity in CBD [17]. The frequency of the TNFα -308 allele is also significantly higher in farmer's lung (asthma to grain dust) patients (0.43) than in controls (0.19) or patients with pigeon breeder's lung (0.16). Increased TNFα production have been implicated in the pathogenesis of alveolitis in farmer's lung [25]. On the other hand, no significant association between the TNFα -308 polymorphism and ancylosing spondylitis, multiple sclerosis, rheumatoid arthritis or chronic obstructive pulmonary disease (COPD) were found [78-83]. Determining whether a TNF variant is involved in a disease process is complicated by the fact that the gene is located in the MHC region, a region central to immune regulation, and a strong linkage disequlibrium exists between alleles across the MHC. It is possible that disease associations are influenced by additional MHC genes which are more distant from the TNFα locus. Therefore, associations between MHC haplotypes and TNFα phenotypes may not be due to the polymophisms within the TNFα gene itself, but rather to variation in a linked gene that directly or indirectly regulates TNFα expression [61,84].

IL-1

IL-1α, IL-1β and IL-1RA are members of the early acting IL-1 family of cytokines, whose action is regulated by the structurally related member, IL-1RA [85]. A number of genetic variations have been described within the IL-1 gene cluster on chromosome 2, which are associated with susceptibility to inflammatory, autoimmune and infectious diseases [86]. The base exchanges at positions +3953 and –511 of the IL-1β gene influence the level of IL-1β protein produced by mononuclear cells [87-89]. IL-1β has been implicated in the pathogenesis of inflammatory bowel disease and periodontal disease [5,90-92]. Previous studies also suggest that composite genotypes of the IL-1β gene are significantly associated with increased risk of inflammatory diseases [92-94]. The frequency of the IL-1β +3953 variant is also increased in patients with insulin-dependent diabetes mellitus in DR3- and DR-4 negative individuals [87]. No association was found between IL-1β polymorphism and susceptibility to COPD or silicosis [18,83].

Two variants in the IL-1α gene, at sites -889 and +4845, are present at an increased frequency in juvenile rheumatoid arthritis, chronic polyarthritis and periodontitis [30,95,96]. The genetic polymorphism at position –889, which is in linkage disequilibrium with +4845 is associated with a 4-fold increase in IL-1α protein levels [30]. On the other hand, no association was reported for Graves'disease, juvenile idiopathic arthritis (JIA) or silicosis [18,97,98].

The third known gene in the IL-1 cluster encodes for IL-1 RA which blocks IL-1 signaling by competing with IL-1 for binding to its receptor. The ratio between IL-1 and IL-1RA is crucial in determining the outcome of inflammatory responses [99,100]. A single base variation is present at position +2018 in the IL-1RA gene [101], which has been implicated in progression of coronary artery disease, fibrosing alveolitis and silicosis [18,76,102]. In silicosis, the IL-1RA(+2018) variant was significantly increased in miners with both moderate and severe silicosis suggesting that this variant effects susceptibility to silicosis rather than severity. An allelic association found between IL-1RA and IL-1α may also represent a susceptibility factor for silicosis as the IL-1/IL-1RA ratio is important in the regulation of inflammatory processes [18]. Within the IL-1RA gene there is also a variable number of tandem repeats (VNTR) consisting of an 86 base pair length of DNA in intron 2 [103]. This VNTR is associated with SLE, lichen sclerosis, alopecia areata, ulcerative colitis, diabetes, psoriasis, and juvenile idiopathic inflammatory myopathies [37,39,50-52,72,104,105]. The repeat region of IL-1RA contains three potential protein-binding sites suggesting that the variable copy number of this repeated region may have functional significance [103]. The IL-1RA variant is associated with increased production of IL-1RA, reduced production of IL-1α, and enhanced production of IL-1β in monocytes [88,106]. There was no association between this variant and Graves' disease, ischemic heart disease or COPD [83,97,107,108].

IL-4 and IL-13

IL-4 and IL-13 are determining factors in immunologic mechanisms related to asthma and autoimmune diseases. It has been shown that polymorphisms in the IL-4 gene sequence are associated with rheumatoid arthritis and asthma [9,11,109]. No association was found for multiple sclerosis or JIA [98,110]. An IL-13 promoter polymorphism at position -1055 was shown to be associated with allergic asthma, altered regulation of IL-13 production, increased binding of nuclear

proteins to the regulatory region of the gene and predisposition to the development of allergic asthma [111]. IL-4 and IL-13 share a common receptor component, IL-4R alpha. A strong association of R576IL-4alpha with the prevalence and clinical severity of asthma has been reported [112]. In a study using asthmatic families, the haplotypes composed of the 5' region polymorphisms in the IL-4 gene (IL-4RP2del, IL-4+33, IL-4-589T) and SNPs in the intergene sequence between IL-4 and IL-13 (IL-4-IL-13SNP3G, IL-4-IL-13SNP4C) can be shown to influence the development of asthma [9].

IL-10

IL-10 is an anti-inflammatory cytokine which inhibits both the synthesis of proinflammatory cytokines and antigen presentation [113,114]. Although a large number of SNPs have been ascribed to the IL-10 gene, only a few possess a functional role [115]. The –627 and –1082 polymorphisms effect IL-10 expression [75,116-118]. The –627 polymorphism is associated with severe asthma and renal disease in SLE patients [119-121]. On the other hand no associations were found between IL-10 promoter polymorphisms and rheumatoid arthritis, multiple sclerosis, PSC, early-onset periodontitis, coronary artery disease, JIA or IBD [40,75,98,109,110,122-124].

IL-6

A bi-allelic polymorphism at position –174 in the regulatory region of the IL-6 gene has been reported to have a negative effect on transcription [125,126]. The –174 polymorphism has been implicated in systemic juvenile chronic arthritis, Alzheimers' and coronary heart disease [125,127,128] and the frequency of this variant was found to be lower in Chinese miners with coal worker's pneumoconiosis than in Caucasian and east Indian populations [129]. On the other hand no association with idiopathic pulmonary fibrosis or JIA were found [98,126,130,131]. Other IL-6 polymorphisms have been identified: Msp I and Bgl I, identify probable base substitutions around the fifth exon and in the 5' flanking region, respectively [132]. Although no disease associations with polymorphisms in the 5' flanking region of the IL-6 variant have been identified, an increase frequency of an Xba I RFLP, likely to be due to 3' flanking region insertions, has been described in some patients with SLE and elevated IL-6 levels [133].

TGFβ

TGFβ is a multifunctional cytokine involved in pro- and anti-inflammatory pathways and is expressed in several cell types. A functional polymorphism at position -509 is reported to be associated with Alzheimers' disease, artherosclerosis and asthma severity [19,134,135] while a SNP at position +915 in the signal sequence, which substitutes codon 25 from arginine to proline, is associated with interindividual variation in TGFβ production [136]. No association was found between variants in the TGFβ gene and multiple sclerosis or periodontitis [137,138].

Interactions

There are several studies showing the association between the composite genotypes or genotype-environment interaction and the clinical course of diseases. The severity of adult periodontitis was reported to be associated with a composite genotype including allele 2 of IL-1β(+3953) and IL-1α(-889) [5,92]. In the case of silicosis, analyses of a relatively large data set indicated that the presence of the IL-1RA(+2018) and TNFα (-308) allelic variants leads to a higher odds of severe silicosis, than the presence of only one or neither of the variants. Also, analysis between each gene-gene interaction and exposure led to several marginal associations. The prevalence of silicosis was increased with increasing exposure, except in the case where both minor variants are present [12]. In the case of early-onset periodontitis (EOP), the IL-1β genotype in combination with smoking, and a combined IL-1β and IL-1RA genotype were found to be risk factors supporting a role for genetic and environmental factors in susceptibility to EOP [94]. In a recent study, a gene-gene interaction between S478P in IL-4RA and the –1111 promoter variation in IL-13 was found to increase an individual's susceptibility to asthma. Individuals with the risk genotype for both genes were at almost five times greater risk for the development of asthma compared to individuals with both non-risk genotypes [10]. In the case of IgA nephropathy, carriage of IL-1β and IL-1RA variants together with non-carriage of a TNFα variant was associated with increased susceptibility [139]. If a composite genotype is associated with disease, it is possible that each polymorphism acts in an additive manner.

SUMMARY

Many environmental and occupational diseases are of a chronic inflammatory nature in which cytokines play a significant role. These diseases are considered multigenic and multifactorial as causation and/or progression are under multiple genetic as well environmental factors. Genes that encode inflammatory cytokines are subject to polymorphisms in their regulatory regions that affect their expression and these common allelic variants may be associated with increased severity or susceptibility to diseases. As such, opportunities currently exist to improve our ability to conduct human risk assessment by utilizing our understanding of the human genome and recently developed techniques to rapidly detect common variants to study gene-

gene and gene-environment interactions. Such studies are complementary and a necessary addition to studies using the whole genome approach to understand the underlying genetics, provide useful prognostic markers and identify novel therapies of chronic inflammatory disorders.

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