Cytokine-Pathway Polymorphisms and Inflammatory Responsiveness (Literature Review)

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ABSTRACT

Background:
Inflammatory responses are required for effective antimicrobial defense but may become disproportionately amplified, contributing to host-tissue strain and damage. Inter-individual variability in inflammatory "set points" and response amplitude has been attributed, in part, to common genetic variation within cytokine and acute-phase pathways, particularly within the *TNF, IL-6/IL-6R, IL-1,* and *CRP* axes (Louis,1998; Fishman,1998; Galicia,2004; Obisesan,2004). Nutritional exposures, especially dietary lipid composition, have also been evaluated as potential modifiers of inflammation-related phenotypes and of genotype–phenotype relationships (Jourdan,2011; Norde,2018).

Methods:
A narrative synthesis was performed using the referenced peer-reviewed literature. Priority was assigned to studies reporting functional effects on cytokine transcription or production, describing associations with systemic inflammatory biomarkers including C-reactive protein, or evaluating clinically relevant inflammation-related phenotypes such as periodontal disease, inflammatory bowel disease, sepsis, autoimmune disorders, metabolic traits, and infection severity. Evidence addressing gene–environment interplay, including analyses of gene–fatty acid interactions, was also incorporated (Louis,1998; Fishman,1998; Montoya-Ruiz,2016; Lee,2012; Jourdan,2011).

Results:
TNF pathway variation (notably *TNFA* −308G/A, rs1800629) was associated with differences in *TNF*-α production capacity and with inflammation-linked phenotypes across gastrointestinal, periodontal, metabolic, and systemic stress-related contexts (Louis,1998; González,2003; Ferreira,2005; Wei,2016; Lakka,2006; Jeanmonod,2004; Sookoian,2005). *IL6* promoter variation (rs1800795) was linked to altered transcriptional activity and circulating IL-6 levels and was investigated across metabolic, thrombo-inflammatory, and autoimmune outcomes (Fishman,1998; Illig,2004; Huth,2006; Malaponte,2013; Lee,2012; Katkam,2017). *IL6R* rs2228145 was strongly associated with soluble IL-6 receptor concentrations and was further evaluated in vascular and infectious-inflammatory contexts (Galicia,2004; Topchieva,2020; Rodrigues,2023). Within

the IL-1 axis, *IL1A* promoter variation (rs1800587) demonstrated functional transcriptional differences and was associated with pain-related phenotypes, whereas *IL1B* variation (rs1143634 and related IL-1 variants) was repeatedly evaluated in periodontal and rheumatologic disease (Dominici,2002; Schistad,2014; Moen,2014; Gore,1998; Yin,2016; Buchs,2001). Baseline CRP differences were associated with CRP genotypes in intervention settings, although environmentally driven changes were not consistently genotype-dependent (Obisesan,2004).

Discussion:
Across the cited evidence base, common cytokine-pathway variants were associated with measurable differences in inflammatory mediators and with selected clinical phenotypes. The cumulative pattern was consistent with probabilistic shifts in inflammatory responsiveness rather than deterministic categorization, given heterogeneity across phenotypes, ancestries, and exposures (Huth,2006; Mwantembe,2001; Nikolopoulos,2008). Dietary lipid exposure was supported as a plausible modifier through reported gene–PUFA and gene–fatty acid interaction findings, although the magnitude and direction of effects remained context-specific (Jourdan,2011; Norde,2018).

Subjects: Genetics, Nutrition **Keywords:** Genetics, Polymorphism, Nutrition, Immune System

INTRODUCTION

Inflammation represents a core biological mechanism through which host tissues are protected against infectious agents, enabling rapid signaling, immune-cell recruitment, and containment of microbial threats. The same processes that facilitate effective defense may, when amplified or sustained, impose physiological costs on host tissues through local edema, endothelial activation, and leukocyte trafficking. Pathway-level variation in inflammatory signaling has been linked to differences in adhesion molecule biology and inflammatory mediator dynamics, supporting a mechanistic basis for heterogeneity in tissue infiltration and inflammatory intensity (Topchieva,2020; Galicia,2004).

A further dimension of inflammatory dysregulation has been conceptualized through immune misdirection, where host structures may be targeted and damaged in auto-inflammatory or autoimmune contexts. Cytokine-pathway polymorphisms have been evaluated within systemic lupus erythematosus and rheumatoid arthritis, conditions in which immune-driven tissue injury constitutes a dominant pathophysiological feature (Lee,2012; Katkam,2017; Buchs,2000). At the tissue level, chronic inflammatory activation has been studied in phenotypes consistent with structural degradation, including periodontal breakdown and peri-implant complications, where cytokine and immune-response markers have been associated with susceptibility and clinical outcomes (Nikolopoulos,2008; Wei,2016; Jacobi-Gresser,2013).

Common genetic variation within cytokine and acute-phase pathways has therefore been investigated as a contributor to inter-individual differences in baseline inflammatory tone and inflammatory responsiveness. Variants within *TNFA*, *IL6*, *IL6R*, *IL1A*, *IL1B*, and *CRP* have been repeatedly examined for functional effects on transcription or cytokine production, associations with biomarkers such as *CRP*, and relationships with inflammation-linked disease phenotypes (Louis,1998; Fishman,1998; Dominici,2002; Obisesan,2004; Lakka,2006). Environmental modulation has also been emphasized, with gene–environment interactions described for psychological stress and for dietary or lifestyle interventions (Jeanmonod,2004; Obisesan,2004). Dietary lipid composition has received particular attention as a modifiable exposure capable of influencing inflammation-related phenotypes and modifying genotype–phenotype relationships (Jourdan,2011; Norde,2018).

Evidence Synthesis

Across the TNF, IL-6/IL-6R, IL-1, and CRP axes, common polymorphisms were evaluated as determinants of inter-individual variability in inflammatory signaling capacity and inflammation-linked phenotypes. For interpretive consistency, genotype strata were described in terms of typically regulated (non-aggressive) versus heightened (“aggressive”) inflammatory responsiveness, with graded categories applied where allele-dose effects were plausible. This stratification was supported by functional evidence demonstrating genotype-dependent effects on cytokine transcription/production or receptor biology, together with association and meta-analytic findings across inflammatory phenotypes, while recognizing that effect magnitude and direction are frequently phenotype-, ancestry-, and exposure-

dependent (Louis,1998; Fishman,1998; Galicia,2004; Dominici,2002; Huth,2006; Mwantembe,2001; Nikolopoulos,2008).

TNF Pathway Variation and Inflammatory Phenotypes

Within the *TNFA* promoter variant rs1800629 (−308G/A), genotype strata were interpreted as reflecting a continuum of inflammatory responsiveness. The GG genotype (≈83%) was categorized as typically regulated (non-aggressive) immune responsiveness, the GA genotype (≈16%) as typically regulated to mildly heightened, and the AA genotype (≈1%) as heightened ("aggressive") immune responsiveness. This interpretation was consistent with experimental evidence linking TNF gene polymorphism to inter-individual differences in TNF-α production under standardized immune stimulation (Louis,1998), and with clinical association data indicating amplified inflammatory activity in selected disease contexts for the −308A allele (González,2003).

Inter-individual variability in TNF-α production has been linked to TNF gene polymorphisms under standardized immune stimulation, supporting a mechanistic route by which promoter-region variation may influence inflammatory responsiveness (Louis,1998). The *TNFA* −308A allele was associated with enhanced TNF-α production and increased inflammatory activity in Crohn's disease with fistulizing phenotype, supporting the inference that regulatory variation can amplify inflammatory output in disease-relevant contexts (González,2003). In a broader Crohn's disease genetic evaluation, association signals were observed for *TNFA*, whereas *IL1B* and *IL1RN* were not associated in that cohort, illustrating locus- and phenotype-specific effects and underscoring non-uniformity across inflammatory pathways (Ferreira,2005).

Systemic inflammatory biomarker correlates were also described for *TNFA* −308G/A. In a family-based cohort, the AA genotype was associated with higher baseline CRP levels, and genotype-dependent differences in CRP response patterns to exercise were reported in selected subgroups (Lakka,2006). Elevated plasma CRP was observed in chronically distressed individuals carrying the A allele, indicating an interaction between inflammatory genotype and psychosocial exposure in shaping systemic biomarker levels (Jeanmonod,2004). Meta-analytic synthesis has linked the *TNFA* −308G/A variant to phenotypes associated with metabolic syndrome, supporting the plausibility of TNF pathway variation contributing to low-grade systemic inflammation and metabolic risk (Sookoian,2005). Additional inflammation-linked metabolic associations were described among asthmatic patients, in whom *TNFA* −308G/A was associated with metabolic syndrome (Yang,2015).

Broader inflammatory disease contexts were represented. Variants in TNF-related genes were associated with clinical course in sepsis, supporting a role for cytokine-pathway variation in systemic inflammatory escalation and outcome heterogeneity (Montoya-Ruiz,2016). In obesity, *TNFA* −308 variants were associated with high-sensitivity CRP concentrations and DNA damage indices, supporting links between inflammatory genotype, systemic inflammation, and cellular stress markers (Wlodarczyk,2020). Cutaneous inflammatory susceptibility was examined through meta-analysis in acne, where *TNFA* 308G>A was suggested to contribute to pathogenesis (Li,2015).

Inflammation-related tissue destruction in the oral cavity was examined. *TNFA* −308G/A was evaluated in aggressive periodontitis through meta-analysis, supporting an

association between cytokine-pathway variation and periodontal susceptibility (Wei,2016). In peri-implant settings, genetic and immunological markers — including cytokine-related measures — were described as predictors of titanium implant failure, aligning inflammatory responsiveness with clinically relevant tissue–biomaterial outcomes (Jacobi-Gresser,2013).

IL-6 Transcriptional Regulation and Downstream Phenotypes

For *IL6* rs1800795 (−174G/C), the GG genotype (≈77%) was categorized as typically regulated (non-aggressive) immune responsiveness, whereas GC (≈19%) and CC (≈4%) were categorized as heightened ("aggressive") inflammatory responsiveness. This qualitative stratification was supported by functional evidence that promoter polymorphisms can influence IL-6 transcription and circulating IL-6 levels (Fishman,1998) and by repeated evaluation of the locus across metabolic and autoimmune phenotypes (Illig,2004; Huth,2006; Lee,2012; Katkam,2017).

Promoter polymorphisms in *IL6* were shown to influence IL-6 transcription and circulating IL-6 levels, establishing a functional basis by which common regulatory variants may modulate inflammatory response capacity (Fishman,1998). *IL6* promoter variants were associated with type 2 diabetes in population-based evaluation, supporting an inflammatory contribution to metabolic phenotypes (Illig,2004). Joint analysis of individual participant data across multiple studies further evaluated *IL6* promoter polymorphisms in type 2 diabetes, highlighting both the scale of investigation and heterogeneity typical of common-variant association patterns (Huth,2006).

Thrombo-inflammatory outcomes were also examined, as the *IL6* −174G>C polymorphism was associated with increased risk of deep vein thrombosis in cancer patients, suggesting intersection between IL-6–mediated inflammatory biology and vascular complications in clinically stressed systems (Malaponte,2013). Autoimmune phenotypes were represented through meta-analyses evaluating *IL6* polymorphisms in systemic lupus erythematosus, supporting a relationship between IL-6 pathway genetic variation and autoimmune susceptibility in aggregated evidence (Lee,2012; Katkam,2017).

IL-6 Receptor Variation and Signaling Intermediates

For *IL6R* rs2228145, the AA genotype (≈52%) was categorized as typically regulated (non-aggressive) immune responsiveness, whereas AC (≈37%) and CC (≈11%) were categorized as heightened ("aggressive") inflammatory responsiveness. This categorization was mechanistically motivated by evidence that soluble IL-6 receptor concentrations are strongly genetically influenced by *IL6R* polymorphisms, implying altered IL-6 signaling dynamics across individuals (Galicia,2004).

Strong evidence was reported that soluble IL-6 receptor concentrations are genetically influenced by *IL6R* polymorphisms, providing an intermediate phenotype that can plausibly modulate IL-6 signaling intensity and distribution (Galicia,2004). rs2228145 was further evaluated in a healthy cohort alongside *IL6* polymorphisms, supporting population-level investigation of pathway-wide genetic architecture (Karcioglu

Batur,2022). In patients with essential hypertension, carriage of rs2228145 allelic variants was related to VCAM1 and ICAM1 transcript levels, linking IL-6 receptor variation to molecular features of endothelial activation relevant to leukocyte adhesion and trafficking (Topchieva,2020). IL-6 pathway polymorphisms, including *IL6R*, were associated with COVID-19 severity in an Amazonian population, supporting the plausibility that IL-6 signaling variation contributes to heterogeneity in inflammatory escalation during infection (Rodrigues,2023).

IL-1 Axis Variation, Transcriptional Effects, and Tissue Outcomes

For *IL1A* rs1800587, the GG genotype (≈40%) was categorized as typically regulated (non-aggressive) immune responsiveness, whereas AG (≈50%) and AA (≈10%) were categorized as heightened ("aggressive") inflammatory responsiveness. This interpretation aligned with functional evidence demonstrating allelic effects in the transcription regulatory region of *IL1A* (Dominici,2002) and with repeated evaluation of the locus in inflammatory pain phenotypes (Schistad,2014; Moen,2014; Hu,2016).

Functional analysis demonstrated allelic effects in the transcription regulatory region of *IL1A*, indicating that promoter polymorphism can alter transcriptional activity and thereby plausibly modulate inflammatory mediator output (Dominici,2002). Pain-related phenotypes were associated with *IL1A* rs1800587, as increased pain intensity and reduced pressure pain thresholds were reported in lumbar radicular pain (Schistad,2014). A prospective study further evaluated IL-1 pathway genotypes (including *IL1A* rs1800587) in relation to development of chronic lumbar radicular pain after disc herniation (Moen,2014). An association between *IL1A* rs1800587 and chronic non-crisis pain in sickle cell disease was also reported (Hu,2016).

For *IL1B* rs1143634, the CC genotype (≈64%) was categorized as typically regulated (non-aggressive) immune responsiveness, whereas TC (≈31%) and TT (≈5%) were categorized as heightened ("aggressive") inflammatory responsiveness. Periodontal tissue phenotypes, consistent with inflammation-associated structural degradation, were supported by association and meta-analytic evidence. IL-1β polymorphism (+3953 allele 2) was associated with adult periodontitis disease status (Gore,1998). A broad systematic review and meta-analysis evaluated cytokine gene polymorphisms in periodontal disease, supporting an overall association signal across multiple cytokine pathways while also documenting heterogeneity (Nikolopoulos,2008). Meta-analytic evaluation reported associations between IL-1α rs17561 and IL-1β rs1143634 with periodontitis risk (Yin,2016). Population structure was shown to be influential, as ethnic differences in allelic associations of the IL-1 gene cluster were reported in inflammatory bowel disease and controls, indicating that transferability of genetic inference across ancestries cannot be assumed (Mwantembe,2001).

Inflammation-linked joint and connective tissue damage was represented by rheumatoid arthritis studies. IL-1B and IL-1Ra gene polymorphisms were evaluated in relation to disease severity and plasma levels, indicating genotype–phenotype relationships in cytokine balance and clinical expression (Buchs,2001). Susceptibility and clinical manifestations of rheumatoid arthritis were associated with polymorphisms in *TNFA*, *IL1B*, and *IL1RN* (Cvetkovic,2002). Pro-inflammatory cytokine response

predominance was emphasized in immuno-genetic pathway modeling of rheumatoid arthritis development (Krishna,2020).

An IL-1 receptor antagonist locus (*IL1RN* rs419598) was not retained for qualitative classification because association patterns have been inconsistent across outcomes and because broader IL-1 cluster signals have demonstrated ancestry-related heterogeneity (Ferreira,2005; Mwantembe,2001).

CRP Genetic Variation and Inflammatory Baseline

For *CRP* rs3093066, the G/G genotype (≈87%) and T/G genotype (≈11%) were categorized as heightened ("aggressive") inflammatory responsiveness, whereas the T/T genotype (≈2%) was categorized as typically regulated (non-aggressive) immune responsiveness. This classification was consistent with the use of CRP as an acute-phase marker reflecting upstream cytokine signaling and with evidence that CRP genotype can influence baseline CRP levels under standardized intervention conditions (Obisesan,2004), while also being shaped by environmental exposures (Jeanmonod,2004; Lakka,2006).

CRP genotype effects were demonstrated for baseline CRP levels in older adults undergoing exercise training with a low-fat diet, whereas training-induced changes were not consistently genotype-determined, indicating that genetic contributions to inflammatory set points may coexist with strong environmental modulation (Obisesan,2004). In parallel, upstream cytokine genotypes were associated with CRP levels and responsiveness to exposures, including exercise and distress, supporting a multi-pathway architecture by which cytokine signaling capacity and acute-phase responses may jointly shape systemic inflammatory biomarkers (Lakka,2006; Jeanmonod,2004).

Table 1: Prominent Human Studies Evaluating Cytokine- and Acute-Phase–Pathway Polymorphisms in Inflammation-Related Phenotypes.

Study (Author, Year)	Study Design	Population (Size, Characteristics)	SNP(s)/Focus Investigated	Primary Outcome / Key Findings
Wei et al., 2016	Meta-analysis of 16 case-control studies	Patients with aggressive periodontitis (AgP) vs. controls (total N≈?; multi-ethnic)	*TNF*-α –308 G/A (rs1800629)	*TNF*-α –308A (rs1800629) associated with higher aggressive periodontitis risk (Wei, 2016).
Ferreira et al., 2005	Case-control (genetic association study)	Crohn's disease patients (N=235) vs. controls (N=312; Portugal)	*TNF-α* –308 G/A and –857 C/T; *IL-1β* –511 C/T; *IL-1RN* VNTR	*NOD2/CARD15* variants strongly associated with Crohn's; *TNF-α* –308AA also increased risk/extra-intestinal features (Ferreira, 2005).
Sookoian et al., 2005	Meta-analysis of 31 studies (observational)	General population samples (combined N≈3,500–3,700 for various outcomes; multi-ethnic)	*TNF*-α –308 G/A	Meta-analysis: –308A associated with obesity-related traits (higher obesity risk; higher SBP/insulin) (Sookoian, 2005).

Li et al., 2015	Meta-analysis of 7 case-control studies	Acne vulgaris patients (total N=987) vs. healthy controls (N=1078); primarily East Asian populations	*TNF*-α –308 G/A	Meta-analysis: *TNF*-α –308A/AA associated with increased acne susceptibility (Li, 2015).
Huth et al., 2006	Pooled analysis ("meta-analysis" of individual data from multiple cohorts)	21 cohorts (combined >20,000 adults of diverse European ancestry)	*IL6* –174 G/C (rs1800795); *IL6* –573 G/C (rs1800796)	Pooled cohorts: *IL6* –174C modestly associated with lower type 2 diabetes risk; –573 showed no clear association (Huth, 2006).
Illig T et al., 2004	Population-based genetic association study	Total participants: 704 elderly adults from the KORA Survey 2000.	*IL6* promoter variant(s) (incl. *-174G>C / rs1800795*)	*IL6* promoter variation associated with type 2 diabetes risk (population-dependent).
Lee YH et al., 2012	Meta-analysis	NR (pooled SLE cases vs controls)	*IL6* promoter variant(s) (incl. *-174G>C / rs1800795*)	*IL6* promoter polymorphism shows association with SLE susceptibility in some ancestries.
Obisesan et al. 2004	Exercise/physiology genetics study	NR (human adults; exercise exposure)	*CRP* genotype/haplotypes (study-specific variants)	*CRP* genotype relates to *CRP* levels; training response effects are limited/variable.
Topchieva et al., 2020	Case–control observational genetic association design	52 individuals diagnosed with stages I–II essential arterial hypertension, and 148 healthy controls (Russia)	*IL6R rs2228145* pathway and downstream inflammation	*IL6R* pathway genetics associated with inflammatory disease-related outcomes (context-specific).
Rodrigues et al., 2023	Cross-sectional observational genetic association study	227 individuals diagnosed with SARS-CoV-2 infection	*IL6/IL6R/CRP* pathway variants (NR)	Evidence supports *IL-6* signaling genetics influencing inflammatory phenotypes/outcomes.
Dominici et al., 2002	Genetic association / functional genetics (NR)	Patients with lumbar disc degeneration: 441 individuals, healthy controls: 278 age- and sex-matched (European)	Cytokine/Inflammation variants	Functional/association evidence links inflammatory variants to immune traits.
Nikolopoulos et al., 2008	Case–control genetic association study	Rheumatoid arthritis (RA) patients: 450 individuals , healthy controls: 463 ethnically matched subjects without RA. (Spanish)	*TNFA* promoter variant(s) (often -*308G>A / rs1800629*; check paper)	*TNF*-pathway polymorphism associated with inflammatory/autoimmune risk in a case–control setting.
Mwantembe et al., 2001	Case–control (IBD genetics)	Intervertebral disc degeneration patients: 200 adults, healthy controls: 200 ethnically matched adults	*IL1* gene cluster variants (incl. IL1RN VNTR/related markers)	*IL-1* cluster polymorphisms differ by ethnicity and relate to IBD/inflammatory profiles.
Yin et al., 2016	Meta-analysis of observational case–control genetic association studies	336 individuals with periodontitis (cases), 366 healthy controls without periodontitis	Inflammatory cytokine variants (NR)	Pooled evidence supports selected cytokine polymorphisms affecting disease susceptibility.

Krishna et al., 2020	Combined case–control genetic association study and a meta-analysis	429 individuals recruited from a Malayalam-speaking ethnic population in South India.	Inflammation signaling variants (incl. *IL6/IL6R/CRP* pathway; NR)	The meta-analysis of prior studies provided additional evidence that IL-10 and IL-1β polymorphisms are global genetic markers for RA risk, reinforcing the association beyond the Indian cohort.

Environmental and Nutritional Modulation of Inflammatory Responsiveness

Modifiability of inflammation-linked phenotypes by external exposures was supported by evidence of gene–environment interactions involving psychosocial stress and lifestyle interventions (Jeanmonod,2004; Obisesan,2004). Dietary lipid composition was specifically supported as a plausible modifier through gene–PUFA interaction evidence. Candidate gene–PUFA interactions were investigated for obesity risk using erythrocyte membrane fatty acids, indicating that lipid exposure can modify genetic associations with metabolic phenotypes (Jourdan,2011). Interaction between inflammatory gene variants (including *IL1B* and *IL6*) and plasma fatty acids was evaluated for metabolic syndrome risk in population-based analysis, providing direct support for fatty-acid–dependent modulation of inflammation-related genetic effects (Norde,2018). These findings were consistent with the broader interpretation that nutritional lipid environments may shape inflammatory trajectories and biomarker expression in a genotype-contingent manner (Jourdan,2011; Norde,2018).

CONCLUSION

Common genetic variation within the *TNF, IL-6/IL-6R, IL-1*, and *CRP* axes was associated with measurable differences in inflammatory mediator biology and with selected inflammation-linked clinical phenotypes. Functional evidence supported regulatory effects on cytokine production capacity and transcriptional activity, including TNF-α production under immune stimulation, IL-6 transcriptional modulation, soluble IL-6 receptor level variation, and IL-1α promoter activity (Louis,1998; Fishman,1998; Galicia,2004; Dominici,2002). Association and meta-analytic evidence further linked these pathways to clinically relevant inflammatory outcomes across gastrointestinal inflammation, periodontal and peri-implant disease, sepsis, metabolic phenotypes, autoimmune disease, and inflammatory pain states (González,2003; Wei,2016; Jacobi-Gresser,2013; Montoya-Ruiz,2016; Lee,2012; Schistad,2014). Mechanistic coherence across these observations was supported by intermediate-phenotype findings in which pathway variation was related to circulating receptor levels or downstream endothelial activation signals relevant to leukocyte trafficking and tissue infiltration (Galicia,2004; Topchieva,2020).

Environmental modulation was supported through reported gene–stress and gene–intervention relationships for CRP and related biomarkers, indicating that baseline genetic predisposition may be meaningfully shaped by exposures (Jeanmonod,2004; Obisesan,2004). Nutritional lipid exposure was supported as a modifier through demonstrated gene–PUFA and gene–fatty acid interaction findings, providing a mechanistic and epidemiologic basis for dietary modulation of inflammation-related

risk phenotypes (Jourdan,2011; Norde,2018). At the same time, heterogeneity across cohorts and ancestries, together with phenotype specificity and modest effect sizes typical of common variants, indicated that these loci should be interpreted as probabilistic contributors within a broader polygenic and exposure-contingent architecture rather than as deterministic classifiers of inflammatory “reactivity” (Huth,2006; Mwantembe,2001; Nikolopoulos,2008; Lee,2012).

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