Inflammation and Immune System

Genetic Pathway Reference

13 Functional Categories • ~75 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of inflammation and innate / adaptive immune regulation, the genes that govern each phase of the inflammatory response, the well-studied common variants in those genes, the cofactors each enzyme or transcription factor depends on, and the supplement and dietary targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on published GWAS literature and peer-reviewed mechanistic studies. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Most common variants catalogued here confer small individual effects (odds ratios 1.05–1.4); clinical significance arises from cumulative patterns and gene-environment interactions. A small number of variants — notably PTPN22 R620W, IL23R R381Q, NOD2 frameshift, CFH Y402H, TYK2 P1104A, and the HLA tag SNPs — have larger and clinically actionable effect sizes for specific autoimmune or infectious disease endpoints.

2. Pathway Biology

2.1 What inflammation is

Inflammation is the coordinated tissue response to infection, injury, or metabolic perturbation. Far from being a single pathway, it is a multi-phase, multi-cell program that integrates innate detection, intracellular signal amplification, systemic cytokine release, leukocyte recruitment, and — critically — active resolution. When any of these phases is miscalibrated, the result is either insufficient host defense (immunodeficiency), excessive acute response (sepsis, cytokine storm), or failed return to homeostasis (chronic low-grade inflammation, autoimmunity, inflammaging) (Medzhitov, Nature 2008; Netea et al., Cell 2016; Franceschi et al., Nat Rev Endocrinol 2018).

2.2 Four temporal phases

A useful mental model divides the inflammatory response into four phases. Phase 1 — detection — is carried out by pattern recognition receptors (PRRs): Toll-like receptors (TLRs) at the cell surface and endosomes, NOD-like receptors (NLRs) in the cytosol, C-type lectin receptors, and RAGE. These sense pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs including HMGB1, S100A proteins, and advanced glycation end products). Phase 2 — amplification — converts detection into transcription through NF-κB, MAPK, JAK-STAT, and inflammasome activation. Phase 3 — effector — produces the pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFNs), the acute phase response from hepatocytes (CRP, SAA, fibrinogen, hepcidin), and the recruitment of leukocytes

via chemokines and adhesion molecules. Phase 4 — resolution — is an active biochemical program that switches off inflammation through specialized pro-resolving mediators (resolvins, protectins, maresins derived from EPA and DHA), IL-10, TGF-β, and efferocytosis of apoptotic neutrophils (Serhan, Nature 2014; Buckley et al., Immunity 2014).

2.3 NF-κB: the master amplifier

NF-κB is the central transcription factor of the innate inflammatory response. In the resting state, p50/p65 dimers are held in the cytoplasm by IκB proteins. Upon receptor signaling, the IKK complex (IKKα, IKKβ, NEMO) phosphorylates IκBα, triggering its ubiquitination and proteasomal degradation, which frees NF-κB to translocate to the nucleus and drive transcription of pro-inflammatory genes. The response is terminated by negative regulators including A20 (TNFAIP3), CYLD, and resynthesized IκBα. Genetic variation at A20 (TNFAIP3) is a major determinant of NF-κB persistence and underlies GWAS signals for SLE, rheumatoid arthritis, and inflammatory bowel disease (Ma & Malynn, Nat Rev Immunol 2012).

2.4 The NLRP3 inflammasome

The NLRP3 inflammasome is a multiprotein complex that activates caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 into their mature, secreted forms. NLRP3 requires two signals: priming (typically TLR → NF-κB → pro-IL-1β transcription) and activation (potassium efflux, mitochondrial ROS, lysosomal damage, or crystal phagocytosis including cholesterol crystals, urate, and asbestos). Aberrant NLRP3 activation drives gout, cryopyrin-associated periodic syndromes, atherosclerosis (CANTOS trial with canakinumab targeting IL-1β — Ridker et al., NEJM 2017), and metabolic inflammation. EPA/DHA-derived mediators and ω-3 fatty acids directly inhibit NLRP3 activation (Yan et al., Immunity 2013).

2.5 The IL-6 / CRP axis and Mendelian randomization

IL-6 is produced by macrophages, T cells, and endothelium in response to TNF-α, IL-1β, and TLR signaling. It drives hepatic production of CRP, SAA, fibrinogen, and hepcidin via JAK2-STAT3. Signaling occurs through two modes: classic signaling via membrane IL-6R (anti-inflammatory effects in some contexts) and trans-signaling via soluble IL-6R (gp130 engagement on cells lacking membrane IL-6R, predominantly pro-inflammatory). The IL6R D358A variant (rs2228145) increases ADAM17-mediated shedding of membrane IL-6R, phenocopying tocilizumab and reducing coronary heart disease risk in large Mendelian randomization studies (IL6R MR Consortium, Lancet 2012). This is the cleanest human genetic evidence that IL-6 signaling is causal in atherosclerosis.

2.6 Resolution of inflammation

Resolution was historically thought to be a passive dilution of inflammatory mediators; it is now known to be an active biochemical program. Lipoxins (from arachidonic acid via 15-LOX and 5-LOX), resolvins E-series (from EPA), resolvins D-series, protectins, and maresins (all from DHA) are generated by transcellular biosynthesis, bind specific GPCRs (FPR2/ALX, ChemR23, GPR32, GPR18), and drive neutrophil apoptosis, macrophage switch to pro-resolving phenotype, efferocytosis, and return to homeostasis (Serhan, Nature 2014). Genetic variation in FADS1/FADS2 (desaturase locus) determines how efficiently dietary ALA is converted to EPA and DHA, and is one of the strongest GWAS signals for plasma fatty acid composition (Schaeffer et al., Hum Mol Genet 2006; Lemaitre et al., PLoS Genet 2011). Population variants at this locus shift the substrate pool available for pro-resolving mediator synthesis.

2.7 Adaptive immunity and the Th1 / Th2 / Th17 / Treg balance

Naïve CD4 T cells differentiate into Th1 (T-bet, IFN-γ; intracellular pathogens), Th2 (GATA3, IL-4/5/13; parasites, allergy), Th17 (RORγt, IL-17; fungi and extracellular bacteria, but also autoimmunity), or regulatory T cells (FOXP3, IL-10/TGF-β; tolerance) under the direction of cytokine milieu and costimulatory signals. Genetic variation at PTPN22, CTLA4, IL23R, STAT4, and FOXP3 shifts this balance and underlies many autoimmune GWAS signals. The IL23R R381Q loss-of-function variant is strongly protective for inflammatory bowel disease, psoriasis, and ankylosing spondylitis (Duerr et al., Science 2006), establishing the Th17 axis as a causal driver of these conditions and providing the biological rationale for anti-IL-23 therapies.

2.8 The complement system

Complement is a parallel, evolutionarily ancient proteolytic cascade activated by three pathways (classical via immune complexes, lectin via MBL recognition of mannose, and alternative via spontaneous C3 tickover). All three converge on C3 cleavage, generating C3b (opsonin), C3a (anaphylatoxin), and the membrane attack complex (C5b-9). Complement is tightly regulated by factor H (CFH), factor I, decay-accelerating factor, and CD59; defects in these regulators drive atypical hemolytic uremic syndrome, C3 glomerulopathy, and age-related macular degeneration. The CFH Y402H variant (rs1061170) is one of the largest common-variant effects in human GWAS, with homozygous AMD odds ratios near 4.6 (Klein et al., Science 2005).

2.9 Oxidative–inflammatory crosstalk

Reactive oxygen species amplify and are amplified by inflammation. Myeloperoxidase (MPO) in neutrophils generates hypochlorous acid from hydrogen peroxide, which oxidizes LDL and inactivates eNOS. Inducible nitric oxide synthase (iNOS / NOS2), upregulated by NF-κB, produces large sustained quantities of NO that react with superoxide to form peroxynitrite. Counterbalancing these are the NRF2-ARE antioxidant program (SOD2, GPX1, catalase, NQO1, HMOX1, glutathione synthesis enzymes) and paraoxonase 1 (PON1) bound to HDL, which hydrolyzes oxidized lipids. Genetic variation at NFE2L2 (NRF2 promoter), SOD2, GPX1, CAT, and PON1 modulates endogenous antioxidant defense (Marzec et al., FASEB J 2007).

2.10 Clinical integration

Chronic low-grade systemic inflammation ("inflammaging") is now recognized as the shared soil for atherosclerosis, insulin resistance, sarcopenia, cognitive decline, and many age-related cancers. High-sensitivity C-reactive protein (hs-CRP) is the most widely used circulating biomarker and a validated predictor of cardiovascular risk independent of LDL (Ridker et al., NEJM 2002, JUPITER 2008). IL-6, fibrinogen, soluble IL-6R, and neutrophil-to-lymphocyte ratio add incremental information. The CANTOS trial (canakinumab, targeting IL-1β) and the COLCOT / LoDoCo2 trials (low-dose colchicine, inhibiting NLRP3) provide the clinical proof that targeting inflammation reduces cardiovascular events independent of lipid lowering (Ridker et al., NEJM 2017; Tardif et al., NEJM 2019; Nidorf et al., NEJM 2020).

3. Functional Categories

The inflammation and immune pathway can be organized into thirteen functional categories, each corresponding to a distinct biochemical or cellular job. The categories below are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	Pattern recognition receptors	Detect PAMPs, DAMPs, AGEs	TLR2, TLR3, TLR4, TLR9, NOD2, AGER (RAGE)
2	NF-κB core signaling	Master amplifier of innate response	NFKB1, TNFAIP3 (A20), IKBKB, REL
3	Inflammasome (NLRP3 axis)	Activate caspase-1 → IL-1β / IL-18	NLRP3, CARD8, IL1B, IL18, MEFV, AIM2
4	Pro-inflammatory cytokines	TNF, IL-6, IL-1, IL-17, IFN-γ, LTA	TNF, IL6, IL6R, IL1B, IL1RN, IL17A, IL4, IFNG, LTA
5	Acute phase response	Hepatic CRP, SAA, fibrinogen	CRP, APCS
6	Resolution & anti-inflammatory	IL-10, TGF-β, resolvin precursors	IL10, TGFB1, ALOX15, FPR2, FADS1, FADS2, ELOVL2
7	T-cell balance & adaptive bridge	Th1/Th2/Th17/Treg differentiation	PTPN22, CTLA4, IL23R, STAT4, FOXP3, TBX21, RORC
8	Oxidative-inflammatory interface	MPO, iNOS, PON1, NRF2 program	MPO, NOS2, PON1, NFE2L2, KEAP1, SOD2, GPX1, CAT
9	Complement system	Alternative / classical / lectin pathways	CFH, C3, CFB, C5, MBL2
10	Chemokines & leukocyte trafficking	Monocyte/neutrophil recruitment	CCR5, CCR2, CXCL8, CX3CR1, CCL2
11	Eicosanoid axis	COX/LOX-derived mediators	PTGS2 (COX-2), ALOX5, ALOX5AP, LTA4H, PLA2G7
12	Type I/II interferon & antiviral	IFN-α/β/λ/γ signaling	IFNL3, IFNL4, IRF5, OAS1, TYK2
13	HLA tag SNPs	Antigen presentation (limited scope)	HLA-DRB1, HLA-C, HLA-DQA1

4. SNP Catalog by Functional Category

Each table below lists the well-studied common variants in the genes for that category, along with the variant name, the functional consequence, and the cofactor(s) required by the associated enzyme or signaling component. Effect sizes and GWAS p-values are noted where well established. The largest-effect and most clinically actionable variants are flagged in the interpretive paragraphs below each table.

4.1 Pattern Recognition Receptors (TLR, NOD, RAGE)

Gene	rsID	Variant	Functional consequence	Cofactor
TLR4	rs4986790	D299G (Asp299Gly)	Blunted LPS response; lower NF-κB activation. Associated with sepsis susceptibility but paradoxically protective for atherosclerosis (Kiechl et al., NEJM 2002; Ferwerda et al., PNAS 2007).	(receptor)
TLR4	rs4986791	T399I (Thr399Ile)	Often in LD with D299G on a common haplotype; similar hyporesponse to LPS.	(receptor)
TLR2	rs5743708	R753Q	Impaired gram-positive recognition; increased susceptibility to staphylococcal and mycobacterial infection (Schröder & Schumann, Lancet ID 2005).	(receptor)
TLR3	rs3775290	L412F	Reduced dsRNA sensing; associated with herpes simplex encephalitis susceptibility (Zhang et al., Science 2007).	(receptor)
TLR9	rs5743836	-1237 T/C	Promoter variant; C allele increases TLR9 expression, associated with autoimmune traits.	(receptor)
NOD2	rs2066844	R702W	Impaired MDP (muramyl dipeptide) sensing. Crohn's disease OR ~2.5 heterozygous (Hugot et al., Nature 2001).	(receptor)
NOD2	rs2066845	G908R	Second Crohn's disease variant at NOD2 (Ogura et al., Nature 2001).	(receptor)
NOD2	rs2066847	3020insC / L1007fs	Frameshift truncation; strongest Crohn's disease variant, homozygous OR >17.	(receptor)
AGER	rs1800625	-429 T/C promoter	C allele ↑ RAGE promoter activity and soluble RAGE levels. Directly relevant to AGE-mediated inflammation (Hudson et al., Diabetes 2001).	Zn
AGER	rs2070600	G82S (Gly82Ser)	Altered ligand binding; strong GWAS signal for lung function and pulmonary fibrosis (Repapi et al., Nat Genet 2010, p<1e-15).	Zn

The TLR/NLR/RAGE receptors are the front door of innate immunity. TLR4 hypo-responsive variants show a recurring paradox in the literature: they increase susceptibility to serious gram-negative infection but protect against atherosclerosis, because atherosclerosis is partly driven by chronic TLR4 engagement by oxidized LDL and endogenous ligands. NOD2 is the strongest single-gene contributor to Crohn's disease risk through common variants. AGER (RAGE) is the mechanistic link between glycation biology and inflammatory signaling — AGEs, HMGB1, and S100 proteins are all RAGE ligands.

4.2 NF-κB Core Signaling

Gene	rsID	Variant	Functional consequence	Cofactor
NFKB1	rs28362491	-94 ins/del ATTG	Del allele ↓ NFKB1 p50 promoter activity. Associated with ulcerative colitis and	Zn, Mg

Gene	rsID	Variant	Functional consequence	Cofactor
			cardiovascular disease (Karban et al., Hum Mol Genet 2004).	
TNFAIP3	rs2230926	F127C (Phe127Cys)	↓ A20 deubiquitinase function → prolonged NF-κB activation. SLE OR ~1.7 (Musone et al., Nat Genet 2008).	Zn
TNFAIP3	rs6920220	intergenic	Strong GWAS signal for rheumatoid arthritis, SLE, psoriasis, celiac disease (Plenge et al., Nat Genet 2007).	Zn
IKBKB	rs5029748	intronic	IKK-β regulatory variant; modulates NF-κB activation kinetics.	Mg, ATP
REL	rs13031237	intronic	c-Rel locus; GWAS for rheumatoid arthritis and ulcerative colitis (Gregersen et al., Nat Genet 2009).	(TF)

TNFAIP3 (A20) is the single most important negative regulator of NF-κB and a major autoimmune GWAS hub. Loss-of-function in A20 extends the duration of every inflammatory signal, not just one specific cytokine. Zinc is a structural cofactor for A20's zinc-finger domains, which is one biochemical rationale for the recurring association between zinc deficiency and dysregulated inflammation.

4.3 Inflammasome (NLRP3 Axis)

Gene	rsID	Variant	Functional consequence	Cofactor
NLRP3	rs10754558	3' UTR C/G	G allele ↑ NLRP3 mRNA stability → ↑ IL-1β secretion. Associated with CAD and inflammatory conditions (Hitomi et al., J Allergy Clin Immunol 2009).	K+ efflux, ROS
NLRP3	rs35829419	Q705K (Gln705Lys)	Gain-of-function; ↑ basal IL-1β secretion. Associated with RA, gout (Verma et al., Ann Rheum Dis 2008).	K+ efflux
CARD8	rs2043211	C10X (Cys10Ter)	Truncation of CARD8, which normally inhibits NLRP3. Loss of inhibition → ↑ IL-1β (Roberts et al., Genes Immun 2010).	(adaptor)
IL1B	rs16944	-511 C/T	T allele ↑ IL-1β production. Gastric cancer risk with H. pylori (El-Omar et al., Nature 2000).	(cytokine)
IL18	rs1946518	-607 C/A	A allele ↑ IL-18 transcription (Giedraitis et al., J Neuroimmunol 2001).	(cytokine)
MEFV	rs3743930	E148Q	Familial Mediterranean fever mild variant; modifier of inflammatory tone in heterozygotes (Booty et al., Arthritis Rheum 2009).	(pyrin)
AIM2	rs1103577	intronic	Alternative cytosolic DNA-sensing inflammasome; limited GWAS data.	dsDNA

The NLRP3 inflammasome is the target of canakinumab (anti-IL-1β) and colchicine. The CANTOS and COLCOT / LoDoCo2 trials provide the clinical proof that NLRP3/IL-1β inhibition reduces cardiovascular events. Omega-3 fatty acids (EPA, DHA) directly inhibit NLRP3 activation through multiple mechanisms including GPR120 signaling and membrane raft disruption (Yan et al., Immunity 2013), providing a mechanistic basis for ω-3 supplementation in inflammatory disease.

4.4 Pro-inflammatory Cytokines

Gene	rsID	Variant	Functional consequence	Cofactor
TNF	rs1800629	-308 G/A	A allele ≈2-fold ↑ TNF-α transcription in reporter assays. Associated with severe sepsis, cachexia, TB susceptibility (Wilson et al., PNAS 1997).	(cytokine)
TNF	rs361525	-238 G/A	Second TNF promoter variant with complex, often opposite, regulatory effects to -308.	(cytokine)
LTA	rs909253	intron 1	Lymphotoxin-α variant; MI risk in Japanese cohort (Ozaki et al., Nat Genet 2002).	(cytokine)
IL6	rs1800795	-174 G/C	C allele associated with lower basal IL-6 in most European cohorts; population-dependent effect.	(cytokine)
IL6R	rs2228145	D358A (Asp358Ala)	A allele ↑ ADAM17 shedding of membrane IL-6R → ↑ sIL-6R and ↓ classic signaling. MR: ↓ CHD risk, phenocopies tocilizumab (IL6R MR Consortium, Lancet 2012, p<1e-8).	(receptor)
IL1B	rs1143634	+3954 C/T	Synonymous; T allele ↑ IL-1β secretion in some studies.	(cytokine)
IL1RN	rs4251961	T/C	Regulates IL-1 receptor antagonist production (Carter et al., Genes Immun 2008).	(antagonist)
IL17A	rs2275913	-197 G/A	A allele ↑ IL-17 production; psoriasis, RA associations (Espinoza et al., Hum Immunol 2011).	(cytokine)
IL4	rs2243250	-590 C/T	T allele ↑ IL-4 promoter activity → Th2 skew, atopy.	(cytokine)
IFNG	rs2430561	+874 T/A	T allele ↑ IFN-γ production; intron 1 NF-κB binding site.	(cytokine)

IL6R rs2228145 is the single most important variant in this table. It is the human genetic evidence that IL-6 signaling is causal in coronary heart disease and the biological basis for considering IL-6 pathway inhibition (tocilizumab, ziltivekimab) as cardiovascular risk reduction. TNF -308 has been studied in thousands of papers with inconsistent results in ethnic subgroups; effect sizes are modest. The IL-17 and IFN-γ variants matter more for autoimmune subtyping than for general inflammatory tone.

4.5 Acute Phase Response

Gene	rsID	Variant	Functional consequence	Cofactor
CRP	rs1205	3'UTR C/T	T allele associated with lower basal CRP (Ridker et al., JAMA 2008).	(protein)
CRP	rs3091244	Triallelic	Regulatory variant at CRP promoter; affects CRP set-point (Carlson et al., Am J Hum Genet 2005).	(protein)
CRP	rs2794520	intergenic	CHARGE GWAS lead SNP for CRP levels, p<1e-200 (Dehghan et al., Circulation 2011).	(protein)
APCS	rs1374486	intronic	Serum amyloid P component levels.	(protein)

CRP is a biomarker, not a driver — Mendelian randomization studies indicate CRP itself is not causal for CHD even though it strongly predicts risk. Nonetheless, CRP genetic variants are clinically useful because they allow discounting genetically-high baseline CRP when interpreting hs-CRP in cardiovascular risk stratification. The genetic CRP set-point is largely determined by these three SNPs plus IL6 and IL6R upstream.

4.6 Resolution and Anti-inflammatory

Gene	rsID	Variant	Functional consequence	Cofactor
IL10	rs1800896	-1082 G/A	G allele ↑ IL-10 production; part of the high-producer haplotype (Turner et al., Eur J Immunogenet 1997).	(cytokine)
IL10	rs1800871	-819 C/T	Part of the IL10 promoter haplotype with -1082 and -592.	(cytokine)
TGFB1	rs1800470	L10P (codon 10)	C allele (Pro) ↑ TGF-β secretion; associated with fibrosis and transplant outcomes (Awad et al., Transplantation 1998).	(cytokine)
ALOX15	rs2619112	intronic	15-lipoxygenase; substrate enzyme for lipoxin biosynthesis (Assimes et al., Hum Mol Genet 2008).	Fe, O2
FPR2	rs1769490	intronic	Formyl peptide receptor 2 (ALX); receptor for resolvin D1 and lipoxin A4.	(receptor)
FADS1	rs174537	intergenic	MAJOR determinant of Δ5-desaturase activity → plasma EPA/AA ratio. T allele slow converter (Schaeffer et al., Hum Mol Genet 2006; p<1e-100 for fatty acid traits).	Fe, O2, NADH
FADS2	rs174575	intronic	Independent Δ6-desaturase signal at FADS locus.	Fe, O2, NADH
ELOVL2	rs953413	intronic	EPA → DPA → DHA elongation; GWAS-associated with plasma DHA and used as a DNA methylation aging biomarker.	NADPH

The FADS1/FADS2/ELOVL2 cluster is one of the most actionable findings in this entire category. Carriers of the slow-converter alleles at FADS1 rs174537 make substantially less EPA and DHA from dietary ALA, which means they depend more on preformed EPA/DHA from

fatty fish or supplements. This single genetic finding can shift a person's entire omega-3 supplementation strategy. Resolution is an active biochemical program, and its substrate supply is genetically modulated — making ω-3 supplementation particularly important in slow-converter genotypes.

4.7 T-cell Balance and Adaptive Bridge

Gene	rsID	Variant	Functional consequence	Cofactor
PTPN22	rs2476601	R620W (Arg620Trp)	Gain-of-function lymphoid tyrosine phosphatase. Strong RA OR ~1.75, T1D, SLE, Hashimoto's (Begovich et al., Am J Hum Genet 2004).	(phosphatase)
CTLA4	rs231775	T49A (Thr17Ala)	Altered CTLA-4 expression on Tregs; Graves', T1D, autoimmune thyroid disease (Ueda et al., Nature 2003).	(coinhibitory R)
IL23R	rs11209026	R381Q (Arg381Gln)	PROTECTIVE loss-of-function. IBD OR ~0.26, psoriasis, ankylosing spondylitis (Duerr et al., Science 2006).	(receptor)
STAT4	rs7574865	intron 3	Th1/Th17 differentiation; RA, SLE risk (Remmers et al., NEJM 2007).	(TF)
FOXP3	rs3761548	-3279 A/C	Treg master regulator promoter variant; modulates Treg function (X-linked).	(TF)
TBX21	rs17250932	intronic	T-bet; master regulator of Th1 commitment.	(TF)
RORC	rs9826	3'UTR	RORγt; master regulator of Th17 commitment.	(TF)

This category contains some of the largest-effect common variants in the entire report. PTPN22 R620W is a major autoimmune risk allele across multiple diseases. IL23R R381Q is notable for being PROTECTIVE — it was the first variant to cleanly implicate the Th17/IL-23 axis in IBD and psoriasis, and it provided the biological rationale for ustekinumab, risankizumab, and guselkumab. The effect sizes here are 2–5× larger than anything in the cytokine category.

4.8 Oxidative–Inflammatory Interface

Gene	rsID	Variant	Functional consequence	Cofactor
MPO	rs2333227	-463 G/A	A allele ↓ MPO promoter activity → ↓ HOCl generation, ↓ oxidative burden (Piedrafita et al., J Biol Chem 1996).	Fe, H2O2
NOS2	rs2297518	S608L (Ser608Leu)	Inducible NOS; variant ↑ iNOS activity → ↑ peroxynitrite in inflammatory states (Dhillon et al., PLoS One 2014).	BH4, NADPH, O2
PON1	rs662	Q192R (Gln192Arg)	R allele has altered substrate specificity; affects HDL antioxidant function and paraoxon detoxification (Mackness et al., Circulation 2003).	Ca2+

Gene	rsID	Variant	Functional consequence	Cofactor
PON1	rs854560	L55M (Leu55Met)	M allele ↓ PON1 protein stability.	Ca2+
NFE2L2	rs6721961	-617 C/A promoter	A allele ↓ NRF2 promoter activity → ↓ antioxidant response element program (Marzec et al., FASEB J 2007).	(TF)
KEAP1	rs1048290	intronic	NRF2 negative regulator; limited but suggestive GWAS data.	Zn, Cys
SOD2	rs4880	V16A (Val16Ala)	Mitochondrial targeting efficiency; Ala variant imports less SOD2 into mitochondria (Sutton et al., Pharmacogenetics 2003).	Mn
GPX1	rs1050450	P198L (Pro198Leu)	Reduced GPx1 activity with L allele.	Se
CAT	rs1001179	-262 C/T	T allele ↓ catalase promoter activity.	Fe, heme

NRF2 (NFE2L2) is the master transcription factor for the antioxidant response element (ARE) program, which induces SOD2, GPX1, catalase, NQO1, HMOX1, and the glutathione synthesis machinery. Reduced NRF2 capacity creates systemic vulnerability across the entire antioxidant network. Sulforaphane (from broccoli sprouts), curcumin, and resveratrol are the best-characterized dietary NRF2 activators. This category is the mechanistic bridge between oxidative stress and inflammation because ROS activate NF-κB and NLRP3, and the products of inflammation generate more ROS — a feed-forward loop that NRF2 capacity interrupts.

4.9 Complement System

Gene	rsID	Variant	Functional consequence	Cofactor
CFH	rs1061170	Y402H (Tyr402His)	LARGE EFFECT. Impaired factor H regulation of C3 convertase. AMD OR ~4.6 homozygous (Klein et al., Science 2005).	(regulator)
CFH	rs1410996	intronic	Independent AMD signal at CFH locus (Maller et al., Nat Genet 2006).	(regulator)
C3	rs2230199	R102G (S/F variant)	Slow vs fast C3 electrophoretic variant; AMD, dense deposit disease (Yates et al., NEJM 2007).	(complement)
CFB	rs641153	R32Q (Arg32Gln)	PROTECTIVE for AMD; reduced alternative pathway activation (Gold et al., Nat Genet 2006).	(complement)
C5	rs17611	V802I (Val802Ile)	Modulates C5 cleavage efficiency; RA severity (Giles et al., Arthritis Rheum 2015).	(complement)
MBL2	rs1800450	B variant / G54D	Reduced MBL oligomerization and function; lectin pathway deficiency (Madsen et al., Immunogenetics 1994).	(lectin)

The CFH Y402H finding was one of the first successful GWAS signals in human disease and remains one of the largest common-variant effects in any GWAS. The complement system is

relatively 'hard-wired' — there are few dietary or supplement interventions that meaningfully shift complement activity. Eculizumab and ravulizumab (anti-C5) and pegcetacoplan (anti-C3) are the therapeutic options, reserved for severe complement-driven disease.

4.10 Chemokines and Leukocyte Trafficking

Gene	rsID	Variant	Functional consequence	Cofactor
CCR5	rs333	Δ32 (32-bp deletion)	Non-functional CCR5 receptor. Homozygous → HIV-1 resistance. Altered inflammation set-point (Samson et al., Nature 1996).	(receptor)
CCR2	rs1799864	V64I (Val64Ile)	Altered monocyte recruitment; HIV progression, CAD associations (Smith et al., Science 1997).	(receptor)
CXCL8	rs4073	-251 T/A	A allele ↑ IL-8 (CXCL8) transcription (Hull et al., Thorax 2000).	(chemokine)
CX3CR1	rs3732378	T280M (Thr280Met)	Reduced fractalkine receptor function; modestly protective for CAD (McDermott et al., Circ Res 2003).	(receptor)
CCL2	rs1024611	-2518 A/G	G allele ↑ MCP-1 (CCL2) production (Rovin et al., BBRC 1999).	(chemokine)

CCR5-Δ32 is the most famous variant in this category, mostly known for HIV resistance but also affecting inflammatory tone in multiple contexts including post-stroke recovery. The chemokine variants collectively modulate the efficiency of leukocyte recruitment from blood into inflamed tissue — a less dramatic but cumulative effect on inflammatory phenotype.

4.11 Eicosanoid Axis

Gene	rsID	Variant	Functional consequence	Cofactor
PTGS2	rs20417	-765 G/C	C allele ↓ COX-2 promoter activity; protective for CAD and MI (Papafili et al., ATVB 2002; Cipollone et al., JAMA 2004).	heme, O2
PTGS2	rs5275	8473 T/C (3'UTR)	Altered mRNA stability; modifies aspirin/NSAID response.	heme, O2
ALOX5	rs2115819	intronic	5-lipoxygenase activity; cardiovascular risk modulator (Dwyer et al., NEJM 2004).	Fe, O2, ATP
ALOX5AP	rs10507391	intronic (HapA tag)	FLAP haplotype A; deCODE MI and stroke risk (Helgadottir et al., Nat Genet 2004).	(adaptor)
LTA4H	rs17525495	intronic	Leukotriene A4 hydrolase; LTB4 synthesis. MI risk in some populations (Helgadottir et al., Nat Genet 2006).	Zn
PLA2G7	rs1051931	A379V (Ala379Val)	Lp-PLA2 activity; cardiovascular biomarker and drug target (Jang et al., ATVB 2006).	Ca2+

This category is where dietary omega-3/omega-6 balance has its clearest mechanistic impact. EPA competes with arachidonic acid as substrate for COX-2 and 5-LOX, shifting production from pro-inflammatory 2-series prostaglandins and 4-series leukotrienes to less inflammatory 3-series and 5-series mediators. This is why the FADS1/FADS2 findings in Section 4.6 and the PTGS2/ALOX5 findings here are mechanistically linked — the substrate pool and the enzyme both matter, and genetic variation in either can shift the balance.

4.12 Type I/II Interferon and Antiviral

Gene	rsID	Variant	Functional consequence	Cofactor
IFNL3	rs12979860	C/T	CC genotype ≈ 3× more likely to spontaneously clear HCV; strongest IFN-λ3 variant (Ge et al., Nature 2009).	(cytokine)
IFNL4	rs368234815	ΔG/TT	ΔG creates functional IFN-λ4 protein; paradoxically associated with worse HCV clearance (Prokunina-Olsson et al., Nat Genet 2013).	(cytokine)
IRF5	rs2004640	intronic	↑ IRF5 expression; SLE risk locus (Graham et al., Nat Genet 2006).	(TF)
OAS1	rs10774671	splice site	2'-5' oligoadenylate synthetase; COVID-19 severity (Zhou et al., Nat Med 2021).	ATP
TYK2	rs34536443	P1104A (Pro1104Ala)	PROTECTIVE partial loss-of-function. Reduced risk of RA, SLE, psoriasis, IBD, T1D (Diogo et al., AJHG 2015; Dendrou et al., Sci Transl Med 2016).	ATP

TYK2 P1104A is noteworthy as the human genetic validation of TYK2 inhibition for autoimmune disease — which led directly to the development of deucravacitinib (selective TYK2 inhibitor approved for psoriasis). The IFNL3/IFNL4 pair is one of the most striking examples of a single locus predicting response to an infectious disease (HCV) and to its therapy.

4.13 HLA Tag SNPs (Limited Scope)

Gene	rsID	Variant	Functional consequence	Cofactor
HLA-DRB1	rs660895	tag for DRB1*04:01	Shared epitope tag; rheumatoid arthritis OR ~4 (Raychaudhuri et al., Nat Genet 2012).	(MHC II)
HLA-C	rs10484554	tag for C*06:02	Strongest psoriasis HLA allele, OR ~3 (Nair et al., Nat Genet 2009).	(MHC I)
HLA-DQA1	rs2187668	tag for DQ2.5	Celiac disease tag; highly sensitive marker (van Heel et al., Nat Genet 2007).	(MHC II)

*Full HLA typing requires specialized sequencing beyond standard WGS SNP calling, but these three tag SNPs serve as proxies for three of the most clinically important HLA haplotypes: the shared epitope for RA, C*06:02 for psoriasis, and DQ2.5 for celiac. Presence of any of these tag alleles warrants formal HLA typing in the clinical setting if the associated condition is suspected.*

5. Category → Cofactor → Supplement Mapping

The table below maps each functional category to the cofactors its enzymes or signaling proteins require, the supplements that supply those cofactors or modulate the pathway pharmacologically, and the dietary and lifestyle levers with evidence for each category. Doses shown are general population references, not individualized recommendations.

Category	Key cofactors	Supplement targets	Dietary / lifestyle levers
PRRs (TLR/NOD/RAGE)	Zn (for A20 and receptor structure)	Zinc 10–20 mg/d if deficient	Reduce AGE load (RAGE); limit high-heat cooking
NF-κB core	Zn, Mg, ATP	Zinc, magnesium glycinate	Polyphenols (curcumin, resveratrol, EGCG)
Inflammasome (NLRP3)	K+ efflux, ROS, lipid rafts	Omega-3 EPA/DHA 2–4 g/d	Low-dose colchicine (Rx); avoid crystal triggers
Cytokines (TNF, IL-6)	(receptors, cytokines)	Omega-3; curcumin; anti-IL-6 (Rx)	Endurance exercise, weight management
Acute phase (CRP)	Hepatic synthesis capacity	Omega-3, curcumin, statin (Rx)	Weight loss, exercise, sleep
Resolution (resolvins)	EPA, DHA, 15-LOX, 5-LOX	EPA/DHA 2–4 g/d — ESPECIALLY in FADS slow converters	Fatty fish 3–4×/wk; low ω-6 ratio
T-cell balance	Vitamin D, zinc	Vitamin D3 2000–5000 IU/d per level; zinc	Sun exposure, microbiome diversity
Oxidative-inflammatory	Se (GPx), Mn (SOD2), Fe (CAT), NADPH	Selenium 100–200 µg/d; NAC/glycine/GSH precursors	Sulforaphane (broccoli sprouts), curcumin, resveratrol (NRF2)
Complement	(hard-wired)	(limited dietary modulation)	Weight, AMD-specific AREDS formula if indicated
Chemokines / trafficking	(receptors)	(no direct)	Statin (pleiotropic chemokine effects)
Eicosanoid axis	Heme, Fe, O2, EPA vs AA substrate	EPA high-dose (icosapent ethyl if indicated)	Low ω-6:ω-3 ratio; aspirin (Rx)
Interferon / antiviral	ATP (kinase activity)	(no direct)	Vaccination; TYK2 inhibitors if indicated (Rx)
HLA	(MHC structure)	(no direct)	Gluten avoidance if DQ2.5 + celiac

6. Complete SNP Lookup Table

The table below lists every SNP catalogued in this reference with its approximate GRCh38 coordinate, to facilitate positional lookup in a VCF file. Coordinates are compiled from dbSNP (build 156 or later). Verify the contig naming convention in any given VCF ('chr1' vs '1') before running positional queries, and note that rs368234815 (IFNL4) is an indel that may require specialized calling beyond simple SNP matching. Indel variants, including CCR5-Δ32 (rs333) and the NFKB1 ATTG indel (rs28362491), may also require format-specific parsing.

Gene	rsID	GRCh38 coord	Category
AGER	rs1800625	6:32181231	PRR (RAGE)
AGER	rs2070600	6:32183793	PRR (RAGE)
AIM2	rs1103577	1:159063318	Inflammasome
ALOX15	rs2619112	17:4633276	Resolution
ALOX5	rs2115819	10:45417921	Eicosanoid
ALOX5AP	rs10507391	13:30712900	Eicosanoid
APCS	rs1374486	1:159590110	Acute phase
C3	rs2230199	19:6677832	Complement
C5	rs17611	9:121800672	Complement
CARD8	rs2043211	19:48217275	Inflammasome
CAT	rs1001179	11:34438684	Oxidative-inflam
CCL2	rs1024611	17:34255165	Chemokine
CCR2	rs1799864	3:46358273	Chemokine
CCR5	rs333	3:46373456	Chemokine (Δ32)
CFB	rs641153	6:31946816	Complement
CFH	rs1061170	1:196690107	Complement
CFH	rs1410996	1:196702810	Complement
CRP	rs1205	1:159712443	Acute phase
CRP	rs2794520	1:159710652	Acute phase
CRP	rs3091244	1:159713301	Acute phase
CTLA4	rs231775	2:203867991	T-cell
CX3CR1	rs3732378	3:39263494	Chemokine
CXCL8	rs4073	4:73740307	Chemokine

Gene	rsID	GRCh38 coord	Category
ELOVL2	rs953413	6:11044661	Resolution
FADS1	rs174537	11:61785208	Resolution
FADS2	rs174575	11:61812749	Resolution
FOXP3	rs3761548	X:49264691	T-cell
FPR2	rs1769490	19:51748020	Resolution
GPX1	rs1050450	3:49357401	Oxidative-inflam
HLA-C	rs10484554	6:31268209	HLA
HLA-DQA1	rs2187668	6:32637406	HLA
HLA-DRB1	rs660895	6:32577380	HLA
IFNG	rs2430561	12:68159741	Cytokine
IFNL3	rs12979860	19:39248147	Interferon
IFNL4	rs368234815	19:39248147	Interferon (indel)
IKBKB	rs5029748	8:42271208	NF-κB
IL10	rs1800871	1:206773552	Resolution
IL10	rs1800896	1:206773289	Resolution
IL17A	rs2275913	6:52186235	Cytokine
IL18	rs1946518	11:112164265	Inflammasome
IL1B	rs1143634	2:112837290	Cytokine
IL1B	rs16944	2:112836810	Inflammasome
IL1RN	rs4251961	2:113097213	Cytokine
IL23R	rs11209026	1:67240275	T-cell
IL4	rs2243250	5:132673462	Cytokine
IL6	rs1800795	7:22727026	Cytokine
IL6R	rs2228145	1:154454494	Cytokine (MR)
IRF5	rs2004640	7:128939577	Interferon
KEAP1	rs1048290	19:10491626	Oxidative-inflam
LTA	rs909253	6:31572779	Cytokine
LTA4H	rs17525495	12:96429572	Eicosanoid

Gene	rsID	GRCh38 coord	Category
MBL2	rs1800450	10:52771475	Complement
MEFV	rs3743930	16:3243338	Inflammasome
MPO	rs2333227	17:58269543	Oxidative-inflam
NFE2L2	rs6721961	2:177234117	Oxidative-inflam (NRF2)
NFKB1	rs28362491	4:102500998	NF-κB (ins/del)
NLRP3	rs10754558	1:247587261	Inflammasome
NLRP3	rs35829419	1:247587794	Inflammasome
NOD2	rs2066844	16:50712015	PRR
NOD2	rs2066845	16:50722629	PRR
NOD2	rs2066847	16:50729867	PRR (frameshift)
NOS2	rs2297518	17:27769571	Oxidative-inflam
OAS1	rs10774671	12:112919388	Interferon
PLA2G7	rs1051931	6:46705354	Eicosanoid
PON1	rs662	7:95308134	Oxidative-inflam
PON1	rs854560	7:95316772	Oxidative-inflam
PTGS2	rs20417	1:186680817	Eicosanoid (COX-2)
PTGS2	rs5275	1:186672878	Eicosanoid (COX-2)
PTPN22	rs2476601	1:113834946	T-cell
REL	rs13031237	2:60916922	NF-κB
RORC	rs9826	1:151820522	T-cell
SOD2	rs4880	6:159692840	Oxidative-inflam
STAT4	rs7574865	2:191099907	T-cell
TBX21	rs17250932	17:47727000	T-cell
TGFB1	rs1800470	19:41354391	Resolution
TLR2	rs5743708	4:153705165	PRR
TLR3	rs3775290	4:186083063	PRR
TLR4	rs4986790	9:117713024	PRR
TLR4	rs4986791	9:117713324	PRR

Gene	rsID	GRCh38 coord	Category
TLR9	rs5743836	3:52255693	PRR
TNF	rs1800629	6:31575254	Cytokine
TNF	rs361525	6:31575324	Cytokine
TNFAIP3	rs2230926	6:137874386	NF-κB (A20)
TNFAIP3	rs6920220	6:137685367	NF-κB (A20)
TYK2	rs34536443	19:10352442	Interferon

Note: GRCh38 positions are compiled from dbSNP and may shift by a few bases depending on reference build. For high-stakes variants (notably CFH Y402H, IL23R R381Q, PTPN22 R620W, TYK2 P1104A, and NOD2 3020insC), verify the exact coordinate against the current dbSNP entry before running positional queries.

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Database resources

dbSNP (NCBI) for rsID-to-coordinate mapping (GRCh38 build 156+).
GWAS Catalog (EBI / NHGRI) for associated-variant lookups.
OMIM for monogenic inflammatory and immunodeficiency disorders.
ClinVar for variant pathogenicity classifications (especially NOD2, CFH, TYK2).
ImmunoBase / Open Targets Genetics for prioritized immune disease variants.

8. Disclaimer

This document is an educational reference. It does not constitute medical advice, does not establish a clinician–patient relationship, and is not a substitute for individualized evaluation by a qualified healthcare provider. Genetic variants are described at the level of common-population biology; clinical interpretation in any individual depends on the full genetic background, lab measurements, medical history, current medications, and other factors that this document does not address.

Most common variants catalogued here confer small individual effects (odds ratios 1.05–1.4). Cumulative significance arises from patterns across multiple variants and from interaction with environmental factors (diet, microbiome, infections, stress, sleep, age, sex, ethnicity). A subset of variants in this document — notably PTPN22 R620W, IL23R R381Q, NOD2 3020insC, CFH Y402H, TYK2 P1104A, CCR5-Δ32, and the HLA tag SNPs — have larger and more actionable effects and warrant direct clinical discussion if found on genotyping.