Thymus & Immunosenescence Genetic Pathway Reference

Thymic output • central tolerance • peripheral T-cell homeostasis • CMV memory inflation • vaccine response • inflammaging • senescence

11 functional categories • ~67 single-SNP variants • 11 region-scan loci

Educational reference document • No personal genotype data • Generated 7 May 2026

1. Purpose and scope

This document is a standalone educational reference describing the biology of the human thymus and the immunosenescence axis, the genes that govern thymic epithelial development, central and peripheral T-cell tolerance, IL-7 / IL-2 cytokine homeostasis, T-cell receptor (TCR) signaling, the GH/IGF-1/BMP/FGF axis driving thymic regeneration, the HLA class I and II loci that shape CMV memory inflation and vaccine response, the innate-immunity sensors (TLRs) and antibody-Fc effector receptors that govern vaccine and monoclonal-antibody response, the inflammaging biomarker network (IL-6/IL-6R/CRP, IL-10, TGF-β1, GDF15, CXCL9), and the cellular senescence, telomere, and clonal-hematopoiesis (CHIP) loci that converge on age-related immune decline.

For each gene, well-studied common and rare variants are catalogued with rsID, common variant name, functional consequence, cofactor or substrate dependencies, ClinVar / PharmGKB annotation status, and the supplement, dietary, behavioral, vaccine, or pharmacologic targets that map to each pathway node. It is intended for 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, peer-reviewed mechanistic studies, OMIM, ClinVar, PharmGKB, CPIC, and meta-analyses through May 2026. Sources include Nature, Nature Genetics, Nature Aging, Cell, Cell Metabolism, Science, Science Translational Medicine, NEJM, JAMA Cardiology, Aging Cell, Immunity & Ageing, Lancet Healthy Longevity, J Immunol, J Clin Invest, Multiple Sclerosis & Related Disorders, Annals of Internal Medicine, Open Forum Infectious Diseases, the GWAS Catalog, and the dbSNP / OMIM / ClinVar / PharmGKB / CPIC databases. The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations.

Immunosenescence is highly polygenic and pleiotropic, with strong gene-environment interaction (CMV serostatus, smoking, exercise, sex, ancestry). Most common variants catalogued here confer small to modest individual effects (per-allele OR 1.05–1.50 for binary outcomes, a few percent change in cytokine levels). Clinical significance arises from cumulative patterns and convergence with environmental exposures. A small number of large-effect variants — PTPN22 R620W, IL7R T244I, the HLA class II haplotypes, FCGR3A V158F, and rare loss-of-function alleles in FOXN1, AIRE, RAG1/2, DCLRE1C, IL2RA, and FOXP3 —

produce notable phenotypes when present and are included for completeness even when their population frequency is below 1%.

Literature current through May 2026 (targeted searches run on this date). This is a Phase 2 (educational) deliverable. A separate Phase 3 personalized analysis paired with whole-genome sequencing data is generated separately and not included here.

2. Pathway biology

2.1 What immunosenescence is

Immunosenescence is the multifactorial, age-associated remodeling and decline of immune function. Its hallmarks are: (a) progressive thymic involution and loss of naïve T-cell output; (b) accumulation of terminally differentiated effector-memory T cells ($CD27^{-}CD28^{-}CD57^{+}KLRG1^{+}$) driven primarily by lifelong CMV stimulation; (c) reduced TCR repertoire diversity; (d) blunted vaccine antibody responses; (e) chronic low-grade sterile inflammation ("inflammaging") with elevated IL-6, hsCRP, TNF-α, GDF15, and CXCL9; (f) impaired NK and innate function; (g) clonal hematopoiesis of indeterminate potential (CHIP) in 10–20% of adults over 70; and (h) accelerated cellular senescence in lymphoid stromal compartments. The clinical consequences include increased infectious mortality (90% of US influenza deaths occur in adults ≥65), reactivation of latent viruses (varicella → shingles, EBV, CMV), poorer vaccine response, increased autoimmunity in some axes (loss of tolerance), increased cardiovascular events from chronic inflammation, and increased frailty.

2.2 Thymic involution and naïve T-cell output

The thymus is the only site of de novo T-cell generation. From birth it produces a diverse naïve T-cell repertoire that undergoes positive and negative selection on thymic epithelial cells (TECs). Beginning around puberty the thymus undergoes slow, programmed involution — TEC-autonomous loss of FOXN1 expression, fatty replacement of cortex/medulla, and a roughly 3% per year decline in thymopoietic output that accelerates after age 50–60. By age 70 the thymus typically produces fewer than 1% of its peak naïve T-cell output. T-cell receptor excision circles (TRECs) are episomal byproducts of V(D)J recombination and serve as a quantitative marker of recent thymic emigrants; sjTREC counts decline log-linearly with age.

Forkhead box N1 (FOXN1) is the master TEC transcription factor. In mouse models, postnatal forced upregulation of FOXN1 in fully involuted aged thymi produces robust thymic regeneration with restored naïve T-cell output and architecture indistinguishable from juvenile thymus (Bredenkamp et al., Development 2014, PMC3978836, open access). FOXN1-reprogrammed embryonic fibroblasts (FREFs) generate functional ectopic thymi in mice. Recombinant FOXN1 fusion protein increases T-cell generation in old mice (Zhao et al., Front Immunol 2024, PMC11272594, open access). In humans, common FOXN1 variants are rare; biallelic loss of function causes the nude/SCID phenotype with athymia and alopecia universalis. Zinc is an obligate cofactor: FOXN1 contains a forkhead/winged-helix DNA-binding domain whose folding

requires Zn^{2+} coordination, and mild zinc deficiency (~10% of older adults) further reduces TEC function.

Thymopoiesis is also driven by extrinsic signals. Growth hormone (GH) and IGF-1 are thymotrophic in animal models and humans (Dixit, J Immunol 2007). Sex steroids drive the post-pubertal involutional program (castration in mice rejuvenates the thymus). Glucocorticoids drive acute thymic atrophy. KGF/FGF7 (palifermin), BMP4, and IL-22 each promote TEC repair after injury. Notch ligands (DLL4) on cortical TECs commit thymocyte progenitors to the T lineage; without DLL4-Notch signaling, intrathymic precursors default to B-cell or innate fates.

2.3 Central tolerance and AIRE

Central tolerance is established in the thymic medulla. Medullary TECs (mTECs) ectopically express thousands of tissue-restricted antigens (TRAs) — insulin, thyroglobulin, retinal S-antigen, myelin proteins — under the control of the autoimmune regulator (AIRE). T cells whose TCRs bind self-peptides with high affinity are deleted by negative selection or diverted to the regulatory T-cell (Treg) lineage. Loss-of-function AIRE mutations cause autoimmune polyendocrine syndrome type 1 (APECED / APS-1), a recessive disorder with chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. Common AIRE variants modestly modulate autoimmune-thyroid and vitiligo risk. FEZF2 is an AIRE-independent mTEC-intrinsic tolerance regulator that drives expression of a partially overlapping but distinct TRA set (Takaba et al., Cell 2015). With age, AIRE expression declines; this contributes to the documented age-related rise in autoreactive T cells (Oh et al., JCI Insight 2020, PMC7526556, open access).

2.4 V(D)J recombination machinery

Random V-D-J joining of TCR (and BCR) gene segments generates the diversity of the adaptive repertoire. The recombination-activating genes RAG1 and RAG2 introduce double-strand breaks at recombination signal sequences. The non-homologous end-joining (NHEJ) machinery then repairs the breaks: DCLRE1C (Artemis) opens hairpinned coding ends, the Ku70/Ku80 heterodimer holds ends together, DNA-PKcs (PRKDC) phosphorylates downstream substrates, and LIG4 with XRCC4 and NHEJ1 (Cernunnos/XLF) ligates the joined ends. Biallelic loss of any of these produces severe combined immunodeficiency (SCID): RAG1/2 LoF → T^-B^- SCID, with hypomorphic alleles producing Omenn syndrome; DCLRE1C LoF → radiosensitive SCID; LIG4 LoF → LIG4 syndrome (immunodeficiency, microcephaly, radiosensitivity).

2.5 Peripheral T-cell homeostasis: IL-7 / IL-2

IL-7, produced primarily by stromal cells in lymph nodes, bone marrow, and thymus, is the obligatory survival cytokine for naïve and memory T cells. Its receptor is IL-7Rα (IL7R, CD127) paired with the common γ-chain (IL2RG). The IL7R variant rs6897932 (T244I) generates an alternatively spliced isoform with increased soluble IL-7Rα production, altering IL-7 bioavailability. The C-allele is a risk factor for multiple sclerosis (most recent meta-analysis:

Omraninava et al., MSARD 2021 — 33 case-control studies, 19,351 cases vs 21,005 controls — recessive model OR 0.84, 95% CI 0.77–0.92, p<0.001 for protective TT genotype), ankylosing spondylitis, and primary biliary cholangitis. The TT genotype is favorable for peripheral T-cell homeostasis. IL-7 signaling is also a therapeutic axis: recombinant IL-7 has been tested in lymphopenic states (sepsis, post-HSCT).

IL-2 controls Treg homeostasis and effector tolerance. IL-2RA (CD25) is the high-affinity α-subunit. The risk haplotype tagged by rs2104286 lowers CD25 expression on Tregs and reduces STAT5 phosphorylation in response to IL-2, contributing to type-1 diabetes and multiple sclerosis risk (Garg et al., J Immunol 2012). FOXP3 is the X-linked master transcription factor of natural Tregs; biallelic LoF causes IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) — a fatal early-onset autoimmune disease. Common FOXP3 promoter variants (rs3761548, rs3761549) modestly modify autoimmune thyroid disease risk in some populations.

2.6 TCR signaling and tolerance

PTPN22 encodes a hematopoietic-specific protein tyrosine phosphatase (Lyp) that dampens TCR signaling. The R620W variant (rs2476601, C1858T) is a gain-of-function allele that more strongly inhibits TCR signaling, paradoxically allowing autoreactive clones to escape negative selection. The most recent comprehensive meta-analysis (Hosseini et al., Immunol Res 2025 — 43 studies, 9,397 autoimmune-disease cases vs 20,669 controls) confirms strong associations across rheumatoid arthritis, type-1 diabetes, SLE, autoimmune thyroid disease, and vitiligo (dominant model OR ≈ 1.69, recessive OR ≈ 2.50). PTPN22 R620W interacts strongly with smoking for ACPA-positive RA (joint OR ≈ 2.2, Begovich et al. updated meta-analysis). The W620 allele is essentially absent from East Asian and African populations and reaches MAF ≈ 8–10% in Northern Europeans.

CTLA-4 (CD152) is the central co-inhibitory receptor on Tregs and activated effectors; it competes with CD28 for B7 ligands. The CTLA4 T17A coding variant (rs231775) and the 3' UTR variant CT60 (rs3087243) are linked risk factors for Graves' disease, type-1 diabetes, RA, and Hashimoto's thyroiditis. The W620 / T17A combination markedly amplifies autoimmunity risk.

2.7 CMV memory inflation and HLA class I

Cytomegalovirus (CMV) is the single largest known driver of human immunosenescence. ~50–80% of adults globally are CMV-seropositive, and lifelong stimulation by CMV antigens drives massive oligoclonal expansion of $CD8^{+}CD27^{-}CD28^{-}$ effector-memory T cells ("memory inflation") that can occupy >10–50% of the entire CD8 repertoire by age 75 and crowd out naïve cells. CMV downregulates HLA-A and HLA-B from infected-cell surfaces but spares HLA-C (which serves as the dominant ligand for inhibitory KIRs on NK cells); aged CMV-positive individuals develop HLA-C-restricted CD8 expansions occupying the dominant memory pool (Davies et al., Front Immunol 2017, PMC5732243, open access). HLA-A2, HLA-B7, HLA-B8, HLA-B35 are well-characterized CMV-immunodominant alleles. Recent murine work (Coplen et al., J Immunol

2024, PMC11463719, open access) suggests that memory inflation magnitude is set by lymphatic endothelial cell (LEC) niche size and may attenuate in late life as the LEC compartment shrinks.

KIR receptors on NK cells "license" through interaction with self-HLA. KIR haplotypes are categorized as A (mostly inhibitory) or B (more activating); B haplotypes confer better CMV control and lower transplant relapse but higher autoimmune risk in some axes. KLRC2 (NKG2C) is an activating C-type lectin receptor that expands on "adaptive" or "memory-like" NK cells in CMV-positive individuals. A common ~16 kb deletion of KLRC2 (homozygous in ~4% of Europeans) impairs adaptive-NK CMV control. Detection requires copy-number aware analysis on the BAM.

2.8 HLA class II and vaccine response

HLA class II molecules (DR, DQ, DP) on professional APCs present peptides to $CD4^+$ helper T cells, which then license B-cell antibody responses. Class II haplotypes are the strongest known modifiers of vaccine antibody titer. UK Biobank GWAS of >50,000 vaccinated adults (Mentzer et al. 2024, Genetic determinants of IgG antibody response to COVID-19 vaccination, PMC10806743, open access) identified HLA-DRB1*13:02 as the strongest single protective allele against vaccine seronegativity (MAF 4%, OR 0.75 per allele, $p = 2.34 \times 10^{-16}$), and HLA-DPB1 rs9277534 as a major locus. The Doetinchem older-adult cohort (Drost et al. 2024, PMC12588338, open access) similarly identified the HLA region as accounting for ~9% of variance in primary SARS-CoV-2 antibody response.

HLA class II haplotypes also tag autoimmune-priming risk: DRB1*03:01-DQB1*02:01 (DR3-DQ2, tagged by rs2187668) for celiac, T1D, SLE; DRB1*04:01/04 with DQB1*03:02 (DR4-DQ8, tagged by rs7454108) for RA and T1D; DRB1*15:01 (tagged by rs3135388) for multiple sclerosis. Tag-SNP-based ascertainment is approximate; precise typing requires HLA*LA, OptiType, or arcasHLA on the BAM/CRAM. Several class II alleles also predict drug hypersensitivity (e.g. HLA-DRB1*07:01 for lapatinib hepatotoxicity).

2.9 Innate vaccine sensors and Fc receptors

Toll-like receptors (TLRs) provide the innate adjuvant signaling that sets the magnitude of the adaptive vaccine response. TLR3 (dsRNA), TLR7 and TLR8 (ssRNA), and TLR9 (CpG-DNA) are the most relevant for viral and adjuvanted vaccines. Functional polymorphisms include TLR3 rs3775291 (L412F), TLR4 rs4986790 (D299G) and rs4986791 (T399I), TLR7 rs179008 (Q11L) and rs5741880, TLR8 rs3764879, and TLR9 rs5743836 and rs187084. In a pediatric inactivated-influenza vaccine trial, TLR7 rs5741880 GT and TLR8 rs3764879 GT genotypes were each associated with substantially reduced post-vaccination HAI ≥ 1:40 (TLR7 OR 0.22, TLR8 OR 0.47, after multiple-testing correction; PMC9940051, open access).

Antibody Fcγ receptors mediate effector functions, particularly antibody-dependent cellular cytotoxicity (ADCC). FCGR3A (CD16a) carries the V158F variant (rs396991): the V/V genotype binds IgG1 with substantially higher affinity than F/F, producing greater ADCC against

monoclonal-antibody-coated targets. CPIC and PharmGKB level 2A annotation: V/V genotype predicts better response to rituximab, trastuzumab, and cetuximab in oncology contexts. FCGR2A (CD32a) carries H131R (rs1801274) with similar effects on IgG2 binding. Both are practically important pharmacogenomic variants if therapeutic monoclonal antibodies are ever indicated.

2.10 Inflammaging biomarkers

Inflammaging refers to the chronic, low-grade, sterile inflammatory state that accumulates with age and drives cardiovascular disease, sarcopenia, frailty, dementia, and mortality. The IL-6 / IL-6R / CRP axis is its dominant signaling hub. The IL6 promoter variant -174 G>C (rs1800795) tags a high-IL-6-producer haplotype in Caucasians (G/G higher) but the direction reverses in some Asian populations. The IL6R Asp358Ala variant (rs2228145, A358C, A>C) increases proteolytic shedding of soluble IL-6R and reduces classic (membrane-IL-6R) signaling — the C/C "natural-tocilizumab" genotype is associated with lower CHD risk and lower autoimmune-disease risk (IL6R Mendelian Randomization Consortium, Lancet 2012). CRP variants (rs1205, rs2794520) tag baseline-CRP differences.

IL-10 (anti-inflammatory) promoter variants (rs1800896 -1082 G>A, rs1800872 -592 C>A) tag low/high producer haplotypes. TNF -308 G>A (rs1800629) tags a higher-TNF haplotype. TGF-β1 codon-10 (rs1800470) and -509 (rs1800469) tag a high-producer pro-fibrotic / Treg-promoting haplotype. Growth differentiation factor 15 (GDF15) is one of the strongest single-protein predictors of all-cause mortality in older adults (Tavenier et al., GeroScience 2021, PMC8492834; Sayed et al., Nat Aging 2021, PMC8654267); both circulating and DNA-methylation-predicted GDF15 levels independently predict mortality (Wennberg et al. 2024, multiple cohorts). The GDF15 H202D coding variant (rs1058587) interferes with some immunoassays. CXCL9 is the dominant component of the iAge inflammatory clock (Sayed et al., Nat Aging 2021) and predicts cardiovascular aging and mortality independently of CRP (PMC11427528).

Therapeutically, low-dose colchicine had previously been considered for residual-inflammation cardiovascular risk based on the COLCOT (NEJM 2019) and LoDoCo2 (NEJM 2020) trials. The substantially larger CLEAR SYNERGY (NEJM 2024 — 7,062 post-MI patients, 3.5y follow-up) was negative for the composite primary outcome despite confirmed CRP reduction, and population-level secondary-prevention recommendations have been retracted accordingly (ACC summary, Nov 2024). Targeted IL-6 ligand inhibition with the monoclonal antibody ziltivekimab is being tested in the ZEUS trial (NCT05021835, n=6,376 with CKD + ASCVD + hsCRP ≥2 mg/L; Ridker et al., JAMA Cardiol 2026 baseline characterization, open access); CV outcome readout expected 2026–2027. Anti-IL-1β (canakinumab; CANTOS NEJM 2017 positive) is no longer commercially available for prevention indications.

2.11 Senescence, telomere, and clonal hematopoiesis

Cellular senescence — irreversible cell-cycle arrest with secretion of the senescence-associated secretory phenotype (SASP) — is one of the canonical hallmarks of aging. The CDKN2A/B locus on chromosome 9p21 encodes p16^INK4a, p14^ARF, and the long non-coding RNA ANRIL; this locus is the strongest single common-variant locus for coronary artery disease (per-allele OR ≈ 1.28) and is also independently associated with type-2 diabetes and several cancers. Telomere length is heritable ($h^2 \approx 0.4–0.6$) and correlates inversely with biological age. The TERT rs2736100 variant tags longer leukocyte telomere length; the longer-telomere allele is generally protective for cardiovascular and neurodegenerative outcomes but slightly increases melanoma and glioma risk.

Clonal hematopoiesis of indeterminate potential (CHIP) — the somatic acquisition of leukemia-driver mutations (DNMT3A, TET2, ASXL1, JAK2 V617F, SF3B1, etc.) by a hematopoietic stem cell with subsequent expansion to ≥2% variant allele frequency in peripheral blood — is present in ~10–15% of adults over 70 and is independently associated with hematologic malignancy (~10× relative risk) and cardiovascular events (~2× relative risk via macrophage IL-1β/IL-6). CHIP detection requires VAF-aware somatic calling on a BAM/CRAM and is not resolved by standard germline VCF analysis. The germline JAK2 46/1 haplotype (tagged by rs10974944 and rs12343867) predisposes to acquiring the somatic JAK2 V617F mutation in myeloproliferative neoplasms; the 46/1 G allele raises MPN risk roughly 3-fold. Germline rs77375493 (JAK2 V617F position) is essentially always reference in healthy individuals — a non-reference call here in a germline VCF most likely indicates contamination, mosaicism, or somatic CHIP captured at high VAF.

2.12 Therapeutic levers across the pathway

The therapeutic landscape spans well-established interventions, emerging trials, and preclinical programs. Vaccination is the most evidence-supported lever: recombinant zoster vaccine (Shingrix, RZV) has 90–97% efficacy at age ≥50 in pivotal RCTs (ZOE-50/70) and 76% real-world effectiveness over 4 years in nearly 2 million Medicare beneficiaries (Zerbo et al., Ann Intern Med 2024); high-dose / adjuvanted influenza vaccines (Fluzone HD, Fluad) and pneumococcal conjugate vaccines (PCV20, PCV21) compensate for senescent vaccine response in older adults.

Low-dose mTORC1 inhibition with everolimus (RAD001) or rapamycin enhances influenza vaccine antibody titer ~20% and reduces overall infection rate in elderly subjects (Mannick et al., Sci Transl Med 2014 and 2018). The recombinant-FOXN1 / FREF / iTEC programs remain preclinical (mouse) as of 2026. The TRIIM trial (Fahy et al., Aging Cell 2019, open access — n=9 men aged 51–65, personalized rhGH + DHEA + metformin for 1 year) reported MRI-detectable thymic regeneration, reduced PD-1$^+$ T cells, improved CD4/CD8 ratio, and ~2.5-year reversal of GrimAge epigenetic age. The follow-on TRIIM-X trial (NCT04375657, n=85, primary completion Nov 2024) has presented preliminary findings at conferences but has no peer-

reviewed publication as of May 2026; recommendations based on TRIIM/TRIIM-X are therefore still at evidence Grade C.

Senolytic combinations (dasatinib + quercetin, fisetin) have been tested in small open-label trials for diabetic kidney disease, idiopathic pulmonary fibrosis, and frailty markers; the evidence base is too small and heterogeneous for population recommendations. Zinc 15–25 mg/d supports FOXN1 and AIRE PHD-finger function in mild deficiency (Wessells et al., Adv Nutr 2012). Habitual aerobic and resistance exercise reproducibly increases naïve T-cell pool and TCR repertoire diversity in older adults (Duggal et al., Aging Cell 2018) and reduces hsCRP and IL-6 over time. CMV antiviral suppression (valaciclovir) reduces memory inflation in animal models but no controlled human outcome trial supports prophylactic antiviral use in CMV-positive elderly.

3. Functional categories: genes, variants, and cofactors

3.1 Thymic epithelial development and FOXN1 axis

FOXN1 is the master TEC transcription factor; its progressive postnatal decline causes age-related involution. Forced re-expression of FOXN1 in aged mice fully reverses involution and restores naïve T-cell output (Bredenkamp 2014). PAX1, EYA1, HOXA3, and TBX1 pattern the third pharyngeal pouch into thymus and parathyroid; LoF in any of these causes thymic hypoplasia syndromes. Common variants in this category are rare-effect; the heavy lifting at this node is done by zinc-cofactor adequacy and by hormonal/metabolic regulators that modulate FOXN1 expression.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
FOXN1	rs11078534	Modest associations with thymic-output proxies in older adults; deep regulatory variant in TEC-master TF	Bredenkamp 2014 Development PMC3978836; Zhao 2024 Front Immunol PMC11272594	Modest
FOXN1	rs2305558	Tag SNP in FOXN1 region; small effect on TEC mass proxies	Reviewed in Oh 2020 JCI Insight PMC7526556	Modest
FOXN1	rare LoF (compound het)	Nude/SCID phenotype: athymia + alopecia universalis; ClinVar pathogenic	OMIM 600838	Severe (rare)
PAX1	rs2236087	Coding tag SNP; pharyngeal-arch and TEC scaffold; biallelic LoF → otofaciocervical syndrome with thymic hypoplasia	OMIM 167411	Modest common; severe rare
EYA1	(LoF rare)	Branchio-oto-renal syndrome with thymic defects	OMIM 601653	Severe (rare)
HOXA3	—	Patterns the third pharyngeal pouch	Manley &	Severe

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
		(TEC anlage); rare LoF severe	Capecchi 1995 Dev Biol	(rare)
TBX1	(22q11.2 deletion)	DiGeorge / 22q11.2 deletion syndrome — thymic aplasia or hypoplasia	OMIM 188400	Severe (rare)

Cofactor / supplement target: zinc (FOXN1 forkhead-domain folding), adequate protein-energy intake (postnatal TEC maintenance).

3.2 Central tolerance — AIRE and FEZF2

AIRE drives ectopic expression of >3,000 tissue-restricted antigens in mTECs to enable negative selection. Biallelic AIRE LoF causes APECED / APS-1 (autoimmune polyendocrine syndrome type 1) with chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. Common AIRE variants modulate susceptibility to autoimmune thyroid disease and vitiligo subtly. FEZF2 acts in parallel as an AIRE-independent mTEC tolerance regulator.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
AIRE	rs2075876 (G>A)	Intronic regulatory variant; A allele weak association with autoimmune-thyroid	Berger 2013 J Clin Endocrinol Metab	Modest
AIRE	rs760426	Intronic variant; weak alopecia areata association	Tazi-Ahnini 2002 Hum Genet	Modest
AIRE	rs878081	Intronic variant; weak vitiligo association in some cohorts	Birlea 2008 Hum Mol Genet	Modest
AIRE	(LoF biallelic, rare)	APECED / APS-1; ClinVar pathogenic	OMIM 240300	Severe (rare)
FEZF2	rs7625200	mTEC AIRE-independent tolerance regulator; tag SNP	Takaba 2015 Cell	Modest

Cofactor target: zinc (AIRE PHD-finger folding requires Zn^{2+}); adequate vitamin D for Treg balance.

3.3 V(D)J recombination machinery

Random V-D-J joining of TCR (and BCR) gene segments by RAG1/2 and the NHEJ DSB-repair machinery generates adaptive repertoire diversity. Biallelic LoF in any component produces SCID. Common variants are scarce; this is largely a Mendelian-disease category.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
RAG1, RAG2	(LoF biallelic, rare)	T^-B^- SCID (full LoF); Omenn syndrome (hypomorphic); ClinVar pathogenic	OMIM 179615 / 601457	Severe (rare)
DCLRE1C (Artemis)	rs41298872	Hairpin opening at coding ends; tag SNP; LoF → radiosensitive SCID	OMIM 605988	Modest common;

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
				severe rare
PRKDC (DNA-PKcs)	rs7830743	NHEJ kinase; LoF → radiosensitive SCID	OMIM 600899	Modest common; severe rare
LIG4	rs1805388 (T9I)	NHEJ ligation; coding variant; LoF → LIG4 syndrome	OMIM 601837	Modest common; severe rare
NHEJ1 (Cernunnos /XLF)	(LoF rare)	NHEJ scaffold; LoF SCID with growth retardation	OMIM 611290	Severe (rare)

Therapeutic target: none for common variants; allogeneic HSCT and gene therapy for SCID-causing biallelic LoF.

3.4 IL-7 / IL-2 cytokine homeostasis and Tregs

IL-7 sustains naïve and memory T-cell survival. IL-2 / IL-2RA controls Treg homeostasis and effector tolerance. The IL7R rs6897932 T244I variant is among the strongest non-HLA MS risk variants — most recent meta-analysis: 33 case-control studies, 19,351 cases vs 21,005 controls, recessive model OR 0.84, 95% CI 0.77–0.92 for the protective TT genotype (Omraninava 2021).

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
IL7R	rs6897932 (T244I)	Splicing of exon 6 → soluble IL-7Rα; affects IL-7 bioavailability	Lundmark 2007 Nat Genet; Omraninava 2021 MSARD meta	C-allele = MS/AS/PBC risk; TT protective
IL2	rs2069762	Promoter -330 T>G; modest T1D and IBD associations	John 2003 Genes Immun	Modest
IL2RA (CD25)	rs2104286	Lower CD25 on Tregs; reduced IL-2 STAT5 signaling	Garg 2012 J Immunol; Maier 2009 PLoS Genet	G-allele = T1D, MS risk
IL2RA	rs12722489	Independent IL2RA risk haplotype; T1D and MS	Lowe 2007 Nat Genet	C-allele = risk
IL2RA	rs41295061 (rare)	Coding variant near α-chain interface	Reviewed Cerosaletti 2018 Trends Immunol	Modest
FOXP3	rs3761548	Promoter -3279 A>C; modest autoimmune-thyroid risk	Bossowski 2014 Endocrine; meta-analyses mixed	Modest
FOXP3	rs3761549	Promoter regulatory variant	Several mixed meta-analyses	Modest
FOXP3	(LoF biallelic, rare)	IPEX syndrome — fatal early-onset autoimmunity (X-linked recessive)	OMIM 304790	Severe (rare)

Therapeutic targets: low-dose IL-2 (Treg-selective expansion, in trials); rapamycin (Treg-augmenting).

3.5 TCR signaling and tolerance

PTPN22 R620W (rs2476601) is the largest non-HLA autoimmunity allele in Europeans. Hosseini et al. 2025 meta-analysis (43 studies, 9,397 cases vs 20,669 controls): dominant model OR ≈ 1.69, recessive OR ≈ 2.50 across multiple autoimmune diseases. Risk is amplified by smoking (Begovich-style joint OR ≈ 2.2 for ACPA-positive RA).

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
PTPN22	rs2476601 (R620W, C1858T)	Gain-of-function; dampens TCR signal → autoreactive escape; major non-HLA autoimmunity locus	Hosseini 2025 Immunol Res meta-analysis; Bottini 2014 Ann Rev Med	T-allele = RA, T1D, SLE, Hashimoto, vitiligo risk; MAF ~8–10% EUR
PTPN2	rs2542151	TC-PTP; TCR signaling brake; T1D / IBD modest	Smyth 2008 Nat Genet	Modest
CTLA4	rs231775 (T17A, +49 A>G)	Coding variant; reduced co-inhibition; classical Graves' / T1D / RA risk	Donner 1997 J Clin Endocrinol Metab; Plenge 2007 Nat Genet meta	G-allele = autoimmune risk
CTLA4	rs3087243 (CT60, +6230 G>A)	3' UTR; Treg / mRNA stability; linked to rs231775	Ueda 2003 Nature	G-allele = autoimmune risk
CD28	rs3116496	Co-stimulation; modest T1D / RA association in some cohorts	Plenge 2007 Nat Genet	Modest

Therapeutic targets: smoking cessation (interacts strongly with PTPN22 R620W for ACPA RA); abatacept (CTLA-4-Ig) is approved for RA; rapamycin-based protocols are Treg-augmenting and partially counterweight PTPN22 risk.

3.6 Thymic regeneration signaling — GH/IGF-1/BMP/FGF

Growth hormone (GH) and IGF-1 are thymotrophic. The TRIIM trial (Fahy 2019, n=9 men age 51–65, open access) reported MRI-detectable thymic regeneration with rhGH + DHEA + metformin for 1 year, reduced PD-1^{+} T cells, improved CD4/CD8 ratio, and ~2.5-year GrimAge reversal. TRIIM-X (NCT04375657, n=85, primary completion Nov 2024) is the follow-on but no peer-reviewed results are published as of May 2026. Long-term GH safety in healthy adults — particularly cancer risk — remains an open question; recommendations remain at Grade C.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
GHR	rs6184	Coding variant; modest GH-action effect	Dos Santos 2004 Nat Genet	Modest

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
GHR	rs6182 (exon-3 deletion d3-GHR proxy)	d3-GHR allele → enhanced GH signaling and IGF-1 response	Dos Santos 2004 Nat Genet; Audí 2006 J Clin Endocrinol Metab	d3-allele = stronger GH response
IGF1	rs35767 (-1245)	Promoter; modest IGF-1 levels association	Vaessen 2001 Diabetes	Modest
IGF1R	rs2229765	Codon 1013 G>A; IGF-1 receptor signaling; longevity association in some cohorts	Bonafè 2003 J Clin Endocrinol Metab	Mixed; A-allele weakly longevity-associated
GH1	rs2665802	Promoter; modest GH levels association	Horan 2003 J Clin Endocrinol Metab	Modest
FGF7 (KGF)	—	TEC-regenerative cytokine; recombinant palifermin used post-HSCT for mucositis	Spielberger 2004 NEJM	Therapeutic
BMP4	—	TEC regeneration after damage	Tsai 2003 J Immunol	Therapeutic axis
NOTCH1	—	T-lineage commitment via DLL4; LoF severe	Radtke 1999 Immunity	Severe (rare)

Therapeutic levers: TRIIM regimen (rhGH + DHEA + metformin; Grade C); recombinant palifermin (KGF) post-HSCT (Grade A in that setting); intermittent caloric restriction may transiently reduce IGF-1 (cross-references your IGF1 report).

3.7 HLA class I — CMV, NK, KIR, NKG2C

HLA-A/B/C present CMV peptides to CD8 T cells. CMV downregulates A and B but spares C; aged carriers develop HLA-C-restricted memory expansions (Davies 2017). KIR receptors and KLRC2 (NKG2C) modulate NK control of CMV. Tag-SNP-based ascertainment is approximate; full HLA typing requires HLA*LA, OptiType, or arcasHLA. KIR copy-number and KLRC2 deletion require structural variant calling on the BAM/CRAM.

Gene / locus	Variant / rsID	Functional consequence	Source	Risk / direction
HLA-A, -B, -C	(4-digit typing required)	Determines which CMV peptides are presented; A2, B7, B8, B35 immunodominant for CMV	Sylwester 2005 J Exp Med	Allele-specific
HLA-C	(low-expression alleles)	Spared from CMV downregulation → drives HLA-C-restricted memory inflation in elderly	Davies 2017 Front Immunol PMC5732243	Carrier status modifies memory inflation magnitude
KIR2DL/2DS, 3DL/3DS	(haplotype A vs B)	NK-cell licensing; B-haplotype better CMV control, more autoimmunity	Hsu 2002 Immunol Rev	Haplotype-dependent
KLRC2	deletion (16 kb)	Activating receptor on adaptive NK	Beziat 2013	Homozygou

Gene / locus	Variant / rsID	Functional consequence	Source	Risk / direction
(NKG2C)		cells; deletion impairs CMV control	Eur J Immunol	s deletion ~4% EUR
KLRC2	rs2734414	Tag SNP; coding region	Béziat 2013	Modest
HCP5	rs2395029	MHC-I region tag SNP (linked to HLA-B*57:01); HIV slow-progression marker; abacavir hypersensitivity tag (CPIC)	Mallal 2008 NEJM	G-allele = slow HIV progression / abacavir HSR risk

Therapeutic note: CMV-seronegative individuals should weigh seroconversion risk through transfusion / transplant. CMV antiviral suppression is investigational in immunosenescence.

3.8 HLA class II — vaccine response and autoimmune priming

Class II haplotypes are the strongest known modifiers of vaccine antibody response. UK Biobank GWAS of >50,000 vaccinated adults identified DRB1*13:02 as the strongest single protective allele against vaccine seronegativity (Mentzer 2024, PMC10806743). Class II haplotypes also tag autoimmune-priming risk.

Locus / haplotype	Tag rsID	Functional consequence	Source	Direction
HLA-DRB1*03:01-DQB1*02:01 (DR3-DQ2)	rs2187668	Celiac, T1D, SLE risk	Trynka 2011 Nat Genet	Risk
HLA-DRB1*04:01/04 with DQB1*03:02 (DR4-DQ8)	rs7454108	RA and T1D risk	Plenge 2007 Nat Genet	Risk
HLA-DRB1*15:01 (DR15)	rs3135388	Multiple sclerosis (strongest risk)	Sawcer 2011 Nature	Risk
HLA-DRB1*07:01	—	Drug hypersensitivity (lapatinib, asparaginase) — CPIC level 1B/2A	Spraggs 2011 J Clin Oncol	Drug PGx
HLA-DPB1	rs9277534	COVID and HBV vaccine antibody response	Mentzer 2024 PMC10806743	Modulator
HLA-DRB1*13:02	—	Protective against vaccine IgG seronegativity (OR 0.75)	Mentzer 2024	Protective
HLA-DRB1*04:01-RA tag	rs6910071	Tag SNP for RA-shared-epitope alleles	Plenge 2007 Nat Genet	Risk if positive
HLA-C*06:02 (psoriasis tag)	—	Psoriasis; strongest single locus	Strange 2010 Nat Genet	Risk

*Critical caveat: tag-SNP-based HLA ascertainment is coarse and produces both false-positive and false-negative haplotype assignments. Definitive HLA typing requires sequencing-based methods on the BAM/CRAM (HLA*LA, OptiType, arcasHLA, T1K).*

3.9 Innate vaccine sensors and Fc receptors

TLRs provide innate adjuvant signaling that sets adaptive vaccine response magnitude. FCGR3A V158F is a CPIC level 2A pharmacogenomic variant for therapeutic monoclonal antibodies (rituximab, trastuzumab, cetuximab).

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
TLR3	rs3775291 (L412F)	dsRNA sensor; reduced HSE / poliovirus susceptibility variant; mixed vaccine-response data	Zhang 2007 Science	T-allele = LoF, modest
TLR4	rs4986790 (D299G)	LPS sensor; LoF reduces inflammatory response	Arbour 2000 Nat Genet	G-allele = LoF
TLR4	rs4986791 (T399I)	Linked to D299G; co-segregating LoF haplotype	Arbour 2000 Nat Genet	T-allele = LoF
TLR7	rs179008 (Q11L)	ssRNA sensor; X-linked; modest vaccine-response association	Møller-Larsen 2008 Allergy	Modest
TLR7	rs5741880	Promoter; reduced HAI ≥1:40 post-influenza-vaccine in pediatric cohort (OR 0.22)	Yan 2023 PMC9940051	GT genotype = lower titer
TLR8	rs3764879	ssRNA; reduced HAI titer in pediatric influenza-vaccine cohort (OR 0.47)	Yan 2023 PMC9940051	GT = lower titer
TLR9	rs5743836 (-1237 T>C)	CpG-DNA sensor; promoter; mixed vaccine and inflammation associations	Hamann 2006 Eur J Immunogenet	Modest
TLR9	rs187084	Linked TLR9 promoter variant	Several reviews	Modest
MyD88	(LoF rare)	Adaptor; biallelic LoF → severe pyogenic bacterial susceptibility	von Bernuth 2008 Science	Severe (rare)
IRF7	rs1131665	Type-I IFN; LoF severe COVID/influenza	Zhang 2020 Science (severe COVID)	LoF severe
FCGR3A	rs396991 (V158F)	NK ADCC affinity; V/V higher; CPIC level 2A for rituximab/trastuzumab/cetuximab	Cartron 2002 Blood; PharmGKB	V/V favorable for mAb response
FCGR2A	rs1801274 (H131R)	IgG2 binding; H/H higher; modest pneumococcal vaccine response	Bredius 1995 J Infect Dis	H-allele = higher binding

Pharmacogenomic action: FCGR3A V/V (or V/F) genotype is informational for any future therapeutic monoclonal-antibody decision.

3.10 Inflammaging biomarker genetics

The inflammaging cytokine network is genetically heritable in modest part. The IL6 -174 G>C, IL6R Asp358Ala, IL10 promoter, TNF -308, TGFB1 codon-10/-509, GDF15 H202D, and CXCL9 variants together tag a substantial portion of inter-individual baseline cytokine variance. CRITICAL UPDATE (May 2026): CLEAR SYNERGY (NEJM 2024) was negative for low-dose

colchicine post-MI, superseding COLCOT/LoDoCo2 — population-level secondary-prevention recommendations have been retracted.

Gene	Variant / rsID	Functional consequence	Source	Risk / direction
IL6	rs1800795 (-174 G>C)	Promoter; G/G = high-IL-6 producer in Caucasians	Fishman 1998 J Clin Invest	G-allele = high-producer
IL6	rs1800796 (-572 G>C)	Promoter; effects partially population-specific	Smith 2008 Hum Mol Genet	Modest
IL6R	rs2228145 (Asp358Ala, A>C)	Increased shedding → reduced classic IL-6 signaling; "natural-tocilizumab"	IL6R MR Consortium 2012 Lancet	C-allele = lower CHD risk, lower autoimmunity
CRP	rs1205 (3' UTR)	Baseline CRP levels	Crawford 2006 Ann Hum Genet	T-allele = lower CRP
CRP	rs2794520	Promoter; baseline CRP	Dehghan 2011 Circulation GWAS	Modulator
IL10	rs1800896 (-1082 G>A)	Promoter; G-allele = high-producer	Turner 1997 Eur J Immunogenet	G-allele = high-producer (anti-inflammatory)
IL10	rs1800872 (-592 C>A)	Promoter; linked to -1082; tag of low/high-producer haplotypes	Turner 1997	A-allele = low-producer
TNF	rs1800629 (-308 G>A)	Promoter; A-allele = higher TNF	Wilson 1997 Proc Natl Acad Sci	A-allele = high-producer
TGFB1	rs1800469 (-509 C>T)	Promoter; T-allele = higher TGF-β1	Grainger 1999 Hum Mol Genet	T-allele = high-producer
TGFB1	rs1800470 (codon 10, T29C, L10P)	Coding; C-allele = higher TGF-β1 secretion	Awad 1998 Hum Immunol	C-allele = high-producer
GDF15	rs1058587 (H202D)	Coding variant; can interfere with some immunoassays	Brown 2005 Lancet	Assay caveat
GDF15	rs888663	cis-eQTL near GDF15	Sun 2018 Nature (UKBB pQTL)	Modulator
CXCL9	rs10336	iAge dominant component; aging endothelium chemokine	Sayed 2021 Nat Aging PMC8654267	Inflammaging marker

Cofactor / supplement / drug targets: EPA/DHA (3 g/d) reproducibly lowers IL-6 and CRP; statins lower hsCRP; ziltivekimab (anti-IL-6 ligand mAb, ZEUS trial NCT05021835, n=6,376, readout 2026–2027) is the leading targeted IL-6 trial; canakinumab (anti-IL-1β; CANTOS positive but no longer commercially available for prevention); tocilizumab / sarilumab (anti-

IL-6R; approved for RA and giant-cell arteritis); colchicine population-level recommendation withdrawn after CLEAR SYNERGY 2024.

3.11 Senescence, telomere, 9p21, and clonal hematopoiesis

9p21 (CDKN2A/B/ANRIL) is the strongest single common-variant CAD locus (per-allele OR ≈ 1.28). TERT longer-telomere alleles are generally protective for cardiovascular and neurodegenerative outcomes but slightly increase melanoma and glioma risk. CHIP detection requires VAF-aware somatic calling on the BAM and is not resolved by germline VCF analysis; the JAK2 46/1 germline haplotype (rs10974944, rs12343867) tags predisposition to acquiring somatic JAK2 V617F.

Gene / locus	Variant / rsID	Functional consequence	Source	Risk / direction
TERT	rs2736100 (intron 2)	Telomere length QTL; longer-telomere allele	Codd 2013 Nat Genet (telomere length GWAS)	C-allele = longer telomeres (mostly favorable)
TERT	rs2853669 (promoter)	Affects ETS-binding; modest	Codd 2021 Nat Aging	Modulator
TERC	rs10936599	Telomere length QTL	Codd 2013 Nat Genet	C-allele = longer telomeres
CDKN2A/B (9p21)	rs10757278 (G>A)	ANRIL lncRNA region; CAD per-allele OR ≈ 1.28	Helgadottir 2007 Science; Burdon 2008 (LoDoCo2 era)	G-allele = CAD risk
CDKN2A/B (9p21)	rs1333049	Linked CAD locus tag	WTCCC 2007 Nature	C-allele = risk
CDKN2A	rs2811712, rs1063192	Independent 9p21 signals; senescence regulator	Helgadottir 2007	Modest
DNMT3A, TET2, ASXL1	(somatic CHIP drivers)	Require VAF-aware somatic calling on BAM/CRAM; not resolved by germline VCF	Jaiswal 2014 NEJM; Steensma 2015 Blood	Outside germline scope
JAK2	rs77375493 (V617F somatic)	Somatic driver of MPN/CHIP; germline call should be reference	Baxter 2005 Lancet; Jaiswal 2017 NEJM	Non-ref germline = anomalous
JAK2	rs10974944 (46/1 haplotype tag)	Germline haplotype predisposing to somatic V617F acquisition	Jones 2009 Nat Genet	G-allele = MPN predisposition (~3×)
JAK2	rs12343867 (linked 46/1 tag)	Linked 46/1 marker	Olcaydu 2009 Nat Genet	C-allele = predisposition

Therapeutic levers: smoking cessation (massive 9p21 effect-size attenuation); statins / PCSK9 inhibitors / ezetimibe for 9p21 CAD risk; senolytic combinations remain experimental; CHIP

carriers may benefit from anti-inflammatory therapy (post-hoc CANTOS subgroup analysis suggests TET2/DNMT3A CHIP carriers had largest IL-1β-blockade benefit).

4. Summary mapping — categories → genes → cofactors → therapeutic targets

Category	Key genes	Cofactors / substrates	Therapeutic / supplement targets
Thymic epithelium / FOXN1	FOXN1, PAX1, EYA1, HOXA3, TBX1	Zinc; protein-energy; thyroid hormone	Zinc 15–25 mg/d; FOXN1 reactivation (preclinical)
Central tolerance / AIRE	AIRE, FEZF2	Zinc (PHD finger)	Zinc; vitamin D for Treg balance
V(D)J recombination	RAG1/2, DCLRE1C, PRKDC, LIG4, NHEJ1	Mn^{2+}/Mg^{2+} for RAG	HSCT / gene therapy for SCID
IL-7 / IL-2 / Treg homeostasis	IL7R, IL2, IL2RA, FOXP3	—	Low-dose IL-2 (trials); rapamycin (Treg-augmenting)
TCR signaling / costimulation	PTPN22, PTPN2, CTLA4, CD28	—	Smoking cessation (PTPN22 risk amplifier); abatacept; rapamycin
Thymic regeneration GH/IGF-1	GHR, GH1, IGF1, IGF1R, FGF7, BMP4, NOTCH1	Zinc, vitamin A, IGF-binding proteins	TRIIM regimen (Grade C); palifermin post-HSCT
HLA class I / CMV / NK	HLA-A/B/C, KIR, KLRC2	—	CMV antiviral suppression (investigational)
HLA class II / vaccine response	HLA-DRB1, DQB1, DPB1	—	Adjuvanted vaccines compensate; consider RZV, high-dose flu, PCV20
Innate sensors / FCGR	TLR3/4/7/8/9, MyD88, IRF7, FCGR3A, FCGR2A	—	FCGR3A V158 informs mAb selection (CPIC 2A)
Inflammaging biomarkers	IL6, IL6R, IL10, TNF, TGFB1, CRP, GDF15, CXCL9	EPA/DHA reduce IL-6, CRP	EPA 2–4 g/d; statins; ziltivekimab (ZEUS, pending); colchicine recommendation withdrawn 2024
Senescence / telomere / 9p21 / CHIP	TERT, TERC, CDKN2A/B/ANRIL, JAK2, DNMT3A, TET2	—	9p21 → aggressive lipid management; CHIP → consider anti-inflammatory in trials

5. Complete SNP lookup table

Single-SNP variants targeted by this pathway panel, with category, gene, common variant name, GRCh38 coordinates (best-effort; rsID-based VCF lookup is the primary mode of

ascertainment), risk-allele direction where established, and approximate European-ancestry minor-allele frequency.

Category	Gene	rsID — variant name	GRCh38 (chr:pos)	Direction	MAF EUR ~
3.1	FOXN1	rs11078534 (intronic)	chr17:28720636	Modest	0.40
3.1	FOXN1	rs2305558	chr17:28738401	Modest	0.30
3.1	PAX1	rs2236087	chr20:21703540	Modest	0.25
3.2	AIRE	rs2075876 (intronic)	chr21:44290929	Modest	0.30
3.2	AIRE	rs760426	chr21:44288516	Modest	0.28
3.2	AIRE	rs878081	chr21:44288903	Modest	0.18
3.2	FEZF2	rs7625200	chr3:121583159	Modest	0.30
3.3	DCLRE1C	rs41298872	chr10:14945838	Modest	0.05
3.3	PRKDC	rs7830743	chr8:48685592	Modest	0.30
3.3	LIG4	rs1805388 (T9I)	chr13:107179621	Modest	0.15
3.4	IL7R	rs6897932 (T244I)	chr5:35874576	C-allele = MS risk; TT protective	0.28 (T)
3.4	IL2	rs2069762 (-330 T>G)	chr4:122113077	Modest	0.25
3.4	IL2RA	rs2104286	chr10:6052735	G-allele = T1D/MS risk	0.25
3.4	IL2RA	rs12722489	chr10:6094698	Risk	0.15
3.4	IL2RA	rs41295061	chr10:6056987	Modest (rare)	0.02
3.4	FOXP3	rs3761548 (-3279 A>C)	chrX:49264952	Modest	0.20 (M)
3.4	FOXP3	rs3761549	chrX:49264830	Modest	0.20 (M)
3.5	CTLA4	rs231775 (T17A)	chr2:203867992	G-allele = autoimmune risk	0.40
3.5	CTLA4	rs3087243 (CT60)	chr2:203874197	G-allele = risk	0.45
3.5	CD28	rs3116496	chr2:203706024	Modest	0.30
3.5	PTPN22	rs2476601 (R620W)	chr1:113834947	T-allele = autoimmune risk	0.10
3.5	PTPN2	rs2542151	chr18:12779948	Modest	0.17

Category	Gene	rsID — variant name	GRCh38 (chr:pos)	Direction	MAF EUR ~
3.6	GHR	rs6184	chr5:43350226	Modest	0.06
3.6	GHR	rs6182	chr5:43350267	Modest	0.07
3.6	IGF1	rs35767 (-1245)	chr12:102399971	Modest	0.18
3.6	IGF1R	rs2229765	chr15:98686062	Mixed; longevity tag	0.45
3.6	GH1	rs2665802	chr17:63919614	Modest	0.45
3.7	KLRC2	rs2734414	chr12:10408431	Modest	0.20
3.7	HCP5	rs2395029 (B*57:01 tag)	chr6:31378724	G-allele = HIV slow-prog / abacavir HSR	0.07
3.8	HLA-DRB1 (DR3-DQ2)	rs2187668	chr6:32612398	T = celiac/T1D/SLE risk	0.13
3.8	HLA-DQB1 (DR4-DQ8)	rs7454108	chr6:32669140	C = RA/T1D risk	0.10
3.8	HLA-DRB1 (DR15)	rs3135388	chr6:32717941	T = MS risk	0.13
3.8	HLA-DPB1	rs9277534	chr6:33064570	Modulator vaccine response	0.45
3.9	TLR3	rs3775291 (L412F)	chr4:186082921	Modest	0.30
3.9	TLR4	rs4986790 (D299G)	chr9:117713024	G = LoF	0.07
3.9	TLR4	rs4986791 (T399I)	chr9:117713324	T = LoF (linked)	0.07
3.9	TLR7	rs179008 (Q11L)	chrX:12885155	Modest (X-linked)	0.20 (M)
3.9	TLR7	rs5741880	chrX:12884298	GT = lower titer	0.20 (M)
3.9	TLR8	rs3764879	chrX:12923331	GT = lower titer	0.30 (M)
3.9	TLR9	rs5743836 (-1237)	chr3:52224520	Modest	0.10
3.9	TLR9	rs187084	chr3:52223627	Modest	0.40
3.9	IRF7	rs1131665	chr11:615554	Modest	0.25
3.9	FCGR3A	rs396991 (V158F)	chr1:161541472	V/V = higher ADCC; CPIC 2A	0.42 (V)
3.9	FCGR2A	rs1801274 (H131R)	chr1:161509956	H = higher IgG2 binding	0.50
3.10	IL6	rs1800795 (-174 G>C)	chr7:22727027	G/G = high-IL-6	0.40

Category	Gene	rsID — variant name	GRCh38 (chr:pos)	Direction	MAF EUR ~
				(Caucasian)	
3.10	IL6	rs1800796 (-572)	chr7:22726604	Modest	0.10
3.10	IL6R	rs2228145 (D358A)	chr1:154426971	C/C = lower classic IL-6 signaling	0.40 (C)
3.10	CRP	rs1205	chr1:159712444	T-allele = lower CRP	0.32
3.10	CRP	rs2794520	chr1:159713302	T-allele = lower CRP	0.32
3.10	IL10	rs1800896 (-1082)	chr1:206773553	G = high-producer	0.45
3.10	IL10	rs1800872 (-592)	chr1:206773063	A = low-producer (linked)	0.25
3.10	TNF	rs1800629 (-308)	chr6:31575255	A = high-producer	0.18
3.10	TGFB1	rs1800469 (-509)	chr19:41353017	T = high-producer	0.30
3.10	TGFB1	rs1800470 (codon 10)	chr19:41354392	C = high-producer	0.40
3.10	GDF15	rs1058587 (H202D)	chr19:18386860	Assay caveat	0.20
3.10	GDF15	rs888663	chr19:18389129	cis-eQTL	0.30
3.10	CXCL9	rs10336	chr4:76921608	Modulator	0.40
3.11	TERT	rs2736100	chr5:1286402	C = longer telomeres	0.50
3.11	TERT	rs2853669	chr5:1295350	Modulator	0.30
3.11	TERC	rs10936599	chr3:169763484	C = longer telomeres	0.25
3.11	CDKN2BAS1 (9p21)	rs10757278	chr9:22124478	G = CAD risk	0.50
3.11	CDKN2BAS1	rs1333049	chr9:22125504	C = CAD risk (linked)	0.50
3.11	CDKN2A	rs2811712	chr9:22085933	Modest	0.30
3.11	CDKN2A	rs1063192	chr9:21999688	Modest	0.40
3.11	JAK2	rs77375493 (V617F)	chr9:5073770	Somatic driver; germline = REF	<0.001
3.11	JAK2	rs10974944 (46/1)	chr9:5018738	G = predisposition (~3× MPN)	0.25
3.11	JAK2	rs12343867 (linked 46/1)	chr9:5026384	C = predisposition	0.30

6. ClinVar pathogenicity and PharmGKB clinical annotation status

Variant	Gene	ClinVar status	PharmGKB level	Notes
rs2476601 (R620W)	PTPN22	Risk factor (multiple AIDs)	Not formally classified	Largest non-HLA autoimmunity allele
rs6897932 (T244I)	IL7R	Risk factor (MS)	Not formally classified	Strong MS GWAS hit
rs231775 (T17A)	CTLA4	Risk factor (Graves'/T1D)	Not formally classified	Classical autoimmune locus
rs396991 (V158F)	FCGR3A	Drug response	Level 2A (rituximab, trastuzumab, cetuximab)	ADCC; oncology PGx
rs1801274 (H131R)	FCGR2A	Drug response	Level 3	IgG2 binding
rs2228145 (D358A)	IL6R	Risk factor (CHD reduced)	Not formally classified	MR confirmed CHD link
rs1800795 (-174)	IL6	Risk factor (varies by phenotype)	Not formally classified	High-producer in Caucasians
rs10757278 (9p21)	CDKN2B-AS1	Risk factor (CAD)	Not formally classified	Strongest single common-variant CAD locus
rs2736100	TERT	Risk factor (cancer / CV mixed)	Not formally classified	Telomere QTL
rs77375493 (V617F)	JAK2	Pathogenic — somatic driver	Not applicable (somatic)	MPN driver; germline = REF
rs2395029 (HCP5 / B*57:01)	HCP5	Drug response (abacavir HSR)	Level 1A (abacavir)	CPIC required testing
FOXN1, AIRE, RAG1/2, IL2RA, FOXP3 LoF	Various	Pathogenic (rare)	Not applicable	Mendelian SCID / IPEX / APECED
HLA-DRB1*15:01 (rs3135388 tag)	HLA-DRB1	Risk factor (MS)	Level 3	Strongest MS allele
HLA-DR3-DQ2 (rs2187668)	HLA region	Risk factor (celiac, T1D, SLE)	Level 2A (azathioprine via TPMT, separate)	Major class II haplotype
HLA-DRB1*07:01	HLA-DRB1	Drug response (lapatinib HSR)	Level 1B	Hepatotoxicity risk

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8. Literature freshness statement

Report generated: 7 May 2026.

Literature current through: May 2026 (targeted searches run on this date).

Underlying knowledge baseline: training data through end of January 2026.

Searches executed during freshness check (Phase 1): 9 searches.

Top topics searched: FOXN1 thymic regeneration; TRIIM-X readout status; IL7R rs6897932 MS meta-analysis; PTPN22 R620W meta-analysis; CMV memory inflation HLA-C; recombinant zoster vaccine real-world effectiveness; GDF15 mortality / inflammaging; CXCL9 iAge; rapamycin / mTOR vaccine response in elderly; CLEAR SYNERGY colchicine post-MI; ziltivekimab ZEUS baseline.

Most consequential update relative to prior knowledge baseline: CLEAR SYNERGY (NEJM 2024 / TCT–AHA presentation) was negative for low-dose colchicine post-MI primary endpoint, superseding COLCOT (NEJM 2019) and LoDoCo2 (NEJM 2020). Population-level secondary-prevention recommendations have been retracted accordingly. This document therefore does NOT recommend low-dose colchicine for population-level cardiovascular inflammaging mitigation. Other major refinements: (a) IL7R rs6897932 MS effect size confirmed and refined by Omraninava 2021 33-study meta-analysis; (b) GDF15 strengthened as a biomarker of biological aging and all-cause mortality (DAN-MONICA, Health ABC, NHANES); (c) CXCL9 confirmed as the iAge dominant component (Stanford 1KIP cohort and replications); (d) ziltivekimab ZEUS trial (NCT05021835) baseline characteristics published Dec 2025 (Ridker, JAMA Cardiol); CV outcome readout expected 2026–2027.

Pending trials with readouts that would change interpretation:

- ZEUS (NCT05021835) — ziltivekimab IL-6 ligand inhibition in CKD + ASCVD + hsCRP ≥2; n=6,376; readout 2026–2027.
- TRIIM-X (NCT04375657) — combination thymus-regeneration trial; n=85; primary completion Nov 2024; peer-reviewed publication pending.
- COLCOT-T2D (NCT05633810) — colchicine in T2D primary prevention; ongoing.

- RAP PAC and RESTOR — rapamycin / rapalog dosing trials; readouts expected 2026–2027.

Open-access proportion: majority of cited core mechanistic and meta-analytic sources are open access (PMC, Nat Aging, Front Immunol, eLife/biorxiv, JAMA Cardiol open access). Pivotal RCTs (CLEAR SYNERGY, COLCOT, LoDoCo2, ZOE-50/70) are not open access; reviewed via ACC/PCRonline/CCJM/Annals of Internal Medicine summaries and primary peer-reviewed full-text where available.

Suggested next refresh: November 2026 (6-month cadence — ZEUS readout expected within window, TRIIM-X publication likely, ongoing senolytic and rapamycin pipeline).