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Short Communication

Genetic Profiles of Vitiligo in South Asian Populations Implications for Targeted Therapy

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DESCRIPTION

Genetic profiles of vitiligo in South Asian populations reveal a complex interplay of polygenic risk, immune dysregulation, and melanocyte vulnerability that is both shared with other ethnic groups and shaped by region specific allele frequencies and environmental exposures, creating a distinctive landscape for targeted therapy. Vitiligo is now recognized as a prototypical autoimmune depigmenting disorder driven by loss of melanocytes through coordinated innate and adaptive immune responses, with strong heritability and clustering of cases in families, a pattern that is also seen across Asian cohorts. However, South Asian populations, including Indian, Pakistani, Bangladeshi, Sri Lankan, and Nepali groups, have unique genetic architectures that modify the distribution and impact of known susceptibility variants. Genome wide association studies in European and East Asian cohorts have identified more than a hundred risk alleles across loci implicated in immune regulation, apoptosis, oxidative stress, and melanocyte biology such as variants in Human Leukocyte Antigen (HLA) class I and II regions, Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22), Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4), Tyrosinase (TYR), and NOD-like Receptor Family Pyrin Domain Containing 1(NLRP1) yet when these alleles are examined in South Asians, several show differential enrichment or depletion, indicating that the magnitude of risk conferred by specific Single Nucleotide Polymorphisms (SNPs) is ancestry dependent. Recent population genomic work focusing on vitiligo associated genes has highlighted that particular risk alleles in glutamate receptor genes like Solute Carrier Family 1 Member 2 (SLC1A2) can be markedly enriched in South Asians compared with global reference populations, while others, such as Ataxin-2 (ATXN2) intronic variants, may be less frequent, under selection, or display distinct patterns compared with Europeans, East Asians, or Africans. These inter population differences hint that neural immune crosstalk and excitotoxic pathways, modulated by glutamate signaling, might play a relatively more prominent role in vitiligo pathogenesis in South Asian groups, opening a potential avenue for therapies that target neuronal or neuroimmune regulators of melanocyte survival. In parallel, meta analyses of candidate gene studies across Asian populations have implicated upstream regulatory variants in pro inflammatory cytokine genes such as Tumor Necrosis Factor alpha (TNF α), where specific promoter Single Nucleotide Polymorphisms (SNPs) demonstrate strong association with vitiligo risk under additive, dominant, and recessive models, consistent with a model in which heightened TNF α expression promotes melanocyte apoptosis and sustains chronic inflammation in genetically susceptible individuals. For South Asians in particular, these findings dovetail with clinical observations of high inflammatory burden, coexistence of other autoimmune disorders, and robust responses to therapies that modulate TNF α and related cytokine networks, suggesting that stratifying patients by TNF α risk genotype could, in the future, inform choice and intensity of immunomodulation. At the same time, not all hypothesized immune polymorphisms show uniform effects. Studies in South Indian cohorts have reported lack of association between certain Interleukin-10 (IL 10) and Interleukin-13 (IL 13) SNPs and non segmental vitiligo, underscoring the need to avoid overgeneralizing data from one ancestry or region to another and to build locally derived genetic panels that reflect the specific allele spectra of sub populations. Beyond immune loci, variants in genes governing oxidative stress responses and Deoxyribonucleic Acid (DNA) repair for example, polymorphisms in Apyrimidinic Endonuclease 1 (APE1) and other base excision repair pathway genes have been linked to increased vitiligo risk in Asian cohorts, with evidence that particular alleles amplify oxidative damage in melanocytes without necessarily altering core enzymatic activity, thereby lowering the threshold at which environmental insults like ultraviolet radiation or chemical exposures precipitate depigmentation; in melanin rich South Asian skin exposed to high Ultraviolet (UV) indices and diverse occupational chemicals, such sensitizing backgrounds may be especially relevant, reinforcing the rationale for antioxidant based adjunctive therapies and stringent photoprotection tailored to individual genetic risk. Taken together, the emerging picture is that South Asian vitiligo reflects convergence of common autoimmune pathways with region specific weighting of cytokine, neuroimmune, and oxidative stress genes, creating

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subgroups with distinct endotypes that could respond differently to targeted interventions. The therapeutic implications are significant. As biologics and small molecule inhibitors become integral to vitiligo management ranging from JAK inhibitors that block interferon γ and C-X-C Motif Chemokine Ligand 10 (CXCL10) signaling to agents that modulate TNF α, Interleukin-17 (IL 17), or other cytokines genetic profiling could guide which pathway to prioritize in a given patient, improving efficacy and minimizing unnecessary immunosuppression. For example, individuals harboring high risk TNF α promoter variants might be more likely to benefit from strategies that indirectly damp TNF α activity or downstream inflammatory cascades, while those with prominent glutamate receptor risk alleles might someday be candidates for therapies aimed at neuroimmune modulation or excitotoxicity reduction, approaches that are still nascent but conceptually supported by the genetic data. Furthermore, polygenic risk scores derived from panels of validated vitiligo associated variants could help identify South Asian patients at high risk of early onset, extensive disease, or association with other autoimmune conditions, allowing pre emptive institution of intensive topical regimens, phototherapy, or early introduction of systemic targeted agents before irreversible melanocyte loss occurs. Importantly, integrating genetic insights with clinical parameters such as pattern of lesions, rate of spread, and presence of halo nevi or other markers could refine prognostication and monitoring; this integration requires robust bioinformatic frameworks and diverse biobanks that adequately represent South Asian ethnic and caste groups, which have historically been under represented in genetic research. Ethical and practical considerations also shape the path from genotype to therapy: equitable access to genetic testing, protection of genomic data, avoidance of stigmatization in communities where vitiligo already carries psychosocial burden, and transparent communication about the probabilistic nature of genetic risk are essential if precision dermatology is to benefit South Asian patients broadly. Ultimately, as our understanding of the genetic profiles of vitiligo in South Asians deepens, the prospect of genuinely targeted therapy where choice of immunomodulator, antioxidant regime, or neuroimmune agent is informed by a patient's inherited risk architecture moves from theoretical aspiration to an achievable goal, promising more durable repigmentation, fewer adverse effects, and care that respects both the biological and cultural specificities of this large and heterogeneous population.