Understanding Atopic Dermatitis in Asian and European Population Cohorts Using Complementary Omics Techniques

Title: Understanding atopic dermatitis in Asian and European population cohorts using complementary omics techniques

Short title: Multi-omics in atopic dermatitis across ethnic populations

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Conflict of interest

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Abstract

Atopic dermatitis (AD) is highly heterogeneous with respect to pathogenesis, clinical manifestations and treatment response. There is evidence that ancestry and skin-type each contribute to this heterogeneity, indicating the need to improve understanding of disease mechanisms in diverse populations. Methods to integrate multi-omics studies have been well described, but this review focuses on the importance and the strategies needed to integrate data across different ancestral groups, focusing, because of data availability, on Asian and European populations. Skin scientists and clinicians will each benefit from an understanding of how the multiple complimentary layers of omics data may inform future clinical management, from insight into disease pathogenesis and treatment targets.

Background:

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition that can affect up to 20% of children and 10% of adults in European and Asian populations (Faye et al., 2023, Maspero et al., 2023). It has a significant impact on quality of life of patients and caregivers. The average annual treatment costs per patient are estimated to be over USD3000 in the United States, USD1540 in Europe and up to USD8000 in Singapore (Emerson et al., 2001, Olsson et al., 2020). The substantial disease burden of AD is characterised by heterogeneity in clinical manifestations and trajectories, with variable and currently unpredictable response to treatment (Irvine and Mina-Osorio, 2019, Suaini et al., 2021, Yew et al., 2019).

The pathophysiological mechanisms of AD broadly consist of skin barrier dysfunction and immune dysregulation, coupled with influence of itch pathways and external factors such as skin microbiome disturbances (Weidinger et al., 2018). Clinical management strategies directed towards these mechanisms have shown varying degrees of success and in recent years, more specific targeted therapies have been developed to address selected pathomechanisms. Examples include dupilumab that targets the IL-4/IL-13 immune pathways, nemolizumab that targets the IL-31 itch pathway as well as *Staphylococcus aureus* bacteriophage therapy targeting the skin microbiome (Kabashima et al., 2022, Shimamori et al., 2020, Simpson et al., 2016). However, the efficacy of such therapies has been variable among patients with different ancestral descent, further illustrating the complex and heterogeneous nature of AD (Bosma et al., 2023, Gu et al., 2022).

Importance and Rationale:

Our understanding of the pathophysiological mechanisms of AD is not complete. Many studies have leveraged upon omics techniques, defined by investigating the "totality of a molecular process within an organism" using multiple areas of biological study including genomics,

epigenomics, transcriptomics, proteomics and metabolomics, (Rogers, 2023) (Box 1) to address these gaps in understanding. This work has been carried out mostly in European cohorts (Bratu et al., 2023, Carrascosa-Carrillo et al., 2024, Nomura and Kabashima, 2021) but there is, emerging evidence from people of other ethnicities and ancestries from different geographical regions. For example, genomic and proteomic studies in East Asian (EA) AD provide support for the hypothesis that East Asian AD is fundamentally different from European AD (Figure 1) (Wen et al., 2018). Indeed, several studies have consistently demonstrated that AD among Asian patients exhibited skin phenotypes that combine the features of AD and psoriasis (Tsai and Tsai, 2022). Compared to Europeans, Asian AD lesions are more well demarcated and show more prominent scaling on clinical examination. Another Asian study noted that discoid eczema, psoriasiform features or features related to pigmentary changes are more commonly seen (Aponso et al., 2023). Histologically, Asian AD skin showed increased hyperplasia, parakeratosis and higher Th-17 activation in comparison to European white AD skin, while sharing a strong Th-2 component and high total IgE (Noda et al., 2015). It is important to appreciate that ethnicities across Asia are also diverse. Broadly, Asians consist of EA, South-East Asians (SEA) and South Asians (SA) (Figure 1). In general, the detailed study of genomics and proteomics in SEA and SA populations has lagged behind studies conducted in white European populations. Furthermore, in addition to genomics and proteomics, the use of epigenomic, metabolomic and other multi-omics approaches are likely to be important to understand and stratify disease endotypes across all AD patients (Akhtar et al., 2024). Applying detailed multi-omic information will be critical in clinical correlations with disease phenotypes and disease stratifications for treatment response in the clinic. The ambition is to identify suitable therapeutic options tailored to a growing body of evidence for specific endotypes of AD, which may be informed at least in part by population and ancestry differences. Specifically, these endotypes include European American versus Asian patients

(Czarnowicki et al., 2015b, Koga et al., 2008), children versus adults (Czarnowicki et al., 2015a, Esaki et al., 2016), intrinsic versus extrinsic (IgE status) disease (Karimkhani et al., 2015, Suarez-Farinas et al., 2013), and patients with and without *FLG* loss-of-function mutations (Czarnowicki et al., 2019, Irvine et al., 2011, Weidinger et al., 2006).

A major limitation to genetic and genomic analysis remains a relative lack of representation of people from African and Hispanic ethnicities. Important work is on-going internationally to address this imbalance (Genomes Project et al., 2015, Limb, 2024). Care is also needed when considering the complexities of race, ethnicity, and ancestry (Khan et al., 2022). In this review, we have focussed on European and Asian populations because of the current wealth of data in these ancestral groups; we will compare and contrast current omics approaches, and review available evidence between the selected European and Asian populations, whilst highlighting that further research is needed.

Current evidence:

Loss-of-function variants in *FLG,* the gene encoding filaggrin (Limb, 2024)

AD is a complex skin disease with multiple known genetic risk factors. It has been estimated that the heritability of AD is about 75%, with loss-of-function variants in *FLG* being the strongest genetic risk factor for AD (Loset et al., 2019). Understanding genetic mechanisms can provide a starting point to unravel the multiple pathophysiological facets of a complex disease that is also strongly affected by environmental factors. Barrier dysfunction, which is one of the key features of AD, is commonly associated with *FLG* null mutations, (Palmer et al., 2006). Despite the similar prevalence of AD across Europe and Asia, the population structure of *FLG* null mutations varies in different populations. p.R501X and c.2282del4 are characteristic *FLG*-null mutations in European populations (Gupta and Margolis, 2020, Palmer et al., 2006), in contrast with Asian studies showing a greater number of different null

mutations in *FLG* exon 3 (On et al., 2017, Park et al., 2015). A study of Chinese AD patients from Singapore revealed a much larger spectrum of *FLG* mutations, compared to that of an Irish AD cohort (Chen et al., 2011). Only 20% of the Singapore Chinese AD cohort had one or more *FLG*-null mutations, and seven different mutations (c.3321delA, c.6950_6957del8, p.S1515X, p.S2706X, p.Q2417X, p.E2422X, p.G323X) accounted for nearly 80% of the whole mutation spectrum. This contrasted with 46% of AD cases in the Irish cohort having one or more *FLG* null mutations, in whom two mutations (p.R501X and c.2282del4) accounted for 80% of the cases with *FLG* mutations. Therefore, while the resultant phenotypic manifestations of barrier dysfunction associated with filaggrin haploinsufficiency appear similar across Asian and European groups, the underlying specific *FLG* null mutations are different. This may have implications if future targeted intervention therapies were to be used to target particular *FLG* variants in different populations.

Other genetic variants identified from genome-wide association studies (GWAS)

In addition to the well-established *FLG* loss-of-function variants that contribute to barrier dysfunction in AD, genome-wide association studies (GWAS) have identified other loci related to barrier development and immunological dysfunctions (Elias et al., 2019, Paternoster et al., 2015). GWAS involving up to 865,000 participants of European ancestry have identified 81 genome-wide significant independent loci with SNP-based heritability of 5.6% (Budu-Aggrey et al., 2023, Mucha et al., 2020, Paternoster et al., 2015). Beyond the differences in *FLG* mutations, an examination of the frequencies of other genetic risk variants between Asian and European populations shows differences in 43 of the 81 variants at a Bonferroni-corrected threshold of 6.17E-04 (Supplementary Table 1)(Ward and Kellis, 2012). Separate GWAS involving East Asian populations have also been performed (Supplementary Table 2) (Hirota et al., 2012, Ishigaki et al., 2020, Kim et al., 2015, Sakaue et al., 2021, Sun et al., 2011, Tanaka

et al., 2021). From these studies, it was noted that European and Japanese populations shared genetic components related to immunological pathways in AD including acquired and innate immune-related pathways, such as NKT and Th1/Th2 pathways. Japanese GWAS studies have also identified variants mapping to *IL18RAP* that were similarly identified in the largest European AD GWAS (Supplementary Tables 1 and 2) (Ishigaki et al., 2020, Paternoster et al., 2015, Sakaue et al., 2021, Tanaka et al., 2021). This is consistent with previous AD skin cytokine profile studies that showed East Asians display a Th-17 profile in addition to the Th-2 activation found in Europeans (Chan et al., 2018). However, a Japanese GWAS reported four novel AD susceptibility loci, of which a missense variant (R243W) with a deleterious functional effect in *NLRP10* and a variant altering expression of CCDC80 via enhancer expression were Asian-specific (Tanaka et al., 2021). Both genes are hypothesized to be modulators in allergic diseases.

In summary, besides differences in the population structure of *FLG* mutations, other genetic variants related to barrier dysfunction and immune dysregulation are also different between population cohorts of diverse ancestry. Therefore, both similar and diverse disease mechanisms may underpin the development of AD, and differences in genetic factors may be of importance when developing targeted therapies.

Genetic factors investigated via candidate gene approaches

Targeted genotyping and use of a case-control comparison has also revealed differences between genetic factors associated with European and Asian AD (Pontikas et al., 2023). By focusing on specific genetic regions of interest and being hypothesis-driven, targeted genotyping has the advantage of lower costs with better computational efficiency and greater statistical power (Jorgensen et al., 2009). A recent systematic review and meta-analysis reported novel genetic loci mapped to *IL18* and *TGFB1* genes in Europeans, compared to

IL12RB1 and *MIF* genes in Asians (Pontikas et al., 2023). This review reported four studies that assessed SNPs mapped to the *IL18* (rs187238) (number of individuals included in meta-analysis = 388) and *TGFB1* (rs1800471, rs1800470) (number of individuals included in meta-analysis = 461) among participants of European descent (Arkwright et al., 2001, Stavric et al., 2012, Trzeciak et al., 2016, Trzeciak et al., 2010). This suggests a possible role of IL-18 in dysregulated Th2 response and TGFB1 protein in allergic reactions. However, no similar associations were noted in the meta-analyses of studies of Asian descent. There was also significant heterogeneity between Asian and European studies for variants related to IL-18 and epidermal barrier function such as *FLG* and *SPINK5*. In contrast, studies of Asian descent found significant associations of *IL12RB1* (rs393548 and rs436857) as well as *MIF* (rs755622) with AD, suggesting a role for immune dysregulation with IL-12 involvement that includes IgE levels and Th2 cellular function (Kim et al., 2019, Kim J. S. et al., 2016). The lack of findings by candidate gene analyses may reflect their small sample size, making it difficult to assess any possible differences in genetic predisposition to AD between Europeans and Asians.

Genetic variants identified by exome sequencing

There remains a significant amount (>73%) of unexplained AD heritability (Mucha et al., 2020) which could be due in part to low frequency and rare variants not detectable by genome-wide SNP association. An additional 12.6% of heritability was accounted for by using exome sequencing data of patients and control participants of European descent (Grosche et al., 2021, Mucha et al., 2020). Variants were enriched in five genes (*IL4R, IL13, JAK1, JAK2* and *TYK2*) and rare variants noted in three (*DUSP1*, *NOTCH4* and *SLC9A4*) (Grosche et al., 2021, Mucha et al., 2020). Some protein products are targets for current therapeutics, including anti-IL-4/IL-13, anti-IL-13 biologics and JAK inhibitors but it is not yet known whether the genetic variants contribute to differential treatment response. Exome sequencing of cohorts of South Asian

descent has confirmed *FLG* as the major AD risk gene (Pigors et al., 2018). Rare variant analysis identified *MTF1, ORM2*, and *TCHHL1* as genes with AD-associated variants and these findings were replicated in a cohort of Irish ancestry (Pigors et al., 2018) but further work is needed to fully define the role of rare, possibly high penetrance variants in the genetic architecture of AD.

Differences in cytokine profiles between Asians and Europeans

The differences in immune dysregulation pathways observed in skin are similarly represented in differing levels of circulating serum biomarkers among Europeans and Asians (Bakker et al., 2021). Decreased Th1/IFN-γ skewing of serum cytokines in Asian AD patients can be explained by a more active Th17 pathway causing a downregulation of the Th1 axis. Both European and Asian AD patients have significant increases in Th2 serum markers such as IL-13, CCL13, CCL17, CCL22 and CCL26, suggesting that the Th2 pathways are similarly activated in AD across different ethnic groups (Bakker et al., 2021, Mansouri and Guttman-Yassky, 2015, Wen et al., 2018). Multiple Th2 cytokines and chemokines such as IL-13, CCL26 and CCL13 also strongly correlate with total IgE levels. However, IL-13 and CCL26, together with absolute eosinophil counts were more elevated among Asians (Wen et al., 2018). Despite a higher Th17 expression in the skin, circulating serum IL-17 markers were similar between racial groups. IL-22 levels appear higher in Asian than European AD (Jin and Yoon, 2018); this may contribute to the epidermal hyperplasia and parakeratosis observed in Asian skin as IL-22 affects keratinocyte proliferation, migration and maturation by inhibiting production of proteins involved in terminal keratinocyte differentiation (Sabat et al., 2014).

Variation in clinical phenotypes between Asians and Europeans

Inherent differences in genetic predisposition and differences in cytokine expression are likely to underpin the phenotypic differences between European and Asian AD. Understanding differences in clinical phenotypes between these groups and correlating with underlying molecular biomarkers therefore provides opportunities to define specific pathophysiological mechanisms. However, there is added complexity given the diversity within and between Asian populations. There are likely to be a different genetic architectures in Asian sub-populations and this may contribute to the different disease prevalences and severities. In a recent population study in Singapore, the prevalence of AD among EA, SEA and SA were 9.2%, 8.4% and 8.5% respectively (Yew et al., 2023). However, those of SEA and SA descent had a significantly higher trans-epidermal water loss, reduced skin surface moisture and a more alkaline skin pH indicating worse barrier dysfunction (Yew et al., 2023). A systematic review highlighted differing AD characteristics between study regions within Asia and among sub-Asian populations (Yew et al., 2019). For example, studies from SEA reported more exudative eczema, truncal involvement, lichenification and prurigo nodularis. EA studies reported more cases with erythroderma, truncal, extensor, scalp and auricular involvement while SA Indian studies reported more flexural involvement (Yew et al., 2019). This was accompanied by significant differences in allele frequencies for 74/81 (91%) of the genetic variants associated with AD across the three Asian ethnic subgroups in a Singaporean population sample (Supplementary Table 1) (Budu-Aggrey et al., 2023, SG10K_Health, 2024). In addition to differences in genetic predisposition, varying environmental and cultural practices also contribute to differences in phenotype from different regions across the Asian continent.

Role of epigenetic effects in AD

Epigenetic modifications affect gene expression without changing the underlying base-pair sequence code and these disturbances in genome regulatory mechanisms may precede disease (Handy et al., 2011). DNA methylation is one of the most well-characterized epigenetic modifications and a key regulator of gene expression and molecular phenotype. Recent studies have highlighted epigenetic events, including DNA methylation, affecting inflammation and skin barrier function (Akhtar et al., 2024, Bratu et al., 2023, Loset et al., 2019, Ma et al., 2022, Schmidt and de Guzman Strong, 2021). A small case-control study by Olisova et al. (including 12 AD patients and 6 controls) showed significant differences in methylation profiles in full thickness skin biopsies (Olisova et al., 2020). This analysis implicated biologically plausible pathways including immune response, lymphocyte activation, cell proliferation, apoptosis and epidermal differentiation (Olisova et al., 2020). Using a targeted approach, a study of 56 individuals, showed changes in methylation driven by AD-associated SNPs in *KIF3A*. Differential methylation was associated with increased trans-epidermal water loss (TEWL) in risk allele carriers, and expression levels of KIF3A protein, which itself can affect TEWL and AD risk (Stevens et al., 2020). The authors have previously identified from murine and human studies that *KIF3A* SNPs were associated with asthma and AD, with one-third of these SNPs creating novel cytosine-phosphate-guanine (CpG) sites (Johansson et al., 2017) where methylation occurs. Methylation in *FLG* adds to the risk of AD associated with loss-of-function variants within *FLG* (Ziyab et al., 2013). Differential methylation can also affect immune dysregulation of relevance to AD including *IL13* in CD4+CLA+ T cells resulting in increased expression of IL-13 mRNA (Acevedo et al., 2020). The examples listed above are from people of white European ancestry; methylation studies among Asian people are limited to date, but whole blood expression-quantitative trait loci (eQTL) data from a Singaporean Chinese cohort

identified the association of CpG-SNP, rs612529T/C in the promoter of *VSTM1* (Kumar et al., 2017) and further work is on-going.

Epigenetic events such as DNA methylation, histone modifications and non-coding RNAs can modulate the activity of transcription factors or transcriptional regulators such as PPARδ, FABP5 and EMSY, resulting in changes in lipid metabolism, keratinocyte differentiation and barrier maturation, thereby affecting overall skin barrier function (Elias et al., 2019, Morgan et al., 2010, Romanowska et al., 2008).

The influence of extrinsic environmental factors on the interactions of gene expression and epigenetic modifications highlights the importance of understanding how the exposome interacts with genetic factors in a diversity of environments across the world (Chong et al., 2022). Exposome is defined as the environmental exposures that an individual encounters throughout life and how they relate to one's health (Wild, 2005). Alterations in the expression of micro RNAs (miRNA) is another mechanism by which the exposome can affect skin phenotype. The incidence of AD increases with industrialization and air pollution, along with psoriasis, skin cancer, and acne (Roberts, 2021). Alterations in the expression of miRNAs include those regulating Th2 polarization, inflammatory processes and keratinocyte properties (Fadadu et al., 2023). For example, maternal smoking during pregnancy results in increased expression of miR-223 and methylation of *FOXP3* which reduces the regulatory T cells at birth (Hinz et al., 2012), while infants with low levels of Tregss have a higher risk of AD (Kim J. E. et al., 2016).

Skin microbiome diversity

It has previously been reported that microbial diversity and particularly an increase in *Staphylococcus aureus* on the skin surface is closely associated with disease flares and

progression of AD (Kong et al., 2012). Other skin commensals including *S. epidermidis* and *Malassezia furfur* have been reported in Caucasian studies to play a role in driving inflammation in AD (Cau et al., 2021, Navarro-Trivino and Ayen-Rodriguez, 2022). The skin microbiome also influences epigenetic events such as DNA/histone modifications and regulation through non-coding RNAs (Chen et al., 2021). Microbial metabolites such butyric acid derivatives result in histone acetylation of *AcH3K9*, which reduces IL-6 production leading to further colonization by *S aureus* (Traisaeng et al., 2019). The effects of microbiome species diversity and interactions with host immunity, epidermal barrier and epigenetic factors differ according to geography, climate and ethnic background. This was illustrated by a comparison of the multi-ethnic Asian populations from Singapore with a white European cohort from Switzerland (Leong et al., 2019) Skin microbiome studies directly comparing Asian and European populations remain scarce, but comparisons of different Asian ancestries (e.g. East Asians versus South Asians) have revealed differences in skin microbiome (Alghamdi et al., 2021, Chen et al., 2021, Leong et al., 2019). The lack of evidence for comparisons of skin microbiome across different ethnic groups and geographic regions highlights the importance of further studies to investigate the skin microbiome diversity among Asian and European AD populations and how this may play a role in the observed phenotypic differences between these populations.

An approach for future transethnic comparative analyses

Many of the susceptibility loci identified from GWAS are located in noncoding regions of the genome (Paternoster et al., 2015). Exceptions are variants in *FLG*, *IL13* and *IL6R* but these account for only approximately 15% of AD heritability (Mucha et al., 2020). A more complete understanding of AD patho-mechanisms requires use of all available omics data, including genetics, epigenetics, transcriptomics, proteomics, metabolomics and metagenomics

(Carrascosa-Carrillo et al., 2024, Rusinol and Puig, 2024). Furthermore, comparison between different populations is required to further refine causal variants and non-coding effects. Large-scale omic studies have been conducted mainly in European population cohorts and more recently East Asians (Cheng et al., 2021, Nomura and Kabashima, 2021). However, in-depth comparisons of similarities and differences between the different ethnic cohorts have not yet been performed.

Current strategies

Current omics analyses are frequently carried out in silico and may be biased by data from one particular ancestral group. There is a need to integrate and cross-compare omics data across platforms and between different populations, to maximize understanding. We therefore propose a structured stepwise approach (Figure 2) for transethnic comparative analysis using the multiple omics data that are increasingly becoming available, as follows:

(1) Identify genetic risk factors

Genetic risk factors for AD are identified using genome-wide SNP analysis and rare variant association. Stratified analyses assess distinct ancestry groups for comparison before meta-analysis. Rare variant association testing identifies variants that are low-frequency ($0.5\% \leq$ minor allele frequency (MAF) $< 5\%$) and rare (MAF $< 0.5\%$). This requires exome sequencing or whole genome sequencing to a depth of 15-20x for reliable detection (Rashkin et al., 2017). Exome sequencing data, combined with genome-wide SNP variants, allows for comparison of European and Asian cohorts to assess overlap in genetic loci or shared functional pathways.

(2) Prioritize candidate genes

Potential candidate genes can be identified based upon proximity (e.g. genes within 10 kb of the sentinel SNP), comparative genomics, integration with regulatory features, gene expression and other omics data, as well as causal analyses as described below.

(3) Investigate gene expression

Gene expression data from publicly available databases and consortia such as the eQTLGen Consortium (including gene expression of whole blood samples from 31,684 individuals), together with tissue specific eQTLs in skin tissue from GTEx (Consortium, 2013, Vosa et al., 2021) provides information on gene expression linked to genotype. However, this data is mainly derived from cohorts of European descent and further assessment of eQTLs in Asian populations is needed. Separate analyses according to individual ethnic groups could then be carried out and subsequently meta-analysed.

(4) Overlay epigenetic data

For epigenetic analysis, loci are overlaid with regulatory features including DNase I hotspots, histone marks and chromatin states from the Roadmap Epigenomic Consortium (Bernstein et al., 2010). Unlike DNA sequences which are static, epigenetic marks may be associated with promotion, activation or repression of nearby gene expression. Studying the epigenetic landscape around disease-associated loci may therefore help to reveal the mechanisms of effect on disease risk or progression through changes in gene expression.

Taken together, these layers of omics data allow causal analyses such as Mendelian Randomization, accompanied by colocalization analyses to triangulate and identify potential

causal pathways from genetic variants to phenotypes, thereby assessing if Europeans and Asian share common downstream functional pathways (Zhu et al., 2016). In addition, it may allow the identification of differences along the causal pathways of relevance to phenotypic differences. Indeed, as most of the current colocalization analysis methods implicitly assume identical linkage disequilibrium (LD) structures between the two association samples, with false discovery rate and power suffering in the case of mismatch (Hukku et al., 2021), it is paramount that sufficiently well-powered sample series of the respective ethnic populations are generated.

Newer methods and integrative strategies

Newer methods and integrative strategies are emerging to better address our understanding of AD in different ancestral groups including steps towards functional analyses, as follows:

Multi-omic data

Functional genomic analyses to confirm or refute genomic findings can be conducted using omics strategies such as plasma metabolomics and serum proteomics data from databases such as the UK Biobank (Sun et al., 2023). These can be replicated with Asian cohorts which are now reaching comparable sample sizes from some population but this remains a limitation for validation and comparison of findings with European datasets. In recognition of this limitation a well-represented population cohort (HELIOS - Health for Life in Singapore) has been established, comprising EA, SEA and SA, with high-quality biological samples collected for future molecular assays accompanied by comprehensive phenotyping, including the measurement of skin physiology such as transepidermal water loss (TEWL) and pH. This represents a valuable resource for AD research (Wang et al., 2024, Yew et al., 2023).

Mendelian Randomization and colocalization analysis

Mendelian randomization (MR), often referred to as 'nature's randomized controlled trial', leverages upon genetic variants which are fixed at conception to assess the causality of an observed association between a modifiable exposure or risk factor and a clinically relevant outcome (Budu-Aggrey and Paternoster, 2019). A summary-based Mendelian randomization (SMR), integrates summary-level data from large-scale GWAS with data from quantitative trait locus (QTL) studies, such as eQTLGen (Vosa et al., 2021). SMR aims to identify genes whose expression levels are associated with a trait due to the effects of a common genetic variant, either by direct causal or pleiotropic effects, rather than due to a genetic linkage (Zhu et al., 2016). By a planned series of SMRs, it is possible to evaluate potentially causal effects of genetic variants to define similarities and differences between European and Asian AD. For example, using the analyses of (i) SNP -> Gene Expression -> Phenotype and (ii) SNP -> Methylation -> Expression, genes likely to be in the causal pathway for a specific phenotype such as AD can be identified, and the second SMR allows prioritization of genes likely to be acting through methylation on gene expression. Subsequent colocalization analysis which compares the association patterns at a locus provides further support for the likelihood if the variant is indeed causal, thereby informing candidate gene prioritization.

Clinical utility and application

In order to bridge the gap between research and clinical application, polygenic risk scores (PRSs) can be used as predictors of the disease, disease trajectories, disease severity and treatment response. PRS combine multiple genetic variants weighted by their effect sizes to improve prediction of disease risk, severity, trajectory or treatment response (Loh and Chambers, 2023). The PRS framework also allows inclusion of environmental factors into the prediction models. A recent study demonstrated that AD PRS could predict AD severity in European American individuals (Arehart et al., 2022). However, as disease specific effect sizes

depend on GWAS results, this highlights the importance of larger, higher-quality GWAS to formulate more accurate PRSs relevant to diverse populations since PRS based on European-derived summary statistics has lower accuracy when applied to non-European populations (Martin et al., 2019). This observation is consistent across 17 anthropometric and blood panel traits. On average, the accuracy of the PRS among the Hispanic/Latino Americans, South Asians, East Asians and Africans was only 25 to 60% of that of the Europeans (Martin et al., 2019).

A relative lack of genomic and other omics data for Asian populations has motivated larger and higher quality population cohorts from Asia, including the HELIOS cohort study (described above) with whole genome sequencing data of 50,000 citizens and permanent residents of Singapore, mostly of Asian descent (Wang et al., 2024).

Other omics can be used to create risk scores, and methylation risk score (MRS) are effective in the study of atopic phenotypes and other forms of chronic low-grade inflammation, providing an opportunity to further improve omics-based risk scoring (Hillary et al., 2024, Kilanowski et al., 2022). Beyond predicting an individual disease risk, a predictive model incorporating PRS/MRS and non-genetic information would be useful to inform treatment selection for clinical management. This personalized approach is particularly relevant because of the heterogeneity of AD and high costs of novel treatments. It is important to advance personalized preventive as well as therapeutic interventions to identify patients at risk of co-morbidities and to inform health economic evaluations for emerging AD therapeutics.

Multiple challenges remain in the clinical application of omics-based risk scores. Fundamentally, it is important to evaluate if the omic-based risk score is actionable with respect to clinical utility in the population of interest, and this requires extensive validation testing.

Other challenges include funding for genotyping costs, efficiency of turnaround time and ethical aspects of molecular analysis.

Conclusions

The majority of knowledge regarding molecular pathomechanisms and disease pathways is based on genomic studies of European cohorts. There is a lack of omics data from Asian AD for functional genomic analyses to identify candidate genes or computation of omics-based risk scores. With an over-representation of studies of European descent, about 20% of the heritability of AD has been explained. More studies with greater diversity that examine genetic factors as well as gene-environment interactions will shed more light on the spectrum of pathomechanisms of AD and generate more specific PRS for clinical utility across diverse populations. Ultimately this will be for the greater good for understanding AD from a global health perspective.

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Legends

Figures

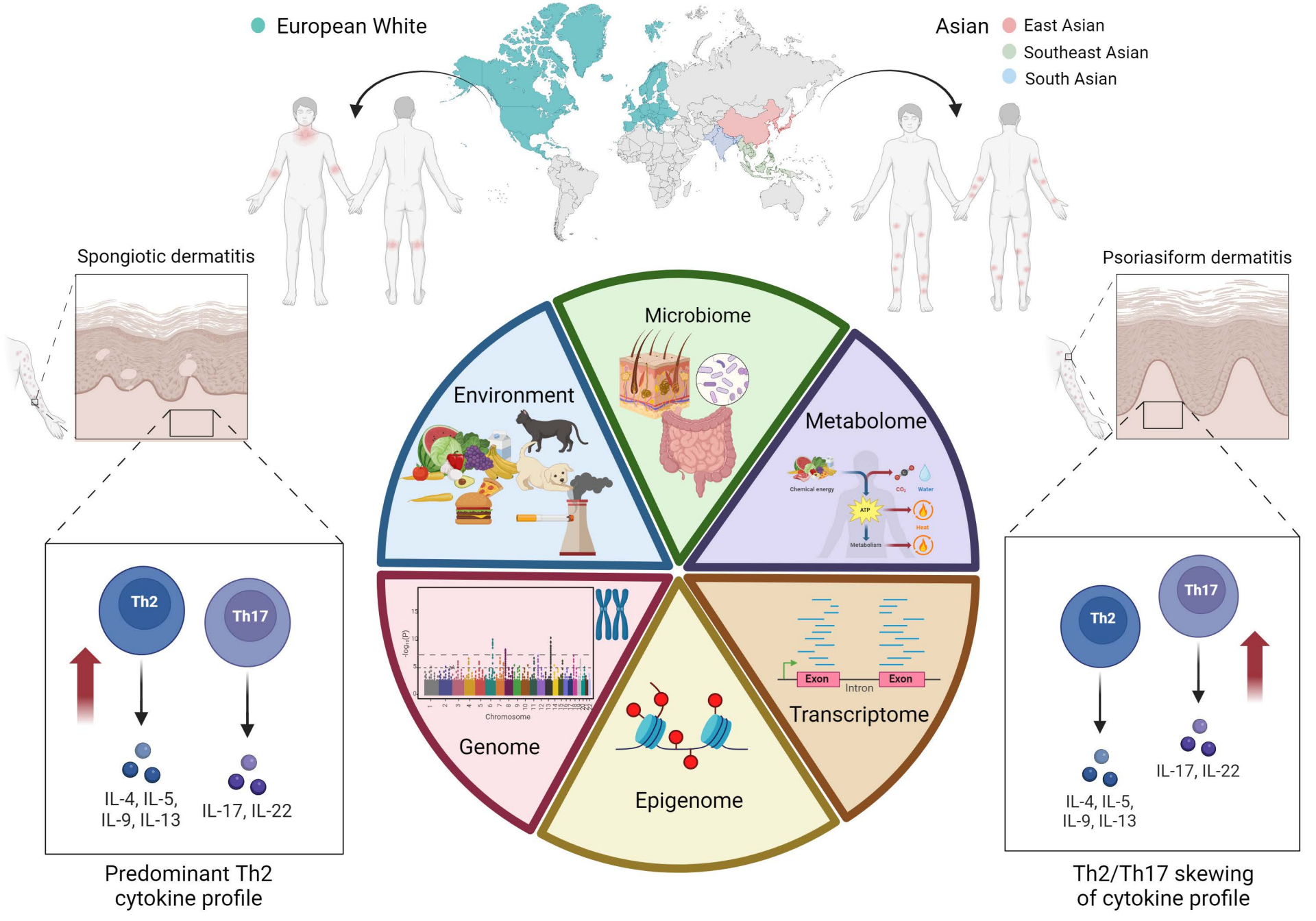
Figure 1. Differences in the phenotype and endotype of atopic dermatitis between European whites and Asians.

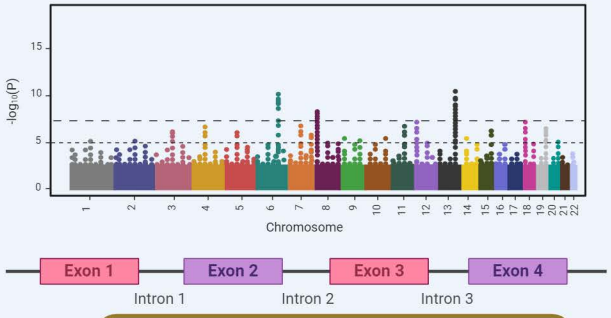
Figure 2. Flow diagram illustrating a structured stepwise approach to analyze multiple omics datasets.

Supplementary Tables

Supplementary Table 1. Frequencies of genetic variants of genome wide association studies (GWAS) involving participants of European ancestry

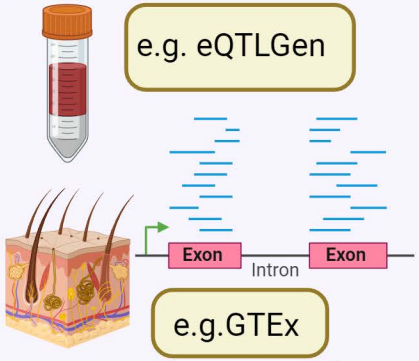
Supplementary Table 2. Identified genetic variants among genome wide association studies (GWAS) involving participants of East Asian ancestry


European White
Asian
East Asian
Southeast Asian
South Asian
Spongiotic dermatitis
Psoriasiform dermatitis
Microbiome
Environment
Metabolome
Genome
Epigenome
Transcriptome
Chemical energy
ATP
Heat
Metabolism
Water
Exon
Intron
Exon
Chromosome
Th2
Th17
IL-4, IL-5,
IL-9, IL-13
IL-17, IL-22
Predominant Th2
cytokine profile
Th2
Th17
IL-4, IL-5,
IL-9, IL-13
IL-17, IL-22
Th2/Th17 skewing
of cytokine profile



Genome-wide SNP association
+
Rare variant association

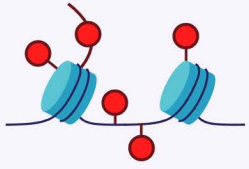
Identifying genetic risk factors



e.g. eQTLGen

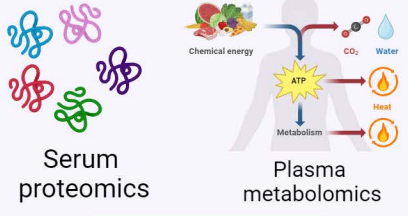
e.g.GTEx

Gene expression data



e.g. Roadmap Epigenomic Consortium

Epigenetic data

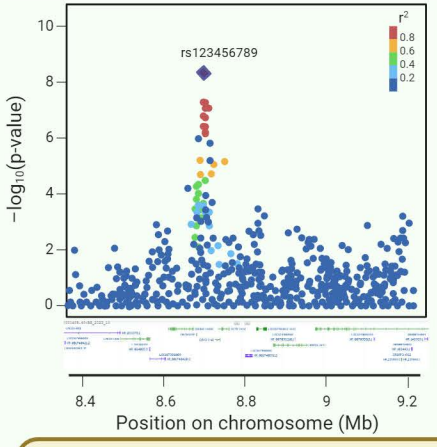


Serum proteomics

Plasma metabolomics

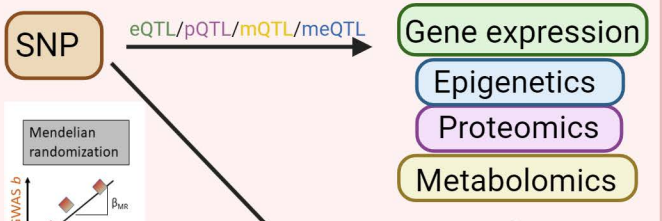
e.g UK biobank, SG100K cohort

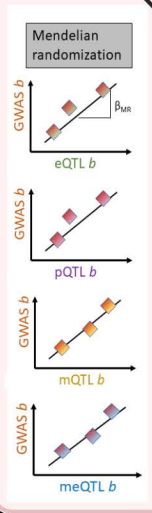
Multi-omic data



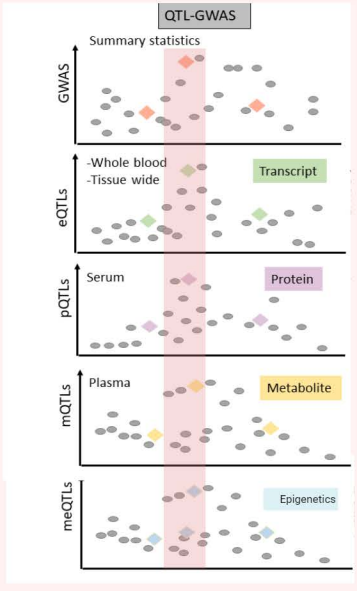
Proximity-genes within 10 kb

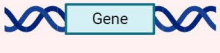
Potential candidate gene identification





Mendelian Randomization





Candidate gene prioritization

Colocalization analysis

Box 1. Omics Technologies

1. Genome wide association study (GWAS) is an approach that tests hundreds of thousands of genetic variants across many genomes to find those that are statistically associated with a particular disease or phenotype. GWAS most commonly involves genotyping using microarrays as a cost-efficient method to detect common variants of a trait or disease.

2. Whole genome sequencing (WGS) is the process of determining the entire DNA sequence, including both protein coding and non-coding protein regions. Depth of sequencing refers to the number of times a region or variant is sequenced. A sufficient depth of WGS (for example 10-20 fold) allows uncommon genetic variants to be identified. However, clinical interpretation of rare and non-coding variants is challenging and these may be termed 'variants of unknown significance'.

3. Whole exome sequencing (WES) involves sequencing all of the protein coding regions of genes (exome) in a genome since many severe disease-causing variants are known to be within the exons. The exons consist of about 1% of the entire human genome therefore this isa relatively efficient way to identify genetic variants e linked to rare diseases, but the interpretation of variants of unknown significance remains a challenge.

4. Rare variant association testing can explain additional disease risk variability on top of common variants' information from GWAS. These include analyses of low-frequency ($0.5\% \leq MAF < 5\%$) and rare ($MAF < 0.5\%$) variants. To improve statistical power of rare variants testing, aggregation tests may be used, to evaluate multiple variants in a gene or region.

5. Proteomics is an omics approach to comprehensively profile the serum proteome or other tissue (eg skin) in order to detect biomarkers in human disease. Mass spectroscopy-based proteomics rely on liquid chromatography separation and recent advances allow untargeted proteomics analysis of more than 15,000 proteins to be profiled simultaneously.

6. Plasma metabolomics is an omics approach to analyze and profile metabolites in biological samples. Metabolites are lower molecular weight intermediates and products from chemical reactions that reflect intrinsic metabolic processes as well as environmental exposures.

7. Epigenetics refers to any process that affects the expression of the genes without changing the DNA sequence. Processes include DNA methylation, histone modification and noncoding RNA action. Environmental exposures are known to drive and affect epigenetic processes.

A. DNA methylation refers to the addition of a methyl group to a cytosine base within a cytosine-guanine pair (CpG) and methylation is usually associated with transcriptional repression. Mapping of the methylation across the genome has largely relied on array-based technology as it is cost effective and requires small amounts of DNA.

B. Histones modifications include the posttranslational changes of acetylation, methylation, phosphorylation and ubiquitination. These lead to changes in chromatin structure with effects on gene expression.

C. Noncoding RNAs can reduce or silence gene expression by recruitment of protein complexes to promote histone methylation or RNA binding proteins that impair histone deacetylation or inhibition of transcription factors binding to promoter regions.

8. The microbiome is a community of microorganisms including bacteria, fungi and viruses inhabiting a range of niches on the human body. The composition and diversity of the microbiome as well as the body's immune reactions to the microbes can have an impact multiple physiological and pathological processes in skin, lung, bowel and brain.

Metagenomics describes the use of nucleotide sequencing techniques to define and quantify microbial species without the need for culture. Examining the relative abundance, diversity and associated functional microbial pathways of the microbiome can contribute insights to underlying disease mechanisms.