# The genetics of skin ageing

D. Gunn

**Genes are encoded within DNA and are activated by cells when their products (proteins) are required. For example, greater activity of keratin genes, which make up the structure of the hair fibre, in scalp skin is associated with increased hair fibre production. DNA sequence variants mainly influence genes (herein termed gene variants) by affecting how a gene is regulated (how and when its activity is changed) or through changing the sequence of amino acids of the protein produced from the gene. The effect of gene variants on protein function can be quite marked, such as ablating most if its function, or quite subtle, such as reducing by a small percent the degree to which a gene can be activated under specific conditions. The extent to which a particular gene variant can affect a feature of skin ageing is determined by the size of effect that variant has on a gene's function along with the degree to which the gene function itself influences that particular feature.**

One of the most important advances in genomic research is the huge increase in the number of DNA variants that can be screened at any one time – variations in all human genes can now be screened in a study compared with only a handful of genes twenty years ago. Twin studies have discovered that skin ageing is influenced more or less equally by genetic and environmental factors (aka 'nature versus nurture') highlighting the potential for GWASs to revolutionise the understanding of skin ageing by identifying the genes that influence the ageing process in skin. [1] However, GWASs also bring challenges to study design including the handling of large numbers of human samples and huge datasets.

## GWASs OF SKIN AND FACIAL AGEING

Whilst gene variant links with skin wrinkling are mainly lacking, bar a tentative link to a gene expressed in the nervous system [2], a number of gene variants have been found to link with pigmented age spots on the face. [3] Most of these variants have also been linked to skin colour, suggesting the protective effects of melanin are reducing the damage in skin that precedes pigmented age spot development. However, the key triggers that induce age spots, once enough damage has accumulated, remains elusive - larger genetic studies might start undercovering these subsequence biological mechanisms.

To determine the impact of gene variants on facial ageing, we conducted the first GWAS study to examine the association between gene variants and perceived age (aka youthful looks - a measure that is also predictive of mortality). [4] In 2,693 participants of the Rotterdam Study and 599 participants of the Leiden Longevity Study we found that variants in the *MC1R* gene had the strongest association with how old the subjects looked for their age (Figure); homozygote minor allele carriers looked almost two years older than homozygote wild-type allele carriers. Although *MC1R* is a key pigmentation gene, the association was unlikely due to variation in sun-exposure as its association was independent of skin wrinkling, skin colour, and pigmented spots (which are strongly linked to skin sun-damage), and persisted through different levels of sun-bed use and summer sun-exposure. [5] Further research to better understand how *MC1R* variants are influencing facial ageing, such as identifying the specific facial ageing features impact by the *MC1R* variants, is now required.

*Figure. Enface average image of 20 women (mean chronological age 69) who looked young for their chronological age (average perceived age after adjusting for wrinkles was 60) (C) and 20 women (mean chronological age 69) who looked old for their chronological age (mean perceived age after adjusting for wrinkles was 78) (D); differences in face shape changes and skin colour are evident. Originally published in Current Biology, 2016 May 9;26(9):1213-20. doi: 10.1016/j.cub.2016.03.008 – republished with permission ©Unilever.*

Unilever R&D, Sharnbrook, Bedfordshire, United Kingdom

To determine whether some skin ageing traits are driven by common underlying biological mechanisms, we investigated which skin ageing specific traits/phenotypes coappear to a similar extent within people. We found 3 primary correlative features of skin ageing which explained 73% of the total variance of the different ageing phenotypes: an hypertrophic/wrinkling component (linked to global wrinkling, perceived age and Griffiths photodamage grading), an atrophic/skin colour component (linked to pigmented spots and telangiectasia) and a cancerous component (linked to actinic Keratosis and keratinocyte cancers). The strength of gene variant associations differed per component with the strongest genetic associations, primarily skin pigmentation genes, found with the atrophic component. This data indicates there are three main sets of biological mechanisms driving skin ageing, highlighting that future genetic studies should focus on these three features separately rather than treat skin ageing as one phenotype.

## The future

Finally, as huge advancements have occurred over the last ten years in DNA sequencing technology; [6,7] now the whole DNA sequence within a human sample (some 3 billion pieces of code) can be read within a day. As a consequence, sequencing technology will make larger experiments more practical and enable gene variants to be measured quickly and at low cost. Indeed, the UK biobank is radically changing the availability of GWAS data, identifying increased numbers of gene variant associations with skin pigmentation and ageing; for example, variation in skin pigmentation associates with nearly 200 gene variants within the UK biobank data.

As GWAS findings continue to grow, further research into the molecular mechanisms that drive the link between gene variants and features of skin ageing is required, particularly why some pigmentation genes link to skin ageing much more strongly than others. To facilitate such research, a new exciting technology is rapidly being adopted - the ability to measure gene variants, mRNA levels and epigenetic modifications in single cells. For example, single cell analysis of inflamed versus normal skin highlights the role of epidermal cell signalling to immune cells in driving an inflamed state. [8] The understanding of gene function at the single cell level will help drive innovations to mimic how genetic mechanisms can slow ageing and drive new anti-ageing products. Hence, sequencing and single cell technologies together will lead to rapid advancements in the understanding of how biological mechanisms drive skin ageing - the future of skin ageing research is very bright indeed.

## References


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## Abstract

Nature or Nurture? – One of the oldest debated questions in human biology. DNA sequence variants (Nature) effect the function and regulation of genes and, as a result, affect how cells and tissues age. Twin studies indicate half of the variation in the appearance of skin ageing features are attributable to DNA sequence variants, indicating they have a substantial influence on skin ageing. Genome Wide Association Studies (GWASs) are employed to identify which DNA sequence variants across the whole human genome most strongly associate with a specific ageing trait. As DNA sequence variants do not change over time, GWASs are more likely to identify biological processes that cause ageing rather than are a consequence of ageing. In effect, GWAS findings identify proteins and biological pathways that can slow the ageing process. Herein, I review progress to-date in GWASs that have identified DNA sequence variants that influence skin and facial ageing.



## Keywords

genetics – GWAS – skin ageing – perceived age



## Correspondence

David Gunn

**Email:** david.gunn@unilever.com