Genetics of facial telangiectasia in the Rotterdam Study: a genome-wide association study and candidate gene approach


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Abstract

Background The severity of facial telangiectasia or red veins is associated with many lifestyle factors. However, the genetic predisposition remains unclear.

Objectives We performed a genome-wide association study (GWAS) on facial telangiectasia in the Rotterdam Study (RS) and tested for replication in two independent cohorts. Additionally, a candidate gene approach with known pigmentation genes was performed.

Methods Facial telangiectasia were extracted from standardized facial photographs (collected from 2010–2013) of 2842 northwestern European participants (median age 66.9, 56.8% female) from the RS. Our GWAS top hits (P-value <10\(^{-6}\)) were tested for replication in 460 elderly women of the SALIA cohort and in 576 additional men and women of the RS. Associations of top single nucleotide polymorphisms (SNPs) with expression quantitative trait loci (eQTL) in various tissues were reviewed (GTEx database) alongside phenotype associations in the UK biobank database. SNP-based associations between known pigmentation genes and facial telangiectasia were tested. Conditional analysis on skin colour was additionally performed.

Results Our most significant GWAS signal was rs4417318 (P-value 5.38\(*10^{-7}\)), an intergenic SNP on chromosome 12 mapping to the SLC16A7 gene. Other suggestive SNPs tagged genes ZNF211, ZSCAN4, ICOS and KCNN3; SNP eQTLs and phenotype associations tagged links to the vascular system. However, the top signals did not pass significance in the two replication cohorts. The pigmentation genes KIAA0930, SLCA45A2 and MC1R, were significantly associated with telangiectasia in a candidate gene approach but not independently of skin colour.

Conclusion In this GWAS on telangiectasia in a northwestern European population, no genome-wide significant SNPs were found, although suggestive signals indicate genes involved in the vascular system might be involved in telangiectasia. Significantly associated pigmentation genes underline the link between skin colour and telangiectasia.

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Conflict of interest

Although no products were tested, it is possible these results could be used to promote anti-ageing products and services that lead to a financial gain for Unilever.

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**Introduction**

Telangiectasia is dilated small blood vessels visible in the skin, which vary in colour from red to blue. These linear or branched-like vessels are typically located on the nose and cheeks. Risk factors for having more extensive facial telangiectasia include environmental factors such as smoking and UV-exposure and intrinsic factors such as ageing, pale skin colour and tendency to develop sunburn.1-4

Facial telangiectasia is regarded as one of the skin ageing features, together with wrinkles, pigmented spots, xerosis and skin sagging. Skin ageing research shows that UV-exposure is an important risk factor for all signs of skin ageing, but other determinants such as for example, skin colour, have different effects in the different features of skin ageing.5,6 Twin studies demonstrate that facial wrinkles are 55% heritable, highlighting a sizeable genetic background to this feature.7 Genome-wide association studies (GWAS) performed on pigmented spots discovered that genetic variations in skin colour genes (IRF4, MC1R, ASIP and BNC2) are important in the amount of facial pigmented spots5; moreover, melanocortin-1-receptor (MC1R) variants are associated with youthful looks.8

Hence, different skin ageing phenotypes are accounted by genes and environmental factors differently and therefore it makes sense to study these separately, in order to understand skin ageing as a whole. Telangiectasia is a less well-studied phenotype and its aetiology and risk factors remain to be fully understood. A recent GWAS study in 1534 Han Chinese women found single-nucleotide polymorphism (SNP) rs191497052 tagging the KIDINS220 gene associated with having more facial telangiectasia.9 In another recent study, the heritability of telangiectasia was estimated to be low.10 However, this does not exclude that specific genetic variants may be associated with susceptibility for degree of telangiectasia.

In this study, we performed a GWAS on facial telangiectasia in 2842 North-West European men and women of the Rotterdam Study (RS). Our results were tested for replication in 460 German women of the SALIA cohort and also in a separate group of 576 RS men and women. Since pigmentation genes are known to influence wrinkling and pigmented spots, we additionally reviewed the association between telangiectasia and known pigmentation genes.

**Methods**

**Study population**

Subjects were included from the RS, a large population-based cohort, which started in 1990 in a suburb of Rotterdam. Today the RS comprises four cohorts (RSI-IV) and new subjects are still being added. Our GWAS includes participants from RSI-III. Extensive details and objectives of the RS have been described elsewhere. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports.11

**Phenotyping**

Collection of our phenotype, facial telangiectasia in the RS, has been validated and described in detail before.12 In short, telangiectasia was digitally extracted from standardized high-resolution facial photographs using a semi-automated script in MATLAB. This resulted in a percentage area of the total facial area which is covered with telangiectasia. Between the start of the dermatological screening in 2010 and July 2013, we included 2842 men and women, after quality control (QC).

**Genotyping and imputation**

DNA extraction was performed using whole blood samples following standardized and previously described protocols.13 Genotyping in the RS was performed using both the Infinium II HumanHap550(-Du) (RSI & RSII) and 610-Quad Genotyping BeadChip (RSI & RSIII; Illumina, San Diego, CA, USA). Imputation of markers was performed using the Haplotype Reference Consortium 1.1 as reference panel.14 RSI, II and III were imputed separately on the Michigan imputation server. In total 39 117 105 genotypes or imputed variants were available. Additionally, markers with poor imputation quality scores ($R^2 < 0.3$) or frequencies lower than 1% were removed.

**Statistical analysis**

We performed a GWAS separately for cohorts RSI, RSII and RSIII using a linear regression with the score test and RVTESTS software package.15 Since the residuals of the linear regression on telangiectasia did not fit a normal distribution, we ln-transformed our outcome measure resulting in approximately normal distribution of the residuals of the regression. Our analyses were adjusted for age, sex and two technical variables which accounted for the variability in analysed batches and flashlight. A conditional analysis was performed by additionally adjusting the analysis for skin colour. Details of all variables have been published.6 To account for possible population stratification and hidden relatedness between participants, we also adjusted for the first four genetic principal components. Subsequently, QC was performed using EasyQC software package with parameter defaults.16 To bundle the results of our three cohorts, we performed a meta-analysis using software METAL and the inverse variance approach.17 Meta-analysis was completed for 8 086 478 markers. P-values < 0.05*10$^{-8}$ were considered genome-wide statistically significant and P-values 0.05*10$^{-8}$ <0.05*10$^{-5}$ genome-wide statistically suggestive.

**Replication and power calculation**

Replication of our top associated SNPs (P-value < 5.0*10$^{-6}$) was performed in two separate cohorts. The first cohort
consisted of 460 German elderly women of the SALIA cohort, where telangiectasia have been scored manually based on photometric grading as part of the SCINEXA™ method.18 Details on this cohort have been described elsewhere.19,20 The GWAS was performed using linear regression, adjusted for age and the first 10 genetic principal components. The second replication cohort consisted of 576 RS participants where photographs were collected between September 2013 and May 2016, available after QC. Here, phenotyping, genotyping and statistical analysis were performed as described in detail above. Additionally, we conducted a power analysis to calculate the power of our analysis and the probability of replicating our top SNP in two independent cohort, using GWAPower tool.21

Candidate gene approach
To assess whether telangiectasia is associated with known pigmentation genes, we reviewed the association between the SNPs on these genes known from their association with pigmented spots,6 tanning response,22 or hair colour23 in three recent state-of-the-art GWAS papers, and telangiectasia in the discovery cohort. This was performed by selecting the dosage of the alleles of the known variants and performing a linear regression. For the skin colour gene MC1R, several functional SNPs have been discovered with known cumulative effects. Therefore, we combined four known functional MC1R variants (rs1805005, rs1805007, rs1805008, rs1805009) into one genetic risk score by adding up the number of risk alleles.8 Additional analyses conditioned on skin colour were performed. The SNP (rs191497052) which was associated with telangiectasia in female Han Chinese9 is not present in our European cohort and therefore was not analysed. P-values < 0.05 were regarded as statistically significant.

Bioinformatics
Single nucleotide polymorphisms were annotated to genes using UCSC genome browser (GRCh37/hg19). To assess how the found associations could influence mRNA expression levels, the association of our top SNPs with expression quantitative trait loci (eQTLs) in different tissues was investigated using the GTEx portal (https://gtexportal.org/) during Q1 2020, and SNP phenotype associations in the UK biobank via Open Targets (https://www.opentargets.org/).24

Results
Population characteristics
Our population consisted of 1521 women (53.5%) and 1321 men (46.5%). The median age was 66.6 years, and the median percentage of facial telangiectasia area was slightly higher in women than in men [men: 0.77%, (interquartile range (IQR) 0.49–1.21); women: 0.96%, (IQR 0.62–1.41)].

GWAS results and replication
In our main GWAS, we did not find any genome-wide significant hits (Fig. 1). The most significantly associated SNP was rs4417318 (P-value 5.38*10^{-5}), an intergenic SNP located on chromosome 12. This SNP is significantly associated with variation in the expression (i.e. an eQTL) of the pseudogene RP11-813P10.2 exclusively in coronary artery tissue as were the other suggestive hits in this locus (Table 1) supporting a vasculature role for this gene locus.

Other associated SNPs with a P-value < 5.0*10^{-6} were located on chromosome 12 as well but also on chromosomes 1, 2, 8, 16 and 19 (Table 1). The second strongest locus that was associated, on chromosome 19, had a significant association with the expression of the ZNF211 in skin, which is the most significant of its eQTL associations. In addition, this SNP is associated with platelet and red cell distribution width in the UK biobank. On chromosome 2, the most significant SNP is nearby to the ICOS gene (inducible T-cell costimulatory) which is linked to skin wound healing including angiogenesis.25 The strongest associating SNP on chromosome 1 is within the gene KCNN3, which is strongly linked with atrial fibrillation.26 SNP rs7463003 on chromosome 8 is between the genes RDH10 and STAU2, both genes are significantly associated with systolic blood pressure in the UK biobank although this SNP itself is not. Finally, the most significant SNP on chromosome 16 was significantly associated with ease of skin tanning in the UK biobank (P-value = 3.0*10^{-170}) and is in the gene PRDM7 but near the MC1R gene, and the most significant eQTL in skin is with the gene CDK10.
Table 1  Top hits genome-wide association study (GWAS) telangiectasia Rotterdam Study, $n = 2842$

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>BASE</th>
<th>EA</th>
<th>OA</th>
<th>fEA</th>
<th>$P$-value</th>
<th>$P$-value in SALIA replication</th>
<th>$P$-value in RS replication</th>
<th>Direction</th>
<th>Mapped gene</th>
<th>Most significant eQTL (tissue type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4417318</td>
<td>12</td>
<td>60620713</td>
<td>c</td>
<td>g</td>
<td>0.6543</td>
<td>5.38E-07</td>
<td>0.091</td>
<td>0.525</td>
<td>--</td>
<td>SLC16A7</td>
<td>RP11-813P10.2 (coronary artery)</td>
</tr>
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<td>60708785</td>
<td>a</td>
<td>c</td>
<td>0.3449</td>
<td>5.96E-07</td>
<td>0.125</td>
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<td>SLC16A7</td>
<td>RP11-813P10.2 (coronary artery)</td>
</tr>
<tr>
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<td>60567404</td>
<td>a</td>
<td>t</td>
<td>0.3448</td>
<td>6.87E-07</td>
<td>0.295</td>
<td>0.462</td>
<td>+++</td>
<td>SLC16A7</td>
<td>RP11-813P10.2 (coronary artery)</td>
</tr>
<tr>
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<td>60558709</td>
<td>t</td>
<td>c</td>
<td>0.3454</td>
<td>9.13E-07</td>
<td>0.273</td>
<td>0.434</td>
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<td>g</td>
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<td>1.26E-06</td>
<td>0.479</td>
<td>0.347</td>
<td>--</td>
<td>ZNF211</td>
<td>ZNF211 (skin not sun-exposed)</td>
</tr>
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<td>t</td>
<td>c</td>
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<td>1.27E-06</td>
<td>0.479</td>
<td>0.349</td>
<td>--</td>
<td>ZNF211</td>
<td>ZNF211 (skin not sun-exposed)</td>
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<td>c</td>
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<td>0.346</td>
<td>--</td>
<td>ZNF211</td>
<td>ZNF211 (skin not sun-exposed)</td>
</tr>
<tr>
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<td>0.343</td>
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<td>ZNF211 (skin not sun-exposed)</td>
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<tr>
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<tr>
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<td>g</td>
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<td>0.342</td>
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<td>ZSCAN4</td>
<td>ZNF211 (skin not sun-exposed)</td>
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<td>a</td>
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<td>SLC16A7</td>
<td>RP11-813P10.2 (coronary artery)</td>
</tr>
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<td>c</td>
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<td>3.87E-06</td>
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<td>0.9379</td>
<td>4.16E-06</td>
<td>0.867</td>
<td>0.334</td>
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<td>g</td>
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<td>90134174</td>
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<td>0.972</td>
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<td>PRDM7*</td>
<td>FAM157C (whole blood)§</td>
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<td>c</td>
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<td>5.00E-06</td>
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<td>0.767</td>
<td>+++</td>
<td>PRDM7*</td>
<td>FAM157C (whole blood)§</td>
</tr>
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</table>

Main results of GWAS telangiectasia in $n = 2842$ individuals ($P$-value $< 5 \times 10^{-8}$). SNP listed on rs number sorted by $P$-value (smallest through largest). CHR, chromosome; BASE, refers to position of SNP on the chromosome; EA, effect allele; OA, other allele; fEA, frequency of the effect allele; SNP, single nucleotide polymorphism; Direction, direction in which the effect of the SNP is per cohort of the Rotterdam Study (RSI, RSII, RSIII); Mapped gene according to UCSC genome browser where * indicates the SNP is in the gene, all others are intergenic SNPs mapped to closest gene/ transcript. $§$ most significant eQTL in skin was with CDK10.

None of the top SNPs could be replicated in the two independent cohorts (Table 1), although this might be explained by lack of power. The power calculation performed indicated at least 950 subjects per cohort would be required to have an 80% power of replicating the associations that were found in the discovery cohort, since the top SNP only explained 2% of the total variance (data not shown). An additional GWAS conditioned on skin colour, revealed similar effect sizes and $P$-values; however, the two SNPs in the PRDM7 gene, near the MC1R gene dropped in significance. This suggests these hits were not (entirely) independent of skin colour.

**Candidate gene approach**

Telangiectasia was significantly associated with known pigmentation SNPs with rs16891982 ($P$-value 0.03) mapping to the SLC45A2 gene and rs11703668 ($P$-value 0.01) mapping to the KIAA0930 gene. In addition, the combined MC1R genetic risk score was also significantly associated with having more telangiectasia ($P$-value 0.03; Table S1, Supporting Information). Conditional analysis revealed that the KIAA0930 gene signal might be partly skin colour independent ($P$-value 0.03) whereas the SLC45A2 gene signal ($P$-value 0.08) and the MC1R genetic risk score ($P$-value 0.26) were not.

**Discussion**

This GWAS study on facial telangiectasia did not reveal genome-wide significant associations between SNPs and facial telangiectasia in a northwestern European population. However, there are tentative links between the genes near some of the suggestive SNPs with the vasculature system, perhaps, indicating some of them are not false positives. In addition, in a candidate gene approach, several significant links with known pigmentation...
genes and telangiectasia were found, confirming the link between skin colour and telangiectasia found in epidemiological studies.

Smoking habits and UV-exposure remain the most importantly associated life style factors associated with the presence of facial telangiectasia.1–4 In addition, pigmentation and skin colour seem to play a role because pale coloured individuals are repeatedly most at risk. In support of this, the current study found two SNPs in known skin colour genes (KIAA0930 and SLCA45A2) and the MCIR genetic risk score to be associated with telangiectasia in addition to the genome-wide suggestive SNPs in the PRDM7 gene which also covers the MCIR locus. The link between pale skin and telangiectasia might be explained by the increased risk of getting sunburn or UV-related damage which is more pronounced in individuals with pale skin. Photo-damaged biopsies in a recent study into photoaging show more elastic damage, sebaceous gland prominence, inflammation and dilated vessels compared to participant matched sun-protected elastic damage, sebaceous gland prominence, inflammation and which is more pronounced in individuals with pale skin. Photo-by the increased risk of getting sunburn or UV-related damage

In conclusion, we conducted a GWAS on facial telangiectasia in a fairly large northwestern European population of men and women in an attempt to explore its' genetic background. We did not find significantly associated SNPs in this study, however, suggestive signals showed tentative links with the vascular system. Significantly associated pigmentation genes KIAA0930, SLCA45A2 and MCIR underline the link between skin colour and telangiectasia in a candidate gene approach. Much larger studies are now required to replicate suggestive signals and to identify the influences of DNA sequence variants on telangiectasia.

**References**


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**Supporting information**

Additional Supporting Information may be found in the online version of this article:

Table S1. Association with known skin pigmentation genes.