DOI: 10.1111/jdv.17014 JEADV

ORIGINAL ARTICLE

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.

Received: 12 May 2020; Accepted: 5 October 2020

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.

Funding sources

This study is funded by Unilever. The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University Rotterdam; Netherlands Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. Author SM is supported by Unilever and author DAG is Unilever employee. The SALIA study was funded by the Deutsche Forschungsgemeinschaft (DFG; HE-4510/2-1, KR 1938/3-1, LU 691/4-1), by the Ministry of the Environment of the state North Rhine-Westphalia (Düsseldorf, Germany), by the Federal Ministry of the Environment (Berlin, Germany) and the DGUV (German statutory accident assurance) VT 266.1. The Genotype-Tissue Expression (GTEx) was supported by the Common Fund of the Office of the Director of the National Institutes of Health, and by NCI, NHGRI, NHLBI, NIDA, NIMH, and NINDS.

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 spots[5]; 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(-Duo) (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 photonumeric 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,[5] tanning response,[22] or hair colour[23] 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 Chinese[9] 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)].

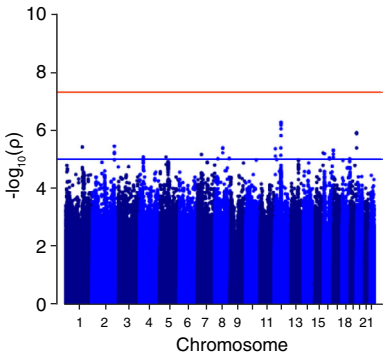

Figure 1 Manhattan plot representing the association between the single nucleotide polymorphisms (SNPs) and the ln-transformed percentage of the face, which is covered with telangiectasia for 2842 men and women. On the *x*-axis the chromosomes are plotted with each dot representing a SNP on corresponding chromosomal locations vs. the −log10(*P*-value) of the association. The red horizontal line represents the threshold for genome-wide-significant, indicating a *P*-value of $5*10^{-8}$. The blue horizontal line represents the threshold for genome-wide-suggestive.

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 $5.38*10^{-7}$), 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 = $3.0*10^{-176}$) 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, $n = 2842$

SNP	CHR	BASE	EA	OA	fEA	*P*-value	*P*-value in SALIA replication	*P*-value in RS replication	Direction	Mapped gene	Most significant eQTL (tissue type)
rs4417318	12	60620713	c	g	0.6543	5.38E-07	0.091	0.525	−−−	*SLC16A7*	RP11-813P10.2 (coronary artery)
rs12230938	12	60708785	a	c	0.3449	5.96E-07	0.125	0.535	+++	*SLC16A7*	RP11-813P10.2 (coronary artery)
rs17602381	12	60567404	a	t	0.3448	6.87E-07	0.295	0.462	+++	*SLC16A7*	RP11-813P10.2 (coronary artery)
rs12227514	12	60558709	t	c	0.3454	9.13E-07	0.273	0.434	+++	*SLC16A7*	RP11-813P10.2 (coronary artery)
rs73573497	19	58165890	a	g	0.0529	1.26E-06	0.479	0.347	−−−	*ZNF211*	ZNF211 (skin not sun-exposed)
rs73573500	19	58166262	t	c	0.0530	1.27E-06	0.479	0.349	−−−	*ZNF211*	ZNF211 (skin not sun-exposed)
rs73573501	19	58166536	t	c	0.0529	1.27E-06	0.479	0.346	−−−	*ZNF211*	ZNF211 (skin not sun-exposed)
rs12610258	19	58167451	c	g	0.9471	1.30E-06	0.479	0.343	+++	*ZSCAN4*	ZNF211 (skin not sun-exposed)
rs12610292	19	58167753	t	c	0.0529	1.32E-06	0.479	0.342	−−−	*ZSCAN4*	ZNF211 (oesophagus - Mucosa)
rs9710520	19	58168922	a	g	0.9472	1.32E-06	0.458	0.342	+++	*ZSCAN4*	ZNF211 (skin not sun-exposed
rs11173337	12	60531507	a	g	0.3488	1.58E-06	0.092	0.379	+++	*SLC16A7*	RP11-813P10.2 (coronary artery)
rs77938763	2	204962815	a	g	0.0210	3.61E-06	0.521	0.407	−−−	*ICOS*	None
rs77766535	1	154746441	a	c	0.0988	3.87E-06	0.995	0.494	+++	*KCNN3**	None
rs7463003	8	74315266	a	c	0.9794	4.16E-06	0.815	0.088	+++	*STAU2-AS1*	None
rs2106823	19	58168641	a	g	0.9379	4.16E-06	0.867	0.334	+++	*ZSCAN4*	Not present in database
rs73351721	12	58830976	a	g	0.0602	4.17E-06	0.843	0.086	+++	*AK093124*	None
rs118021692	8	74313389	a	g	0.0207	4.24E-06	0.815	0.086	−−−	*STAU2-AS1*	None
rs7198289	16	90134174	a	c	0.1768	4.89E-06	0.972	0.766	+++	*PRDM7**	FAM157C (whole blood)[$]
rs7198471	16	90134260	a	c	0.1768	5.00E-06	0.972	0.767	+++	*PRDM7**	FAM157C (whole blood)[$]

Main results of GWAS telangiectasia in $n = 2842$ individuals (*P*-value $\leq 5*10^{-6}$). 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 *SCLC45A2* 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 *MC1R* genetic risk score to be associated with telangiectasia in addition to the genome-wide suggestive SNPs in the *PRDM7* gene which also covers the *MC1R* 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. Photodamaged biopsies in a recent study into photoaging show more elastic damage, sebaceous gland prominence, inflammation and dilated vessels compared to participant matched sun-protected buttock skin[27] which indicates that UV-damaged skin has more telangiectasia than sun-protected skin. The *KIAA0930* gene locus was recently discovered to be associated with tanning response to sun exposure,[22] hair colour and sunburn,[28] revealing association with multiple pigmentation traits. The SNP tagging the *KIAA0930* gene remained significantly associated with greater telangiectasia when additionally correcting for skin colour, although with marginal significance level (*P*-value 0.03) given the fairly large sample size. The results tagging the *MC1R* gene and the *SLC45A2* gene, in contrast, were more likely driven by their association with skin colour. Overall these results indicate pigmentation genes do not associate fundamentally with telangiectasia independently of skin colour. This is in contrast to other skin ageing phenotypes, e.g. pigmented spots, where several pigmentation genes were very significantly associated with the amount of acquired facial pigmented spots, even when additionally adjusted for skin colour.[5] This highlights different genetic pathways for different skin ageing phenotypes.

Our GWAS results indicate that there are no single gene variants with strong association with telangiectasia. In conjunction, as the heritability of telangiectasia is low,[10] it suggests that very large studies (e.g. >10 000 subjects) might be needed to identify any gene variants that do associate on a genome-wide level. The only SNP previously reported to be significantly associated with telangiectasia, rs191497052, could not be replicated in our discovery cohort nor in two other smaller Caucasian cohorts, since it was not present.[9] This highlights the need for further replication of rs191497052 in Asian populations and better understanding of the genetic background of skin ageing features across different populations.

Although the genes tagged by the top SNPs are linked to the vasculature system, the links were quite disparate. For example, the top SNP linked to RP11-813P10.2 expression in coronary artery tissue, ICOS is linked to angiogenesis, SNPs in ZNC211 are linked with platelet and red cell parameters in the UK biobank, KCNN3 is linked with atrial fibrillation, and RDH10 and STAU2 are linked with systolic blood pressure. Hence, replication of these SNP associations is required before vasculature associated variants can be determined to be driving the appearance of telangiectasia. Future, larger studies might also investigate the relation between pigmentation and the vasculature system as one can imagine vasculature differences in different skin colours (maybe resulting in more or less telangiectasia).

Strengths to this study are that the telangiectasia method has been validated and was successfully used in lifestyle studies.[4,12] Also, we added two independent cohorts for external validation of our results. However, the sample size of our cohorts was too small to discover and replicate SNPs with small effect sizes in traits with low heritability. Alternatively, the suggestive SNPs in the discovery cohort could be false positives.

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 *MC1R* 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.

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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.