



## King's Research Portal

DOI:

[10.1016/j.jid.2016.09.014](https://doi.org/10.1016/j.jid.2016.09.014)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Ribero, S., Sanna, M., Visconti, A., Navarini, A., Aviv, A., Glass, D., ... Bataille, V. (2017). Acne and Telomere Length: A New Spectrum between Senescence and Apoptosis Pathways. *Journal of Investigative Dermatology*, 137(2), 513-515. DOI: 10.1016/j.jid.2016.09.014

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# Accepted Manuscript

Acne and telomere length. A new spectrum between senescence and apoptosis pathways

S. Ribero, M. Sanna, A. Visconti, A. Navarini, A. Aviv, D. Glass, T.D. Spector, C. Smith, M. Simpson, J. Barker, M. Mangino, M. Falchi, V. Bataille

PII: S0022-202X(16)32456-3

DOI: [10.1016/j.jid.2016.09.014](https://doi.org/10.1016/j.jid.2016.09.014)

Reference: JID 536

To appear in: *The Journal of Investigative Dermatology*

Received Date: 23 March 2016

Revised Date: 30 August 2016

Accepted Date: 1 September 2016

Please cite this article as: Ribero S, Sanna M, Visconti A, Navarini A, Aviv A, Glass D, Spector T, Smith C, Simpson M, Barker J, Mangino M, Falchi M, Bataille V, Acne and telomere length. A new spectrum between senescence and apoptosis pathways, *The Journal of Investigative Dermatology* (2016), doi: 10.1016/j.jid.2016.09.014.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Acne and telomere length. A new spectrum between senescence and apoptosis pathways.

Ribero S<sup>1,2\*</sup>, Sanna M<sup>1\*</sup>, Visconti A<sup>1</sup>, Navarini A<sup>3</sup>, Aviv A<sup>4</sup>, Glass D<sup>1</sup>, Spector TD<sup>1</sup>, Smith C<sup>3</sup>, Simpson M<sup>5</sup>, Barker J<sup>3</sup>, Mangino M<sup>1</sup>, Falchi M<sup>1#</sup> and Bataille V<sup>1,6#</sup>

<sup>1</sup>Department of Twin Research & Genetic Epidemiology, King's College London, UK

<sup>2</sup>Department of Medical Sciences, Section of Dermatology, University of Turin, Italy

<sup>3</sup>St John's Institute of Dermatology, Division of Genetics and Molecular Medicine, Kings College London, UK

<sup>4</sup>Center of Human Development and Aging, The State University of New Jersey, New Jersey Medical School, Newark, NJ 07103, USA

<sup>5</sup>Department of Medical Genetics, Division of Genetics and Molecular Medicine, Faculty of Life Sciences and Medicine, Kings College London, UK

<sup>6</sup>Department of Dermatology, West Herts NHS Trust, Herts, UK

\* RS, SM contributed equally to this work

#FM, BV share senior authorship

**Short title: Telomere length, p53 and acne susceptibility**

**Address for correspondence:**

Simone Ribero, MD, PhD

Department of Twin Research and Genetic Epidemiology, King's College London

St Thomas' campus, Westminster Bridge Road, London, SE1 7EH

email: simone.ribero@unito.it

Tel: 01442-287467 Fax: 01442-287588

Acne is a multi-factorial disease with many factors thought to play a role including the skin microflora and nutrition as well as hormonal influences and stress (Suh and Kwon, 2015). Acne patients have increased sebum secretion, and both acne and activity of the sebaceous glands are under significant genetic control (Mourelatos et al., 2007; Bataille et al., 2002). Recent Genome Wide Association Studies (GWAS) have identified several

variants linked to acne susceptibility (Wang et al., 2015; He et al., 2014; Navarini et al., 2014; Zhang et al., 2014).

It has long been noticed by dermatologists that acne patients have reduced skin ageing, often observed many years after the acne has recovered. Signs of ageing, such as wrinkling and skin thinning appear later in acne patients compared to non-affected individuals. This was speculated to be due to increased sebum secretion during a lifetime but other factors are likely to be involved (Downing et al., 1986).

In this study, we investigated leucocyte telomere length (LTL) in subjects with acne compared to controls using data from the TwinsUK registry (<http://www.twinsuk.ac.uk/>). Telomeres are repeat TTAGGG sequences at the end of linear chromosomes guarding against loss of genetic material during cellular replication. Repeated cell cycles eventually lead to a critically shortened LTL signalling cellular senescence and triggering apoptosis. Hence, LTL has been shown to be predictive of biological ageing (Hewitt et al., 2012).

Volunteers in the TwinsUK cohort were not recruited on the basis of any specific trait or disease and have been shown to have diseases and lifestyle characteristics similar to the general population (Andrew et al., 2001). Guy's and St Thomas' Hospital NHS Trust Research Ethics Committee approved the study, and all twins provided informed written consent. For historical reasons the TwinsUK registry involves mainly females and males were therefore excluded from this study. The history of acne was self-reported during a nurse-administered questionnaire and the female twins were asked if they had ever suffered from acne and whether their acne was self treated, treated by a GP or by a dermatologist (Bataille et al., 2002). 293 out of 1,205 twin volunteers (24.3%) had experienced acne in their lifetime.

LTL was measured using Southern Blot and was available for all the subjects included in this study (Valdes et al., 2007; see Supplementary Material for details). Mean LTL in the 1,205 subjects was 7.08 kb (median=7.06 kb, range: [5.70-8.67] kb). Mean weight was 67 kg (median: 65 kg; range: [40-115] kg) and mean height was 162 cm (median: 162 cm; range: [144-182] cm). The mean age of the twins at the time of DNA extraction was  $48 \pm 12$  years.

Linear regression (see Supplementary Material for details) showed that acne cases had longer LTL (mean  $7.17 \pm 0.64$  kb) compared to controls (mean  $6.92 \pm 0.02$  kb) after adjustment for age, twin relatedness, weight and height ( $\beta=0.11$ ;  $se=0.05$ ;  $p=0.01$ ). Using score tests under a logistic regression model, we further investigated the association between acne and a set of SNPs previously reported to be associated with LTL in a sample of 1,893 cases of severe acne and 5,132 population controls from the UK Acne Genetic study (Codd et al., 2013; Mangino et al., 2015; Navarini et al., 2014). No LTL SNPs were significantly associated with acne after correction for multiple testing. However, rs3027234 in the CTS Telomere Maintenance Complex Component 1 gene (*CTC1*), was nominally significant (Supplementary Table 1). Finally, we performed a mixed effect logistic regression analysis in whole genome data from healthy skin samples comparing acne cases and controls. The expression data was measured in 705 female individuals from the TwinsUK registry (<http://www.mother.ac.uk/>) of whom 346 had data on acne history. We selected 195 controls twins who were perfectly age-matched to 39 twins with acne and gene expression data (see Supplementary Material for details). Only the *ZNF420* gene (probe ILMN\_1720431) was significantly associated with acne history at FDR 5%, showing a higher expression in controls ( $p=7.73 \times 10^{-7}$ ; Table 1 and Figure 1), Interestingly, *ZNF420* is one of the 30% most expressed genes in skin.

This study investigates reduced skin ageing observed in acne by assessing telomere length in circulating white cells and gene expression in the skin. Acne cases showed longer telomeres after adjusting for age, height and twin relatedness suggesting that the delayed skin ageing may be due to reduced senescence. Only one SNP predicting LTL was found to be associated with acne at nominal significance. This SNP is located within the *CTC1* gene which is a component of the CST complex and plays an important role in protecting telomeres against degradation (Sarek et al., 2015). The reduced expression of the gene *ZNF420* in normal skin in acne cases which encodes the protein Apak (ATM and p53-associated KRAB-type zinc-finger protein) suggests that p53 is up-regulated in acne cases as the *ZNF420* gene is a negative regulator of p53-mediated apoptosis.

Considering longer telomeres and the up-regulation of the p53 pathway in acne cases, it could be speculated that acne susceptibility may be linked to the biology of cancer. A recent study from the Nurses' Health study II, a large USA cohort involving more than 99,000 female nurses (Zhang et al., 2015) found an increased risk of cancer in acne cases (Zhang et al., 2015). Additionally, recent GWASs have reported significant associations between acne and genes involved in cancer susceptibility, including the *MYC* gene and genes linked to the TGF $\beta$  cell signalling pathway (Zhang et al., 2014; Navarini et al., 2014). Further work is needed to investigate the associations between cell senescence, acne, and cancer susceptibility but this work shed new light on this very common and often debilitating skin disease.

The authors state no conflict of interest

**Acknowledgments.** We wish to express our appreciation to all study participants of the TwinsUK. MS, AV, and MF wish to acknowledge S. Burbidge of the Imperial College High-Performance Computing service for their assistance.

**FUNDING.** TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union (EU), and the National Institute for Health Research (NIHR)- funded BioResource, Clinical Research Facility, and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. MF, VB and AV are supported by BSF grant n. 5044i.

## REFERENCES

- Andrew T, Hart DJ, Snieder H, de Lange M, Spector TD, MacGregor AJ. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Res.* 2001;4:464-77.
- Bataille V, Snieder H, MacGregor AJ, Sasieni P, Spector TD. The influence of genetics and environmental factors in the pathogenesis of acne: a twin study of acne in women. *J Invest Dermatol.* 2002;119(6):1317-22.
- Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL et al. Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet.* 2013;45:422-7
- Downing DT, Wertz PW, Stewart ME. The role of sebum and epidermal lipids in the cosmetic properties of skin. *Int J Cosmet Sci.* 1986 Jun;8(3):115-23.
- He L, Wu WJ, Yang JK, Cheng H, Zuo XB, Lai W et al. Two new susceptibility loci 1q24.2 and 11p11.2 confer risk to severe acne. *Nat Commun.* 2014;5:2870.
- Hewitt G, Jurk D, Marques FD, Correia-Melo C, Hardy T, Gackowska A, et al. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. *Nat Commun.* 2012;3:708.
- Mangino M, Christiansen L, Stone R, Hunt SC, Horvath K, Eisenberg DT et al. DCAF4, a novel gene associated with leucocyte telomere length. *J Med Genet.* 2015;52:157-62
- Mourelatos K, Eady EA, Cunliffe WJ, Clark SM, Cove JH. Temporal changes in sebum excretion and propionibacterial colonization in preadolescent children with and without acne. *Br J Dermatol* 2007; 156:22– 31.
- Navarini AA, Simpson MA, Weale M, Knight J, Carlavan I, Reiniche P et al. Genome-wide association study identifies three novel susceptibility loci for severe Acne vulgaris. *Nat Commun.* 2014;5:4020
- Sarek G, Marzec P, Margalef P, Boulton SJ. Molecular basis of telomere dysfunction in human genetic diseases. *Nat Struct Mol Biol.* 2015 Nov;22(11):867-74.
- Suh DH, Kwon HH. What's new in the physiopathology of acne? *Br J Dermatol.* 2015 Jul;172 Suppl 1:13-9.

Valdes AM, Richards JB, Gardner JP, Swaminathan R, Kimura M, Xiaobin L, et al. Telomere length in leukocytes correlates with bone mineral density and is shorter in women with osteoporosis. *Osteoporosis Int* 2007; 18: 1203-1210.

Wang H, Guo M, Shen S, He L, Zhang X, Zuo X, et al. Variants in SELL, MRPS36P2, TP63, DDB2, CACNA1H, ADAM19, GNAI1, CDH13 and GABRG2 interact to confer risk of acne in Chinese population. *J Dermatol*. 2015 Apr;42(4):378-81.

Zhang M, Qureshi AA, Hunter DJ, Han J. A genome-wide association study of severe teenage acne in European Americans. *Hum Genet*. 2014 Mar;133(3):259-64.

Zhang M, Qureshi AA, Fortner RT, Hankinson SE, Wei Q, Wang LE, et al. Teenage acne and cancer risk in US women: A prospective cohort study. *Cancer*. 2015 May 15;121(10):1681-7.



## TABLES AND FIGURES

**Table 1.** Whole genome differential expression between acne cases and controls using a mixed linear model to control for intra-pair phenotypic correlation. The table reports the top 20 hits from the mixed effect logistic regression analysis. P values (P), Storey's Q value (Q), effect sizes (Beta) and standard errors (SE) are reported. Only the *ZNF420* gene remained significant after multiple testing at 5% false discovery rate ( $Q < 0.05$ ).

Gene	Beta	SE	P	Q
<i>ZNF420</i>	-36.52	7.39	$7.73 \times 10^{-7}$	0.02
<i>KRTAP13-1</i>	16.03	4.24	$1.54 \times 10^{-4}$	0.85
<i>TP53INP1</i>	-4.11	1.24	$9.01 \times 10^{-4}$	0.85
<i>PTPN9</i>	8.32	2.53	$1.01 \times 10^{-3}$	0.85
<i>GOLGA4</i>	-4.70	1.44	$1.14 \times 10^{-3}$	0.85
<i>BCLAF1</i>	-2.87	0.89	$1.17 \times 10^{-3}$	0.85
<i>ZC3H10</i>	4.88	1.51	$1.23 \times 10^{-3}$	0.85
<i>VGLL1</i>	-6.35	1.98	$1.35 \times 10^{-3}$	0.85
<i>GOLGA5</i>	-3.68	1.15	$1.42 \times 10^{-3}$	0.85
<i>C20orf106</i>	6.88	2.16	$1.45 \times 10^{-3}$	0.85
<i>FAM3A</i>	3.22	1.02	$1.66 \times 10^{-3}$	0.85
<i>ALDH3A1</i>	2.03	0.65	$1.78 \times 10^{-3}$	0.85
<i>SUV420H1</i>	-8.68	2.80	$1.93 \times 10^{-3}$	0.85
<i>TNFAIP3</i>	-2.91	0.95	$2.10 \times 10^{-3}$	0.85
<i>PREB</i>	4.27	1.39	$2.18 \times 10^{-3}$	0.85
<i>HCFC1R1</i>	2.74	0.90	$2.22 \times 10^{-3}$	0.85
<i>ING1</i>	-3.88	1.27	$2.22 \times 10^{-3}$	0.85
<i>WDR17</i>	-8.95	2.93	$2.22 \times 10^{-3}$	0.85
<i>CXorf1</i>	-7.07	2.31	$2.22 \times 10^{-3}$	0.85
<i>RAPH1</i>	-2.96	0.97	$2.37 \times 10^{-3}$	0.85

**Figure 1:** Gene expression levels for *ZNF420* (probe ILMN\_1720431) in acne cases and controls. Gene expression levels are adjusted by age and twin relatedness and have been scaled between 0 and 1. Main plot: *ZNF420* expression levels in controls (N=195) and cases (N=39). Inset plot: *ZNF420* expression levels in moderate acne cases, which were treated only by the GP (N=31) and severe acne cases which were treated by a dermatologist (N=8). Reported p values are from logistic regression.

