Facial Appearance Reflects Human Familial Longevity and Cardiovascular Disease Risk in Healthy Individuals

David A. Gunn,1 Anton J. M. de Craen,2 Joanne L. Dick,1 Cyrena C. Tomlin,1 Diana van Heemst,2 Sharon D. Catt,1 Tamara Griffiths,3 Stephanie Ogden,3 Andrea B. Maier,2 Peter G. Murray,1 Christopher E. M. Griffiths,3 P. Eline Slagboom,4,5 and Rudi G. J. Westendorp2,5

1Unilever Discover, Colworth House, Sharnbrook, Bedfordshire, UK.
2Department of Gerontology and Geriatrics, Leiden University Medical Center, The Netherlands.
3Dermatological Sciences, Salford Royal Hospital, University of Manchester, Manchester Academic Health Science Centre, UK.
4Section of Molecular Epidemiology, Department of Medical Statistics and Bioinformatics and 5Netherlands Consortium for Healthy Aging (NCHA), Leiden University Medical Center, The Netherlands.

Address correspondence to David A. Gunn, Unilever Discover, Colworth House, Sharnbrook, Bedfordshire, UK.
Email: david.gunn@unilever.com

Background. As facial appearance can be readily quantified and skin tissue easily accessed, they could be valuable tools for determining how biological mechanisms influence tissue degeneration with age and, consequently, human health and lifespan. It is unknown, however, whether appearance reflects disease risk or lifespan independently of factors already known to associate with both health and appearance.

Methods. In a cross-sectional study, we compared the amount of skin wrinkling on a sun-protected site (upper inner arm) and the facial appearance of 261 offspring (mean age 63.2 y) of nonagenarian siblings with 253 age-matched controls (mean age 62.7 y), all with no reported disease history. We next examined whether any appearance features that significantly associated with familial longevity also associated with the Framingham cardiovascular disease (CVD) risk score. All analyses were adjusted for chronological age, smoking, photodamage, and body mass index.

Results. Female and male offspring had reduced upper inner arm skin wrinkling ($p = .03$ and $p < .001$, respectively), and the male offspring looked 1.4 y younger than the controls ($p = .002$). There were no significant associations between CVD risk and upper inner arm skin wrinkling. Women in the lowest quartile of CVD risk looked more than 2 y younger for their age than those in higher risk quartiles ($p = .002$). Systolic blood pressure was the most significant ($p = .004$) CVD risk factor that was associated with perceived age in women.

Conclusions. Facial appearance and skin wrinkling at a sun-protected site reflect the propensity to reach an extreme old age, and facial appearance reflects the risk of succumbing to CVD independently of chronological age, smoking, photodamage, and BMI.

Key Words: Perceived age—Longevity—Cardiovascular disease—Skin—Aging.

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Despite anecdotal beliefs that an individual’s appearance reflects how well they are aging systemically, very few studies have investigated such links. The perceived age of elderly individuals (over 70 years of age) in passport-type photographs has been found to be predictive of mortality, associated with physical and cognitive functioning, and leukocyte telomere length (1). In addition, skin wrinkling at a sun-protected site has been found to be a marker of self-assessed health (2) in individuals over 70 years of age. These findings suggest that perceived age and skin wrinkling at a sun-protected site are markers of health and longevity and, hence, indicative of systemic aging/biological age (3). However, such links could be specific to elderly populations and sequelae of disease; that is, the presence of disease leads to an older appearance. It is also not clear if links between perceived age and health are independent of factors that are already known to associate with both health and appearance, namely smoking, body mass index (BMI), and the effects of sun-exposure. Indeed, smoking has been associated with increased mortality (4), greater skin wrinkling (5,6), and looking older for one’s age (7). High and low BMI have been associated with increased mortality (8,9) and low BMI with looking older for one’s age (7). Furthermore, increased sun-exposure in Caucasians is associated with reduced all cause and cardiovascular disease (CVD) mortality (10) but increased skin wrinkling and perceived age (7,11). Thus, to determine the utility of using appearance as a marker of systemic aging, new
studies are required to investigate whether associations between health and appearance are driven predominantly by factors already known to influence both.

Studies on the longest lived individuals demonstrate that longevity coincides with an active and healthy mid to late life-stage free of morbidity (12–15). In addition, parents, siblings, and offspring of centenarians or long-lived nonagenarian siblings have lower disease prevalence than age-matched controls (16–19). Thus, such long-lived families offer a unique cohort to study systemic aging and health alongside established markers such as the Framingham CVD risk score, which predicts outcome over a 10-y period (20). Understanding how biological pathways influence tissue degeneration and, as a consequence, disease risk, and lifespan will help identify new ways to promote healthy aging.

Here, we investigated whether appearance is a marker of systemic aging as determined by familial longevity and CVD risk, before the onset of disease and independently of smoking, photodamage, and BMI. The Leiden Longevity Study consists of siblings who have lived to an exceptionally old age (over 89 y of age), their offspring, and the partners of their offspring as age-matched controls (18). We first compared the clinical features of facial and skin aging between offspring and controls. In particular, skin wrinkling via subjective (grading of facial photographs) and objective measures (optical profilometry of skin, [21]) on the face and upper inner arm, pigmented spots on the face, lip size, and perceived facial age were all analyzed. Any significant findings were then compared with CVD risk to determine if they were also markers of systemic aging in the general population.

Methods

Study Design

The Leiden Longevity Study consists of men and women over 89 and 91 y of age, respectively, with at least one sibling who passes the same age criterion, the offspring of either long-lived sibling, and the partners of the offspring (ie, married to or in a civil partnership with the offspring, see [19] for more information). Offspring and their partners were recruited by sending information packs to those on the Leiden Longevity Study database; there was no selection based on demographic data. The partners of the offspring were included in the study as age-matched controls and have similar morbidity and mortality as the wider Dutch population (19). The study protocol was approved by the Medical Ethics Committee for the Leiden University Medical Centre, and participants gave informed written consent. In total, 337 women and 333 men were included in the study.

Measurement of Appearance Features

All participating assessors of the subjective measures were unaware of participants’ ages and age ranges, and images were presented to them in a randomized order.

The methodology used for generating perceived age has been reported elsewhere (22,23). In brief, participants were asked not to use any hair styling or face products (eg, creams, make-up) on or near the face or neck on the day of the study. An en-face and a 45 degree photograph of the face were acquired for all participants and the images were cropped around the neck and hair line. Both images were presented in a randomized order to naive age assessors via a computer screen where they chose a 5-year age range dependent on how old they thought the participants looked. The mean perceived ages for 337 women and 332 men (one male was excluded due to the presence of facial skin grafts) were generated from an average of 60 independent assessments of age. Assessors were predominantly British and Caucasian. Although age assessors were of mixed gender and of varying age, assessor gender and age have been shown to have little effect on the mean perceived ages of participants when large numbers of age assessors are used (22).

Photodamage, skin wrinkling, and pigmented spot grading of the facial images were carried out on 337 women and 293 men (men with beards but not moustaches were excluded) as previously reported (23,24) utilizing grading from two skin-aging experts; the mean value was used for further analyses. Skin replicas or moulds were taken from the lateral eye area (crow’s feet region), cheek, and upper inner arm. The topography of the skin replicas was analyzed as an indicator of skin texture or wrinkling using the PRIMOS software (21). The parameters—maximum wrinkle depth (Wt), skin roughness or average distance between skin furrows/lines (Sm), and overall skin uniformity (Sa)—were selected for analysis as they had independent prediction of perceived age (data not shown). One technical failure meant that data were unavailable for one participant for arm wrinkling. Lip height, as a measure of lip size was measured as previously detailed ([23], also see Supplementary Material for further details).

Data Collection

Smokers were classified via self-report as those currently smoking or having quit within a year of the study-site visit. BMI was calculated from measurements of weight (in kilograms) divided by height (in meters squared). Four blood pressure measures were taken from the arm while participants were seated, and the average of the four measures were used for further analyses. Medical history was obtained from the participants’ general practitioner and medication use from the participants’ pharmacists. Disease data was available for cancer, myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular accident, and diabetes mellitus; the latter defined as those either reported to be diabetic or on diabetic medication. Total cholesterol and high density lipoprotein cholesterol were measured in non-fasted serum samples using the Hitachi Modular P 800 from Roche, Almere, The Netherlands.
Data Analyses
Participants with missing disease data (n = 85) were included and assumed to be disease free; of these, 18 were likely to have had disease giving a disease misclassification rate of less than 3% for the total cohort. Of the 670 participants, those with a disease history (n = 122) were excluded along with those with missing appearance data (additional 34 participants leaving a total of 514 participants (230 men and 284 women) for analyses.

All analyses were carried out in SAS v9.2. For comparisons between offspring and controls, perceived age, skin wrinkling and pigmented spot grading, lip height, and the log of the skin replica data from the eye, cheek, and upper inner arm (nine variables) were used as response variables (total of 13 variables) each in an analysis of variance. Chronological age, smoking status, photodamage grading, and BMI were included as covariates.

The Framingham algorithm was used to calculate CVD risk; BMI was used as a replacement for missing cholesterol or high density lipoprotein data (n = 7; see D’Agostino and coworkers 2008 [20] for more details). The log of CVD risk was used to ensure normality of the data. An analysis of variance was first used to determine whether the CVD risk score was associated with appearance. Chronological age, offspring/control status, smoking, photodamage, and BMI were retained in the models to determine if CVD risk was associated with appearance independently of these factors. Finally, an analysis of variance was used to determine which individual CVD risk factors (ie, BMI, smoking, total cholesterol, high density lipoprotein cholesterol, antihypertensive medication use, and systolic blood pressure) were driving any associations between CVD risk and appearance; diabetics had already been excluded. Chronological age, gender, offspring/control status, and photodamage were retained in the models as before (smoking and BMI were already included as CVD risk factors).

Facial Averages/Composites
To merge photographs together for comparisons of facial appearance in men and women, facial images were merged or averaged together as previously detailed using face shape, color, and texture information ([23, 25]; also see Supplementary Material for further information).

CVD Risk and Appearance
To test whether skin wrinkling on the upper inner arm (Wt variable) and perceived facial age were also markers of health in the general population, the Framingham CVD risk score was calculated for each participant and compared with the two appearance measures. As it was already known that the offsprings have a lower CVD risk than the controls (23), offspring/partner status was included in the analyses to ensure any results were independent of the familial longevity findings detailed earlier. After controlling for smoking, photodamage, and BMI, there were no significant findings for skin wrinkling at the arm (Supplementary Table 2), but women with a lower CVD risk looked younger for their age than women with a higher CVD risk (p = .002, Table 2). To determine the strength of relationship between perceived age and CVD risk, women were grouped into quartiles of CVD risk, and those in the lowest risk group were found to look just over 2 y younger than women in the other quartiles (p = .002, Supplementary Figure 1).

We next determined if any individual CVD risk factors (n = 6) predicted perceived age. Systolic blood pressure was a significant predictor of perceived age in women (those with high systolic blood pressure looked older p = .004, Table 3) and smoking a significant predictor of perceived age.
The findings for women, but not men, remained significant after a Bonferroni multiple testing correction for the number of CVD risk factors tested (n = 6, new significance threshold of p = .008).

Table 2. Comparison Between the Appearance of the Offspring From Long-Lived Families and Age-Matched Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Females (n = 284)</th>
<th>Males (n = 230)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in Means (standard error)</td>
<td>p Value</td>
</tr>
<tr>
<td>Lip height (%)*</td>
<td>−0.07 (0.16)</td>
<td>.660</td>
</tr>
<tr>
<td>Perceived age (years)</td>
<td>−0.05 (0.42)</td>
<td>.898</td>
</tr>
<tr>
<td>Pigmented spot (grades 1–9)</td>
<td>0.10 (0.12)</td>
<td>.398</td>
</tr>
<tr>
<td>Wrinkle grading (grades 1–9)</td>
<td>0.01 (0.04)</td>
<td>.808</td>
</tr>
<tr>
<td>Skin wrinkling eye (µm)*</td>
<td>−0.07 (0.06)</td>
<td>.258</td>
</tr>
<tr>
<td>Skin wrinkling cheek (µm)*</td>
<td>0.05 (0.04)</td>
<td>.199</td>
</tr>
<tr>
<td>Skin wrinkling arm (µm)*</td>
<td>−0.09 (0.04)</td>
<td>.032</td>
</tr>
</tbody>
</table>

Notes: Chronological age, smoking, body mass index, and photodamage were additionally included in each model. A negative value for the difference in means indicates a lower value in the offspring.

* Lip height as a percentage of face height.
† For clarity, only the skin replica parameter with the most significant difference between offspring and controls is given (log of Wt µm); see Supplementary Table 1 for the other replica parameters.

Table 3. Cardiovascular Disease (CVD) Risk Prediction of Perceived Age. CVD Risk Score Prediction of Perceived Age (A) and CVD Risk Factor Prediction of Perceived Age (B) in Analyses of Variances

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Females (n = 284)</th>
<th>Males (n = 230)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (standard error)</td>
<td>p Value</td>
</tr>
<tr>
<td>A* Cardiovascular disease risk score</td>
<td>1.48 (0.47)</td>
<td>.002</td>
</tr>
<tr>
<td>B† Smoking</td>
<td>0.65 (0.73)</td>
<td>.373</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>−0.01 (0.06)</td>
<td>.959</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.22 (0.20)</td>
<td>.273</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.93 (0.60)</td>
<td>.122</td>
</tr>
<tr>
<td>Hypertension medication use</td>
<td>−0.24 (0.56)</td>
<td>.670</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>0.03 (0.01)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Notes: Slope values represent the change in perceived age for a 1-unit increase of a covariate or difference between the group means for a classification variable; for example, male smokers looked 1.42 years older than non smokers and for a systolic blood pressure increase of 1mm of mercury (mm Hg) women looked 0.03 years older (equated to an increase of 29 mm Hg for every year women looked older).

*Framingham CVD risk score prediction of perceived age adjusting for chronological age, offspring/control status, smoking, photodamage, and body mass index.
†CVD risk factors prediction of perceived age adjusting for chronological age, offspring/control status, and photodamage.

age in men (smokers looked older p = .0435, Table 3). The findings for women, but not men, remained significant after a Bonferroni multiple testing correction for the number of CVD risk factors tested (n = 6, new significance threshold of p = .008).

Facial Features That Link Perceived Age With Familial Longevity and CVD Risk

To visualize facial features likely responsible for the perceived age association with familial longevity in men and with systolic blood pressure in women, we created composite/average facial images. We first created facial composite images of male offspring who look young for their age and male partners who look old for their age whilst controlling for smoking, photodamage, and BMI (Figure 1). In addition, we created facial composite images of women with relatively low blood pressure who looked young for their age and women with higher blood pressure who looked old for their age, controlling for the number of offspring in each group, smoking, photodamage, and BMI (Figure 2). Differences in facial features associated with changes to subcutaneous tissue were evident between the images, whereas there was little difference in skin wrinkling (see [23] for comparative perceived age composites illustrating strong skin wrinkling differences).

Discussion

Familial Longevity and Appearance

The offspring of nonagenarian siblings have been previously demonstrated to have a lower risk of mortality and morbidity as well as greater insulin sensitivity and a lower prevalence of metabolic syndrome than age-matched controls (19,26). Here, we demonstrate that reduced skin wrinkling on a sun-protected site (the upper inner arm) was significantly associated with familial longevity. Furthermore, the male offspring looked significantly younger than the controls. These findings existed before the onset of disease and independently of chronological age, smoking, BMI, and photodamage. This is the first time that measures of appearance have been linked to familial...
longevity and, specifically, aspects of appearance linked to intrinsic aging (ie, features that are little influenced by sun exposure [27], and as illustrated in Figure 1).

These findings indicate that biological mechanisms underlying familial longevity may directly influence aging processes in a wide range of organs. Indeed, skin fibroblasts from the upper inner arms of a subset of offspring studied here had greater resistance to oxidative and hyperglycemic stress than fibroblasts from age-matched controls (28,29), supporting a direct action of longevity mechanisms in skin. Hence, facial appearance and skin tissue from the upper inner arm could now be used to determine which biological mechanisms known to contribute to familial longevity (eg, insulin sensitivity [26]) are responsible for the links found here and how they influence aging within skin tissue and cells.

CVD Risk and Appearance

To determine if perceived age and wrinkling on the upper inner arm are also markers of disease risk in the general population, we compared these biomarkers of familial longevity to the Framingham CVD risk score (20). Perceived age was significantly associated with CVD risk in women. Hence, these data demonstrate that perceived age is a marker of familial longevity and CVD risk. It is important to note, though, that techniques used to measure perceived age vary and address different physiological features (examined in 22,23). Indeed, adjusting the perceived age data for factors already known to associate with appearance and health targeted the analyses to facial features other than skin wrinkling (Figures 1 and 2). In addition, the significance of the perceived age findings were weaker when only chronological age was adjusted for (Supplementary
suggestive that skin wrinkling was suppressing the associations between perceived age and familial longevity and CVD risk. Thus, findings from future studies will depend on the technique used to measure perceived age, whether men or women are studied, and what factors are controlled for in any analyses.

The individual CVD risk factors with significant independent prediction of perceived age were systolic blood pressure and smoking. While previous studies have already linked smoking to skin wrinkling and perceived age (5–7), there have been few studies investigating the link between blood pressure and facial appearance. There are links, though, between high CVD risk (30) and high blood pressure (31) to reduced microvascular function in skin, suggestive that blood pressure could directly influence skin aging. However, due to the cross-sectional nature of this study, a causal relationship cannot be established. Longitudinal studies are now required to understand whether blood pressure or correlated parameters drive the deterioration of facial appearance over time and whether this is predominately via skin or subcutaneous tissue.

There is some evidence that appearance is a motivator in behavior change (32), although public CVD health messages involving references to appearance are scant to the best of our knowledge. Along with other studies (1), however, this study could be used to give credibility to public health messages such as “keep your heart healthy – stay younger looking.”

**Gender Differences**

The perceived age and longevity associations were significant in men but not women, whereas CVD risk and perceived

![Figure 2. Facial features that related to systolic blood pressure in women. (A) Enface and 45-degree composite/average images of 12 women (mean age, 60.9) who had a relatively low blood pressure (mean systolic blood pressure, 121) and looked young for their age (mean perceived age, 52.7). (B) Composite images of 12 women (mean age 61.1) with higher blood pressure (mean systolic blood pressure, 153) who looked old for their age (mean perceived age, 62.4). Differences between the young- and older-looking composite images are evident for lower lip size, skin color, and the angle of the nasolabial fold; few differences in skin wrinkling are evident.](http://biomedgerontology.oxfordjournals.org/Downloaded from at Leiden University on January 8, 2013)
age associations were significant in women but not men. As estrogen is strongly linked to facial and skin aging in women (33–35), it is possible that the effects of estrogen on skin are directly responsible for the gender differences found here. However, this would suggest a role for estrogens in CVD risk, which is currently ambiguous (reviewed in ref. 36), and hence further investigations are required to determine whether they are primarily and directly responsible for the gender differences reported here.

**Conclusions**

These data demonstrate that individuals from long-lived families had less skin wrinkling at a sun-protected site than age-matched controls. In addition, perceived facial age was a marker of familial longevity in men and CVD risk in women. These links were present before the onset of disease and independently of smoking, photodamage, and BMI. Hence, skin tissue and facial appearance can be used to better understand how aging mechanisms underlying variations in CVD risk and lifespan in human populations influence tissue degeneration with age.

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**Supplementary Material**

Supplementary material can be found at: [http://biomedgerontology.oxfordjournals.org/](http://biomedgerontology.oxfordjournals.org/)

**Acknowledgements**

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**References**


Supplemental Figure Legends

Figure S1. Effect of dietary restriction and rapamycin on tissues weights relative to body weight. Tissues weights relative to body weights in Fat depots (A), organs (B), and hindlimb muscles (C) of AL (open bars), Rapa (solid bars), and DR (grey bars) mice. The data were obtained from 11-12 mice per group and expressed as mean ± SEM. Data were analyzed using one-way ANOVA with the Turkey’s post-hoc test; an asterisk denotes those values that are significantly different (p≤0.05) from AL mice, a number sign denotes those values that are significantly different (p≤0.05) from AL and Rapa mice, and a percent sign denotes those values that are significantly different (p≤0.05) from Rapa mice. Specific p-values are denoted in the figure.

Figure S2. Effect of dietary restriction and rapamycin on tissues weights. Tissues weights in Fat depots (A), organs (B), and hindlimb muscles (C) of AL (open bars), Rapa (solid bars), and DR (grey bars) mice. The data were obtained from 11-12 mice per group and expressed as mean ± SEM. Data were analyzed using one-way ANOVA with the Turkey’s post-hoc test; an asterisk denotes those values that are significantly different (p≤0.05) from AL mice, a number sign denotes those values that are significantly different (p≤0.05) from AL and Rapa mice, and a percent sign denotes those values that are significantly different (p≤0.05) from Rapa mice. Specific p-values are denoted in the figure.

Figure S3. Nuclear protein levels of Cyclin D1, p21, and p53. Representative western blot analysis of Cyclin D1, p21, and p53 liver nuclear protein levels measured in AL, DR, and Rapa fed mice (A). Quantification of western blot using Imagequant analysis software with protein levels of Cyclin D1, p21, and p53 expressed as percent relative to AL (B). The data were obtained from 11-12 mice per group and expressed as mean ± SEM. Data were analyzed using
one-way ANOVA with the Turkey’s post-hoc test; an asterisk denotes those values that are significantly different (p≤0.05) from AL mice.

**Table S4. Primers for qRT-PCR analysis.** Table S3 list the primers used in the qRT-PCR analysis (Figure 5A and 5B). The 5’ primer and the 3’ primer are listed.
Fok et al, Supplemental Figure S1
A) Fat Weights

B) Tissue Weights

C) Muscle Weights

Fok et al, Supplemental Figure S2
Fok et al, Supplemental Figure S3
<table>
<thead>
<tr>
<th>Gene</th>
<th>5' primer</th>
<th>3' primer</th>
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<tr>
<td>Gapdh</td>
<td>GATGCCCGCATGTTTGAT</td>
<td>GGTGAGCCCTTCCACAA</td>
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<tr>
<td>Cyclin D1</td>
<td>GTGACCGGACTGCTCCGT</td>
<td>TGCAGGCCAGACCAGCTCT</td>
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<td>p16</td>
<td>GAAGCCGGGCTTGCGGCAAA</td>
<td>GCACCGGCGGAGAAGGTA</td>
</tr>
<tr>
<td>p21</td>
<td>ACATTCAGAGCCACAGGCACCA</td>
<td>GCTCAGCAATCACGGCGCAA</td>
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<tr>
<td>p53</td>
<td>AGGAGGGCTCACTCCAGTACC</td>
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<tr>
<td>Sirt1</td>
<td>TCCTGTTGACCGAAGAGCACCTCA</td>
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</tr>
<tr>
<td>Sirt2</td>
<td>GGTGCAAGAGGCTCGAGATTCAG</td>
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<tr>
<td>Sirt3</td>
<td>TGGCCCTGCCCCTTGAGGCATT</td>
<td>CGGAAACGACCATCCGGTTTC</td>
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<td>Sirt4</td>
<td>GGCGGCTCTGAGCCTTCTGTGGA</td>
<td>CGGACCTCTGTCGAGCCCTGAA</td>
</tr>
<tr>
<td>Sirt5</td>
<td>TCGTGTCAGCCACTGTTCCGCA</td>
<td>CCTCCTCGACCGGGGAAGTT</td>
</tr>
<tr>
<td>Sirt6</td>
<td>CGGAAGCCGGACCTACAGGAGG</td>
<td>TCGTGTCAGGATCTCGCGGC</td>
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<td>Sirt7</td>
<td>TGACCGGAGCTGACGGTCA</td>
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Fok et al, Supplemental Table S4