

ASSOCIATION STUDIES ARTICLE

# Combined analysis of keratinocyte cancers identifies novel genome-wide loci

Upekha E. Liyanage<sup>1,\*†</sup>, Matthew H. Law<sup>1</sup>, Xikun Han<sup>1,‡</sup>, Jiyuan An<sup>1</sup>, Jue-Sheng Ong<sup>1,¶</sup>, Puya Gharakhani<sup>1</sup>, Scott Gordon<sup>2</sup>, Rachel E. Neale<sup>3</sup>, Catherine M. Olsen<sup>4,5</sup>, 23andMe Research Team, Stuart MacGregor<sup>1,§</sup> and David C. Whiteman<sup>4,§</sup>

<sup>1</sup>Statistical Genetics Lab, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia, <sup>2</sup>Genetic Epidemiology, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia, <sup>3</sup>Cancer Aetiology and Prevention, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia, <sup>4</sup>Cancer Control Group, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia and <sup>5</sup>Faculty of Medicine, The University of Queensland, Brisbane, QLD 4006, Australia

\*To whom correspondence should be addressed at: Statistical Genetics Lab, QIMR Berghofer Medical Research Institute, 300 Herston Road, Brisbane, QLD 4006, Australia. Tel: 0738453713; Fax: +6133620111; Email: upekha.liyanage@qimrberghofer.edu.au

## Abstract

The keratinocyte cancers (KC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common cancers in fair-skinned people. KC treatment represents the second highest cancer healthcare expenditure in Australia. Increasing our understanding of the genetic architecture of KC may provide new avenues for prevention and treatment. We first conducted a series of genome-wide association studies (GWAS) of KC across three European ancestry datasets from Australia, Europe and USA, and used linkage disequilibrium (LD) Score regression (LDSC) to estimate their pairwise genetic correlations. We employed a multiple-trait approach to map genes across the combined set of KC GWAS (total  $N = 47\,742$  cases, 634 413 controls). We also performed meta-analyses of BCC and SCC separately to identify trait specific loci. We found substantial genetic correlations (generally 0.5–1) between BCC and SCC suggesting overlapping genetic risk variants. The multiple trait combined KC GWAS identified 63 independent genome-wide significant loci, 29 of which were novel. Individual separate meta-analyses of BCC and SCC identified an additional 13 novel loci not found in the combined KC analysis. Three new loci were implicated using gene-based tests. New loci included common variants in *BRCA2* (distinct to known rare high penetrance cancer risk variants), and in *CTLA4*, a target of immunotherapy in melanoma. We found shared and trait specific genetic contributions to BCC and SCC. Considering both, we identified a total of 79 independent risk loci, 45 of which are novel.

<sup>†</sup>Upekha E. Liyanage, <http://orcid.org/0000-0003-4588-4084>

<sup>‡</sup>Xikun Han, <http://orcid.org/0000-0002-3823-7308>

<sup>¶</sup>Jue-Sheng Ong, <http://orcid.org/0000-0002-6062-710X>

<sup>§</sup>Equal contribution.

Received: March 14, 2019. Revised: May 30, 2019. Accepted: June 3, 2019

© The Author(s) 2019. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

## Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common cancers of the skin. Together, they are known as keratinocyte carcinomas (KC), so named because the cells of origin are the abundant, keratin-producing cells of the epidermis. BCC and SCC both arise in the epidermis but are histologically and clinically distinct from each other (Supplementary Material, Fig. S1) (1). BCC and SCC tend to be slow growing skin cancers when compared with melanoma, which is the most aggressive form (2). SCC has a lower prevalence than BCC, but accounts for the most KC-related deaths (2). While the principal treatment modalities for KC (surgery, curettage and destruction) are highly effective in the majority of cases, they cause pain and scarring, carry risks of infection and represent the second highest expenditure on cancer healthcare in Australia (3,4). In the USA the average annual cost of skin cancer (melanoma and keratinocyte cancers) treatment was \$8.1 billion, with ~4.9 million patients treated for skin cancer from 2007 to 2011 (5).

BCC and SCC share the major risk factors of ultraviolet radiation (UVR) exposure and fair skin, and as such occur most commonly on sun exposed sites (6). Consequently, KC are extremely frequent in fair-skinned populations living in areas with high UVR such as Australia and the southern United States (2). The age-standardized incidence rate in Australia for BCC is 770 per 100 000 person years; for SCC it is 270 per 100 000 person years (7). In addition to the role of UVR, immunosuppression increases the risk of both SCC and BCC, reinforcing the importance of the immune system in early elimination of cancerous cells (6).

Both skin cancer and its established risk factors, such as pigmentation, have a heritable component. A recent large twin study estimated the heritability of keratinocyte cancer to be 43% [95% confidence interval (CI), 26–59%] (8). Previous genome-wide association studies (GWAS) and related approaches have identified 29 loci associated with BCC susceptibility and 11 loci associated with SCC (9–14). Seven of these loci are associated with both BCC and SCC, suggesting shared genetic pathways in keratinocyte cancer etiology. Some of these common single nucleotide polymorphisms (SNPs) have a functional role in pigmentation (e.g. *MC1R*, *IRF4*, *TYR*) and freckling tendency (*BNC2*) (10,12), consistent with the strong causal role of UVR in keratinocyte cancer risk. Identifying additional risk loci may uncover novel genetic pathways underpinning cancer risk and identify new drug targets to assist in the development of future cancer therapies (15).

We first conducted a series of GWAS across four large datasets of ethnically homogenous ancestry (White British/European) from Australia, Europe and the USA. In addition to performing GWAS of BCC and SCC cases, where possible we also analysed a single case group combining all KC cases. For the QSkin and electronic medical records for genetic research (eMERGE) GWAS datasets, while histology records confirmed the occurrence of a KC, a specific diagnosis of BCC or SCC was not available for all participants (Methods). For these two cohorts all cases were included in the KC phenotype.

Given the overlap in the risk loci identified to date in BCC and SCC (e.g. *BNC2*, *MC1R*, *ASIP*) (11,12), it is likely these traits have an overlapping genetic basis. To explore this hypothesis, we tested for genetic correlation between the BCC, SCC and the KC phenotype GWAS using linkage disequilibrium (LD) score regression (LDSC) (16). Finding a high degree of genetic correlation across the KC phenotypes, we performed a combined KC analysis bringing together the BCC, SCC and KC GWAS

using multiple trait analysis of GWAS (MTAG), a method that accounts for incomplete genetic correlation across traits as well as sample overlap (17). As the genetic correlations across BCC, SCC and the KC phenotype were high but not complete, there are likely genetic variants that contribute to either BCC or SCC specifically. We explored this by performing individual separate meta-analyses of BCC and SCC alone.

## Results

### Genetic correlations across BCC, SCC and KC

For each of the contributing GWAS there was little to no evidence for inflation due to population stratification (Supplementary Material, Table S1). Using LDSC we found moderate or high genetic correlations between SCC, BCC and combined KC phenotypes (Fig. 1, Supplementary Material, Table S1). For example, UK Biobank (UKBB) BCC GWAS versus the 23andMe SCC GWAS  $R_g = 0.79$  (CI 0.54–1.03,  $P$ -value =  $2.6 \times 10^{-10}$ ), while the QSkin BCC GWAS versus the UKBB SCC GWAS was  $R_g = 0.56$  (CI 0.11–1.00,  $P$ -value = 0.01). These correlations indicated that a multivariate analysis using MTAG was likely to be more powerful for identifying loci than separate analyses of BCC or SCC. Moreover, the generally high correlations justified including the ~8000 additional KC cases for which type-specific histology (i.e. BCC or SCC) was not available (Table 1).

### Combined multi-trait analysis of KC

Following the multi-trait analysis of the UKBB KC GWAS, 23andMe BCC, 23andMe SCC, QSkin KC and eMERGE KC GWAS (Table 1), the adjusted output for the UKBB KC GWAS identified 78 independent genome-wide significant SNPs assigned to 63 to risk loci, 29 of which are novel (Table 2, complete results for all independent SNPs can be found in Supplementary Material, Table S2).

A number of the newly identified KC SNPs are expression quantitative trait loci (eQTLs) for nearby genes, or are associated with other traits (Table 3; results for all SNP can be found in Supplementary Material, Table 2). Two of the novel KC loci highlight genes that are existing drug targets (Supplementary Material, Table S2). The first, rs231779 on chromosome 2, is an eQTL for *CTLA4*, which is a target for immunotherapy medications including ipilimumab and tremelimumab, which are already in use for melanoma. The second, rs12576996 on chromosome 11 is an eQTL for *MAP3K11*, which has been investigated as a drug target for Parkinson's disease using CEP-1347.

### Meta-analysis of BCC and SCC GWAS

After conducting the overall multi-trait KC GWAS, we performed individual meta-analysis of BCC and SCC using a fixed effects meta-analysis to identify any regions reaching genome-wide significance for a specific type of KC (Supplementary Material, Table S3). Seventy three loci were associated with either BCC or SCC, and the majority overlapped (Materials and Methods) with the MTAG KC analyses. A single locus previously reported for each of BCC and SCC reached genome-wide significance in the individual analyses but not in the KC MTAG analysis (rs9419958/OBFC1 and rs13301660/SEC16A, respectively, Supplementary Material, Table S3). We further identified 13 new loci by conducting BCC or SCC GWAS meta-analysis; these loci did not reach genome-wide significance in our KC MTAG analyses

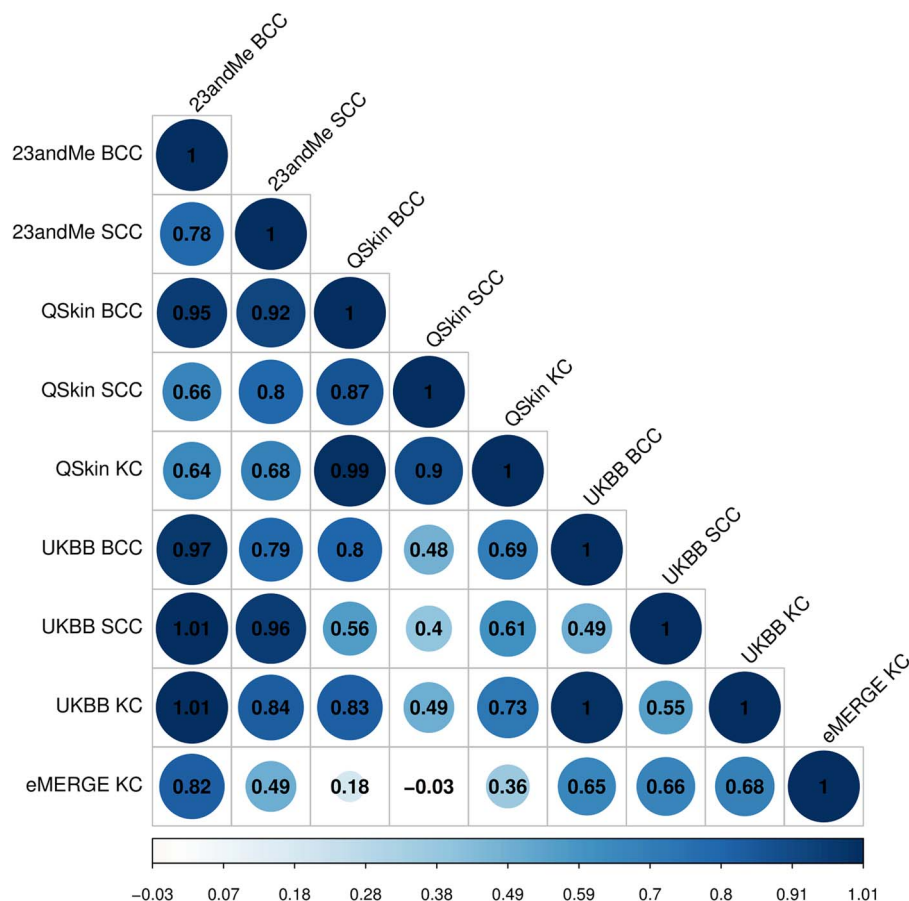


Figure 1. Genetic correlation between BCC, SCC and KC cancers. With the exception of the comparisons between the smallest datasets, all correlations values are significant at  $P$ -value  $< 0.05$  (eMERGE KC versus QSkin BCC  $P$ -value = 0.37; eMERGE KC versus QSkin SCC  $P$ -value = 0.88; full results in [Supplementary Material, Table S1](#)).

Table 1. Sample sizes used for GWAS analysis

Study sample	BCC		SCC		KC	
	Cases	Controls	Cases	Controls	Cases	Controls
QSkin	1995	4797 <sup>a</sup>	821	4797 <sup>a</sup>	8145	4797 <sup>a</sup>
UKBB	16 847	340 302 <sup>a</sup>	2274	340 302 <sup>a</sup>	18 538	340 302 <sup>a</sup>
eMERGE KC	-	-	-	-	1565	8756
23andMe	12 945	274 252 <sup>a</sup>	6579	280 558 <sup>a</sup>	19524 <sup>b</sup>	280 558 <sup>b</sup>
Total	31 787	619 351	9674	625 657	47 742	634 413

<sup>a</sup>Control sets for QSkin, 23andMe and UKBB GWAS are overlapping. <sup>b</sup>Combined KC analysis GWAS set for 23andMe reported to illustrate effective sample size for the combined KC analysis using MTAG (which accounts for sample overlap); only individual BCC and SCC GWAS were available for 23andMe.

and previous studies (Tables 4 and 5; full results including annotation can be found in [Supplementary Material, Table S3](#)). The chromosome 2 locus with peak SNP rs7563677 is an eQTL for *ITGB6*, representing a potentially novel drug target for KC. *ITGB6* is a target of intetumumab currently in use for the treatment of prostate adenocarcinoma; additional drugs in use for this gene's product are abituzumab for metastatic colorectal cancer, and STX-100 for idiopathic pulmonary fibrosis and melanoma [Supplementary Material, Table S3](#).

### Heritability of BCC and SCC

$h^2_{\text{SNP}}$  (SNP-heritability) estimates for BCC and SCC were 13.1% (95% CI = 9.7–16.5%) and 6.8% (95% CI = 0.9–12.7%), respectively. Of that, GWAS significant loci contributed ~5.9% to BCC  $h^2_{\text{SNP}}$  and 2.7% for SCC.

### Consistency of effect sizes across traits

Having identified loci associated with both the KC phenotype, and with BCC and SCC alone, we compared the effect size for the lead SNP from each of the independent loci identified across the three datasets (Methods; [Supplementary Material, Table S8](#)).

Most of the SNPs identified in the KC MTAG analysis including rs231779 (*CTLA4*), rs7328654 (*BRCA2*) and rs3213737 (*HAL*) had consistent effect estimates in the BCC and SCC meta-analysis. However, we noted that when SNPs differed they tended to have larger effect sizes for BCC than SCC, particularly for rs79522206 (*RNU6ATAC37P*) and rs6707137 (*RNY4P15*). This may be due to the effect of winner's curse bias as the majority of our meta-analysis and MTAG sample set was comprised of BCC GWAS (47). However, some variants have larger effects in the SCC meta-analysis including in genes involved in pigmentation

Table 2. Novel KC loci identified using MTAG

CHR	BP	SNP	EA/NEA	P	OR [95% CI]	Nearest protein coding gene
1	110 724 488	rs535930	G/A	$2.08 \times 10^{-8}$	0.95 [0.94–0.97]	KCNC4
1	114 303 808	rs6679677	C/A	$6.50 \times 10^{-11}$	1.10 [1.07–1.13]	PHTF1
1	154 984 363	rs1870940	G/A	$7.88 \times 10^{-11}$	0.94 [0.92–0.96]	ZBTB7B
1	242 023 898	rs4149909	G/A	$2.35 \times 10^{-9}$	1.16 [1.10–1.21]	EXO1
2	5 684 786	rs62112661	C/A	$4.40 \times 10^{-8}$	0.95 [0.94–0.97]	SOX11
2	7 704 860	rs79522206	G/A	$4.38 \times 10^{-16}$	0.81 [0.77–0.85]	RNF144A
2	37 189 296	rs3845780	T/C	$1.85 \times 10^{-9}$	0.95 [0.94–0.97]	STRN
2	38 298 139	rs1800440	T/C	$4.50 \times 10^{-12}$	1.08 [1.06–1.10]	CYP1B1
2	88 554 351	rs6707137	G/A	$5.80 \times 10^{-22}$	1.19 [1.15–1.23]	THNSL2
2	204 734 487	rs231779	T/C	$9.66 \times 10^{-15}$	0.94 [0.92–0.95]	CTLA4
3	98 447 140	rs7620634	G/A	$1.82 \times 10^{-8}$	1.06 [1.04–1.08]	ST3GAL6
5	149 192 846	rs17110447	G/A	$1.66 \times 10^{-9}$	0.94 [0.93–0.96]	PPARGC1B
6	4 979 956	rs1246946	T/C	$5.32 \times 10^{-15}$	0.94 [0.92–0.95]	RPP40
6	90 976 768	rs72928038	G/A	$1.24 \times 10^{-20}$	1.11 [1.09–1.14]	BACH2
7	6 418 673	rs836489	T/G	$1.23 \times 10^{-8}$	0.95 [0.94–0.97]	RAC1
7	29 132 279	rs117744081	G/A	$2.07 \times 10^{-19}$	0.79 [0.75–0.83]	CPVL
7	50 176 163	rs10228836	G/A	$1.70 \times 10^{-10}$	0.95 [0.93–0.96]	ZPBP
8	98 367 884	rs4735451	T/C	$4.75 \times 10^{-9}$	1.06 [1.04–1.08]	TSPYL5
8	120 082 971	rs13261635	T/C	$1.43 \times 10^{-8}$	0.95 [0.93–0.97]	COLEC10
9	106 858 192	rs3739737	G/A	$3.55 \times 10^{-8}$	1.05 [1.03–1.07]	SMC2
10	10 771 564	rs12767525	T/C	$5.49 \times 10^{-9}$	1.05 [1.04–1.07]	CELF2
10	64 402 433	rs10995255	G/A	$6.51 \times 10^{-11}$	0.94 [0.93–0.96]	ZNF365
11	64 107 735	rs663743	G/A	$2.35 \times 10^{-9}$	0.95 [0.93–0.97]	CCDC88B
11	65 580 638	rs12576996	T/G	$3.77 \times 10^{-11}$	1.07 [1.05–1.09]	OVOL1
12	96 379 806	rs3213737	G/A	$1.11 \times 10^{-8}$	1.05 [1.03–1.07]	HAL
13	32 954 561	rs7328654	G/A	$5.82 \times 10^{-10}$	1.05 [1.04–1.07]	N4BP2L1
14	75 935 908	rs77100309	G/A	$1.65 \times 10^{-8}$	0.91 [0.89–0.94]	JDP2
19	1 106 845	rs2075710	T/C	$1.68 \times 10^{-8}$	1.06 [1.04–1.08]	GPX4
20	49 399 007	rs62202837	T/C	$2.23 \times 10^{-13}$	0.93 [0.91–0.95]	BCAS4

Hg19 chromosome (CHR) and base pair (BP) positions are provided for each SNP. Odds ratios (OR) and P-values are from the MTAG analysis of five GWAS datasets; UKBB KC, eMERGE KC, 23andMe BCC, 23andMe SCC and QSkin KC (sample sizes reported in Table 1). The OR and 95% confidence interval is for the effect allele (EA); the non-effect allele (NEA) is also reported. We also report the nearest protein coding gene for each SNP; more complete gene annotation data can be found on Supplementary Material, Table S2.

e.g. rs1805007 (MC1R), rs1805008 (TUBB3) and rs12203592 (IRF4) (11,14). Similar magnitude of effect estimates for BCC and SCC was noted for other pigmentation variants, including rs1126809 (TYR) and rs35407 (SLC45A2) (11). Some of the previously known variants associated with BCC or SCC but not associated with pigmentation pathway particularly, rs2853677 (TERT) and rs78378222 (TP53) (48,49), showed significantly larger effect estimates on BCC risk than SCC risk.

### Gene-based approaches for KC

FastBAT gene-based test for KC revealed an additional three genes in two loci not identified in the single SNP analyses for KC, BCC or SCC (Methods; novel genes marked in bold in Supplementary Material, Table S4). We also conducted a gene-set enrichment analysis using the KC GWAS results (Methods), which identified that there was significant enrichment for the gene-sets ‘T cell selection’ (P-value =  $2.1 \times 10^{-7}$ , Bonferroni-corrected P-value = 0.002) and ‘keratin filament’ (P-value =  $1.9 \times 10^{-6}$ , Bonferroni-corrected P-value = 0.02).

As a parallel approach we performed a transcriptome wide association study (TWAS), as implemented in MetaXcan, using two skin and a whole blood expression set from GTEx Supplementary Material, Tables S5, S6 and S7. This approach determines the genetically predicted change in gene expression due to variants associated with KC, and can predict the potential functional target gene at loci that reach significance

(Materials and Methods) in the MTAG analysis. In addition TWAS can identify additional regions where imputed gene expression levels are associated with KC at significance but no single SNP reaches genome-wide significance. A number of imputed genes are associated with KC in regions identified in the single SNP MTAG results, and an additional gene on chromosome 10 is significantly associated with KC (SLC35G1 P-value =  $1.69 \times 10^{-6}$  sun-exposed skin, highlighted in bold in Supplementary Material, Table S5). When considered together, the FastBAT and TWAS approaches highlight a total of four genes in three loci (ASXL2, RABEPK, HSPA5, SLC35G1) that are significant a P-value < 0.05 corrected for the number of genes and are not identified in the single SNP analyses.

### Discussion

In this well-powered analysis of keratinocyte cancer, we have assembled large GWAS datasets examining BCC, SCC and, for the majority of cohorts, KC. We showed substantial genetic correlation between discrete GWAS of BCC, SCC and the KC phenotype (Fig. 1, Supplementary Material, Table S1), and leveraged this correlation in a multiple trait combined KC GWAS analysis to identify 83 independent genome-wide significant genetic variants in 63 loci (Table 2, Supplementary Materials, Tables S2 and S3). Thirty-four of these loci have been previously reported for BCC or SCC alone using a range of approaches (9–12,14),

Table 3. Annotation of novel KC loci

CHR	BP	SNP	eQTL skin	eQTL whole blood	eQTL other tissue	PheWAS summary
1	110 724 488	rs535930	-	-	-	Educational level
1	114 303 808	rs6679677	-	-	-	Hyper/hypothyroidism, medications for cholesterol, blood pressure, T1D, RA
1	154 984 363	rs1870940	ZBTB7B, ADAM15	-	ZBTB7B, ADAM15, DCST2, RP11-307C12.11	Anthropometric measures, BMI, BMR
1	242 023 898	rs4149909	-	-	-	-
2	5 684 786	rs62112661	-	-	-	-
2	7 704 860	rs79522206	-	-	-	-
2	37 189 296	rs3845780	-	STRN	GPATCH11, STRN	Leg fat percentage
2	38 298 139	rs1800440	-	-	-	-
2	88 554 351	rs6707137	-	-	-	-
2	204 734 487	rs231779	-	-	CTLA4	Hyper/hypothyroidism
3	98 447 140	rs7620634	DCBLD2, ST3GAL6-AS1	-	ST3GAL6, ST3GAL6-AS1, PDLIM1P4	-
5	149 192 846	rs17110447	-	-	-	-
6	4 979 956	rs1246946	-	-	RPP40, RP11-428J1.4, RP11-428J1.5	-
6	90 976 768	rs72928038	-	-	-	Asthma, T1D, hypothyroidism
7	6 418 673	rs836489	DAGLB	DAGLB, FAM220A	RAC1, DAGLB, FAM220A	Anthropometric measures
7	29 132 279	rs117744081	-	-	CTB-113D17.1	-
7	50 176 163	rs10228836	-	-	C7orf72	-
8	98 367 884	rs4735451	-	-	-	-
8	120 082 971	rs13261635	-	-	MAL2, NOV, COLEC10	Height
9	106 858 192	rs3739737	-	SMC2	SMC2, RP11-82L2.1	-
10	10 771 564	rs12767525	-	-	-	-
10	64 402 433	rs10995255	-	ADO	ADO	-
11	64 107 735	rs663743	CCDC88B, PPP1R14B	AP003774.1	AP003774.1, CCDC88B, PPP1R14B, PLCB3	-
11	65 580 638	rs12576996	CTSW, EIF1AD, KRT8P26, MAP3K11	MAP 3K11	BANF1, CTSW, EFEMP2, EIF1AD, FIBP, KRT8P26, MAP3K11, NEAT1, OVOL1, SNX32	Asthma, allergy, eczema, arm impedance
12	96 379 806	rs3213737	HAL, RP11-256L6.3	-	AMDHD1, RP11-256L6.3	Tanning
13	32 954 561	rs7328654	-	-	-	-
14	75 935 908	rs77100309	-	-	-	-
19	1 106 845	rs2075710	GPX4	-	GPX4	-
20	49 399 007	rs62202837	-	-	-	KC*

Hg19 chromosome (CHR) and base pair (BP) positions are provided for each SNP. Only genes reaching the significance threshold of  $2 \times 10^{-6}$ , or for PheWAS traits reaching  $5 \times 10^{-8}$  are shown. KC, keratinocyte cancer; BMI, body mass index; BMR, basal metabolic rate; T1D, type 1 diabetes; RA, rheumatoid arthritis. Full details are provided in [Supplementary Material, Table S2](#). \*Associated with KC at genome-wide significance in the UKBB alone.

while 29 of them are novel ([Supplementary Material, Table S2](#)). Most of the variants affected both BCC and SCC, with a small subset affecting only one or the other of these cancers ([Supplementary Material, Table S8](#)). However, few loci, which were GWAS significant in previous studies, were not replicated in our study (e.g. rs192481803 (2p22.3), rs74899442 (11q23.3) for SCC (11) and rs78097823 (22q 12.1), rs1050529 (6p 21.33) for BCC (12). Some of these were rare SNPs (rs192481803, rs74899442) and were filtered out in MTAG analysis.

For the first time we found an SNP in the cytotoxic lymphocyte-associated antigen-4 (CTLA4) gene associated with KC risk (2q33.2, rs231779 OR=0.94; 95% CI=0.92-0.95, P-value =  $9.7 \times 10^{-15}$ ; [Supplementary Material, Table S2](#)). The importance of this finding is that the CTLA4 protein plays a key role in activating the anti-tumour response against cancer cells (50). In addition, according to a previous animal study CTLA4 mediates the effects of UV-induced immunosuppression, which is particularly important in the development of skin cancer (51).

Ipilimumab (antibodies targeting CTLA4) are currently in use to treat melanoma patients with stage III or IV disease (43,50). However, this particular SNP has not been identified in GWAS of melanoma (52,53). Identification of this SNP highlights the potential future avenue to use Ipilimumab for KC therapy.

SNP rs7563677 at 2q24.2 is an eQTL for ITGB6, representing a putatively novel drug target for KC, with an associated drug STX-100 currently in a Phase I clinical trial for melanoma. This SNP only reaches formal significance in the BCC analysis, although in practice this particular SNP fails quality control (QC) in some KC/SCC only datasets. However, the effect estimates of the proxy SNP, rs6736111 LD ( $r^2 = 0.55$ ) were similar across all traits suggesting that it is a KC SNP (see [Supplementary Material, Table S8](#)). Furthermore, the KC associated SNP rs12576996 (11q13.1) is an eQTL for a gene (MAP3K11) that is a potential drug target (CEP-1347), which is currently in clinical trials for Parkinson's disease, and our findings may support repurposing for KC.

**Table 4.** Novel loci from meta-analysis of BCC or SCC GWAS

CHR	BP	SNP	EA/NEA	P	OR [95% CI]	Nearest protein coding gene
2	11 526 716	rs12466910	A/G	$2.97 \times 10^{-8}$	0.95 [0.94–0.97]	ROCK2
2	161 356 717	rs7563677	C/G	$4.58 \times 10^{-8}$	0.93 [0.91–0.96]	RBMS1
5	44 412 065	rs11741260	A/G	$8.74 \times 10^{-10}$	1.07 [1.05–1.10]	FGF10
5	67 751 221	rs42905	A/C	$2.82 \times 10^{-8}$	1.05 [1.03–1.06]	PIK3R1
6	15 535 321	rs9383064 <sup>a</sup>	C/G	$1.29 \times 10^{-8}$	1.10 [1.06–1.14]	DTNBP1
6	150 353 556	rs12205199	A/C	$1.13 \times 10^{-8}$	1.05 [1.03–1.07]	RAET1L
8	116 632 819	rs2721936	A/T	$2.06 \times 10^{-9}$	1.05 [1.03–1.07]	TRPS1
9	681 645	rs9408674	A/G	$2.88 \times 10^{-9}$	1.05 [1.03–1.07]	KANK1
9	19 059 865	rs60269255	C/G	$1.94 \times 10^{-8}$	1.07 [1.04–1.09]	HAUS6
10	13 740 917	rs1887004	T/C	$6.65 \times 10^{-10}$	0.95 [0.93–0.96]	RP11-295P9.3
15	79 237 293	rs2289702	T/C	$2.57 \times 10^{-9}$	1.09 [1.06–1.11]	CTSH
19	50 151 686	rs7508601	A/T	$3.23 \times 10^{-8}$	0.95 [0.94–0.97]	SCAF1
20	37 746 454	rs209901	T/G	$2.84 \times 10^{-8}$	0.95 [0.93–0.97]	DHX35

CHR, chromosome; BP, base pair position; SNP, single nucleotide polymorphism; EA, effect allele; NEA, non-effect allele; P, P-value, OR [95% CI], odds ratio, 95% confidence interval. <sup>a</sup>The chromosome 6 region with peak SNP rs9383064 is associated with SCC; all other tabulated regions are associated BCC. We reported the nearest protein coding gene; for more detailed gene annotation see [Supplementary Material, Table S3](#).

**Table 5.** Annotation of novel loci from meta-analysis of BCC or SCC GWAS

CHR	BP	SNP	eQTL skin	eQTL whole blood	eQTL other tissue	PheWAS
2	11 526 716	rs12466910	-	-	LINC00570	-
2	161 356 717	rs7563677	-	-	ITGB6	-
5	44 412 065	rs11741260	-	-	-	-
5	67 751 221	rs42905	-	-	-	-
6	15 535 321	rs9383064 <sup>a</sup>	-	-	DTNBP1	-
6	150 353 556	rs12205199	-	-	-	Alopecia areata
8	116 632 819	rs2721936	-	-	-	Anthropometric measures
9	681 645	rs9408674	-	-	KANK1	-
9	19 059 865	rs60269255	-	-	HAUS6	-
10	13 740 917	rs1887004	-	-	-	-
15	79 237 293	rs2289702	CTSH	CTSH	CTSH	Lung cancer, T1D
19	50 151 686	rs7508601	-	-	-	Hypothyroidism/myxoedema, vitiligo
20	37 746 454	rs209901	-	-	-	-

CHR, chromosome; BP, base pair position; SNP, single nucleotide polymorphism; T1D, type 1 diabetes mellitus. <sup>a</sup>The chromosome 6 region with peak SNP rs9383064 is associated with SCC; all other tabulated regions are associated BCC. Full details are provided in [Supplementary Material, Table S3](#).

One of the novel KC SNPs we identified, rs7328654, lies in an intron of BRCA2 (13q13.1). BRCA2 is a tumor suppressor gene; rare variants in this gene, including rs11571833, are associated with a dramatically increased risk of various cancers including breast, lung, ovarian and prostate (54–57). A recent study conducted by Rafnar et al. (58) identified that K3326\* variant (BRCA2) is associated with SCC of the skin (OR=1.69; 95% CI=1.26–2.26,  $P=4.2 \times 10^{-4}$ ). However, similar effect estimates were noted (OR=1.94; 95% CI=1.10–3.38) for rs11571833 (A/T) with a P-value of 0.02 in our SCC meta-analysis. The common variant that we identified (rs7328654) is not in LD with the rare high penetrance variants (e.g. for rs11571833  $r^2=0.001$ ; the other pathogenic BRCA2 variants are also very rare and so cannot be in strong LD with our common variant). The common variant we identify (rs7328654) has not been reported for any cancer although it is associated with LDL cholesterol levels (59).

As expected, many of the KC risk variants are involved in pigmentation. rs6059655 (ASIP) in 20q11.22, rs1805007 (MC1R) in 16q24.3, rs12203592 (IRF4) in 6p25.3, rs1126809 (TYR) in 11q14.3 and rs16891982 (SLC45A2) in 5p15.33 are non-synonymous SNPs, or enhancers, which regulate gene expression. These SNPs have previously been found to be associated with SCC, BCC and

melanoma risk (9–12,51–53,60–62). We found an association between rs3213737 (HAL, 12q23.1) and KC. This SNP was recently identified as associated with vitamin D levels (63) in the GeneAtlas database of UKBB data (64), and is genome-wide significantly associated with ease of skin tanning. This gene encodes an enzyme required to produce urocanic acid, which protects skin against UVR damage and UVR-induced immune suppression (65). A study conducted by Welsh et al. (66) did not find association for rs7297245 (HAL) with overall BCC or SCC risk; however, stratified analysis revealed that rs7297245 (A/A) (LD  $r^2=0.2$  with our lead SNP rs3213737) is associated with SCC in women alone. While we are unable to perform sex-stratified analyses, the T allele of rs7297245 [Haplotype reference consortium (HRC) reports for the other strand] is not associated with KC (UKBB MTAG output for rs7297245  $P=0.3$ ) suggesting our signal is independent to the one reported by Welsh et al. Several of the implicated genes are involved in functions relating to immune response. Our gene-set enrichment analysis implicated the positive T-cell selection pathway. As previously reported for BCC and SCC, we identified associations in the major histocompatibility complex (MHC) region (rs9271611/HLA-DQA16 in p21.32, and

rs9277332/HLA-DPA1 in 6p21.32, rs2507999/HLA-B in 6p21.33) (67,68). In addition to the previously mentioned CTLA4 locus, the new loci with peak SNPs rs6679677 and rs72928038 are associated with autoimmune-related traits (Table 3).

In addition to the multi-trait analysis of KC, we also performed individual separate meta-analyses of BCC and SCC, as the differing clinical outcomes and high but incomplete genetic correlation between SCC and BCC suggests that there may be both overlapping and discrete genetic risks for these conditions. While the majority of the loci overlapped with the KC analysis, there were a further 12 BCC and 1 SCC loci that did not overlap (Supplementary Material, Table S3). In terms of genes/loci common to both BCC and SCC, in addition to pigmentation genes (e.g. MC1R), overlapping pathways include immune response (e.g. rs2507999/HLA-B and rs231779/CTLA4) and telomere length (rs9419958/OBFC1) (Supplementary Material, Table S8). Associations of note specific to BCC include rs78378222 near TP53, which is critical for DNA repair and cell cycle control (69), and rs9383064 near DTNBP1, which is associated with SCC alone (Supplementary Material, Table S8).

Of note, identification of these novel loci associated with KC improves the predictability of polygenic risk scores, but marginally as the new variants have relatively smaller effect sizes.

### Strengths and limitations

Our study is the largest genetic study of KC to date and as a result we have more than doubled the number of significant loci. One major advantage of using MTAG is it allows the combination of genetically correlated traits, which would not necessarily be clinically similar traits. As we discuss above BCC and SCC are two different skin cancers with an overlapping risk factors and genetic susceptibility, and we used a range of approaches to identify overlapping and unique genetic risks.

Our study comprised (multi-trait) meta-analyses of GWAS where each individual study included ancestry matched, ethnically homogeneous cases and controls, reducing the likelihood that our associations were due to differences in population substructure.

A limitation is that a proportion of our cases were derived from self-reported data. Since people may misreport the type of KC they have, this may make it difficult to accurately assess the true genetic correlations between KC subtypes. Histology reports were obtained only for a subset of QSkin participants; the remainder did have histologically-confirmed keratinocyte cancers but the type-specific histology was not available for analysis. For this latter group, we included them only in the combined KC analysis. 23andMe included self-reported data; however, a separate sub study confirmed the validity of using self-report of KC type, which had high sensitivity (93%) and specificity (99%) compared with medical records (11).

We did not perform anatomical site specific analysis of KC or the analysis to determine genetic basis of having a single, multiple or recurrent KC lesions because the relevant data was not uniformly available across the datasets. Another possible limitation is that we were unable to perform histological subtype-specific GWAS meta-analysis (e.g. limited to the micronodular BCC subtype) as we did not have the requisite data. Even though we implicitly assume that the genetic risk is similar in all subtypes in our analysis, we acknowledge that the genetic signals we identify may derive from common subtypes rather than the rarer because the majority of our samples will represent the common forms of BCC and SCC.

Our most powerful analysis leveraged the strong genetic correlation between the input traits to maximize power for identifying new loci using the MTAG software. MTAG makes the assumption that the genetic correlations across traits are relatively homogeneous across the genome; while this seems likely in our situation (the effect sizes for previously identified BCC and SCC loci are broadly similar, in keeping with their high genome-wide genetic correlation), this is difficult to test formally. While MTAG maximizes our power for KC discovery generally, as our numbers for SCC are much smaller than those for BCC there may be additional SCC loci that we failed to identify due to poor statistical power.

Finally although our analysis identified new genes (including potential novel drug targets for KC), further fine-mapping and molecular genetic characterization is essential to pinpoint the underlying causal variants and to reveal the biological functions of the peak SNPs. Further, while we report potential drug targets for genes we identified as associated with KC, these would need to be assessed through preclinical models and clinical trials to fully evaluate their efficacy, safety, benefits versus risks before repurposing.

### Conclusions

Keratinocyte carcinomas are the most numerous of the cancers in countries with populations primarily of European ancestry. While mortality is low, morbidity is considerable and they impose substantial burdens on health systems around the world. With our large GWAS meta-analysis, and by combining a range of approaches, we were able to identify 45 novel regions associated with skin cancer risk, providing new insights into disease etiology and putatively novel drug targets for KC. However, replication studies are warranted to confirm these novel genome-wide associations.

### Materials and Methods

#### Study participants

**QSkin.** QSkin is a large prospective study on KCs; it comprises a cohort of 43 794 men and women aged 40–69 years (18). The aim of the study is to identify the environmental and genetic risk factors for skin cancer. At baseline in 2011, data on participants' phenotype, lifestyle and exposures to environmental risks were collected using a self-administered questionnaire. KCs are not routinely registered in Australian cancer registries, so health administration data from Medicare were used to identify treatments for KCs for the period from date of consent though to June 30, 2014. Exact diagnoses of BCC and SCC were established through further linkage with pathology records. Medicare is Australia's universal health insurance scheme with virtually 100% coverage. The eight Medicare item codes for billing claims for excision of histologically confirmed KC have very high concordance (~97%) with histopathologic diagnoses (19).

Genotyping of 17 965 participants using Illumina Global Screening Array (San Diego, CA, USA) was conducted in 2017, which included 8803 individuals undergoing excision for one or more KC during the follow-up period 2011–2014. Prior to GWAS QC (see methods). Pathology records were able to confirm a BCC diagnosis for 2066 of these individuals, and for 854 SCC. Pathology records confirming the specific type of KC was unavailable for the remaining cases, allowing their use only in the KC phenotype analyses. Controls were QSkin individuals

who reported no history of actinic skin lesions prior to baseline, and for whom no KC excisions were observed during follow-up.

**UKBB.** The UKBB is a biorepository database, which has information on genetics and more than 2000 phenotypes acquired through self-report, hospital records and linkage to registries for about half a million participants in the UK (20). This large prospective cohort study data recruitment was conducted from 2006 to 2010, aiming to collect a wide range of physical, biological, lifestyle measures and clinical outcomes of these voluntary participants. Further, these data have been embedded in national electronic health records for further clarification, completeness and accuracy (20).

We used clinically and histopathologically defined ICD9 and ICD10 definitions to classify BCC and SCC cases (Table 1; for full details of selection of case see the Supplemental Methods). We selected the cancer-free controls on the basis of not having (a) a current or prior cancer registry history of cancer, or benign or *in situ* tumors, including C44, unspecified malignant neoplasms of skin; and (b) not having self-reported cancer at the time of enrollment of the study (21) (for final numbers see following sections). Genotyping was conducted using Affymetrix UK Biobank Axiom array (Santa Clara, CA, USA) and Affymetrix UK BiLEVE Axiom array (22).

**eMERGE.** eMERGE is a database that contains a collection of genetic and phenotypic data identified through electronic medical records in five participating groups in the USA (23). A more detailed description of this cohort is available via the dbGaP website (dbGaP ID phs000360) (24). Briefly, cases were those with a KC phenotype, derived from at least two reports of ICD9 code of 173–173.9, V10.83, 209.31–209.26 or 173.00–173.99. KC free controls were those without any report of ICD9 code 172–173.99. Prior to GWAS QC (see following sections) there was GWAS data available for 1666 KC cases and 9643 KC free controls. eMERGE KC cases and cancer-free controls were genotyped on the Illumina Human660W-Quad\_v1\_A array (San Diego, CA, USA) (24).

**23andMe.** 23andMe is a personal genetics company located in Mountain View, California (25). GWAS data were available for participants who self-reported a history of SCC or BCC (11,12). A separate, sub study has been performed to ascertain the validity of self-reported skin cancer status by Chahal et al. (11). In this, randomly selected patients from the Stanford outpatient clinics were given the same questionnaire as used by 23andMe and were followed up in medical records to check the concordance between self-report data and medical records. A high percentage of true positives and true negatives were identified (sensitivity, specificity: BCC 93% and 99%, SCC 92% and 98%, respectively) (11,12). Hence, these figures support the accuracy of the self-reported questionnaire used in 23andMe data. Genotyping was conducted using four different arrays (V1, V2, V3, V4), which included custom variants as well as content from the Illumina HumanHap550+ BeadChip, and Illumina OmniExpress+ BeadChip arrays (12).

## GWAS analyses

**QSkin.** We filtered out 189 387 SNPs from the Illumina Global Screening array (San Diego, CA, USA) array data if the GenTrain score was  $<0.6$ , Hardy–Weinberg equilibrium (HWE) *P*-value was  $<1 \times 10^{-6}$  and/or minor allele frequency (MAF) was  $<1\%$  using GenomeStudio and PLINK (v1.9) (26), leaving 496 695 SNPs. We

excluded participants with  $>5\%$  missing genotypes from the initial set of 17 965 QSkin participants (remaining  $N=17\,643$ ).

Using the University of Michigan Imputation Server genotypes were phased by Eagle 2 (27) and imputed to the Haplotype reference consortium (HRC) version r1.1 (28) via minimac version 3 (29). Following imputation, identity by descent (IBD) as measured by PLINK v1.9 was used to drop one individual from pairs with  $>0.1875$   $PI_{HAT}$  scores ( $N=400$  individuals) from the analysis. Further, we identified and removed prior to analysis 378 individuals with ancestral principal component values more than six standard deviations (SD) away from European HapMap populations. In total, 776 individuals were removed as one IBD pair were also principal components analysis (PCA) outliers.

Of the 16 687 post QC samples there were 8145 individuals with any KC diagnosis confirmed by Australian Medicare records, of which 1995 had a histologically confirmed BCC diagnosis and 821 a histologically confirmed SCC diagnosis. There were also 4797 controls who were cancer free without a history of actinic lesions. Using the same control set we performed a BCC, SCC and a KC GWAS (Table 1).

SNPs with MAF  $>0.01$  and imputation quality score  $>0.3$  were analysed with PLINK 2.0, with the first 10 principal components (PC), age, age<sup>2</sup>, sex, sex \* age and sex \* age<sup>2</sup> fitted as covariates. Following this we used the univariate LDSC approach (30) to ensure that our GWAS results were not inflated due to the biases such as model misspecification, population stratification and cryptic relatedness. The LDSC intercept for the SCC, BCC and KC GWAS was 1.01–1.04 indicating the majority of apparent inflation ( $\lambda \sim 1.1$ ) is polygenic signal (Supplementary Material, Table S1).

**UKBB.** A detailed description of the UKB GWAS QC procedures has been provided elsewhere (22) and is summarized here. We restricted our analysis to 438 870 participants who were either white-British or were genetically similar to white-British UKBB participants based on PCA (e.g. Irish ancestry) (21). In total, we included 2274 SCC cases, 16 847 BCC cases and 340 302 cancer free controls in the study. Using a common control set we performed a BCC, SCC and by combining the BCC and SCC case set as a KC phenotype GWAS. Note that there were 583 people who had both BCC and SCC and we included them in the individual BCC and SCC analyses as a case (Table 1).

The relatedness among individuals in UKBB is higher than that in a random population sample (30.3% of UKBB participants had third degree or closer relationships) (22). Hence, we used BOLT-LMM v1.2 (31) for our association analysis. BOLT-LMM uses linear mixed models to have better control over population stratification and cryptic relatedness than standard methods (31). We first used a sparse set of 368 802 genotyped autosomal SNPs to calibrate the Bayesian prior used for the actual BOLT-LMM association tests. We obtained association estimates for 97 million imputed SNPs. SNPs with poor imputation scores (INFO  $<0.4$ ) or MAF  $<0.01$  were discarded, yielding results for 7.6 million SNPs. Given that BOLT-LMM assumes that our trait of interest is quantitative, we applied a formula (32) to transform the linear-scale beta(s) into values on the log (OR) scale—using BOLT-LMM in this way is valid for analysis of large, non-ascertained population cohorts such as UKBB (31). The LDSC intercepts for the UKBB BCC and SCC GWAS were 1.03 and 1.00, respectively (Supplementary Material, Table S1).

**eMERGE.** We performed genotype QC using PLINK v1.90b5.4 (26,33) by removing SNPs with call rate  $<97\%$ , MAF  $<0.01$  and



HWE  $P$ -value  $<10^{-4}$  in controls and  $P$ -value  $<10^{-10}$  in cases. Individuals with  $>3\%$  missing genotypes were removed. Autosomal markers were used to compute IBD in PLINK, and one of each pair of related individuals with PI\_HAT scores  $>0.2$  were removed from the analysis. We conducted the PCA in PLINK using all the participants and reference samples of Northern European ancestry (1000G British, CEU, and Finland). We removed the ancestry outliers with PC1 and PC2 values more than six SD from the mean of the reference panel. Following QC there were 1565 cases with a KC diagnosis, 8756 cancer free controls, and 310 260 SNPs available for imputation (Table 1).

Phasing of the genotyped SNPs was performed in ShapeIT (34), and imputation in Minimac3 through the Michigan imputation server (29). We used HRC version r1.1 (28) as the reference panel for imputation. SNPs with MAF  $>0.001$  and imputation quality ( $r^2$ )  $>0.3$  were used for association analysis. We performed the association testing using PLINK v2.00a2LM (26) under an additive genetic model adjusted for sex and the first 10 PCs. The LDSC intercept for the eMERGE GWAS was 1.00 [standard error (SE)=0.007], indicating that there was very little evidence for stratification or structural biases (Supplementary Material, Table S1).

**23andMe.** For detailed QC information see (12,35); this is summarized briefly here. Individuals with  $<97\%$  European ancestry were identified and excluded using an ancestry deconvolution model (36). SNPs with genotype call rate  $<95\%$ , HWE  $P$ -value  $<10^{-20}$  were removed from the analysis. If the allele frequencies were different in 23andMe compared to the European 1000 Genomes reference panel, they were also excluded from the analysis. Phasing of genotyped SNPs was performed using Beagle (version 3.3.1) (37). Imputation to version 3 release of the 1000 Genomes reference haplotypes (38) was conducted using Minimac2 (35). GWAS data using an overlapping set of controls were available for European ancestry participants of 23andMe for SCC (6579 cases and 280 558 controls) and BCC (12 945 cases and 274 252 controls) (Table 1). In our analysis we included 9 061 544 SNPs after excluding those variants with a MAF  $<0.01$  and an imputation score  $<0.3$ . LDSC indicated little to no evidence of residual inflation (intercept SCC 1.04, BCC 1.06, Supplementary Material, Table S1).

### Genetic overlap

In light of the previously identified common risk factors and shared genes of SCC and BCC risk we hypothesized that BCC and SCC may have a high genetic correlation. Hence, we explored the genetic overlap between these skin cancers using the bivariate LDSC v.1.0.0 method (16). LDSC is a feasible way of estimating genetic correlations between traits using GWAS summary statistics (Supplementary Material, Table S1). Furthermore, the LDSC method appropriately accounts for overlapping samples when analysing GWAS summary statistics.

### Multiple trait analysis of KC

To model the high but incomplete correlation between BCC and SCC, we conducted a meta-analysis using multi-trait analysis of GWAS (MTAG), a method-of-moments framework, which requires only GWAS summary statistics for the included traits (39,40). MTAG models the incomplete correlation between the input traits using bivariate LDSC. MTAG has the useful property that due to the modelling done in LDSC, it accounts for sample overlap across the input traits (39,40). This feature is

important as some of the datasets used in our analysis have a large degree overlap among the control sets (Table 1).

We performed a multiple trait combined KC GWAS analysis using; UKBB KC (18 538 cases, 340 302 controls), eMERGE KC (1565 cases, 8756 controls), 23andMe BCC (12 945 cases, 274 252 controls), 23andMe SCC (6579 cases, 280 558 controls) and QSkin KC (8145 cases, 4797 controls) (Methods; Table 1). MTAG has the advantage of outputting a result for each input trait adjusted by all other input traits; the results we present here are the MTAG output for the UKBB KC GWAS. (Supplementary Material, Table S2). Manhattan plot, Q-Q plot and the regional plots for the output of the UKBB KC GWAS MTAG output can be found in Supplementary Materials, Figures S2, S3 and S8.

### Conditional analysis and locus assignment

To identify all independent SNPs associated with KC in the MTAG analysis, we performed a joint conditional analysis using the GCTA v1.26 software (41), with stepwise model selection and the parameters set to distance of SNPs 2000Kb, threshold  $P$ -value  $5 \times 10^{-8}$  and the collinearity between the SNPs to 0.05 (Supplementary Material, Table S2). A LD reference panel was constructed using 5000 randomly selected participants from the UKBB. Independent SNPs within 1 mb (mega base) of each other were assigned to the same locus with the exception of SNPs around ASIP at 20q11 where long-range LD has been observed and a wider boundary of 2.5 mb was used.

### BCC and SCC meta-analyses

To identify genetic variants specific to BCC and SCC, we performed meta-analyses of the individual cancers using METAL (39). For BCC meta-analyses we used samples from UKBB BCC (16 847 cases, 340 302 controls), 23andMe BCC (12 945 cases, 274 252 controls) and QSkin BCC (1995 cases, 4797 controls). SCC GWAS was conducted using UKBB SCC (2274 cases, 340 302 controls), 23andMe SCC (6579 cases, 280 558 controls) and QSkin SCC (821 cases, 4797 controls). The full results for these analyses can be found in Supplementary Material, Table S3. Conditional analysis was performed for the BCC and SCC meta-analyses as above, and BCC and SCC loci were deemed the same as those identified in the KC analysis if they were within 1 mb of each other; the LD  $r^2$  between lead SNPs and the matching KC locus can be found in Supplementary Material, Table S3. Manhattan plots, Q-Q plots and the regional plots for the output of the BCC and SCC meta-analyses can be found in Supplementary Materials, Figures S4–S7, S9, S10.

### Estimating heritability

We calculated the heritability due to common SNPs ( $h^2_{\text{SNP}}$ ) estimates on the liability scale using LDSC and assuming that the prevalence of BCC to be 3.5% and SCC to be 0.5%, respectively, in the UK (prevalence calculated using the proportions within UKBB). Briefly, GWAS results for UKBB BCC and UKBB SCC analyses were filtered to SNPs MAF  $>0.01\%$ , and present in the Hapmap3 reference list provided by LDSC.

Then we computed the  $h^2_{\text{SNP}}$  following the removal of the GWAS significant loci for BCC and SCC, respectively. For each loci we filtered out the top independent SNP and all SNPs within 1 mb either side. For HLA and MC1R this window was expanded

to 2 mb, and for ASIP we removed 31 to 36 mb of chr20 due to the long range LD exhibited at this locus.

### Comparison of effect estimates between BCC, SCC and KC

To further explore the concordance in effect sizes for genetic variants identified in the multiple trait combined KC GWAS, or the BCC and SCC specific meta-analyses, we extracted the effect sizes and SE for each independent SNP from the three datasets. We used the difference between SCC and BCC log (OR) and its SE (computed under the approximation of independence across the samples) to test for a difference in log (OR). In total 95 independent SNPs were extracted, and P-value  $< 5 \times 10^{-4}$  was assigned as the significance threshold (Supplementary Material, Table S8).

### Gene-based methods

We performed gene-based tests using the fastBAT (42) software, based on a Bonferroni-corrected significance threshold of  $0.05/23957 = 2.1 \times 10^{-6}$ . Gene-based results with peak single SNP results  $> 5 \times 10^{-8}$  (that is, gene-based results not derived from genes containing a genome-wide significant SNP in their own right) are shown in Supplementary Material, Table S4. To ensure we were not capturing long-range LD with loci discovered in the single SNP GWAS, genes with significant gene-based results were deemed as novel loci if  $> 1$  mb from an SNP with a single SNP result P-value  $< 5 \times 10^{-8}$ , and that the peak SNP in each gene region was not in LD ( $r^2 > 0.01$ ) with any single SNP with a GWAS P-value  $< 5 \times 10^{-8}$  within 2 mb. Adjacent gene-based results were combined into a single locus if within 1 mb of each other (Supplementary Material, Table S4).

### Post-GWAS analysis

The overall GWAS results for BCC, SCC and KC were further examined using FUMA (43) to test whether any predefined gene sets show enrichment, based on the GWAS results (MAGMA gene set analysis). GWAS loci were also characterized in terms of eQTL data and potential drug targets using the Open Targets platform (44) and the Gtex portal (v7) (45) using the strongest single SNP within in each gene region (Tables 3 and 4; full results are in Supplementary Material, Table S2, Supplementary Material, Table S3, and Supplementary Material, Table S4).

### Analysis of predicted gene expression

To further understand the biological mechanisms of novel genome-wide SNPs, we performed a TWAS using the MetaXcan software, a method for relating predicted tissue expression levels of genes to phenotypes (46). We specifically investigated gene expression in whole blood (6759 genes), sun-exposed skin (7637 genes) and skin not exposed to the sun (5802 genes) from GTEx (45) (Supplementary Materials, Tables S5, S6 and S7). Associations were deemed significant at the Bonferroni-corrected threshold of  $0.05/(20198) = 2.48 \times 10^{-6}$ .

### Supplementary Material

Supplementary Material is available at HMG online.

### Acknowledgements

We thank Scott Wood and John Pearson from QIMR Berghofer for IT support. We thank the research participants and employees of 23andMe who contributed to this study.

### Contributors to the 23andMe Research Team

M. Agee, B. Alipanahi, A. Auton, R. K. Bell, K. Bryc, S. L. Elson, P. Fontanillas, N. A. Furlotte, D. A. Hinds, K. E. Huber, A. Kleinman, N. K. Litterman, M. H. McIntyre, J. L. Mountain, E. S. Noblin, C. A. M. Northover, S. J. Pitts, J. Fah Sathirapongsasuti, O. V. Sazonova, J. F. Shelton, S. Shringarpure, C. Tian, J. Y. Tung, V. Vacic and C.H. Wilson.

### QSkin

We would like to thank and acknowledge the staff of the sample processing group at QIMR Berghofer, and staff at Erasmus Medical Center, Rotterdam for genotyping and SNP calling. Imputation was performed University of Michigan Imputation Server. We thank and acknowledge the staff at QIMR Berghofer the maintenance of the High Performance Cluster, which was used for data analysis.

### dbgap (eMERGE)

The dbgap data we used in this study included samples from the University of Washington, Mayo Clinic, Marshfield Clinic, the Northwestern University and the Vanderbilt University. In the following paragraphs, we acknowledge each study separately:

### Group Health Cooperative/University of Washington

Funding support for Alzheimer's Disease Patient Registry (ADPR) and Adult Changes in Thought (ACT) study was provided by a U01 from the National Institute on Aging (Eric B. Larson, PI, U01AG006781). A gift from the 3M Corporation was used to expand the ACT cohort. DNA aliquots sufficient for GWAS from ADPR probable AD cases, which had been enrolled in genetic differences in Alzheimer's cases and controls (Walter Kukull, PI, R01 AG007584) and obtained under that grant, were made available to eMERGE without charge. Funding support for genotyping, which was performed at Johns Hopkins University, was provided by the NIH (U01HG004438). Genome-wide association analyses were supported through a Cooperative Agreement from the National Human Genome Research Institute, U01HG004610 (Eric B. Larson, PI).

### Mayo Clinic

Samples and associated genotype and phenotype data used in this study were provided by the Mayo Clinic. Funding support for the Mayo Clinic was provided through a cooperative agreement with the National Human Genome Research Institute (NHGRI), Grant #: UOIHG004599; and by grant HL75794 from the National Heart Lung and Blood Institute (NHLBI). Funding support for genotyping, which was performed at The Broad Institute, was provided by the NIH (U01HG004424).

### Marshfield Clinic

Research Foundation Funding support for the Personalized Medicine Research Project (PMRP) was provided through a

cooperative agreement (U01HG004608) with the National Human Genome Research Institute (NHGRI), with additional funding from the National Institute for General Medical Sciences (NIGMS). The samples used for PMRP analyses were obtained with funding from Marshfield Clinic, Health Resources Service Administration Office of Rural Health Policy grant number D1A RH00025, and Wisconsin Department of Commerce Technology Development Fund contract number TDF FYO10718. Funding support for genotyping, which was performed at Johns Hopkins University, was provided by the NIH (U01HG004438).

### Northwestern University

Samples and data used in this study were provided by the NUGene Project ([www.nugene.org](http://www.nugene.org)). Funding support for the NUGene Project was provided by the Northwestern University's Center for Genetic Medicine, Northwestern University and Northwestern Memorial Hospital. Assistance with phenotype harmonization was provided by the eMERGE Coordinating Center (Grant number U01HG04603). This study was funded through the NIH, NHGRI eMERGE Network (U01HG004609). Funding support for genotyping, which was performed at The Broad Institute, was provided by the NIH (U01HG004424).

### Vanderbilt University

Funding support for the Vanderbilt Genome-Electronic Records (VGER) project was provided through a cooperative agreement (U01HG004603) with the National Human Genome Research Institute (NHGRI) with additional funding from the National Institute of General Medical Sciences (NIGMS). The dataset and samples used for the VGER analyses were obtained from Vanderbilt University Medical Center's BioVU, which is supported by institutional funding and by the Vanderbilt CTSA grant UL1RR024975 from NCR/NIH. Funding support for genotyping, which was performed at The Broad Institute, was provided by the NIH (U01HG004424).

Assistance with phenotype harmonization and genotype data cleaning was provided by the eMERGE Administrative Coordinating Center (U01HG004603) and the National Center for Biotechnology Information (NCBI). The datasets used for the analyses described in this manuscript were obtained from dbGaP at <http://www.ncbi.nlm.nih.gov/gap> through dbGaP accession number phs000360.v1.p1.

### Ethical approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (reference number 06/MRE09/65), and at recruitment all participants gave informed consent to participate in UK Biobank and be followed up, using a signature capture device.

The QSkin study, and the overall combined KC analysis project, was approved by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute. Each participant in QSkin provided written informed consent to take part in the study.

23andMe's human subjects protocol was approved by Ethical and Independent Review Services, an Association for the Accreditation of Human Research Protection Programs (AAHRPP) accredited Institutional review board (IRB). All participants have given written informed consent to participate in the study.

The eMERGE study was approved by the Institutional Review Board of Vanderbilt University Medical Center and written

informed consent has taken from the participants informing them that their genetic information will be used for research.

### Data availability

The full GWAS summary statistics for the 23andMe dataset will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit [research.23andme.com/collaborate](http://research.23andme.com/collaborate) for more information and to apply to access the data.

UK Biobank data are available through the UK Biobank Access Management System <https://www.ukbiobank.ac.uk/>.

*Conflict of interest statement.* None declared.

### Funding

Australian National Health and Medical Research Council (NHMRC; project grant APP1063061, Program grant APP1073898). This work was conducted using the UK Biobank Resource (application number 25331). Australian Research Council Future Fellowship (to S.M.). Research Fellowships from the NHMRC Australia (to R.E.N., S.M. and D.C.W.). University of Queensland and QIMR Berghofer Medical Research Institute (scholarship to U.L.).

The UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council (UK), Department of Health (UK), Scottish Government and Northwest Regional Development Agency. It also had funding from the Welsh Assembly Government, British Heart Foundation, and Diabetes UK.

### References

- Paolino, G., Donati, M., Didona, D., Mercuri, S.R. and Cantisani, C. (2017) Histology of non-melanoma skin cancers: an update. *Biomedicine*, **5**, 71.
- Apalla, Z., Lallas, A., Sotiriou, E., Lazaridou, E. and Ioannides, D. (2017) Epidemiological trends in skin cancer. *Dermatol. Pract. Concept.*, **7**, 1–6.
- Fahradyan, A., Howell, A.C., Wolfswinkel, E.M., Tsuha, M., Sheth, P. and Wong, A.K. (2017) Updates on the management of non-melanoma skin cancer (NMSC). *Healthcare (Basel)*, **5**, 1–24.
- Australian Institute of Health and Welfare (2013) Health system expenditure on cancer and other neoplasms in Australia: 2008–09. AIHW. <https://www.aihw.gov.au/>. Accessed on December 26, 2018.
- Guy, G.P., Machlin, S.R., Ekwueme, D.U. and Yabroff, K.R. (2015) Prevalence and costs of skin cancer treatment in the U.S., 2002–2006 and 2007–2011. *Am. J. Prev. Med.*, **48**, 183–187.
- Didona, D., Paolino, G., Bottoni, U. and Cantisani, C. (2018) Non melanoma skin cancer pathogenesis overview. *Biomedicine*, **6**, 1–15.
- Pandeya, N., Olsen, C.M. and Whiteman, D.C. (2017) The incidence and multiplicity rates of keratinocyte cancers in Australia. *Med. J. Aust.*, **207**, 339–343.
- Mucci, L.A., Hjelmberg, J.B., Harris, J.R., Czene, K., Havelick, D.J., Scheike, T., Graff, R.E., Holst, K., Moller, S., Unger, R.H. et al. (2016) Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*, **315**, 68–76.
- Stacey, S.N., Helgason, H., Gudjonsson, S.A., Thorleifsson, G., Zink, F., Sigurdsson, A., Kehr, B., Gudmundsson, J., Sulem, P., Sigurgeirsson, B. et al. (2015) New basal cell carcinoma susceptibility loci. *Nat. Commun.*, **6**, 6825.

10. Asgari, M.M., Wang, W., Ioannidis, N.M., Itnyre, J., Hoffmann, T., Jorgenson, E. and Whittemore, A.S. (2016) Identification of susceptibility loci for cutaneous squamous cell carcinoma. *J. Invest. Dermatol.*, **136**, 930–937.
11. Chahal, H.S., Lin, Y., Ransohoff, K.J., Hinds, D.A., Wu, W., Dai, H.-J., Qureshi, A.A., Li, W.-Q., Kraft, P., Tang, J.Y. et al. (2016) Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma. *Nat. Commun.*, **7**, 12048.
12. Chahal, H.S., Wu, W., Ransohoff, K.J., Yang, L., Hedlin, H., Desai, M., Lin, Y., Dai, H.-J., Qureshi, A.A., Li, W.-Q. et al. (2016) Genome-wide association study identifies 14 novel risk alleles associated with basal cell carcinoma. *Nat. Commun.*, **7**, 12510.
13. Siiskonen, S.J., Zhang, M., Li, W.Q., Liang, L., Kraft, P., Nijsten, T., Han, J. and Qureshi, A.A. (2016) A genome-wide association study of cutaneous squamous cell carcinoma among European descendants. *Cancer Epidemiol. Biomarkers Prev.*, **25**, 714–720.
14. Nan, H., Xu, M., Kraft, P., Qureshi, A.A., Chen, C., Guo, Q., Hu, F.B., Curhan, G., Amos, C.I., Wang, L.E. et al. (2011) Genome-wide association study identifies novel alleles associated with risk of cutaneous basal cell carcinoma and squamous cell carcinoma. *Hum. Mol. Genet.*, **20**, 3718–3724.
15. Nelson, M.R., Tipney, H., Painter, J.L., Shen, J., Nicoletti, P., Shen, Y., Floratos, A., Sham, P.C., Li, M.J., Wang, J. et al. (2015) The support of human genetic evidence for approved drug indications. *Nat. Genet.*, **47**, 856–860.
16. Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.-R., ReproGen Consortium, Psychiatric Genomics Consortium, Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Duncan, L. et al. (2015) An atlas of genetic correlations across human diseases and traits. *Nat. Genet.*, **47**, 1236–1241.
17. Turley, P., Walters, R.K., Maghziyan, O., Okbay, A., Lee, J.J., Fontana, M.A., Nguyen-Viet, T.A., Wedow, R., Zacher, M., Furlotte, N.A. et al. (2018) Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.*, **50**, 229–237.
18. Olsen, C.M., Green, A.C., Neale, R.E., Webb, P.M., Cicero, R.A., Jackman, L.M., O'Brien, S.M., Perry, S.L., Ranieri, B.A. and Whiteman, D.C. (2012) Cohort profile: the QSkin sun and health study. *Int. J. Epidemiol.*, **41**, 929–929i.
19. Thompson, B.S., Olsen, C.M., Subramaniam, P., Neale, R.E. and Whiteman, D.C. (2016) Medicare claims data reliably identify treatments for basal cell carcinoma and squamous cell carcinoma: a prospective cohort study. *Aust. N. Z. J. Public Health*, **40**, 154–158.
20. Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M. et al. (2015) UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.*, **12**, e1001779.
21. Ong, J.S., An, J., Law, M.H., Whiteman, D.C., Neale, R.E., Gharahkhani, P. and MacGregor, S. (2018) Height and overall cancer risk and mortality: evidence from a Mendelian randomisation study on 310,000 UK Biobank participants. *Br. J. Cancer*, **118**, 1262–1267.
22. Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J. et al. (2017) Genome-wide genetic data on ~500,000 UK Biobank participants. doi:10.1101/166298.
23. Kho, A.N., Pacheco, J.A., Peissig, P.L., Rasmussen, L., Newton, K.M., Weston, N., Crane, P.K., Pathak, J., Chute, C.G., Bielinski, S.J. et al. (2011) Electronic medical records for genetic research: results of the eMERGE consortium. *Sci. Transl. Med.*, **3**, 79re1.
24. Home—dbGaP—NCBI. <https://www.ncbi.nlm.nih.gov/gap/>. Last accessed December 2, 2018.
25. Stoeklé, H.-C., Mamzer-Bruneel, M.-F., Vogt, G. and Hervé, C. (2016) 23andMe: a new two-sided data-banking market model. *BMC Med. Ethics*, **17**, 19.
26. Chang, C.C., Chow, C.C., Tellier, L.C., Vattikuti, S., Purcell, S.M. and Lee, J.J. (2015) Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*, **4**, 7.
27. Loh, P.-R., Palamara, P.F. and Price, A.L. (2016) Fast and accurate long-range phasing in a UK Biobank cohort. *Nat. Genet.*, **48**, 811–816.
28. McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A.R., Teumer, A., Kang, H.M., Fuchsberger, C., Danecek, P., Sharp, K. et al. (2016) A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.*, **48**, 1279–1283.
29. Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E.Y., Levy, S., McGue, M. et al. (2016) Next-generation genotype imputation service and methods. *Nat. Genet.*, **48**, 1284–1287.
30. Bulik-Sullivan, B.K., Loh, P.-R., Finucane, H.K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson, N., Daly, M.J., Price, A.L. and Neale, B.M. (2015) LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.*, **47**, 291–295.
31. Loh, P.R., Tucker, G., Bulik-Sullivan, B.K., Vilhjalmsdottir, B.J., Finucane, H.K., Salem, R.M., Chasman, D.I., Ridker, P.M., Neale, B.M., Berger, B. et al. (2015) Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.*, **47**, 284–290.
32. Lloyd-Jones, L.R., Robinson, M.R., Yang, J. and Visscher, P.M. (2018) Transformation of summary statistics from linear mixed model association on all-or-none traits to odds ratio. *Genetics*, **208**, 1397–1408.
33. Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A., Bender, D., Maller, J., Sklar, P., de Bakker, P.I., Daly, M.J. et al. (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.*, **81**, 559–575.
34. Delaneau, O., Marchini, J. and Zagury, J.-F. (2011) A linear complexity phasing method for thousands of genomes. *Nat. Methods*, **9**, 179–181.
35. Fuchsberger, C., Abecasis, G.R. and Hinds, D.A. (2015) minimac2: faster genotype imputation. *Bioinformatics*, **31**, 782–784.
36. Durand, E.Y., Do, C.B., Mountain, J.L. and Michael Macpherson, J. (2014) Ancestry composition: a novel efficient pipeline for ancestry deconvolution. doi:10.1101/010512.
37. Browning, S.R. and Browning, B.L. (2007) Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *Am. J. Hum. Genet.*, **81**, 1084–1097.
38. 1000 Genomes Project Consortium, Abecasis, G.R., Altshuler, D., Auton, A., Brooks, L.D., Durbin, R.M., Gibbs, R.A., Hurles, M.E. and McVean, G.A. (2010) A map of human genome variation from population-scale sequencing. *Nature*, **467**, 1061–1073.

39. Willer, C.J., Li, Y. and Abecasis, G.R. (2010) METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, **26**, 2190–2191.
40. Turley, P., Walters, R.K., Maghziyan, O., Okbay, A., Lee, J.J., Fontana, M.A., Nguyen-Viet, T.A., Wedow, R., Zacher, M., Furlotte, N.A. et al. (2017) MTAG: multi-trait analysis of GWAS. doi:10.1101/118810.
41. Yang, J., Lee, S.H., Goddard, M.E. and Visscher, P.M. (2011) GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.*, **88**, 76–82.
42. Bakshi, A., Zhu, Z., Vinkhuyzen, A.A.E., Hill, W.D., McRae, A.F., Visscher, P.M. and Yang, J. (2016) Fast set-based association analysis using summary data from GWAS identifies novel gene loci for human complex traits. *Sci. Rep.*, **6**, 32894.
43. Watanabe, K., Taskesen, E., van Bochoven, A. and Posthuma, D. (2017) Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.*, **8**, 1826.
44. Carvalho-Silva, D., Pierleoni, A., Pignatelli, M., Ong, C., Fumis, L., Karamanis, N., Carmona, M., Faulconbridge, A., Hercules, A., McAuley, E. et al. (2018) Open Targets Platform: new developments and updates two years on. *Nucleic Acids Res.*, **47**, 1–11.
45. Carithers, L.J. and Moore, H.M. (2015) The Genotype-Tissue Expression (GTEx) project. *Biopreserv. Biobank.*, **13**, 307–308.
46. Barbeira, A.N., Dickinson, S.P., Bonazzola, R., Zheng, J., Wheeler, H.E., Torres, J.M., Torstenson, E.S., Shah, K.P., Garcia, T., Edwards, T.L. et al. (2018) Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat. Commun.*, **9**, 1825.
47. Xiao, R. and Boehnke, M. (2009) Quantifying and correcting for the winner's curse in genetic association studies. *Genet. Epidemiol.*, **33**, 453–462.
48. Shay, J.W. (2016) Role of telomeres and telomerase in aging and cancer. *Cancer Discovery*, **6**, 584–593.
49. Wang, Y., Wu, X.-S., He, J., Ma, T., Lei, W. and Shen, Z.-Y. (2016) A novel TP53 variant (rs78378222 A > C) in the polyadenylation signal is associated with increased cancer susceptibility: evidence from a meta-analysis. *Oncotarget*, **7**, 1–11.
50. Seidel, J.A., Otsuka, A. and Kabashima, K. (2018) Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front. Oncol.*, **8**, 86.
51. Schwarz, A., Beissert, S., Grosse-Heitmeyer, K., Gunzer, M., Bluestone, J.A., Grabbe, S. and Schwarz, T. (2000) Evidence for functional relevance of CTLA-4 in ultraviolet-radiation-induced tolerance. *J. Immunol.*, **165**, 1824–1831.
52. Ransohoff, K.J., Wu, W., Cho, H.G., Chahal, H.C., Lin, Y., Dai, H.-J., Amos, C.I., Lee, J.E., Tang, J.Y., Hinds, D.A. et al. (2017) Two-stage genome-wide association study identifies a novel susceptibility locus associated with melanoma. *Oncotarget*, **8**, 17586–17592.
53. Law, M.H., Bishop, D.T., Lee, J.E., Brossard, M., Martin, N.G., Moses, E.K., Song, F., Barrett, J.H., Kumar, R., Easton, D.F. et al. (2015) Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma. *Nat. Genet.*, **47**, 987–995.
54. Casey, G. (1997) The BRCA1 and BRCA2 breast cancer genes. *Curr. Opin. Oncol.*, **9**, 88–93.
55. McLaughlin, J.R., Rosen, B., Moody, J., Pal, T., Fan, I., Shaw, P.A., Risch, H.A., Sellers, T.A., Sun, P. and Narod, S.A. (2013) Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2. *J. Natl. Cancer Inst.*, **105**, 141–148.
56. Liu, Q., Tong, D., Liu, G., Yi, Y., Xu, J., Yang, X., Wang, L., Zhang, J., Ye, J., Zhang, Y. et al. (2018) A novel BRCA2 mutation in prostate cancer sensitive to combined radiotherapy and androgen deprivation therapy. *Cancer Biol. Ther.*, **19**, 669–675.
57. American Association for Cancer Research (2014) BRCA2 mutation linked to lung cancer risk. *Cancer Discov.*, **4**, OF1.
58. Rafnar, T., Sigurjonsdottir, G.R., Stacey, S.N., Halldorsson, G., Sulem, P., Pardo, L.M., Helgason, H., Sigurdsson, S.T., Gudjonsson, T., Tryggvadottir, L. et al. (2018) Association of BRCA2 K3326\* with small cell lung cancer and squamous cell cancer of the skin. *J. Natl. Cancer Inst.*, **110**, 967–974.
59. Spracklen, C.N., Chen, P., Kim, Y.J., Wang, X., Cai, H., Li, S., Long, J., Wu, Y., Wang, Y.X. and Takeuchi, F. (2018) Association analyses of East Asian individuals and trans-ancestry analyses with European individuals reveal new loci associated with cholesterol and triglyceride levels. *Hum. Mol. Genet.*, **27**, 1122.
60. Brown, K.M., Macgregor, S., Montgomery, G.W., Craig, D.W., Zhao, Z.Z., Iyadurai, K., Henders, A.K., Homer, N., Campbell, M.J., Stark, M. et al. (2008) Common sequence variants on 20q11.22 confer melanoma susceptibility. *Nat. Genet.*, **40**, 838–840.
61. Bishop, D.T., Demenais, F., Iles, M.M., Harland, M., Taylor, J.C., Corda, E., Randerson-Moor, J., Aitken, J.F., Avril, M.-F., Azizi, E. et al. (2009) Genome-wide association study identifies three loci associated with melanoma risk. *Nat. Genet.*, **41**, 920–925.
62. Barrett, J.H., Iles, M.M., Harland, M., Taylor, J.C., Aitken, J.F., Andresen, P.A., Akslen, L.A., Armstrong, B.K., Avril, M.F., Azizi, E. et al. (2011) Genome-wide association study identifies three new melanoma susceptibility loci. *Nat. Genet.*, **43**, 1108–1113.
63. Manousaki, D., Dudding, T., Haworth, S., Hsu, Y.-H., Liu, C.-T., Medina-Gómez, C., Voortman, T., van der Velde, N., Melhus, H., Robinson-Cohen, C. et al. (2018) Low-frequency synonymous coding variation in CYP2R1 has large effects on vitamin D levels and risk of multiple sclerosis. *Am. J. Hum. Genet.*, **103**, 1053.
64. Canela-Xandri, O., Rawlik, K. and Tenesa, A. (2018) An atlas of genetic associations in UK Biobank. *Nat. Genet.*, **50**, 1593–1599.
65. de fine Olivarius, F., Wulf, H.C., Crosby, J. and Norval, M. (1996) The sunscreens effect of urocanic acid. *Photodermatol. Photoimmunol. Photomed.*, **12**, 95–99.
66. Welsh, M.M., Karagas, M.R., Kuriger, J.K., Houseman, A., Spencer, S.K., Perry, A.E. and Nelson, H.H. (2011) Genetic determinants of UV-susceptibility in non-melanoma skin cancer. *PLoS One*, **6**, e20019.
67. Wang, W., Jorgenson, E., Whittemore, A.S. and Asgari, M.M. (2018) Susceptibility loci-associated cutaneous squamous cell carcinoma invasiveness. *J. Invest. Dermatol.*, **138**, 557–561.
68. Ioannidis, N.M., Wang, W., Furlotte, N.A., Hinds, D.A., 23andMe Research Team, Bustamante, C.D., Jorgenson, E., Asgari, M.M. and Whittemore, A.S. (2018) Gene expression imputation identifies candidate genes and susceptibility loci associated with cutaneous squamous cell carcinoma. *Nat. Commun.*, **9**, 4264.
69. Olivier, M., Hollstein, M. and Hainaut, P. (2010) TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb. Perspect. Biol.*, **2**, a001008.