A Genome-Wide Association Study of Cutaneous Squamous Cell Carcinoma among European Descendants

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Abstract

Background: No GWAS on the risk of cutaneous squamous cell carcinoma (SCC) has been published. We conducted a multistage genome-wide association study (GWAS) to identify novel genetic loci for SCC.

Methods: The study included 745 SCC cases and 12,805 controls of European descent in the discovery stage and 551 controls of European ancestry in the replication stage. We selected 64 independent loci that showed the most significant associations with SCC in the discovery stage (linkage disequilibrium $r^2 < 0.4$) for replication.

Results: Rs8063761 in the DEF8 gene on chromosome 16 showed the strongest association with SCC ($P = 1.7 \times 10^{-9}$ in the combined set; $P = 1.0 \times 10^{-6}$ in the discovery set and $P = 4.1 \times 10^{-6}$ in the replication set). The variant allele of rs8063761 (T allele) was associated with a decreased expression of DEF8 ($P = 1.2 \times 10^{-6}$). Besides, we validated four other SNPs associated with SCC in the replication set, including rs9689649 in PARK2 gene ($P = 2.7 \times 10^{-8}$ in combined set; $P = 3.2 \times 10^{-5}$ in the discovery; and $P = 0.02$ in the replication), rs754626 in the SRC gene ($P = 1.1 \times 10^{-8}$ in combined set; $P = 1.4 \times 10^{-5}$ in the discovery and $P = 0.02$ in the replication), rs9643297 in ST3GAL1 gene ($P = 8.2 \times 10^{-8}$ in combined set; $P = 3.3 \times 10^{-5}$ in the discovery; and $P = 0.04$ in the replication), and rs17247181 in ERBB2IP gene ($P = 4.2 \times 10^{-6}$ in combined set; $P = 3.1 \times 10^{-7}$ in the discovery; and $P = 0.048$ in the replication).

Conclusion: Several genetic variants were associated with risk of SCC in a multistage GWAS of subjects of European ancestry.

Impact: Further studies are warranted to validate our finding and elucidate the genetic function of these variants. Cancer Epidemiol Biomarkers Prev; 25(4); 1–7. ©2016 AACR.
(T2D_HPFS), a coronary heart disease case–control study nested within the NHS (CHD_NHS), and a coronary heart disease case–
case control study nested within the HPFS (CHD_HPFS). Overlapped
samples among the component datasets were excluded. Detailed
descriptions of the study population were presented in the Sup-
plementary Materials and Methods and were published previously
(12, 13).

To define SCC in the Harvard GWAS, the participants in the
NHS and HPFS reported newly diagnosed cancers biennially.
With their permission, medical records were obtained and
reviewed by physicians to confirm their self-reported diagnosis.
We included the pathologically confirmed invasive SCC cases
with no previously diagnosed cancer as the eligible cases in the
SCC GWAS. The controls were defined as those who did not
report any type of major cancers. The study protocol was
approved by the Institutional Review Board of Brigham and
Women’s Hospital and the Harvard School of Public Health
(Boston, MA).

**The Rotterdam study.** The Rotterdam Study (RS) is a prospective
population-based follow-up study of the determinants and
prognosis of chronic diseases in the elderly including skin
diseases and cancer in participants living in Rotterdam, the
Netherlands. The design has been prescribed in detail (14).
In brief, the RS consists of a major cohort (RS-I) and two
extensions (RS-II and RS-III). The cohort is predominantly
(95%) Caucasian and the overall response rate for all three
cycles at baseline was 72.0%. The Medical Ethics Committee
of the Erasmus Medical Center and the review board of the
Dutch Ministry of Health, Welfare and Sports have ratified the
RS. From each participant, written informed consent was
obtained. For this study, we included participants from the
RS-I and RS-II cohorts, as the number of SCC cases in RS-III was
very small.

To ascertain histologically confirmed SCC cases, all participants
from the RS were linked with the nationwide network and registry
of histo- and cytopathology in the Netherlands (PALGA; up to
23rd September 2011; ref. 15). PALGA was founded in 1971 and
achieved complete national coverage in 1991. Every obtained
pathology excerpt contains encrypted patient data, a report iden-
tifier, a conclusion of the pathologist (often differentiating
between biopsy and excision and stating the localization of the
SCC), and a PALGA diagnosis line derived from Systematized
Nomenclature of Medicine (15). We used a previously published
approach to identify unique SCC cases based on date of diagnosis,
biotherapy/excision and/or tumor localization (16). If the diagnosis
or the number of unique SCC remained unsure, the medical files
were hand searched and cases that remained dubious were
excluded.

**Replication study.** In the replication stage, a fast-track replication
was conducted among 531 SCC cases and 551 healthy controls in
the skin cancer case–control study nested within NHS and HPFS
(skin cancer study). All the cases and controls in this study were
from the subcohorts of NHS and HPFS who had given a blood
specimen. Eligible cases consisted of pathologically confirmed
invasive SCC cases diagnosed after the baseline up to 2006 follow-
up cycle for both cohorts, who had no previously diagnosed
cancer. Controls were randomly selected from participants who
were free of diagnosed cancer up to and including the question-
aire cycle in which the case was diagnosed. One or two controls
were matched to each case by age (±1 year). Cases and their
matched controls were selected in the same cohort.

Information on pigmentation traits were collected from pro-
spective questionnaires in both NHS and HPFS using similar
wording. We used categorical variables to indicate the natural hair
color (red, blonde, light brown, dark brown, and black), tanning
ability (practically none, light tan, average tan and deep tan in
NHS; painful burn and peel, burn then tan, tan without burn in
HPFS), and the total number of lifetime severe sunburns (none,
1–2, 3–5, 6, and more).

**Genotyping, imputation, and quality control**

SCC GWAS. We previously performed genotyping in the com-
ponent sets of Harvard GWAS using the Affymetrix 6.0 array
(12, 13). We used the MACH program (17) to impute
2,543,887 autosomal SNPs based on haplotypes from the Hap-
Map (18) database phase II data build 35 (CEU) in all of the four
component sets, including T2D_NHS, T2D_HPFS, CHD_NHS,
and CHD_HPFS (19). Samples from the four studies were imput-
ed separately. We observed high imputation quality in each
cohort’s imputation. SNPs with imputation r2 > 0.95 and minor
allele frequency (MAF) > 0.01 in each study were included in
meta-analysis. Finally, a total of 1,777,244 SNPs were included in
the Harvard GWAS.

Genotyping from participants of the RS has been described
before (14). In brief, DNA from whole blood was extracted fol-
lowing standard protocols. The Infinium II HumanHap550K
Genotyping BeadChip version 3 was used to genotype both RS-I
and RS-II cohorts. Next, the RS-I and RS-II cohorts were imput-
ed separately using the HapMap Phase II CEU reference panel
(Build 36) as the reference panel and using a two-step procedure
imputation algorithm implemented in the program MACH. SNPs
with imputation r2 < 0.03, MAF < 0.02 for RS-I, and MAF < 0.08 for
RS-II were excluded. After quality control, a total of 2,356,032
SNPs from RS-I and 1,956,891 SNPs from RS-II were available for
GWAS and meta-analysis.

**Replication study.** We selected 64 independent SNPs [linkage
disequilibrium (LD) r2 < 0.4] showing the strongest associations
with SCC in the discovery stage for replication in the skin cancer
study. We genotyped these SNPs using TaqMan OpenArray system
at the Dana Farber/Harvard Cancer Center Polymorphism Detec-
tion Core. Laboratory personnel were blinded to the case–control
status, and blinded quality control samples were inserted to
validate genotyping procedures; concordance for the blinded
samples was 100%. Primers, probes, and conditions for genotyping
assays are available upon request. We excluded five SNPs
(rs4980694, rs12210050, rs13156707, rs11263585, and
rs3099065) that failed genotyping in the replication set. The rest
59 SNPs were successfully genotyped with call rate >85% and
Hardy–Weinberg P value > 0.01. Detailed information of these
SNP was presented in Supplementary Table S1.

Seven common MC1R variants (Val60Leu, Val92Met, 
Arg151Cys, Ile155Thr, Arg160Trp, Arg163Gln, and
Asp294His) were previously genotyped among a subgroup of the skin cancer
case–control study (257 SCC cases and 282 controls). Detailed
descriptions of this subgroup study were previously published (5).

**Statistical analysis**

We used logistic regression to test associations between minor
allele counts and SCC risk in the discovery and replication sets. In

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the discovery stage, we used the imputed genotype data based on HapMap phase II data build 35 (CEU). We analyzed the three component GWASs in the discovery set separately. We adjusted for age, gender, and the three largest principal components of genetic variation of each GWAS in the regression model. These principal components were calculated for all individuals on the basis of ca. 10,000 unlinked markers using the EIGENSTRAT software (20). We additionally adjusted for the component study set in the Harvard GWAS. We used PLINK for the GWAS analyses in this study. Associations in each GWAS were combined in an inverse variance weighted meta-analysis using METAL (21). Age and gender were adjusted in the skin cancer replication set. The same meta-analysis was conducted to combine the discovery set and the replication set.

Results

We combined three component studies in the discovery stage of this SCC GWAS, which included the Harvard GWAS, the RS-I, and the RS-II. We used the skin cancer case–control study nested in the Harvard cohorts in the replication stage. The details of each component study of this multi-stage SCC GWAS were summarized in Table 1. In the discovery stage, we analyzed a total of 2,392,512 autosomal SNPs imputed from HapMap phase II data build 35 (CEU) after quality control for their associations with SCC. The quantile-quantile (Q–Q) plot of the SCC GWAS did not demonstrate a systematic deviation from the expected distribution (Supplementary Fig. S1). The overall genomic control inflation factor ($\lambda_{GC}$) was 1.00. The Manhattan plot of this SCC GWAS was presented in Supplementary Fig. S2. We selected 64 independent SNPs (LD $r^2 < 0.4$) that showed the strongest associations (by $P$ values) with SCC in the discovery stage for replication. Detailed information of these selected SNP was presented in Supplementary Table S1. Five SNPs (rs4980694, rs12210050, rs13156707, rs11263585, and rs3099065) that failed genotyping in the replication set were excluded.

After combining the discovery set and the replication set, we identified the SNP rs8063761 on chromosome 16 most significantly associated with SCC risk ($P = 1.7 \times 10^{-5}$ in the combined set; $P = 1.0 \times 10^{-6}$ in the discovery set; and $P = 4.1 \times 10^{-4}$ in the replication set). The variant allele of this SNP (T allele; MAF, 0.33) was associated with an increased risk of SCC with odds ratio (OR) of 1.34 [95% confidence interval (CI) 1.22–1.47] compared with the wild allele (A allele; Table 2). This SNP was located in the intron region of the differentially expressed in FDCP 8 homolog (DEF8) gene. We additionally evaluated the association of all the SNPs within 200 kb surrounding this gene with SCC risk and presented the regional plot of DEF8 gene in Fig. 1. As shown in the regional plot, the SNP rs8051733 was in high LD with the identified SNP rs8063761 (LD $r^2 > 0.8$). The SNP rs8051733 was also in the intron region of DEF8 gene, and the variant allele of the SNP rs8051733 (G allele; MAF, 0.30) was associated with an increased risk of SCC with OR of 1.37 [95% CI, 1.16–1.61; $P = 2.0 \times 10^{-4}$ in the discovery set] compared with the wild allele (A allele).

We additionally tested the association between the SNP rs8063761 and human pigmentation traits as well as the risk of other skin cancers based on our published GWAS data (2). As summarized in Supplementary Table S2, we found that the variant allele of this SNP (T allele) was associated with lighter hair color ($P = 6.9 \times 10^{-9}$), poorer tanning ability

### Table 1. The component datasets of the SCC GWAS

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Total</th>
<th>SCC cases/controls</th>
<th>Platform</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard GWAS</td>
<td>5,509</td>
<td>424/5,085</td>
<td>Affymetrics 6.0</td>
<td>1,777,244b</td>
</tr>
<tr>
<td>RS-I</td>
<td>5,892</td>
<td>258/5,634</td>
<td>Affymetrics 6.0</td>
<td>2,356,032c</td>
</tr>
<tr>
<td>RS-II</td>
<td>2,149</td>
<td>63/2,086</td>
<td>Affymetrics 6.0</td>
<td>1,956,891d</td>
</tr>
<tr>
<td>All (meta-analysis)</td>
<td>13,550</td>
<td>745/12,805</td>
<td></td>
<td>2,392,512</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Replication set</th>
<th>Sample size</th>
<th>Genotype</th>
<th>Number of imputed SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer study</td>
<td>1,082</td>
<td>531/551</td>
<td>TaqMan OpenArray</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, and the first three principal components in each study.

*Filtered by imputation $r^2 > 0.95$ and MAF > 0.01.

*Filtered by imputation $r^2 > 0.3$ and MAF > 0.02.

*Filtered by imputation $r^2 > 0.3$ and MAF > 0.08.

*64 SNPs were selected for replication but five of them failed in genotyping.

### Table 2. Association between the SNP rs8063761 in the intron region of DEF8 gene and the risk of SCC

<table>
<thead>
<tr>
<th>Dataset</th>
<th>AA</th>
<th>AT</th>
<th>TT</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>$P_{	ext{heterogeneity}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery set</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvard GWAS</td>
<td>178/2,427</td>
<td>192/2,167</td>
<td>54/490</td>
<td>1.26 (1.09–1.47)</td>
<td>2.23E–03</td>
<td></td>
</tr>
<tr>
<td>RS-I</td>
<td>96/2,710</td>
<td>125/2,405</td>
<td>37/519</td>
<td>1.42 (1.38–1.7)</td>
<td>1.66E–04</td>
<td></td>
</tr>
<tr>
<td>RS-II</td>
<td>26/189</td>
<td>29/908</td>
<td>8/989</td>
<td>1.25 (0.86–1.71)</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>All (meta-analysis)</td>
<td>300/5,326</td>
<td>346/5,480</td>
<td>99/1,998</td>
<td>1.32 (1.18–1.47)</td>
<td>1.01E–06</td>
<td>0.60</td>
</tr>
<tr>
<td>Replication set</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin cancer study</td>
<td>211/267</td>
<td>229/222</td>
<td>79/50</td>
<td>1.38 (1.16–1.65)</td>
<td>4.09E–04</td>
<td></td>
</tr>
<tr>
<td>Combined set (meta-analysis)</td>
<td>134/1,227</td>
<td>174/1,47</td>
<td>134/1,227</td>
<td>1.34 (1.22-1.47)</td>
<td>1.74E–09</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Adjusted for age, and gender.
(P = 2.1 × 10^{-44}), and increased number of previous sunburns (P = 3.7 × 10^{-11}). No significant association was found between this SNP and the risk of BCC (P = 0.06) or the number of non-melanoma skin cancer (P = 0.06) or the number of non-melanoma skin cancer (P = 0.06). 

We compared the association between the SNP rs8063761 and SCC risk before and after adjustment of human pigmentation traits in the skin cancer study. As shown in Supplementary Table S3, this association remained significant, but substantially attenuated after additionally adjusted for hair color, tanning ability, and the number of sunburns (P = 4.1 × 10^{-4} before adjustment and P = 0.01 after adjustment).

Of interest, we found that the SNP rs8063761 was associated with the expression of DEF8 gene based on the published data of expression quantitative trait loci derived from a GWAS of global gene expression in the lymphoblastoid cell lines of 550 individuals of British descent (22). The variant allele of the SNP rs8063761 (T allele) was associated with a decreased expression of DEF8 gene (β = −0.14; SE = 0.03; P = 1.2 × 10^{-4}). These data were available online from the Real-time Engine of eQTLs uploaded by Dr. Liang (23).

However, we noticed that the MC1R gene (previously known pigmentation gene associated with SCC risk) is located close to the DEF8 gene. The SNP rs1805007 in the MC1R gene is in weak LD with the SNP rs8063761 in the DEF8 gene (LD r^2 = 0.3). The variant allele of the SNP rs1805007 (T allele; MAF, 0.07) was associated with an increased risk of SCC with OR of 1.31 (95% CI, 1.07–1.62; P = 9.6 × 10^{-3} in the discovery set) compared with the common allele (C allele). After mutual adjustment by each SNP in the Harvard GWAS set, the association between the SNP rs8063761 and SCC risk remained significant (P = 9.8 × 10^{-3}; OR, 1.23; 95% CI, 1.05–1.45), while the association of the SNP rs1805007 was no longer significant (P = 0.34). We further adjusted for all 7 common MC1R variants (Val60Leu, Val92Met, Arg151Cys, Ile155Thr, Arg160Trp, Arg163Gln, and Asp294His) among a subgroup of the skin cancer case-control study (257 SCC cases and 282 controls genotyped for all 7 MC1R SNPs) and the association of the DEF8 SNP rs8063761 became nonsignificant (P = 0.85; OR, 1.04; 95% CI, 0.71–1.51 after adjustment vs. P = 4.2 × 10^{-3}; OR, 1.44; 95% CI, 1.12–1.85 before adjustment).

In addition, we validated the association between four other SNPs and SCC risk in the replication set, which were rs9689649 in the intron of parkinson protein 2 (PARK2) gene on chromosome 6 (P = 2.7 × 10^{-6} in the combined set; P = 3.2 × 10^{-5} in the discovery set and P = 0.02 in the replication set), rs754626 in the intron of v-src avian sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC) gene on chromosome 20 (P = 1.1 × 10^{-4} in the combined set; P = 1.4 × 10^{-3} in the discovery set and P = 0.02 in the replication set), and rs643297 in the intron of ST3 beta-galactoside alpha-2,3-sialyltransferase 1 (ST3GAL1) gene.
chromosome 8 ($8.2 \times 10^{-6}$ in the combined set; $3.3 \times 10^{-5}$ in the discovery set and $P = 0.04$ in the replication set), and rs17247181 in the intron of erb2 interacting protein (ERBB2IP) gene on chromosome 5 ($4.2 \times 10^{-5}$ in the combined set; $3.1 \times 10^{-5}$ in the discovery set and $P = 0.048$ in the replication set; Table 3).

We also checked the associations between the previously reported SCC risk SNPs identified by candidate gene-based approach for their associations in this study and observed significant associations with consistent directions of effect for the SNPs in $IRF4$ (rs12203592, OR = 1.54 for T allele, $P = 2.57 \times 10^{-4}$), $UBAC2$ (rs73530546, OR = 1.19 for G allele, $P = 0.03$), and $EXOC2$ (rs12210050, OR = 1.34 for T allele, $P = 2.33 \times 10^{-4}$). The SNP in $CITLA4$ (rs3087243) was not associated with SCC risk in our study population ($P = 0.47$). The $XRCC1$ SNPs (rs25487 and rs1799782) were not tested in this study.

### Discussion

In this study, we identified several genetic loci associated with SCC risk by a multi-stage SCC GWAS. To the best of our knowledge, this is the first reported GWAS on SCC to date, which sheds new lights on the genetic basis of SCC development.

The most significant locus identified in this SCC GWAS was the SNP rs8063761 in the intron of $DEF8$ gene. This SNP was also associated with human pigmentation traits, including hair color ($6.9 \times 10^{-9}$), tanning ability ($2.1 \times 10^{-44}$), and the number of sunburns ($3.7 \times 10^{-11}$) in our cohort population. Given that human pigmentation traits are susceptibility factors for skin cancer (1, 24), we compared the association of this SNP with SCC before and after adjustment of pigmentations traits. We found that this association substantially attenuated after adjusted for hair color, tanning ability, and the number of sunburns in the skin cancer study in the Harvard cohorts ($4.1 \times 10^{-6}$ before adjustment and $P = 0.01$ after adjustment), suggesting a mediated association of this SNP with SCC through pigmentation. Of interest, we found this SNP was also strongly associated with the expression level of $DEF8$ gene based on the published eQTL database ($1.2 \times 10^{-5}$; ref. 23).

However, the genetic function of $DEF8$ gene was largely unknown. Furthermore, we noticed that the $DEF8$ gene was close to the $MCIR$ gene, which is a well-known pigmentation gene and has been associated with skin cancer risk (3–5). In this SCC GWAS, only one SNP in the $MCIR$ gene, rs1805007, was in weak LD with the SNP rs8063761 ($L^2 = 0.3$; based on HapMap phase II data build 35, CEU). After adjusting for the SNP rs1805007 in the Harvard GWAS set, the association of the SNP rs8063761 with SCC risk remained significant ($9.8 \times 10^{-3}$; OR, 1.23; 95% CI, 1.05–1.45). However, further adjustment of all 7 common $MCIR$ variants (Val60Leu, Val92Met, Arg151Cys, Ile155Thr, Arg163Gln, and Asp294His) in a subgroup of the replication study (257 SCC cases and 282 controls) eliminated such an association ($P = 0.85$ after adjustment vs. $4.2 \times 10^{-3}$ before adjustment), suggesting such an association may be driven by the $MCIR$ SNPs.

Other genetic loci identified in this study for the association with SCC include polymorphisms within the $ST3GAL1$, SRC, ERBB2IP and $PARK2$ genes. Although their associations didn’t reach GWAS significance, the replication of these findings suggested potential effects of these loci on SCC risk. The $ST3GAL1$ gene encodes a sialyltransferase, β-galactoside α-2,3-sialyltransferase 1 ($ST3Gal1$), which has been reported to play a role in the development of multiple tumors (25–28). A previous study found high expression of $ST3Gal1$ in human cutaneous SCC lesions (29), which further supported our findings. However, this is the first study to report an association between a genetic polymorphism in $ST3GAL1$ gene and skin cancer risk.

The $SRC$ gene is as a well-known proto-oncogene. Genetic abnormalities in this gene have been largely reported in multiple cancers (30–32), including melanoma (33). However, no previous studies have found genetic variants in $SRC$ associated with SCC risk. The $ERBB2IP$ gene encodes the Erbin protein, which is a binding partner of the Erb-B2 protein and regulates Erb-B2 function and localization. Erbin has also been shown to affect the Ras signaling pathway by disrupting Ras–Raf interaction (34). Altered expression of Erbin and Erb-B2 has been found in skin BCC tumors in a previous study, but not in SCC (35). The Parkinson disease–associated gene, $PARK2$, has also been associated with human malignancies in previous studies, including lung cancer (36, 37), glioblastoma (38, 39), and breast cancer (40), but no studies have reported on skin cancer. The precise function of this gene remains largely unknown.

A major strength of this study is the large sample size of pathologically confirmed SCC cases and healthy controls in this study and it is the first reported SCC GWAS so far. With the sample size of 745 SCC cases and 12,805 healthy controls, we estimated the power of 80% to detect the effect size of 1.40, 1.30, 1.20, and 1.15 for the genetic variants with minor allele frequency of 0.05, 0.10, 0.25, and 0.5, respectively, based on a two-sided test of 0.05. Besides, we were able to collect information on human pigmentation traits prospectively in our cohort population for mediation analyses.

In summary, we identified several novel genes and genetic loci associated with SCC risk using a multi-stage GWAS design. The identification of these genetic loci may help us understand the complex mechanisms of developing SCC and suggest new therapeutic targets for this common skin cancer. Further studies are warranted to validate our findings and extend to other populations. Functional studies are needed to elucidate the genetic functions of these identified genes and loci in SCC development.
Disclosure of Potential Conflicts of Interest

A.A. Qureshi is a consultant/advisory board member for Abbvie, Amgen, Centers for Disease Control, Janssen, Merck, Novartis, and Pfizer. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data and declare that the funding sources had no role in the conduct, analysis, interpretation, or writing of this manuscript.

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Conception and design: S.J. Siiskonen, M. Zhang, T. Nijsten, J. Han, A.A. Qureshi
Development of methodology: M. Zhang, P. Kraft, T. Nijsten, J. Han, A.A. Qureshi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Nijsten, J. Han
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.J. Siiskonen, M. Zhang, W.-Q. Li, L. Liang, P. Kraft, T. Nijsten, J. Han, A.A. Qureshi
Writing, review, and/or revision of the manuscript: S.J. Siiskonen, M. Zhang, W.-Q. Li, P. Kraft, J. Han, A.A. Qureshi
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Zhang, W.-Q. Li, J. Han, A.A. Qureshi
Study supervision: M. Zhang, T. Nijsten, J. Han, A.A. Qureshi

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