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LETTER TO THE EDITOR

Identification of telomere maintenance gene variations related to lung adenocarcinoma risk by genome-wide association and whole genome sequencing analyses

Dear editor,

Lung carcinoma is responsible for the highest fatality rate among cancer-related deaths globally, with lung adenocarcinoma (LADC) emerging as the prevailing subtype. LADC is characterized by two distinctive attributes in individuals of Asian ancestry: firstly, Asian patients with LADC are more frequently non-smokers (approximately 40%) than their European counterparts (around 10%) [1]; secondly, approximately 50% of Asian LADC patients have oncogenic mutations in the epidermal growth factor receptor (*EGFR*) gene, whereas this frequency is around 10% in European and American patients [2]. Hence, it is plausible that risk factors exerting a more pronounced influence in Asian than in European/American populations contribute to LADC pathogenesis, irrespective of smoking status. To date, over 50 genomic loci associated with heightened susceptibility to lung carcinoma have been unearthed through genome-wide association studies (GWAS) investigating single nucleotide polymorphisms (SNPs) in East Asian and European/American patients [2–5]. A subset of these loci, including 5p15 (telomerase reverse transcriptase, *TERT*) and 3q28 (tumor protein p63, *TP63*), are associated with LADC risk in both populations. Hence, despite genetic disparities between Caucasian and Asian populations, the populations share genetic factors contributing to lung carcinoma susceptibility.

We performed a meta-analysis encompassing two novel GWAS, comprising 5,416 individuals diagnosed with LADC and 29,696 control subjects (Supplementary Tables S1-S2, Supplementary Figure S1). Additionally, we compared susceptibility loci identified in European ancestry populations with our GWAS data. Five variants were associated with LADC risk in both our GWAS ($P < 5.0 \times 10^{-6}$) and a previous GWAS meta-analysis [3] (Supplementary Table S3). We also compared our findings with top associated SNPs from the latest GWAS [5] (Supplementary Table S4). Subsequently, the most strongly associated SNPs on conditional analysis in non-major histocompatibility complex (HLA) (Supplementary Table S5, Supplementary Figure S2) and HLA regions (Supplementary Table S6, Supplementary Figure S3) were validated in an independent dataset comprising 11,670 patients with LADC and 121,958 controls (Supplementary Figure S4). We detected significant associations of 19 genomic loci and LADC risk, characterized by highly significant *P* values (6.9×10^{-11} to 4.8×10^{-134}). Notably, four of these loci harbor three genes, telomerase RNA component (*TERC*), *TERT*, and protection of telomeres 1 (*POT1*), involved in regulating telomere maintenance (Supplementary Table S7). Associations with 10 loci previously reported in Asian populations (including two loci in *TERT*) [2, 4] and two loci reported in a Caucasian population [3] were validated in the present study (Supplementary Table S7). Additionally, we identified seven novel associated loci: protein tyrosine phosphatase receptor type G (*PTPRG*), *TERC*, butyrophilin subfamily 2 member A1 (*BTN2A1*), major histocompatibility complex, class I, C (*HLA-C*), major histocompatibility complex, class II, DQ beta 1 (*HLA-DQB1*), BCL2 antagonist/killer 1 (*BAK1*), and ankyrin repeat and SOCS box containing 15 (*ASB15*) (Supplementary Table S7).

We also inferred the biological effects of other LADC risk-associated SNP-containing loci identified in the

List of abbreviations: GWAS, genome-wide association studies; LADC, lung adenocarcinoma; WGS, whole genome sequencing; SNP, single nucleotide polymorphism; EGFR, epidermal growth factor receptor; TERT, telomerase reverse transcriptase; TP63, tumor protein p63; TERC, telomerase RNA component; POT1, protection of telomeres 1; PTPRG, protein tyrosine phosphatase receptor type G; BTN2A1, butyrophilin subfamily 2 member A1; HLA-C, major histocompatibility complex, class I, C; HLA-DQB1, major histocompatibility complex, class II, DQ beta 1; BAK1, BCL2 antagonist/killer 1; ASB15, ankyrin repeat and SOCS box containing 15; SECISBP2L, SECIS binding protein 2 like; TERF1, telomeric repeat binding factor 1; TINF2, TERF1 interacting nuclear factor 2; OBFC1, OB-fold-containing 1; TRF1, telomeric repeat binding factor 1; RAP1, TERF2 interacting protein; LTL, leukocyte telomere length.

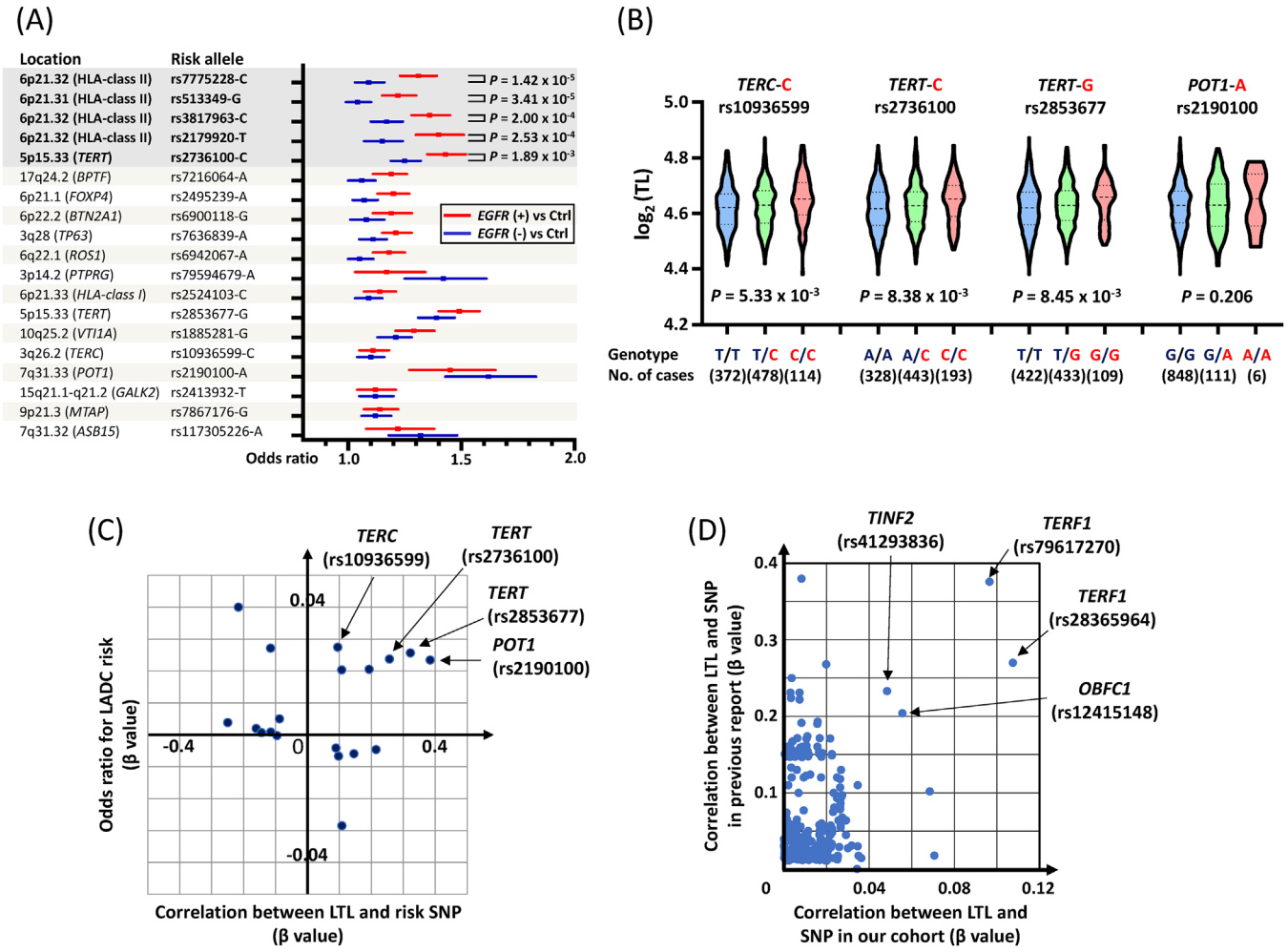

FIGURE 1 Association of novel susceptibility loci with risk for lung adenocarcinoma according to *EGFR* mutation types and association between genotype and leukocyte telomere length. (A) A Forest plot showing associations between 19 SNPs and the presence or absence of *EGFR* mutations. Odds ratios were adjusted for age, sex, smoking status (never vs. ever smoking), and the top five principal components. Combined meta-analysis was performed using a fixed-effects model. *P*-values of SNPs that differed significantly between patients with LADC with and without *EGFR* mutations in case-case analysis are shown. (B) Association between *TERC, TERT*, and *POT1* genotypes and LTL. (C) Association between LADC risk and LTL in 19 LADC risk-associated SNPs. (D) Association between SNPs in telomere maintenance genes and LTL in our cohort (X-axis) and in GWAS catalog data (Y-axis).

Abbreviations: *EGFR*, epithelial growth factor receptor; Ctrl, control; KGP p3, 1000 genomes project phase 3; RSQR, imputation quality; LADC, lung adenocarcinoma; LTL, leukocyte telomere length; *TERC*, telomerase RNA component; *TERT*, telomerase reverse transcriptase; *POT1*, protection of telomeres 1; TL, telomere length; SNP, single nucleotide polymorphism; *TINF2*, TERF1 interacting nuclear factor 2; *OBFC1*, OB-fold-containing 1.

present study through differential expression analysis in normal lung or blood cells: SECIS-binding protein 2-like (*SECISBP2L*; which encodes a putative tumor suppressor protein substrate of Aurora-A kinase), *BAK1* (encoding a pro-apoptotic BCL2 family protein), and *BTN2A1* (encoding a butyrophilin-like protein involved in regulation of $\gamma\delta$ T-cell development and differentiation) (Supplementary Figure S5). Our data indicate that the identified risk-associated loci likely exert an impact on LADC development and immune evasion. Furthermore, we assessed the relationship between the 19 significantly associated SNPs and LADC risk based on somatic *EGFR* mutations in tumor cells (Figure 1A and Supplementary Table S8). Intriguingly, 15 of the 19 SNPs had higher odds ratios in patients with *EGFR*-mutated tumors than in those without such mutations (Supplementary Table S9). Notably, the differences in association according to somatic *EGFR* mutations attained statistical significance for *TERT* and HLA-class II SNPs, reinforcing findings from our previous small-scale GWAS [2]; however, further validation studies are needed to more accurately assess the associations of these SNPs with risk of LADC with *EGFR* mutations.

The associations between SNPs in three genes responsible for telomere maintenance (*TERT*, *TERC*, and *POT1*) and risk of LADC prompted us to explore how these genetic variations influence telomere biology. To accomplish this, we conducted whole-genome sequencing (WGS) of tumor and non-tumor DNA samples obtained from 964 patients with LADC (Supplementary Table S10). Consistent with previous investigations [6], we found that women had longer leukocyte telomere lengths (LTLs) than men, and that LTLs decreased with advancing age, thereby validating the accuracy of our LTL estimation method (Supplementary Figure S6). Notably, the presence of *TERT* and *TERC* risk variants tended to be indicative of elevated LTL ($P < 0.01$) regardless of sex (Figure 1B, Supplementary Figure S7, Supplementary Table S11). Further, variants in the *TERT*, *TERC*, and *POT1* genes were nominally associated with LADC risk and longer LTL ($P < 0.01$) (Figure 1C). Furthermore, we investigated the associations between 398 variants previously linked to both LADC risk and LTL (compiled from the GWAS catalog, https://www.ebi.ac.uk/gwas/) with LTL in our cohort. Intriguingly, we observed that four risk variants in three additional genes involved in telomere maintenance, namely, telomeric repeat-binding factor 1 (*TERF1*), TERF1-interacting nuclear factor 2 (*TINF2*), and OB-fold-containing 1 (*OBFC1*), exhibited a tendency toward association with longer LTLs ($P < 0.01$) (Figure 1D, Supplementary Table S12) and LADC risk. Further validation studies are needed. Physiologically, LTL is tightly governed by telomerase enzymes, including TERC, TERT, and OBFC1, along with shelterin proteins, such as telomeric repeat-binding factor 1 (TRF1), TERF2-interacting protein (RAP1), TERF1, and POT1, which bind to specific DNA sequences at chromosome termini [6]. The current discovery aligns harmoniously with a recent study indicating that hereditary *POT1* mutations were associated with extended telomere length and conferred a predisposition to a familial clonal hematopoiesis syndrome accompanied by development of various solid tumors [7]. A recent Mendelian randomization analysis study established a positive association between longer telomere length and an elevated risk of developing LADC [8]. Building on this discovery, our findings shed further light by demonstrating that common variants within telomere maintenance genes contribute to telomere elongation and increase susceptibility to LADC in Asian populations. Intriguingly, these variants exhibited associations with LTL, while demonstrating no association with telomere length, structural variant count, or tumor mutational burden in 642 patients with LADC (Supplementary Figure S8, Supplementary Table S13). These findings imply that genetic polymorphisms in telomere maintenance genes facilitate telomere elongation, thus prolonging lung epithelial cell survival. The extended lifespan of these cells increases the likelihood of their transformation into malignant cells over time, without influencing somatic alterations during tumor initiation and progression.

Here, we conducted an extensive GWAS, leading to the identification of 19 susceptibility loci associated with LADC. By WGS analysis of 964 samples from patients with LADC, we discovered that risk alleles within the *TERT* and *TERC* genes were linked to elongated telomeres in non-tumor cells, while having no impact on telomere length, mutation status, or structural characteristics of tumor cells. These findings indicate that the presence of long telomeres, conferred by genetic polymorphisms in individuals of Asian descent, fosters the survival of lung epithelial cells and heightens their propensity to undergo malignant transformation. Further elucidation of the distinct and cumulative effects of the 19 LADC risk-associated loci will significantly augment our comprehension of this disease, thereby advancing endeavors toward its treatment and prevention.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Ko.S. and Ta.K. undertook conceptualization. GWAS was performed by Ko.S.; A.T.; Yu.M.; Y.D.; T.Ka.; M.K.; H.I.; F.M.; Y.K.; and Ke.M. Clinical and/or genetic information on study subjects was collected by H.K.; S.M.; H.H; A.G.; Ta.H.; Ki.S.; M.Sa.; Yu.O.; S.W.; K.G.; M.T.; Kat.T.; Ma.K.; Yoh.M.; Ka.T.; Hi.S.; D.M.; Tak.Y.; Ta.M.; Tai.Y.; Y.G.; Ta.Yo.; Ta.Ya.; M.So.; S.To.; K.Y.; Ka.M.; F.T.; M.H.; N.F.; S.S.N.; N.M.; T.S.; Y.N.; K.Ku.; K.Tak.; K.Tan.; Y.Y.; Ku.S.; T.H.; T.M.; Ha.N.; T.N.; Y.O.; N.S.; Y.M.; K.Ku.; K.Take.; Ko.T.; Y.Y.; Ku.S.; T.H.; Tai.M.; H.N.; T.Y.; T.N.; Y.O.; K.Im.; Yo.M.; K.O.; Ka.I.; K.W.; A.S.; M.Y.; M.I.; Ko.M.; J.I.; and Y.M. Omics analysis was undertaken by Ko.S.; S.K.; D.T.; A.S.; S.Ta.; T.A.; A.T.; M.M.; Y.S.; H.S.; T.Y.; M.A.; H.T.; K.Im.; K.Taka.; K.Ko.; H.N.; R.H.; and Y.K. **All authors** reviewed the manuscript draft and revised it critically for intellectual content. **All authors** approved the final version of the manuscript to be published.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participating studies obtained informed consent from the participants by following the protocols approved by their institutional ethical committees. The present study was approved by the ethical committees of each participating institution (ethics approval numbers: 2005-109, 2013-060, 2015-159, 2015-278, 2011-044).

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

Genome data are available from the National Bioscience Database Center (NBDC) Human Database (research ID: hum0014 and hum0012.v1). Summary GWAS1 and GWAS2 data can be freely downloaded from https://epi.ncc.go.jp/cgi-bin/cms/public/index.cgi/jcge/en/download/index.

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