INTRODUCTION

Coronary heart disease (CHD) is one of the most common cardiovascular diseases, and one of the most common causes of death and disability globally (Sacks et al., 2017). The pathophysiological mechanism of coronary heart disease is atherosclerosis, which is characterized by the deposition of excessive cholesterol in the arterial intima (Lusk et al., 2014). The majority of CHD cases can be explained by the interaction of genetic and environmental factors (Peyser, 1997).
Because CHD is an age-related disease, however, interindividual variation in risk of CHD might result from variation in the rate of biological aging (Coronary Artery Disease, 1938). Telomeres are protein-bound DNA repeat structures that are located at the extreme ends of chromosomal DNA where they play an important role in maintaining genomic stability (Rhyu, 1995). They are also a marker of biological aging (Blasco, 2005). In previous studies, mean leukocyte telomere length (LTL) was found to be a predictor of CHD events in middle-age (Spyridopoulos et al., 2009). A case–control study confirmed the association between shorter LTL and an increased risk of coronary artery disease in European populations, which supports the hypothesis that differences in biological aging might contribute to the differences in disease risk and age of CHD onset (Li et al., 2017). In recent years, more studies have revealed that several genes and gene variants are strongly associated with CHD, including TN1P1, MPHOSPH6 and ZNF208 (Song et al., 2017), SH2B3 and SMARCA4 (Li et al., 2017), TERT (Han et al., 2017), and APOB (Al-Bustan, Ismael, Al-Serri, & Al-Rashdan, 2017).

RTEL1 (OMIM: 608833) is a DNA helicase that plays important roles in setting telomere length, maintaining telomeres, and repairing DNA in mice (Barber et al., 2008). Recently, genome-wide association studies (GWAS) have shown that RTEL1 dysfunction appears to be closely related to certain cancers and age-related diseases such as lung cancer (Yan et al., 2016), glioma (Du et al., 2014), astrocytoma (Jin et al., 2015, 2013), stroke (Cai et al., 2017a), and colorectal cancer (Li et al., 2016). However, few studies have investigated the association between genetic variants in RTEL1 and the risk of CHD. We performed a case–control study to analyze the association between six single nucleotide polymorphisms (SNPs) in RTEL1 and the risk of CHD in a Chinese Han population.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

The study protocol was approved by the ethics committee of Haikou People’s Hospital. Written informed consent was obtained from all participants after a full explanation of the study. All samples were coded to protect donor identity. The experimental protocol was implemented in accordance with the approved guidelines.

2.2 | Study subjects

This study included 596 CHD patients and 603 healthy controls. All subjects in our study were recruited from Haikou People’s Hospital, Hainan, China. Patients were unrelated subjects ages 19–83 years old. The controls were recruited from routine healthy examinations in the same hospital. Patients were diagnosed with CHD using standard coronary angiography. Coronary angiography had to reveal 50% narrowing of the lumina of at least one of the major coronary arteries for a patient to be included in the study. Subjects with myocardial infarction, stable angina, and unstable angina were classified as CHD subjects. Non-CHD controls have no congenital heart disease, familial hypercholesterolemia, end-stage renal disease, or known vasculitides.

2.3 | SNP genotyping

Five SNPs in RTEL1 with minor allele frequencies (MAF) of >0.05 were identified in an association analysis of a Beijing Chinese population. The selected SNPs were reported to be associated with CHD and other cardiovascular disease risk. The SNP was found within an intronic region and was unlikely to possess any functional significance, according to the RegulomeDB. The GTEx result for this SNP shows that it is not known to be associated with gene expression in the most

| TABLE 1 | Basic characteristics |
|----------|----------------------|
| Parameters | Case | Control | p value |
| No        | 596 | 603   | <0.001 |
| Males     | 376 (63.1%) | 469 (77.8%) |
| Females   | 220 (36.9%) | 134 (22.2%) |
| Mean age  | 61.44 ± 11.16 | 48.24 ± 13.05 | <0.001 |
| ALT (U/L) | 31.17 ± 2.13 |
| AST (U/L) | 36.62 ± 2.15 |
| GGT (U/L) | 44.59 ± 3.82 |
| TP (g/L)  | 66.43 ± 0.31 |
| GLU (mmol/L) | 6.35 ± 0.11 |
| TG (mmol/L) | 1.80 ± 0.06 |
| TC (mmol/L) | 4.09 ± 0.07 |
| HDL-C (mmol/L) | 1.14 ± 0.01 |
| LDL-C (mmol/L) | 1.93 ± 0.03 |
| APOA1 (g/L) | 1.27 ± 0.01 |
| APOB (g/L) | 1.01 ± 0.02 |
| Lp(a)(mg/L) | 240.1 ± 12.11 |
| PLT (109/L) | 169.47 ± 3.55 |
| PCT (%)   | 1.14 ± 0.15 |
| MPV (fl)  | 13.12 ± 0.32 |
| PDW (%)   | 14.22 ± 0.16 |

Note. p < 0.05 indicates statistical significance.

ALT: alanine aminotransferase; apoA: apolipoprotein A; APOB: apolipoprotein B; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; GLU: glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Lp(a): lipoprotein; MPV: Mean Platelet Volume; PCT: plateletcrit; PDW: platelet distribution width; PLT: platelet; TC: total cholesterol; TG: triglyceride; TP: total protein.
relevant tissue (vascular or peripheral nerve); however, the SNP and the associated variants in LD are known as eQTLs in artery tissue (Supporting information Table S2).

A GoldMag-Mini Purification Kit (GoldMag Co. Ltd Xian City, China) was used to extract genomic DNA from whole-blood samples. DNA samples were stored at −80°C prior to analysis. DNA concentrations were measured using a NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA). Agena MassARRAY Assay Design 4.0 software was used to design a multiplexed SNP MassEXTEND assay, and SNP genotyping was performed using the Agena MassARRAY RS1000 with manufacturer protocols. The PCR primers for each SNP are shown in Supporting information Table S1. Agena Typer 4.0 software was used to perform data management and analyses.

2.4 | Statistical analysis

All statistical analyses were performed using SPSS 19.0 software for Windows (SPSS, Chicago, IL). Allele and genotype frequencies were determined using direct counts. Hardy–Weinberg equilibrium values for each SNP were determined using an exact test to compare the expected frequencies of genotypes in controls. Allele and genotype frequencies in CHD patients and controls were calculated using chi-squared and Fisher’s exact tests. Associations between SNPs and the risk of steroid-induced CHD were tested in genetic models using PLINK software (Version 1.07). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression analysis with adjustment for gender and age (Bland & Altman, 2000). Finally, the Haploview software package (version 4.2) and SHEsis software platform (http://www.nhggr.org/analysis/) were used to estimate pairwise linkage disequilibrium (LD), haplotype construction, and genetic association at polymorphism loci (Barrett, Fry, Maller, & Daly, 2005; Shi & He, 2005). All p values were two-sided, and p ≤ 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the participants

A total of 596 CHD cases (376 men and 220 women; mean age, 61.44 ± 11.16 years) and 603 controls (469 men and 134 women; mean age, 48.24 ± 13.05 years) were included in the study. The clinical characteristics of the cases and controls are shown in Table 1. There were no significant differences in the age and gender distributions between the case and control groups (p < 0.05).

3.2 | Associations between RTEL1 SNPs and CHD risk

Five SNPs within the RTEL1 locus were genotyped in CHD patients and healthy controls (Table 2). Using chi-square tests, we determined that rs6010620 and rs4809324 were associated with a decreased risk of CHD (rs6010620: OR = 0.78, 95% CI = 0.65–0.93, p = 0.005; rs4809324: OR = 0.08, 95% CI = 0.04–0.16, p = 2.7E-21).

3.3 | Associations between genotype frequencies and CHD risk

As is shown in Table 3, logistic regression analyses revealed that the rs6010620 polymorphism in the RTEL1 gene conferred a decreased risk of CHD in the codominant model (adjusted: OR = 0.52, 95% CI = 0.31–0.88, p = 0.007 for the “G/G” genotype) and the recessive model (adjusted: OR = 0.49, 95% CI: 0.30–0.80, p = 0.004 for the “G/G” genotype).

3.4 | Associations between haplotype analyses and CHD risk

Linkage disequilibrium and haplotype analyses of the SNPs in the case and control samples were further studied. Haplotype analysis revealed the block in the RTEL1 genes.

### Table 2 Allele frequencies in cases and controls and odds ratio

| SNP      | Chromosome | Position | Allele | MAF | Case    | Control | HWE p | OR (95% CI)    | p<sup>a</sup> | p<sup>b</sup> |
|----------|------------|----------|--------|-----|---------|---------|-------|----------------|-------------|-------------|
| rs6089953 | 20         | 62291008 | G/A    | 0.261 | 0.280   | 0.840   | 0.91   | (0.76–1.09)    | 0.297       | 0.0594      |
| rs6010620 | 20         | 62309839 | G/A    | 0.265 | 0.317   | 0.500   | 0.77   | (0.65–0.93)    | **0.005**   | **0.001**   |
| rs6010621 | 20         | 62310872 | G/T    | 0.263 | 0.271   | 0.837   | 0.96   | (0.80–1.15)    | 0.677       | 0.133       |
| rs4809324 | 20         | 62318220 | C/T    | 0.098 | 0.107   | 0.526   | 0.08   | (0.04–0.16)    | **2.7E-21** | **5.4E-22** |
| rs2297441 | 20         | 62327582 | A/G    | 0.317 | 0.325   | 0.517   | 0.96   | (0.81–1.14)    | 0.677       | 0.133       |

Note. 95% CI: 95% confidence interval; HWE: Hardy–Weinberg equilibrium; OR: odds ratio.

Bold highlights the value of p and OR(95%CI) with statistical significance.

<sup>a</sup>p < 0.05 indicates statistical significance.

<sup>b</sup>p < 0.01 indicates statistical significance.

*p values were calculated from a chi-square test or Fisher’s exact test. **p values were adjusted by Bonferroni correction.
### TABLE 3  Genotypic model analysis of the relationship between SNPs and coronary heart disease risk

| SNPs     | Model       | Genotype | control | case          | OR (95% CI) | \(p^a\)-value | \(p^b\)-value |
|----------|-------------|----------|---------|---------------|-------------|---------------|---------------|
| Rs6089953| Codominant  | A/A      | 311 (51.6%) | 317 (53.3%)  | 1           | 0.71          | 0.142         |
|          |             | A/G      | 246 (40.8%) | 245 (41.2%)  | 1.02 (0.78–1.33) |               |               |
|          |             | G/G      | 46 (7.6%)   | 33 (5.5%)    | 0.81 (0.47–1.39) |               |               |
|          | Dominant    | A/A      | 311 (51.6%) | 317 (53.3%)  | 1           | 0.91          | 0.182         |
|          |             | A/G-G/G  | 292 (48.4%) | 278 (46.7%)  | 0.98 (0.76–1.28) |               |               |
|          | Recessive   | A/A-A/G  | 557 (92.4%) | 562 (94.5%)  | 1           | 0.41          | 0.082         |
|          |             | G/G      | 46 (7.6%)   | 33 (5.5%)    | 0.80 (0.47–1.36) |               |               |
|          | Log-additive| ---      | ---       | ---           | 0.96 (0.77–1.18) | 0.67          | 0.134         |

| Rs6010620| Codominant  | A/A      | 270 (47.2%) | 315 (52.9%)  | 1           | 0.007*        | 0.0014*       |
|          |             | A/G      | 241 (42.1%) | 246 (41.3%)  | 1.19 (0.90–1.59) |               |               |
|          |             | G/G      | 61 (10.7%)  | 35 (5.9%)    | 0.52 (0.31–0.88) |               |               |
|          | Dominant    | A/A      | 270 (47.2%) | 315 (52.9%)  | 1           | 0.79          | 0.158         |
|          |             | A/G-G/G  | 302 (52.8%) | 281 (47.1%)  | 1.04 (0.79–1.36) |               |               |
|          | Recessive   | A/A-A/G  | 511 (89.3%) | 561 (94.1%)  | 1           | 0.004*        | 0.0008*       |
|          |             | G/G      | 61 (10.7%)  | 35 (5.9%)    | 0.49 (0.30–0.80) |               |               |
|          | Log-additive| ---      | ---       | ---           | 0.90 (0.73–1.10) | 0.31          | 0.062         |

| Rs6010621| Codominant  | T/T      | 318 (52.9%) | 317 (53.2%)  | 1           | 0.76          | 0.152         |
|          |             | G/T      | 240 (39.9%) | 244 (40.9%)  | 1.10 (0.84–1.45) |               |               |
|          |             | G/G      | 43 (7.2%)   | 35 (5.9%)    | 0.98 (0.57–1.69) |               |               |
|          | Dominant    | T/T      | 318 (52.9%) | 317 (53.2%)  | 1           | 0.54          | 0.108         |
|          |             | G/T-G/G  | 283 (47.1%) | 279 (46.8%)  | 1.09 (0.84–1.41) |               |               |
|          | Recessive   | T/T-G/T  | 558 (92.8%) | 561 (94.1%)  | 1           | 0.83          | 0.166         |
|          |             | G/G      | 43 (7.2%)   | 35 (5.9%)    | 0.94 (0.56–1.60) |               |               |
|          | Log-additive| ---      | ---       | ---           | 1.05 (0.85–1.29) | 0.68          | 0.136         |

| Rs4809324| Codominant  | T/T      | 479 (79.4%) | 457 (81.2%)  | 1           | 0.92          | 0.184         |
|          |             | T/C      | 119 (19.7%) | 102 (18.1%)  | 0.96 (0.69–1.35) |               |               |
|          |             | C/C      | 5 (0.8%)    | 4 (0.7%)     | 1.26 (0.30–5.25) |               |               |
|          | Dominant    | T/T      | 479 (79.4%) | 457 (81.2%)  | 1           | 0.88          | 0.176         |
|          |             | T/C-C/C  | 124 (20.6%) | 106 (18.8%)  | 0.98 (0.70–1.36) |               |               |
|          | Recessive   | T/T-T/C  | 598 (99.2%) | 559 (99.3%)  | 1           | 0.74          | 0.148         |
|          |             | C/C      | 5 (0.8%)    | 4 (0.7%)     | 1.27 (0.31–5.28) |               |               |
|          | Log-additive| ---      | ---       | ---           | 0.99 (0.72–1.35) | 0.95          | 0.190         |

| Rs2297441| Codominant  | G/G      | 271 (44.9%) | 276 (46.3%)  | 1           | 0.86          | 0.172         |
|          |             | A/G      | 272 (45.1%) | 262 (44%)    | 0.96 (0.73–1.26) |               |               |
|          |             | A/A      | 60 (9.9%)   | 58 (9.7%)    | 1.09 (0.69–1.72) |               |               |
|          | Dominant    | G/G      | 271 (44.9%) | 276 (46.3%)  | 1           | 0.88          | 0.176         |
|          |             | A/G-A/A  | 332 (55.1%) | 320 (53.7%)  | 0.98 (0.76–1.27) |               |               |
|          | Recessive   | G/G-A/G  | 543 (90%)   | 538 (90.3%)  | 1           | 0.64          | 0.128         |
|          |             | A/A      | 60 (9.9%)   | 58 (9.7%)    | 1.11 (0.71–1.73) |               |               |
|          | Log-additive| ---      | ---       | ---           | 1.01 (0.83–1.23) | 0.93          | 0.186         |

*Note.* 95% CI: 95% confidence interval; OR: odds ratio; SNP: single nucleotide polymorphism.

Bold highlights the value of \(P\) and OR(95%CI) with statistical significance.

\(*p < 0.05\) indicates statistical significance.

\(*p^a < 0.01\) indicates statistical significance.

\(*p^b < 0.01\) indicates statistical significance.

\(*p\) values were calculated by unconditional logistic regression analysis with adjustments for age and gender. \(p^b\) values were adjusted by Bonferroni correction.
Regulator of Telomere Elongation Helicase 1 (RTEL1), an essential DNA helicase, is located in 20q13.3 and includes 40 exons. RTEL1 disassembles a variety of DNA secondary structures to facilitate DNA replication, repair, and recombination processes, thereby helping to maintain telomere integrity (Vannier, Sarek, & Boulton, 2014). Several studies have shown that a substantial proportion of the marked interindividual variation in mean telomere length is genetically determined (Slagboom, Droog, & Boomsma, 1994). In combination, this suggests that individuals who have inherited and shorter telomeres might be more prone to coronary heart disease. It is thus possible that the association of shorter telomeres with an increased risk of coronary heart disease may have a genetic basis (Codd et al., 2013). Any genetic susceptibility could be exacerbated or retarded by postnatal effects on telomere length. If true, this observation could not only partially explain the genetic basis of coronary heart disease, but also its variable age of onset.

Furthermore, previous studies have revealed overexpression of the RTEL1 genomic locus in several cancers such as breast, lung, esophagus, gastric, and colorectal cancer (Muleris, Almeida, Gerbault-Seureau, Malfoy, & Dutrillaux, 1995). Additionally, a mouse model study revealed that RTEL1 could support cell growth by participating in Wnt/β-catenin signaling, which suggests that RTEL1 may be considered to be an oncogene (Wu, Sandhu, Nabi, & Hao, 2012). However, in the past decade, RTEL1 variants have been associated with the decreased risk of several brain cancers and age-related disease including glioma, astrocytoma, glioblastomas, and congenital dyskeratosis. In our study, we investigated six SNPs in RTEL1: rs6089953, rs6010620, rs6010621, rs2297440, rs4809324, and rs2297441. Among these SNPs, Ding Y et al., (Ding et al., 2017) reported the presence of rs4809324 was associated with increasing the COPD risk. The presence of rs2297441 was found to be associated with Crohn's disease in Canadian children (Amre et al., 2009). The presence of rs6010620 was found to increase the risk of glioma (Zhao, Bian, Zhu, Zou, & Tang, 2014). Cai et al. (2017b) reported the associations between single nucleotide polymorphisms in the RTEL1 gene and stroke risk, and the result showed that the rs6010620, rs6010621, and rs6089953 were associated with
an increased risk of stroke. However, Olivier, Charbonnel, Amiard, White, and Gallego (2018) showed RAD51 and RTELI gene could compensate telomere loss and protect cell stability when telomere was absent. And another study indicated that the presence of rs6010620 and rs2297440 resulted in a decreased risk of astrocytoma (Jin et al., 2013). Rong et al. (2017) found rs6089953, rs6010621, and rs2297441 were also associated with a decreased risk of HAPE. In our study, we found that the presence of rs6010620 and rs4809324 was associated with a decreased risk of CHD. This is consistent with previous research results. As far as we know, we are the first to report the association between the RTELI polymorphisms rs6010620 and rs4809324, and CHD risk. More studies should investigate these SNPs using more clinical data with bigger samples. This result may provide a new data to facilitate earlier diagnosis and promote early prevention, and shed light on the new candidate genes and new ideas for the study of subsequent occurrence mechanism of CHD. However, some potential limitations in our current study should be considered when analyzing the results. Our study only conducted preliminary basic research. Moreover, further functional studies and larger population-based prospective studies are required to fully understand the genetic factors underlying CHD.

5 | CONCLUSION

Our results indicate that the rs6010620 and the rs4809324 polymorphisms in RTELI are associated with CHD in a Chinese Han population. These SNPs may serve as prognostic biomarkers for CHD in the Chinese Han population.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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REFERENCES

Al-Bustan, S. A., Ismael, F. G., Al-Serri, A., & Al-Rashdan, I. (2017). Increased risk of the APOB rs11279109 polymorphism for CHD among the Kuwaiti population. Disease Markers, 2017(5), 1–8.

Amre, D. K., Mack, D. R., Morgan, K., Fujiwara, M., Israel, D., Deslandres, C., … Krupoves, A. (2009). Investigation of reported associations between the 20q13 and 21q22 loci and Pediatric-onset Crohn's disease in Canadian Children. American Journal of Gastroenterology, 104(11), 2824–2828. https://doi.org/10.1038/ajg.2009.430

Barber, L. J., Youds, J. L., Ward, J. D., Mcilwraith, M. J., O’Neil, N. J., Petalcorn, M. I. R., … Auclair, M. (2008). RTELI maintains genomic stability by suppressing homologous recombination. Cell, 135(2), 261–271. https://doi.org/10.1016/j.cell.2008.08.016

Barrett, J. C., Fry, B., Maller, J., & Daly, M. J. (2005). Haploview: Analysis and visualization of LD and haplotype maps. Bioinformatics, 21(2), 263–265. https://doi.org/10.1093/bioinformatics/bth457

Bland, J. M., & Altman, D. G. (2000). Statistics notes. The odds ratio. BMJ, 320(7247), 1468.

Blasco, M. A. (2005). Telomerases and human disease: Ageing, cancer and beyond. Nature Reviews Genetics, 6(8), 611–622. https://doi.org/10.1038/nrg1656

Cai, Y., Zeng, C., Su, Q., Zhou, J., Li, P., Dai, M., … Long, F. (2017a). Association of RTELI gene polymorphisms with stroke risk in a Chinese Han population. Oncotarget, 8(70), 114995–115001.

Cai, Y., Zeng, C., Su, Q., Zhou, J., Li, P., Dai, M., … Long, F. (2017b). Association of RTELI gene polymorphisms with stroke risk in a Chinese Han population. Oncotarget, 8(70), 114995–115001.

Codd, V., Nelson, C. P., Albrecht, E., Mangino, M., Deelen, J., Buxton, J. L., … Surakka, I. (2013). Identification of seven loci affecting mean telomere length and their association with disease. Nature Genetics, 45(4), 1–2. https://doi.org/10.1038/ng.2528

Coronary Artery Disease (1938). Coronary artery disease. California and Western Medicine, 49(4 Suppl), 8.

Ding, Y., Xu, H., Yao, J., Xu, D., He, P., Yi, S., … Tian, Z. (2017). Association between RTELI gene polymorphisms and COPD susceptibility in a Chinese Han population. International Journal of Chronic Obstructive Pulmonary Disease, 12, 931–936.

Du, S. L., Geng, T. T., Feng, T., Chen, C. P., Jin, T. B., & Chen, C. (2014). The RTELI rs6010620 polymorphism and Glioma Risk: A meta-analysis based on 12 case-control studies. Asian Pacific Journal of Cancer Prevention, 15(23), 10175. https://doi.org/10.7314/APJCP.2014.15.23.10175

FIGURE 2  RTELI (rs6010620) expression in coronary artery tissues
Sacks, F. M., Lichtenstein, A. H., Wu, J., Appel, L. J., Creager, M. A., Kris-Etherton, P. M., ... Robinson, J. G. (2017). Dietary fats and cardiovascular disease: A presidential advisory from the American Heart Association. *Circulation*, 136(3), e1. https://doi.org/10.1161/CIR.0000000000000510

Shi, Y. Y., & He, L. (2005). SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Research*, 15(2), 97–98. https://doi.org/10.1038/sj.cr.7290272

Slagboom, P. E., Droog, S., & Boomsma, D. I. (1994). Genetic determination of telomere size in humans: A twin study of three age groups. *American Journal of Human Genetics*, 55(5), 876–882.

Song, Y., Yan, M., Li, J., Li, J., Jin, T., & Chen, C. (2017). Association between TNIP1, MPHOSPH6 and ZNF208 genetic polymorphisms and the coronary artery disease risk in Chinese Han population. *Oncotarget*, 8(44), 77233–77240. https://doi.org/10.18632/oncotarget.20432

Spyridopoulos, I., Hoffmann, J., Aicher, A., Brümmerendorf, T. H., Doerr, H. W., Zeiher, A. M., & Dimmel, S. (2009). Accelerated telomere shortening in leukocyte subpopulations of patients with coronary heart disease: Role of cytomegalovirus seropositivity. *Circulation*, 120(14), 1364. https://doi.org/10.1161/CIRCULATIONAHA.109.854299

Vannier, J. B., Sarek, G., & Boulton, S. J. (2014). RTEL1: Functions of a disease-associated helicase. *Trends in Cell Biology*, 24(7), 416–425. https://doi.org/10.1016/j.tib.2014.01.004

Wu, X., Sandhu, S., Nabi, Z., & Hao, D. (2012). Generation of a mouse model for studying the role of upregulated RTEL1 activity in tumorigenesis. *Transgenic Research*, 21(5), 1109–1115. https://doi.org/10.1007/s11248-011-9586-7

Yan, S., Xia, R., Jin, T., Ren, H., Yang, H., Li, J., ... Chen, M. (2016). RTEL1 polymorphisms are associated with lung cancer risk in the Chinese Han population. *Oncotarget*, 7(43), 70475–70480.

Zhao, W., Bian, Y., Zhu, W., Zou, P., & Tang, G. (2014). Regulator of telomere elongation helicase 1 (RTEL1) rs6010620 polymorphism contribute to increased risk of glioma. *Tumor Biology*, 35(6), 5259–5266. https://doi.org/10.1007/s13277-014-1684-8

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.