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Polymorphisms in *TP53*, *MDM2* Genes and Risk of Renal Cell Carcinoma in a Mongolian Population

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Objective: Renal cell carcinoma (RCC) is one of the most common malignancies of the kidney, with genetic factors playing a critical role in its development. Among the key genetic factors, *TP53* and *MDM2* gene polymorphisms have been implicated in cancer susceptibility, but their association with RCC remains unclear in different populations. This study evaluated the association of *TP53* and *MDM2* gene polymorphisms with RCC risk among Mongolian individuals. **Method:** In a hospital-based case-control study, 88 RCC cases and 88 matched controls were analyzed for *TP53* and *MDM2* variants using RFLP-PCR based genotyping. **Results:** The *TP53* CG and CC genotypes and *MDM2* TG and GG genotypes were not significantly associated with RCC risk when considered individually. However, individuals carrying the *MDM2* GG and *TP53* CC genotypes showed elevated RCC risk, although statistical significance was not reached. No strong interaction effects between genotypes and clinical risk factors such as smoking or urinary tract disease were observed. **Conclusion:** While *TP53* and *MDM2* polymorphisms showed trends toward association with RCC, larger studies are warranted to clarify their roles in genetic susceptibility within the Mongolian population.
Keywords: *TP53, MDM2*, Renal cell carcinoma, Polymorphism, Mongolia, Case-control

Introduction

Renal cell carcinoma (RCC) is the most common form of kidney cancer, accounting for over 90% of all malignant renal tumors.[1] Globally, RCC incidence has been increasing,

with Mongolia observing a particularly sharp rise in recent years.[2–5] Despite advancements in diagnosis and treatment, RCC remains a challenge due to its resistance to conventional chemotherapy, late-stage detection, and the absence of reliable early biomarkers.[6–8]

The development of RCC is driven by both environmental exposures and inherited genetic factors. Known environmental risks include tobacco smoking, obesity, hypertension, and urinary tract diseases (UTDs).[5,6,9] In Mongolia, high smoking rates, dietary factors, and limited access to early screening further compound the burden of RCC. However, environmental factors alone do not fully explain RCC pathogenesis—genetic susceptibility plays a significant role.[2,4,10]

Among genes implicated in cancer susceptibility, the tumor suppressor gene *TP53* and its key regulatory partner *MDM2* are central to cell cycle control, DNA repair, and apoptosis. *TP53* (*TP53*), located on chromosome 17p13.1, is often called the "guardian of the genome." A single nucleotide polymorphism at codon 72 (Arg72Pro) has been shown to alter the protein's apoptotic potential, potentially influencing cancer risk.[11] The *MDM2* gene, located on chromosome 12q15, encodes a protein that negatively regulates *TP53* through ubiquitination and proteasomal degradation.[12] A well-studied polymorphism in the *MDM2* promoter region (SNP309, T>G) increases *MDM2* expression, leading to reduced *TP53* activity and possibly promoting tumorigenesis.[12,13]

In addition to *TP53* and *MDM2*, other genes such as *VHL* (von Hippel-Lindau), *PBRM1* (Polybromo 1), *SETD2* (SET Domain Containing 2), and *BAP1* (BRCA1 Associated Protein 1) are well-known for their roles in RCC pathogenesis.[14] *VHL* is a tumor suppressor gene that regulates cellular responses to hypoxia, and its inactivation is a hallmark of clear cell RCC (ccRCC).[15] *PBRM1*, a chromatin remodeling gene, is frequently mutated in RCC, leading to altered gene expression and chromatin structure.[16] *SETD2*, a histone methyltransferase, is involved in maintaining genomic stability, and its loss is associated with aggressive RCC phenotypes.[17] *BAP1*, another tumor suppressor gene, is implicated in chromatin regulation and DNA damage response, with mutations linked to poor prognosis in RCC patients.[18]

While studies have linked *TP53* and *MDM2* polymorphisms to various cancers such as lung, breast, and bladder cancer, their roles in RCC are not well-established and may differ across populations.[11–13] In the context of Mongolia with its unique environmental exposures, high-altitude living, and genetic background investigating these polymorphisms may offer insights into RCC risk stratification and early detection.

This study aimed to evaluate the association between *TP53* (Arg72Pro) and *MDM2* (SNP309) polymorphisms and RCC risk in the Mongolian population. We also examined the potential interaction of these genetic variants with lifestyle factors such as tobacco and alcohol use, hypertension, and UTDs. Understanding these associations could contribute to improved risk assessment and targeted prevention strategies for RCC in Mongolia.

Material and Methods

Study Design and Participants

This hospital-based case-control study was conducted to assess the association between *TP53* and *MDM2* gene polymorphisms and the risk of renal cell carcinoma (RCC) in the Mongolian population. A total of 176 participants were included: 88 patients with histologically confirmed RCC and 88 cancer-free controls matched by age and sex. All participants were recruited from the First Central Hospital of Mongolia between 2019 and 2024.

Eligibility criteria for RCC cases included Mongolian nationality, histopathological confirmation of RCC, and no prior history of other malignancies. Controls were selected from individuals undergoing routine medical checkups or minor non-malignant surgical procedures. Exclusion criteria for both groups included a history of genetic disorders, prior cancer, or organ transplantation.

Data Collection

Demographic and clinical data were collected using a structured questionnaire administered by trained personnel. Information collected included age, sex, body mass index (BMI), smoking status, alcohol consumption, exercise habits, history of hypertension, diabetes mellitus, and urinary tract diseases (UTDs).

Sample Collection and DNA Extraction

Peripheral blood samples (3 mL) were obtained from all participants and stored in EDTA tubes at −20°C until analysis. Genomic DNA was extracted from leukocytes using the Qiagen QIAamp DNA Blood Mini Kit (Qiagen, USA), following the manufacturer's protocol. DNA purity and concentration were

assessed using a NanoDrop spectrophotometer and agarose gel electrophoresis.

Genotyping of TP53 and MDM2

TP53 (Arg72Pro, rs1042522) and *MDM2* (SNP309 T>G, rs2279744) polymorphisms were analyzed using polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis.

- *TP53* Genotyping: PCR amplification was performed using specific primers flanking Arg72Pro. The PCR product was digested with BstUI restriction enzyme, which distinguishes between the Arg and Pro alleles. Digested fragments were visualized by electrophoresis on a 2% agarose gel stained with ethidium bromide under UV light.
- *MDM2* Genotyping: SNP309 was detected using PCR-RFLP with appropriate primers. The amplified product was digested using MspA1I enzyme and analyzed on a 3% agarose gel to distinguish between TT, TG, and GG genotypes.

All reactions were performed in a final volume of 25 µL containing genomic DNA, primers, dNTPs, Taq polymerase, and buffer. Negative controls (no DNA template) were included in each batch of PCRs to ensure assay specificity.

Statistical Analysis

Statistical analysis was conducted using Stata version 13.0 (StataCorp, USA). Descriptive statistics summarized baseline characteristics. Categorical variables were compared between groups using Pearson's chi-square test. Crude odds ratios (cORs) and 95% confidence intervals (CIs) were calculated using univariate logistic regression to estimate the association between each genotype and RCC risk.

Multivariate logistic regression was used to calculate adjusted odds ratios (aORs), controlling for confounders such as alcohol use, tobacco use, and history of UTD. Genotype distributions were tested for Hardy-Weinberg equilibrium. A p-value less than 0.05 was considered statistically significant.

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Scientific Research Committee of the Mongolian National University of Medical Sciences (Approval No: 2023/04/21–2023/3-04). All participants provided written informed consent before enrollment.

Results

Baseline Characteristics

A total of 176 individuals were included in this study, consisting of 88 histologically confirmed renal cell carcinoma (RCC) cases and 88 age- and sex-matched cancer-free controls. The mean age was 51.9 years in both groups. Sex distribution

Table 1. Baseline characteristics of study population

Variables		Total	Controls	RCC	cOR [95% CI]
		n (%)	n (%)	n (%)	
Age	20-29	8 (4.5)	4 (4.5)	4 (4.5)	-
	30-39	18 (10.2)	9 (10.2)	9 (10.2)	-
	40-49	56 (31.8)	28 (31.8)	28 (31.8)	-
	50-59	38 (21.6)	19 (21.6)	19 (21.6)	-
	60-69	42 (23.9)	21 (23.9)	21 (23.9)	-
	70<	14 (8)	7 (8)	7 (8)	-
Sex	Male	68 (38.6)	34 (38.6)	34 (38.6)	-
	Female	108 (61.4)	54 (61.4)	54 (61.4)	-
BMI	18.5 - 24.9	3 (1.7)	3 (3.4)	0 (0)	-
	25.0 - 29.9	60 (34.1)	34 (38.6)	26 (29.5)	1
	30.0 - 34.9	90 (51.1)	42 (47.7)	48 (54.5)	1.512 [0.786 - 2.907]
	35.0<	23 (13.1)	9 (10.2)	14 (15.9)	2.143 [0.785 - 5.851]
	Total	176 (100)	88 (100)	88 (100)	

P value for Pearson's chi-square test, 1 - reference category, CI - confidence interval, cOR - crude odds ratio for conditional binary logistic

Key clinical and lifestyle variables showed statistically significant differences between cases and controls. Tobacco use was more frequent among RCC cases (48.9%) compared to controls (20.5%) (cOR = 3.778, 95% CI =1.812–7.876, P <0.001). Alcohol consumption was also higher in the RCC group (28.4% vs 9.1%; cOR =5.25, 95% CI =1.802–15.294, P =0.001). A striking difference was observed for hypertension (53.4% in cases vs 2.3% in controls; cOR = 65.289, 95% CI =5.941–717.513, P <0.001). History of urinary tract diseases (UTDs) was also significantly associated with RCC (33% vs 4.5%; cOR =13.5, 95% CI =3.21–56.77, P <0.001).

No significant associations were observed for diabetes mellitus, coffee consumption, BMI, or physical activity (Table 2).

Table 2. Association of Lifestyle and Health Factors with Renal Cell Carcinoma (RCC) Risk

Variables		Total	Controls	RCC	cOR [95% CI]
		n (%)	n (%)	n (%)	
Alcohol use	Yes	33 (18.8)	8 (9.1)	25 (28.4)	5.25 [1.802 - 15.294]*
	No	143 (81.3)	80 (90.9)	63 (71.6)	
Tobacco use	Yes	61 (34.7)	18 (20.5)	43 (48.9)	3.778 [1.812 - 7.876]*
	No	115 (65.3)	70 (79.5)	45 (51.1)	
Hypertension	Yes	49 (27.8)	2 (2.3)	47 (53.4)	65.289 [5.941 -717.513]*
	No	127 (72.2)	86 (97.7)	41 (46.6)	
Diabet	Yes	28 (15.9)	11 (12.5)	17 (19.3)	1.667 [0.729 - 3.808]
	No	148 (84.1)	77 (87.5)	71 (80.7)	
Exercise	Yes	23 (13.1)	11 (12.5)	12 (13.6)	1.111 [0.451 - 2.734]
	No	153 (86.9)	77 (87.5)	76 (86.4)	
	No	116 (65.9)	55 (62.5)	61 (69.3)	
History of UTD	Yes	33 (18.8)	4 (4.5)	29 (33)	13.5 [3.21 - 56.77]*
	No	143 (81.3)	84 (95.5)	59 (67)	
Total		**176 (100)**	**88 (100)**	**88 (100)**	

P value for Pearson's chi-square test

Association of *TP53* and *MDM2* Genotypes with RCC

The *TP53* GG genotype was the most prevalent overall (54.5%), followed by CG (31.3%) and CC (14.2%). Compared to the GG genotype, the CG genotype showed a non-significant decreased risk (aOR =0.677, 95% CI =0.267–1.713, P =0.41), while the CC genotype showed a non-significant increased risk (aOR =1.754, 95% CI =0.491–6.265, P =0.387). The combined CG+CC group was not significantly associated with RCC risk (aOR =0.885, 95% CI =0.383–2.042, P =0.774).

For the *MDM2* SNP309 variant, TG was the most common genotype (50.6%), followed by GG (23.3%) and TT (26.1%). Compared to the TT genotype, both TG (aOR =2.576, 95% CI =0.806–8.234, P =0.111) and GG (aOR =2.413, 95% CI =0.632–9.219, P =0.198) genotypes showed elevated but non-significant odds of RCC. The combined TG+GG group showed a trend toward increased risk (aOR =2.532, 95% CI =0.816–7.857, P =0.108) (Table 3).

Combined Genotype Effects

An exploratory analysis of combined genotypes indicated that individuals carrying both the *TP53* CC and *MDM2* GG

genotypes had a higher, though statistically non-significant, risk of RCC (aOR =4.107, 95% CI =0.331–50.923, P =0.271). Other combinations of *TP53* and *MDM2* genotypes did not show significant associations (Table 5).

Table 3. *TP53* and *MDM2* genotypes in relation risk of renal cell carcinoma

Variables	*TP53*	Total	Controls	RCC	cOR [95% CI]	aOR [95% CI]
		n (%)	n (%)	n (%)		
TP53	GG	96 (54.5)	45 (51.1)	51 (58)	1	1
	CG	55 (31.3)	32 (36.4)	23 (26.1)	0.666 [0.347 - 1.276]	0.677 [0.267 - 1.713]
	CC	25 (14.2)	11 (12.5)	14 (15.9)	1.073 [0.444 - 2.592]	1.754 [0.491 - 6.265]*
TP53	GG	96 (54.5)	45 (51.1)	51 (58)	1	1
	CG+CC	80 (45.5)	43 (48.9)	37 (42)	0.76 [0.419 - 1.38]	0.885 [0.383 - 2.042]
MDM2	TT	46 (26.1)	27 (30.7)	19 (21.6)	1	1
	TG	89 (50.6)	42 (47.7)	47 (53.4)	1.701 [0.791 - 3.66]	2.576 [0.806 - 8.234]
	GG	41 (23.3)	19 (21.6)	22 (25)	1.801 [0.726 - 4.469]	2.413 [0.632 - 9.219]
MDM2	TT	46 (26.1)	27 (30.7)	19 (21.6)	1	1
	TG+GG	130 (73.9)	61 (69.3)	69 (78.4)	1.727 [0.822 - 3.63]	2.532 [0.816 - 7.857]

**P<0.05, 1 - reference category, CI - confidence interval, cOR - crude odds ratio for conditional binary logistic, aOR - adjusted odds ratio for conditional binary logistic regression (adjusted by alcohol use, tobacco use, history of UTD) regression*

Table 5. Combined effects of *TP53* and *MDM2* on RCC risk

MDM2	*TP53*	Total	Controls	RCC	cOR [95% CI]	aOR [95% CI]
		n (%)	n (%)	n (%)		
TT	GG	23 (13.1)	12 (13.6)	11 (12.5)	1	1
TT	CG	15 (8.5)	11 (12.5)	4 (4.5)	0.448 [0.106 - 1.899]	1.114 [0.142 - 8.74]
TT	CC	8 (4.5)	4 (4.5)	4 (4.5)	1.063 [0.242 - 4.658]	1.987 [0.222 - 17.756]
TG	GG	49 (27.8)	21 (23.9)	28 (31.8)	1.387 [0.468 - 4.111]	3.191 [0.623 - 16.349]
TG	CG	31 (17.6)	16 (18.2)	15 (17)	1.138 [0.357 - 3.625]	1.856 [0.301 - 11.448]
TG	CC	9 (5.1)	5 (5.7)	4 (4.5)	0.846 [0.157 - 4.57]	4.183 [0.353 - 49.538]
GG	GG	24 (13.6)	12 (13.6)	12 (13.6)	1.114 [0.322 - 3.856]	2.111 [0.352 - 12.654]
GG	CG	9 (5.1)	5 (5.7)	4 (4.5)	0.925 [0.166 - 5.142]	1.69 [0.1 - 28.633]
GG	CC	8 (4.5)	2 (2.3)	6 (6.8)	3.032 [0.475 - 19.348]	4.107 [0.331 - 50.923]

**P<0.05, 1 - reference category, CI - confidence interval, cOR - crude odds ratio for conditional binary logistic, aOR - adjusted odds ratio for conditional binary logistic regression (adjusted by alcohol use, tobacco use, history of UTD) regression*

Tumor Stage, Histology, and Volume by Genotype

Among RCC cases, 56.8% were diagnosed at stage I, followed by stages III (19.3%), IV (12.5%), and II (11.4%). No statistically significant association was found between tumor stage and TP53 or MDM2 genotype (P >0.05 for both).

Histologically, clear cell RCC was the predominant subtype (87.5%), followed by papillary (6.8%) and chromophobe (5.7%) carcinomas. Genotype distributions did not differ significantly across histological types.

Notably, tumor volume <10 cm^3 was more common among patients with the TP53 CC genotype (60.9%) compared to those with TP53 GG (37.3%) and TP53 CG (39.1%) genotypes, showing a statistically significant association (P =0.029). No such trend was seen with MDM2 variants (P =0.715) (Table 4).

Table 4. Stages of renal cell carcinoma cases in the study

Variables		P 53			MDM2			
			GG	CG	CC	TT	TG	GG
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Stage	Stage I	50 (56.8)	28 (54.9)	16 (69.6)	6 (42.9)	9 (47.4)	24 (51.1)	17 (77.3)
	Stage II	10 (11.4)	8 (15.7)	2 (8.7)	0 (0)	1 (5.3)	7 (14.9)	2 (9.1)
	Stage III	17 (19.3)	11 (21.6)	1 (4.3)	5 (35.7)	6 (31.6)	10 (21.3)	1 (4.5)
	Stage IV	11 (12.5)	4 (7.8)	4 (17.4)	3 (21.4)	3 (15.8)	6 (12.8)	2 (9.1)
Histology type	Clear cell	77 (87.5)	45 (88.2)	20 (87)	12 (85.7)	18 (94.7)	42 (89.4)	17 (77.3)
	Chromopobe	5 (5.7)	5 (9.8)	0 (0)	0 (0)	1 (5.3)	3 (6.4)	1 (4.5)
	Papilar	6 (6.8)	1 (2)	3 (13)	2 (14.3)	0 (0)	2 (4.3)	4 (18.2)
Cancer volume*	<10 cm	35 (39.8)	19 (37.3)	14 (60.9)	2 (14.3)	6 (31.6)	22 (46.8)	7 (31.8)
	10 - 40 cm	49 (55.7)	30 (58.8)	9 (39.1)	10 (71.4)	12 (63.2)	23 (48.9)	14 (63.6)
	>40 cm	4 (4.5)	2 (3.9)	0 (0)	2 (14.3)	1 (5.3)	2 (4.3)	1 (4.5)

**P<0.05, 1 - reference category, CI - confidence interval, cOR - crude odds ratio for conditional binary logistic, aOR - adjusted odds ratio for conditional binary logistic regression (adjusted by alcohol use, tobacco use, history of UTD) regression*

Discussion

This study evaluated the association between *TP53* and *MDM2* gene polymorphisms and renal cell carcinoma (RCC) risk in a Mongolian population. While no statistically significant associations were found for individual or combined genotypes, several important trends and observations emerged that warrant further exploration.

The TP53 Arg72Pro polymorphism (rs1042522) has been implicated in various cancers due to its impact on the tumor suppressor protein's ability to induce apoptosis.[11,12] The Pro variant (CC genotype) is believed to be less efficient at triggering apoptosis compared to the Arg variant (GG genotype), potentially allowing damaged cells to survive longer and accumulate mutations. In our study, the CC genotype showed a non-significant increase in RCC risk (aOR =1.754), and was more frequently associated with smaller tumor size (<10 cm^3, P =0.029). This finding is intriguing and may reflect differences in tumor growth dynamics or early-stage detection, but it requires further mechanistic study.

MDM2, a key negative regulator of *TP53*, can impair *TP53*'s tumor suppressor function when overexpressed.[12,13] The SNP309 T>G polymorphism (rs2279744) in the *MDM2* promoter has been shown to enhance *MDM2* expression, attenuating *TP53* activity and promoting tumor development. Although we observed increased RCC risk in individuals carrying the *MDM2* TG (aOR =2.576) and *MDM2* GG (aOR =2.413) genotypes compared to *MDM2* TT, these findings were not statistically significant. The combined *MDM2* TG+GG group also showed a trend toward increased risk (aOR =2.532, P =0.108), consistent with prior studies suggesting *MDM2* SNP309 as a moderate risk factor in various malignancies.

When analyzing combined genotypes, the presence of both high-risk alleles (*TP53* CC and *MDM2* GG) was associated with an increased RCC risk (aOR =4.107), though statistical significance was not reached, likely due to limited sample size. These results suggest potential gene-gene interaction effects that may become significant in larger populations.

Importantly, strong associations were found between RCC and environmental/lifestyle factors such as smoking, alcohol consumption, hypertension, and UTDs.[19,20] These findings align with global literature and emphasize the critical role of modifiable risk factors in RCC development.[21,22] Notably, smoking showed a 3.8-fold increased risk (P <0.001), and UTDs were associated with a 13.5-fold increase in RCC risk (P <0.001). These exposures may exacerbate the effects of underlying genetic susceptibility.

Previous studies in other populations have reported mixed results regarding the role of *TP53* and *MDM2* polymorphisms in RCC, likely due to differences in ethnicity, environmental exposures, and gene-environment interactions.[23–25] The lack of significant findings in this study may reflect the modest effect sizes of these variants or the need for larger samples to detect subtle associations.

Our findings indicate a significant association between *TP53* genotypes and tumor volume in RCC patients, with the *TP53* CC genotype being more frequently observed among those with smaller tumors (<10 cm^3) compared to the *TP53* GG and CG genotypes. Specifically, 60.9% of patients with the CC genotype exhibited smaller tumor volumes, while this was observed in only 37.3% and 39.1% of those with the GG and CG genotypes, respectively. This suggests that the *TP53* CC genotype may be linked to a more favorable tumor profile, potentially reflecting a more effective tumor suppression capacity of this variant.

The *TP53* gene, often referred to as the "guardian of the genome," plays a critical role in regulating cell cycle arrest, apoptosis, and DNA repair.[13,16] Variations in this gene, such as the CC genotype, may influence its functional capacity, contributing to differences in tumor growth dynamics. Our results align with previous studies that have highlighted the role of *TP53* polymorphisms in modifying cancer susceptibility and progression.[26,27]

In contrast, no significant association was observed between *MDM2* variants and tumor volume (P =0.715). This lack of association may be due to the complex regulatory interactions between *MDM2* and *TP53*, where *MDM2* primarily functions as a negative regulator of *TP53*, and its impact on RCC may be influenced by other genetic or environmental factors not captured in this study.[27–29]

These findings emphasize the importance of considering genetic variations such as *TP53* polymorphisms in understanding tumor characteristics and potentially tailoring patient management.[30] However, further research with larger sample sizes and comprehensive genetic profiling is warranted to validate these associations and explore underlying mechanisms.

Limitations of this study include the relatively small sample size, which may limit statistical power and the ability to detect significant gene-gene or gene-environment interactions. In addition, only two polymorphisms were analyzed. RCC is a complex disease likely influenced by multiple genetic and epigenetic alterations, and future studies should incorporate broader panels of genes involved in cell cycle regulation, DNA repair, and inflammation. Another limitation is that gene expression or protein activity levels were not measured, so functional impact remains speculative.

Strengths include the matched case-control design, thorough genotyping using validated PCR-RFLP methods, and incorporation of environmental and lifestyle risk factors into the analysis. This study provides foundational data on genetic susceptibility to RCC in the Mongolian population a group that has been underrepresented in genetic cancer research.

Conclusion

Although *TP53* and *MDM2* polymorphisms were not significantly associated with RCC risk on their own, the observed trends strongly suggest their potential contribution to susceptibility, particularly when combined with environmental risk factors. The high prevalence of modifiable exposures, such as smoking and UTDs, further underscores the critical need for an integrated approach to risk assessment, incorporating both genetic and lifestyle factors. These findings not only highlight an urgent need for large-scale, multi-gene studies to unravel the complex genetic architecture of RCC in Mongolia but also pave the way for precision prevention strategies tailored to this population.

Authors Contribution

G.B, M.T and Sh.A conceived the project and designed the research. G.B, M.P, B, B.D, N.D, TS.Sh, G.Yu, M.T, Y.M and Sh.A contributed to study conception, planning experiments and tech-nical support. G.B, M.T and Sh.A conducted data analysis and data interpre-tation. G.B, M.T and Sh.A participated in the result discussion and technical support. G.B, M.T and Sh.A wrote the manuscript. All authors read and approved the final.

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