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Decoding the Genetic Alteration in Genes of PARP Family and the Possible Association with HNSCC

Harita Ravikumar [a], J. Vijayashree Priyadharsini [a≡*], A. S. Smiline Girija [a≡], P. Sankar Ganesh [aφ] and Nidhi Poddar [b#]

[a] *Department of Microbiology, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai - 600 077, Tamil Nadu, India.*
[b] *Clinical Genetics Laboratory, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai - 600 077, Tamil Nadu, India.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Genetic alterations have long been associated with the transformation of normal cells into malignant cells. Several genes are related to exhibiting the phenotype. The *PARP* gene family is mainly involved in maintaining genome stability. They play an important role in DNA repair and the programmed cell death process.
Aim: To analyse the genetic alteration in PARP family and to determine its association with HNSCC.
Materials and Methods: Cbioportal was used as the primary database for identifying the mutations and variations. The data generated in the form of oncoprint was further assessed for frequency of occurrence, type and novelty.
Results and Discussion: It can be observed that greater amplification was found in the *TIPARP* gene which is 14% among all the 17 genes of the family. Also to add on, *PARP 14* and *PARP 15* show amplification patterns in similar groups of patients. Several types of mutations such as truncated, splicing deep deletion were found in most of the genes. The *TIPARP* gene was up-regulated in HNSCC patients. The Caucasians experiencing low/medium expression of *TIPARP*

≡*Associate Professor;*
φ*Assistant Professor;*
#*Research Scholar;*
**Corresponding author: E-mail: vijayashreej.sdc@saveetha.com;*

showed greater rates of survival than highly expressed African Americans. Similarly, males presenting with low or medium expression of TIPARP showed a greater rate of survival than the highly expressed females.
Conclusion: *TIPARP* could be a promising prognostic marker for screening populations vulnerable to acquiring HNSCC.

Keywords: HNSCC; PARP gene family; genetic alteration; gene expression; novel variants; polymorphism; innovative techniques and innovative technologies.

1. INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) which is the major type of cancer that is most common world wide. Mutation in the TP53 gene sequence which is the somatic genomic alteration that potentially gives rise to HNSCC. Several other gene mutations have also been implicated in the development of oral cancer. The treatment procedure involves surgery, chemotherapy, radiotherapy etc. [1]. HNSCC occurs majorly in 5 anatomical sites which consist of oral cavity, oropharynx, Nasopharynx, hypopharynx and larynx. HNSCC is the cancer that can be cured if it is detected early and often there won't be any symptoms visible, hence it can be avoided at the earliest and detected only when it becomes severe [2]. Tobacco smoking is the primary reason for HNSCC and it is mainly seen in males rather than females. The detection and the diagnosis involves immunohistochemistry, PCR, in situ hybridisation [3].

Poly (ADP-ribose) polymerases (PARPs) are a family of enzymes that exhibit the ability to catalyze the transfer of ADP-ribose to target proteins. Cellular processes, transcription, replication, recombination and DNA repair are a few pathways to mention where PARPs play a vital role. With a special emphasis on the involvement of PARP proteins in DNA repair is of great interest, because certain transformed cells principally rely on PARP mediated DNA repair for survival. Several reports on PARP inhibitors have been shown to increase tumor sensitivity to DNA-damaging agents [3,4]. It is seen that among *PARP, PARP1* and *PARP2* has a catalytic activity and is useful when there is DNA breakage [5]. Genetic alteration has a different pathway and is seen when there is high DNA damage and it is also the multistep accumulation in the genomic landscapes which develops into HNSCC due to overexpression of oncogenes, silenced tumor suppressor [6].

Numerous in silico methods have been used to identify potential variations or mutations in the genome, which could act as potential drivers in triggering disease phenotypes. In the study conducted by Aparna et al, it was seen that matrix metalloproteinases and their association in HNSCC since *MMP* are involved in malignant transformation of a tumor and studied the expression of *MMP* in HNSCC patients [7]. The PARP inhibitors have been found to be useful in HNSCC treatment and the study conducted by Wurtser showed the association of the *PARP* gene family with HNSCC [8]. Based on the previous research it can be seen that there was very little study on the *PARP* gene family and also negligible research done on its association with HNSCC.Our team has extensive knowledge and research experience that has translate into high quality publications [9–20,21–25,26,27,28]. This research aims to decode the genetic alteration in the genes of the *PARP* gene family and their association with HNSCC.

2. MATERIALS AND METHODS

2.1 Data Source

It is a retrospective study and the patient's data has been derived from cBioportal [29] which contains all the patient's details obtained from different cohorts. Information about the genetic alterations throughout the genomic landscape of HNSCC patients are deposited in the repository [30]. The complete profiling of each case in the data set and the demographic details are given in Table 1. Genes used in this study were *PARP1, PARP2, PARP3, PARP4, TNKS, TNKS2, PARP6, TIPARP, PARP8, PARP9, PARP10, PARP11, PARP12, ZC3HAV1, PARP14, PARP15, PARP16*. The genes were queried among the HNSCC dataset and the results were used for further analysis.

2.2 Oncoprint Data Analysis

The information obtained includes the allele frequency, variation, protein coding, amino acid, deletion, insertion etc. the putative association

involving the variations, genome, novel variation and the disease phenotype [29,31].

2.3 gnomAD Data Analysis

This type of investigation involves the large scale sequencing projects and the dataset containing unrelated sequences and public release and compares the variants documented and reported gnomAD repository [29,31].

2.4 Gene Expression and Survival Analysis

The expression of the gene presenting with highest frequency of gene alteration in HNSCC was analysed using the UALCAN (http://ualcan.path.uab.edu/cgi-bin/TCGA-survival) database. Survival curve analysis based on the tumor grade and expression profile was performed to demonstrate the putative role of *PARP* family of genes with HNSCC. Combined survival effect analysis of gene expression and other clinical parameters such as race, gender, tumor grade, cancer subtypes were assessed using a log-rank test that generated a p value which was further used to indicate statistical significance of survival correlation between groups. The test that was used is log rank test [32].

3. RESULTS

cBioportal database was the primary source to obtain the information of patients with head and neck squamous cell carcinoma. The Table 1 shows the demographic details of the patients and the age group of patients was between 19-90 years. Table 2 shows the gene alteration in PARP family and it contains total of 17 genes including *PARP1, PARP2, PARP3, PARP4,TNKS, TNKS2, PARP6, TIPARP, PARP8, PARP9, PARP10, PARP11, PARP12, ZC3HAV1, PARP14, PARP15, PARP16.* Among these genes it was found that *TIPARP* showed 14% of genetic alterations and which is greatest. The *PARP8* gene contains 16 gene alterations and is highest on comparing all the 17 genes. *PARP1, PARP2, PARP6, TIPARP, PARP9, PARP10, PARP11, PARP14, PARP15* shows amplification of genes, *PARP3, PARP4* shows deep deletion. *TNKS, TNKS2, PARP8, PARP12, ZC3HAV1* have both amplification and deep deletion. Under *PARP2,* the N129K gene shows an already existing mutation. Under *PARP4,* E216Q, P120L, EL067K; under TNKS, R245C, V697M, S132F; under *PARP8*, R488H; under *PARP9,* R617Q; under *PARP10,* R753C, ZC3HAV1, R455T, I574V; under *PARP14,* P988L shows already existing mutation others contain novel mutation.

Table 1. Showing the demographic details of patients analyzed in the present study (as obtained from the cBioportal site)

Gender	Male (n = 386) Female (n = 142)
Mutation count	6-3181
Diagnosis age	19-90 years
Smoking status	Smokers: 515 Data not available: 12 Unknown: 1
Alcohol history	Yes – 352 No – 165 Data not available: 11
Neoplasm Histologic grade	Grade 1: 63 Grade 2: 311 Grade 3: 125 Grade 4: 7 Grade GX: 18 Data not available: 4
Race category	White: 452 African: 48 Asian: 11 American Indian or Alaska native: 2 Data not available: 15

Table 2. Showing the gene alteration in the PARP family of genes

Gene	Protein encoded	Cytogenetic loci	% of genetic alterations	Gene alterations	Variant allele frequency	gnomAD frequency
PARP 1	Poly(ADP-ribose) polymerase 1	1q42.12	2	Amplification		
				S274F	0.23	Novel
				P881L	0.04	Novel
				F586L	0.01	Novel
				E456Q	0.27	Novel
				P174T	0.54	Novel
PARP 2	Poly(ADP-ribose) polymerase 2	14q11.2	2.4	Amplification		
				A541dup	0.26	Novel
				M432I	0.10	Novel
				N129K	0.16	rs139090502
PARP 3	Poly(ADP-ribose) polymerase family member 3	3p21.2	1.2	Deep deletion		
				E277D	0.67	Novel
				R472Q	0.11	Novel
PARP 4	Poly(ADP-ribose) polymerase family member 4	13q12.12	2.6	Deep deletion		
				E216Q	0.72	rs145170390
				A637T	0.16	Novel
				H803Q	0.22	Novel
				D952N	0.24	Novel
				W1573R	0.19	Novel
				P120L	0.31	rs199585627
				E1067K	0.06	rs372126761
				P1336S	0.13	Novel
				Q174*	0.13	Novel
TNKS	Tankyrase	8p23.1	5	Amplification		
				Deep deletion		
				E441K	0.23	Novel
				G1013C	0.28	Novel
				R245C	0.26	rs773491393
				V697M	0.85	rs1043487769
				N555KFS*2	0.15	Novel
				S1264N	0.43	Novel
				S132F	0.18	rs774407820
TNKS2	Tankyrase 2	10q23.32	1.8	Amplification		
				Deep deletion		
				G677D	0.05	Novel
				N271S	0.16	Novel
				H597N	0.23	Novel
				V246E	0.52	Novel
				A1062V	0.29	Novel
				A219V	0.45	Novel
PARP6	Poly(ADP-ribose) polymerase family member 6	15q23	0.6	Amplification		
				I213V	0.37	Novel
				E568=	0.63	Novel
TIPARP	TCDD inducible poly(ADP-ribose) polymerase	3q25.31	14	Amplification		
				G239E	0.15	Novel
				H354Y	0.07	Novel

PARP8	Poly(ADP-ribose) polymerase family member 8	5q11.1	10	Amplification		
				Deep deletion		
				S761G	0.79	Novel
				R416T	0.14	Novel
				H426Y	0.12	Novel
				I183S	0.26	Novel
				X476_splice	0.16	Novel
				R488H	0.29	rs1421801606
				R616K	0.16	Novel
				S468C	0.08	Novel
				R88K	0.16	Novel
				E443Q	0.25	Novel
				E532Q	0.47	Novel
				Y581F	0.18	Novel
				Q556*	0.19	Novel
				F340L	0.03	Novel
PARP9	Poly(ADP-ribose) polymerase family member 9	3q21.1	5	Amplification		
				H408Q	0.26	Novel
				G17C	0.49	Novel
				E824Q	0.57	Novel
				R617Q	0.51	rs559272508
PARP10	Poly(ADP-ribose) polymerase family member 10	8q24.3	12	Amplification		
				F906L	0.16	Novel
				R753C	0.22	rs139166854
				A781S	0.23	Novel
				P98S	0.24	Novel
PARP11	Poly(ADP-ribose) polymerase family member 11	12p13.32	4	Amplification		
				T160M	0.21	Novel
				T29K	0.37	Novel
				R296*	0.32	Novel
PARP12	Poly(ADP-ribose) polymerase family member 12	7q34	2.6	Amplification		
				Deep deletion		
				W381C	0.36	Novel
				Q157*	0.28	Novel
				R531*	0.11	Novel
				K428R	0.30	Novel
				C195R	0.27	Novel
				G19Afs*16	0.33	Novel
ZC3HAV1	Zinc finger CCCH-type containing, antiviral 1	7q34	2.4	Amplification		
				Deep deletion		
				R455T	0.37	rs1403439859
				L126H	0.70	Novel
				I574V	0.27	rs150148096
				Q255*	0.07	Novel

PARP 14	Poly(ADP-ribose) polymerase family member 14	3q21.1	7	Amplification		
				N401Kfs*4	0.31	Novel
				S1754L	0.20	Novel
				T1566Nfs*3	0.14	Novel
				I1515M	0.08	Novel
				P988L	0.19	rs771490414
				Q465K	0.53	Novel
				I172V	0.18	Novel
				G5D	0.23	Novel
				E964K	0.20	Novel
				G1135E	0.21	Novel
				D189H	0.18	Novel
				Q1276*	0.15	Novel
				N1099Ifs*17	0.11	Novel
				G1499E	0.17	Novel
PARP 15	Poly(ADP-ribose) polymerase family member 15	3q21.1	5	Amplification		
				Q357H	0.63	Novel
				P438T	0.44	Novel
PARP 16	Poly(ADP-ribose) polymerase family member 16	15q22.31	0.2	W200*	0.20	Novel

TIPARP showed higher frequency of gene amplification, *TNKS* showed more deep deletion. *PARP4, TNKS, PARP8, PARP11, PARP12, ZC3HAV1, PARP14, PARP16* showed truncating mutations. *PARP2* showed inframe mutation. *PARP6, PARP8* showed splice-site mutation. Except *PARP16,* all the other genes had missense mutations. *PARP12* and *ZC3HAV1* showed amplification and deep deletion in the same patients. *PARP14 & PARP15* showed the same pattern amplification in the same patients.

The expression of *TIPARP* was upregulated in HNSCC individuals in comparison to normal individuals. The p value was found to be 1.82 x 10^{-1} which was found to be insignificant (Fig. 2). Upon analysing survival probability based on the Kaplan Meier analysis of *TIPARP* gene expression classified based on race, it was found that low/medium expression in caucasian individuals showed maximum survival rate when compared to the high expression African-American, the p value was found to be p = 0.045 (Fig. 3a). The Kaplan Meier analysis of *TIPARP* expression level classified based on gender showed that low/medium expression male have greater survival rate when compared to high expression females and the p value was found to be p = 0.027 (Fig. 3b).

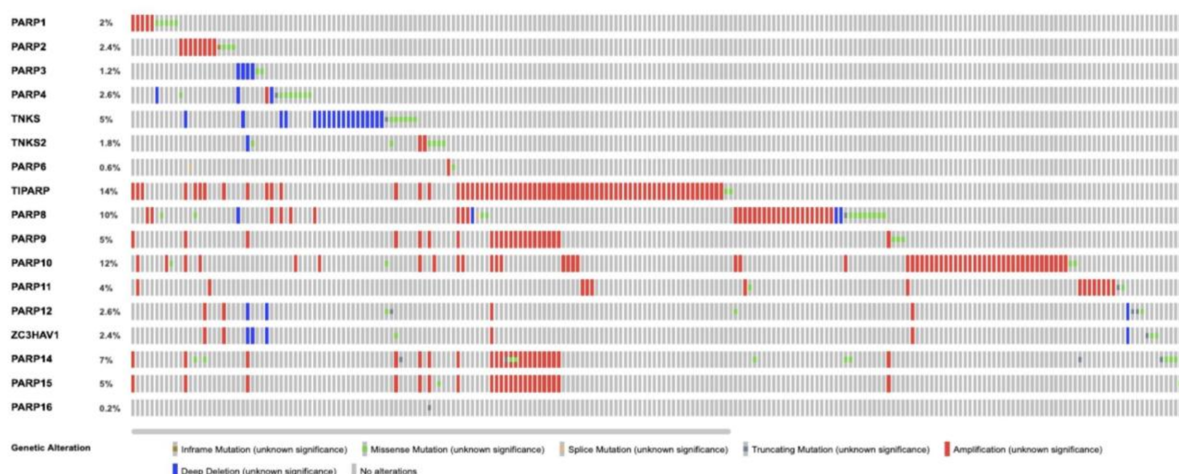

Fig. 1. Showing the oncoprint data that is demonstrating the alterations in the PARP gene family in the HNSCC patients

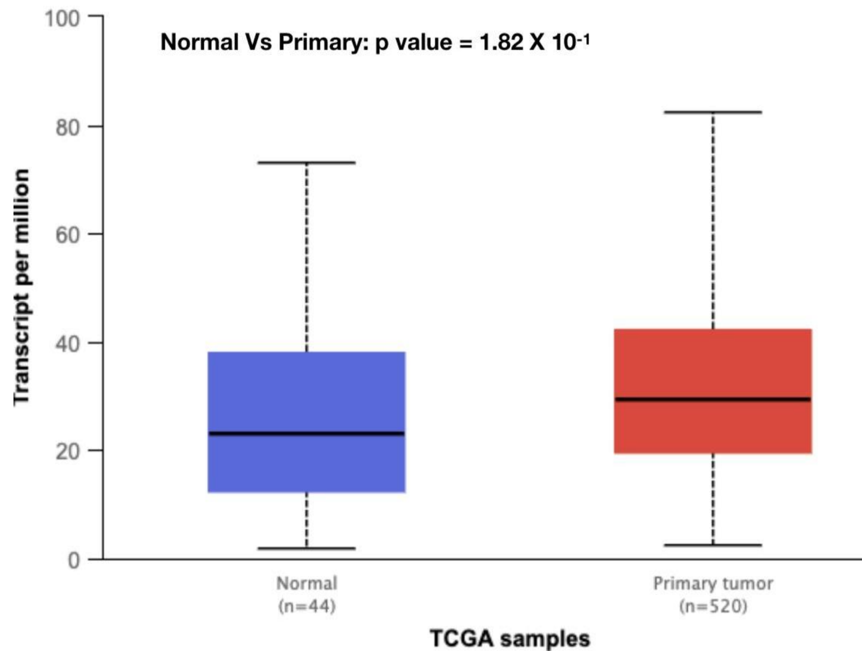

Fig. 2. Box-Whisker plot showing relative expression profile of *TIPARP* gene (Normal vs primary tumor). The X axis denotes the TCGA samples (blue bar indicates normal and red bar indicates primary tumor) and Y axis denotes the transcripts per million values. The comparison of gene expression patterns between normal vs primary tumor was insignificant (p = 1.82 X 10^{-1}). A p value less than 0.05 was considered to be significant

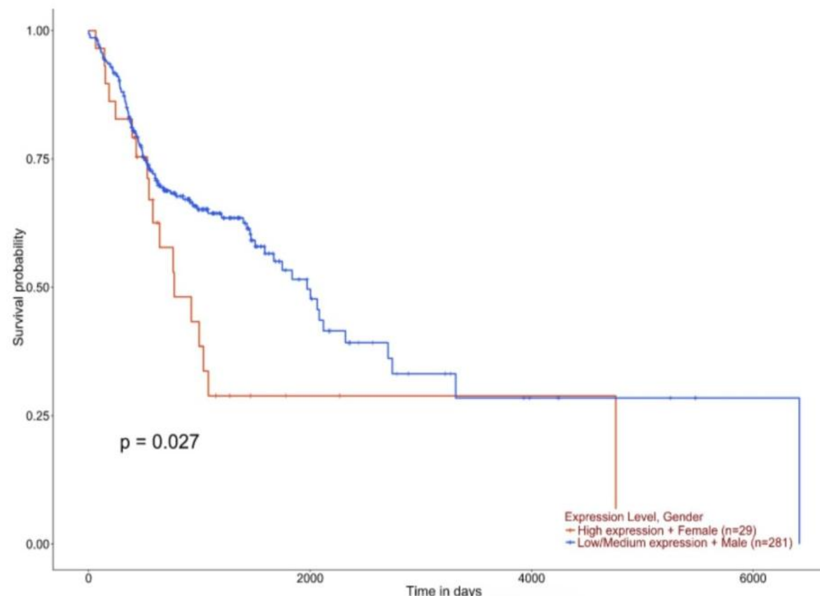

Fig. 3(a). Kaplan Meier plot showing the effect of *TIPARP* expression level classified based on gender of HNSCC patients. The x-axis represents the time in days and the y-axis represents the survival probability. The blue line indicates low expression of *TIPARP* in males and the red line indicates high expression in females. A significant difference in the level of gene expression between the two groups was observed (p=0.027); p<0.05- significant

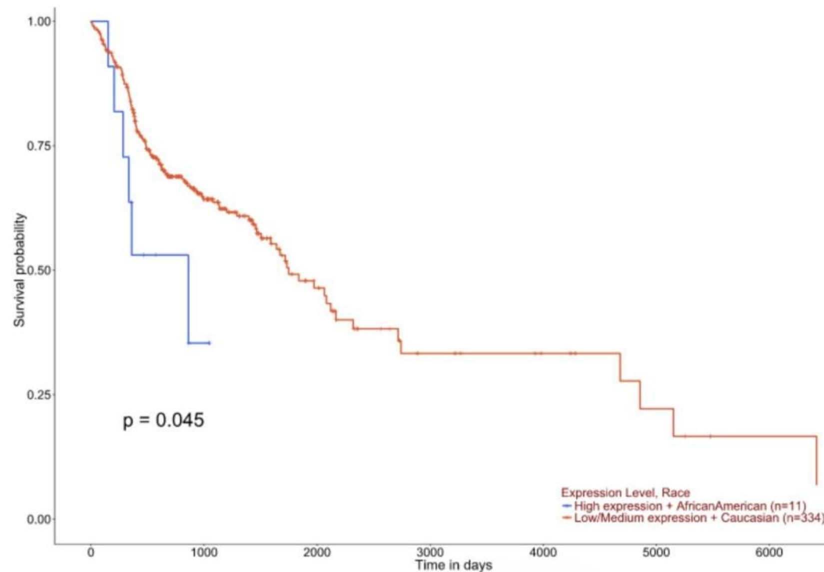

Fig. 3(b). Kaplan Meier plot showing the effect of TIPARP expression level classified based on race of HNSCC patients. The x-axis represents the time in days and the y-axis represents the survival probability. The red line indicates low/medium expression of TIPARP in Caucasians and the blue line indicates high expression in African American population. A significant difference in the level of gene expression between the two groups was observed (p=0.045); p<0.05-significant

4. DISCUSSION

Head and neck squamous cell carcinoma is the most common type of cancer which is diagnosed every year [33]. The study is done to understand the alterations that were observed in the *PARP* gene family and their involvement in HNSCC. This study provides us with information that is already not available and usage of data sources to easily obtain information about patients and perform basic research to accumulate preliminary data. Genetic alteration is a very time consuming procedure when done manually and expensive too. PARP plays an important role in DNA repair pathways (Vyas et al., 2013), with a special emphasis on base excision repair (BER), which is involved in DNA repair of single strand breaks (SSBs). Since in most of the cancer types BER is impaired eventually leading to inhibition of poly (ADP-ribose) polymerase (PARP). This results in the conversion of SSBs to double strand breaks (DSBs).

The expression of *PARP1* is increased in oral squamous cell carcinoma. The expression of PARP was seen at subcellular level. The over-expression in premalignant tumors also paved the way for diagnosed OSCC in the future [34]. According to the study conducted by Maria et al, it was found that the expression of PROX1 gene was found to be expressed as tumor suppressor gene [35]. A study conducted by Gesche indicated that XIAP is involved in the oral squamous cell carcinoma and also the Kaplan Meier curve indicated the XIAP association in unfavourable prognosis of oral squamous cell carcinoma and other curve showing the survival rate that was insignificant [35,36]. The study that was conducted by Yao et al, found that usage of microRNAs in association with OSCC and observed that fibroblast transfers microRNA to oral squamous cell carcinoma cells. Overexpression of miR-34a-5p could lead to tumorigenesis and contribute to the aggressiveness of the cells [37]. Usage of Rab5a was seen in many different types of cancer. A study conducted by Dizhang et al. showed that in 49.3% of OSCC patients Rab5a was overexpressed [37,38]. The gene alteration studies on various genes have also been done for HNSCC and other cancers as well [39,40,41,42,43,44,45].

5. CONCLUSION

The present study brings in a conclusion that *TIPARP* could be considered as a prognostic marker in the case of HNSCC. Although the gene expression pattern between normal and tumor tissues do not produce a significant variation, the

expression level in different races and genders contributed to significant change in the survival of HNSCC patients. More clinical studies have to be carried out to derive an association between *TIPARP* and HNSCC.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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