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High Prevalence of Plasminogen Activator Inhibitor-1 4G/5G Polymorphism among Patients with Venous Thromboembolism in Kerala, India

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Abstract

Venous thromboembolism (VTE) is a multifactorial clotting disorder in which inherited and environmental factors synergistically contribute to its pathogenesis. The aim of this case–control study was to analyze the prevalence of hereditary thrombophilic risk factors, provoking and non-provoking environmental risk factors in patients with VTE from Kerala, India. We have observed a low prevalence of factor V Leiden (7%), prothrombin G20210A (2%), and prothrombin G20030A (2%) mutations and a high prevalence of plasminogen activator inhibitor-1 (*PAI-1*) 4G/5G (52%), *PAI-1* 4G/4G (24%) genotypes in the VTE patients ($n = 147$). Deficiency of anticoagulants, antithrombin (3.4%), and protein C (4.1%) was relatively low. None of the risk factors were observed in 17% of the patients. Majority of VTE patients were younger than 50 years with a median age of 43 years. In conclusion, our results indicate a high prevalence of PAI-1 4G/5G polymorphism among the VTE patients which is in concordance with previous studies in the Asian population. The PAI-1 4G/5G polymorphism could be a potential biomarker for assessing VTE risk, particularly among the Indian population.

Keywords
- venous thromboembolism
- risk factors
- MTHFR C677T
- factor V Leiden
- plasminogen activator inhibitor-1
- prothrombin gene
- C-reactive protein
- genetic mutations

Introduction

Venous thromboembolism (VTE) is a major health concern due to the high morbidity and mortality and high rates of recurrence. Annually, it occurs at a rate of 1 in 10,000 in individuals younger than 40 years and 1 in 1,000 individuals older than 75 years.[1] VTE is usually triggered when the homeostasis between procoagulant and anticoagulant factors is affected and results in the excess thrombin production, which can be due to increased concentration of the clotting factors such as factor V and prothrombin (PT), or deficiency of anticoagulation factors such as protein S, protein C, and antithrombin (AT).[1] The provoking environmental risk factors including pregnancy, cancer, prolonged immobilization, trauma, and surgery and the non-provoking environmental risk factors such as age, sex, race, hormone therapy, obesity, and use of oral contraceptives increase the susceptibility to VTE by stimulating a prothrombotic environment.[1–5]

Among the many genetic variations leading to VTE, G1691A mutation in the factor V gene (*FV* Leiden [*FVL*]),

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C677T mutation in the methylene tetrahydrofolate reductase (*MTHFR*) gene, 4G/5G polymorphisms present at 675 bp upstream of promoter region of the plasminogen activator inhibitor-1 (*PAI-1*) gene, and several mutations in the *PT* gene have been reported in association with VTE.[6–10] The genetic variants associated with VTE vary among the population of different ethnicities. Routine screening for the genetic markers of VTE in most of the laboratories in India involves only FVL and PT G20210A mutations, which have a very low prevalence rate. This case–control study was aimed at identifying the prevalence of the procoagulant risk factors such as *FVL*, *MTHFR* C677T, *PT* 3′ region, *PAI*-1 (4G/5G) polymorphisms, and deficiencies of anticoagulants, protein S, protein C, and AT along with provoking and non-provoking environmental risk factors associated with VTE in patients from Kerala, India.

Methods

Patient Selection

A total of 147 consecutive patients presenting with first or recurring episodes of deep vein thrombosis (DVT) with or without pulmonary embolism (PE) with a follow-up period from 2015 to 2020 and 150 age- and gender-matched healthy controls were included in this study. Patients with known current pregnancy were excluded from the study. VTE was confirmed by ultrasonography/Doppler/computed tomography scan, or magnetic resonance imaging (MRI). Details of the provoking risk factors such as pregnancy, cancer, prolonged immobilization, trauma, and surgery and the non-provoking environmental risk factors such as age, sex, race, hormone therapy, obesity, use of oral contraceptives, ethnicity, and the presence of comorbidities, disease course, number of thrombotic events, geographical data, and total year of illness were obtained from the patient medical records. The study was approved by the Institutional Ethics Committee and was performed at the tertiary care center in Kerala, India.

Detection of Genetic Risk Factors

Genomic DNA was isolated from the patients' blood samples using QIAamp DNA Mini Kit (Qiagen, Germany) as per the manufacturer's instructions and quantified to using BioPhotometer D30 (Eppendorf, Germany). The primer sequences used for the detection of FVL, prothrombin, MTHFR mutations, and PAI-1 genotyping are listed in ►Table 1.

To detect the mutations in the FVL, PT (exon 13, exon 14, and 3′UTR), and MTHFR C677T genes, PCR mix was prepared in a reaction volume of 25 µL containing 10 PM of respective forward and reverse primers, 1× concentration of the EmeraldAmp GT PCR Master Mix (Takara Bio Inc, Japan), and ~100 ng of the genomic DNA isolated from the patient samples as template DNA. The PCR conditions were as follows: an initial denaturation at 94 °C for 5 minutes, 35 cycles of denaturation at 94 °C for 30 seconds, annealing at 55 °C for 30 seconds, extension at 72 °C for 45 seconds, and final extension at 72 °C for 10 minutes. PCR-RFLP method was used to detect FVL and MTHFR C677T mutations. The FV (220 bp) and MTHFR (387 bp) PCR products were subjected to restriction digestion by *Mnl* I and *Hinf* I (Thermo scientific, USA), respectively, and electrophoresed in 3% agarose gels. To detect the gain-of-function mutations G20030A, A20207C, C20209T, G20210A, A20218G, T20219A, C20221T in the 3′ region of *PT* gene, the 486 bp amplicons obtained from the amplification of the PT gene were subjected to cycle sequencing using BigDye Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher, USA) and were analyzed on an ABI 3130 XL genetic analyzer (Applied Biosystems, USA). *PAI-1* 4G/5G genotyping was performed using allele-specific PCR. Amplification of genomic DNA was performed using 1× concentration of the EmeraldAmp GT PCR Master Mix (Takara Bio Inc, Japan), 20 pMPAI-5G or PAI-4G, 10 PM control upstream primer (PAI-1u), and common downstream primer (PAI-2d) with 100-ng genomic DNA as template. The allele-specific PCR conditions included an initial denaturation at 95 °C for 5 minutes; 10 cycles of 95 and 65 °C for 1 minute each; and 23 cycles of 95, 63, and 72 °C for 1 minute each. The PCR products for 4G (139 bp) and 5G (140 bp) specific amplifications along with the 257 bp control band were checked on ethidium bromide–stained 2% agarose gel. The sequence-specific PCR products of PAI-1 4G and PAI-1 5G polymorphism were confirmed by sequencing.

Analysis of Thrombophilia Markers in Plasma

AT activity, protein C activity, protein S activity, and lupus anticoagulant (LA) were measured using the automated analyzer STA Compact 2 (Stago, USA). Analysis of the protein C, protein S, and AT deficiencies was performed before the

Table 1 Primer sequences used in this study

Gene	Primer sequences (5′→3′)	PCR product (bp)	Reference
FVL	F: TGCCCAGTGCTTAACAAGACCA R: CTTGAAGGAAATGCCCCATTA	220	11
PT	F: TTACAAGCCTGATGAAGGA R: CCATGAATAGCACTGGGAGCATTGAAG	486	12
MTHFR	F: AGTCCCTGTGGTCTCTTCATC R: GGAGATCTGGGAAGAACTCAG	387	13
PAI-1	PAI-1u: AAGCTTTTACCATGGTAACCCCTGGT PAI-2d: TGCAGCCAGCCACGTGATTGTCTAG PAI-5G: GTCTGGACACGTGGGGG PAI-4G: GTCTGGACACGTGGGGA	257-IC 140–5G 139–4G	14

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initiation of anticoagulation therapy. Detection of the LA test was based on the results of two tests of different principles, that is, LA-responsive activated partial thromboplastin time and diluted Russell's viper venom reagents as per the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) guidelines. C-reactive protein (CRP) levels were measured using immuno-turbidimetric method on Roche Cobas-8000 using CRP Gen.3 kit (Roche, Germany).

Results

Of the 147 patients, 116 patients (78.91%) had DVT alone and 31 patients (21.09%) had both DVT and PE. Eighty-seven patients (59.2%) had left lower limb thrombosis, 34 (23.1%) had right lower limb thrombosis, 23 (15.6%) had bilateral lower limb thrombosis, and 3 (2.1%) had right upper limb thrombosis. Recurrent thrombosis was observed in 22.4% of the patients. The prevalence of VTE was more among males (62.6%) than in females (37.4%). The median age of the VTE patients was 43 years (range, 21–80 years).

Genetic risk factors of VTE were identified using the genomic DNA isolated from peripheral blood of the patients. PCR-RFLP technique was used to detect FVL and MTHFR C677T mutations. Presence of the 153 bp fragment indicated FVL mutation (►Fig. 1A) while restriction of the 387 bp PCR fragment into 235 bp and 152 bp indicated MTHFR mutation (►Fig. 1B). Sequence analysis of the 3′ region of prothrombin gene revealed two mutations—PT G20210A (►Fig. 1C, D) and PT G20030A (PT-Amrita) (►Fig. 1E, F). PAI-1 4G/5G polymorphisms at the -675 bp of the promoter region were detected using allele-specific PCR (►Fig. 2A, B). The allele-specific PCR products were sequenced to confirm the primer specificity (►Fig. 2C–E).

Analysis of the prevalence of the genetic risk factors in VTE patients revealed that *FVL* mutation had a prevalence of 7% and all the patients with this mutation were heterozygous. *MTHFR* C677T mutation was found in 15% of the patients. *PT* G20210A and *PT*-Amrita (PT G20030A) mutations were detected in 2% of the patients. Both these *PT* mutations were found only in heterozygous condition and only in males. The other rare *PT* mutations A20207C,

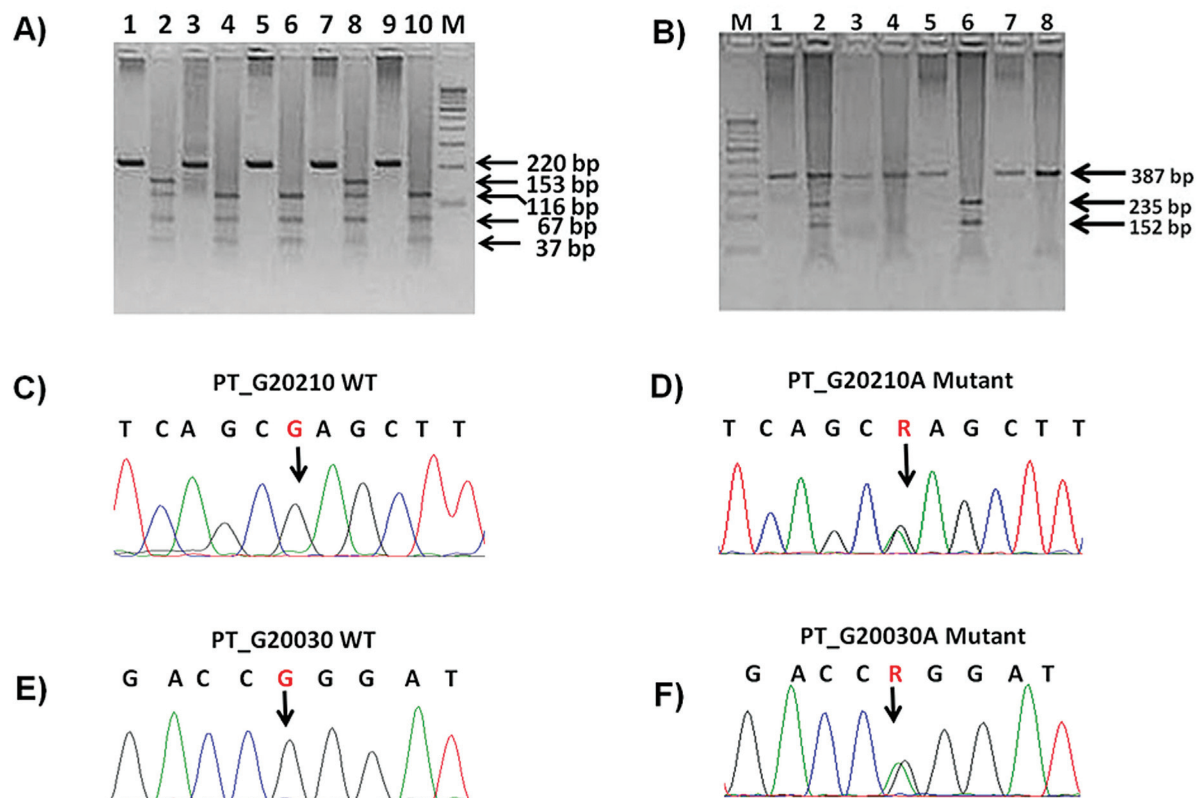

Fig. 1 Detection of genetic variants. (**A**) Agarose gel image showing *factor V* Leiden (*FVL*) mutation analysis by PCR-RFLP. Lanes 1, 3, 5, 7, and 9 show the PCR products of five samples (220 bp); the consecutive lanes 2, 4, 6, 8, and 10 show the restriction pattern after *MnlI* digestion. Lanes 2 and 8: heterozygous *FVL* mutation (153, 116, and 67 bp); lanes 4, 6, and 10: wild-type pattern (116 and 67 bp). (**B**) Agarose gel image showing *MTHFR* C677T mutation analysis by PCR-RFLP. Lanes 1, 3, 5, and 7 show the PCR products of the samples (387 bp); the consecutive lanes 2, 4, 6, and 8 show the restriction pattern after *Hinf* I digestion. Lane 2: heterozygous *MTHFR* mutation (387, 235, and 152 bp); lanes 4 and 8: wild-type pattern (387 bp); and lane 6: homozygous *MTHFR* mutation (235 and 152 bp). Representative electropherograms showing the wild-type *PT* 20210 (**C**) and its heterozygous mutant *PT* G20210A (**D**), wild-type *PT* 20030 (**E**) and its heterozygous mutant *PT* G20030A (**F**).

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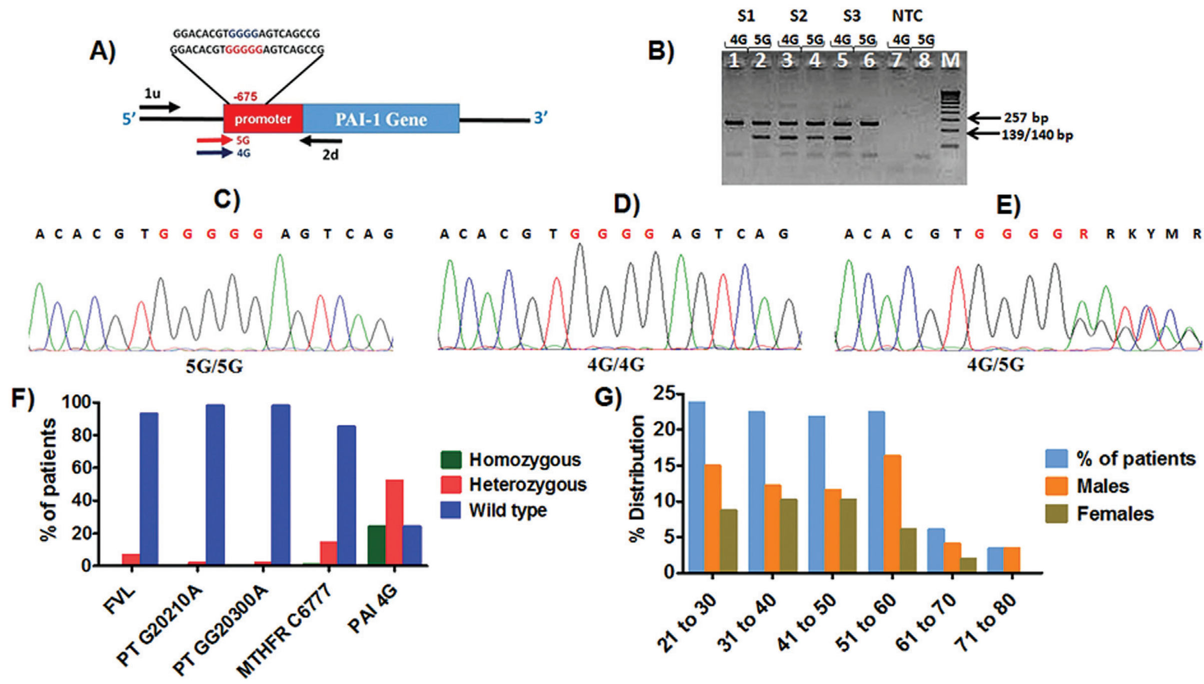

Fig. 2 Detection of PAI-1 polymorphisms by allele-specific PCR method. (**A**) Schematic representation of *PAI-1* 4G/5G allele-specific PCR. (**B**) Agarose gel image of the allele-specific PCR products of *PAI-1*. Lanes 1, 3, 5, and 7 show the 4G-specific PCR products (139 bp) and the consecutive lanes 2, 4, 6, and 8 show 5G-specific PCR products (140 bp) of the samples S1, S2, S3, and NTC. S1: homozygous for 5G allele; S2: heterozygous for 4G and 5G alleles; S3: homozygous for 4G allele; NTC: no template control. Lane 9: M-100 bp ladder. Amplification of 257 bp by the PAI-1u and 2d primers acts as a positive control. Representative electropherograms showing *PAI-1* genotypes 5G/5G (**C**), 4G/4G (**D**), and 4G/5G (**E**), R:A/G; K:G/T; Y:C/T; M:A/C. (**F**) Prevalence of genetic variants associated with VTE. (**G**) Incidence of VTE in patients in different age groups by gender.

C20209T, A20218G, T20219A, C20221T were not detected in any of the patients. *PAI*-1 4G/5G polymorphisms were the most prevalent genetic variants (76%) associated with VTE: of which *PAI*-1 4G/4G genotype was found in 24% of patients, while *PAI*-1 4G/5G genotype was found in 52% of patients (►**Fig. 2F**). 65.3% of the patients had only one of the genetic risk factors (*PAI-1* 4G/4G: 17.7%; *PAI-1* 4G/5G: 42.9%; *FVL*: 2%; *PT* G20210A and G20030A: 0.7%; *MTHFR* C677T: 2%). More than one predisposing genetic risk factor was present in 17.6% of the patients (double mutations: 15.6%; triple mutations: 2%): for example, majority of the patients harboring heterozygous *MTHFR* C677T mutation also carried *PAI-1* 4G/4G genotype and all patients positive for *PT* G20210A mutation also had *PAI-1* 4G/5G genotype. None of the tested genetic risk factors were present in 17% of the patients. The allele frequencies of *PAI-1* 4G were 0.5 and 0.4 in patients and healthy controls, respectively, while for *PAI-1* 5G allele frequencies were 0.5 and 0.6, respectively. *FVL* and *PT* mutations were not detected in any of the healthy controls. *MTHFR* C677T mutation was found in 3.2% of the healthy controls.

Analysis of the plasma levels of natural anticoagulant factors in the VTE patients revealed that 10.9% of the patients had protein S deficiency (<50% protein S), 4.1% had protein C deficiency (<70% functional protein C), 3.4% had AT deficiency (enzymatic activity < 80%), and homocysteine levels were elevated more than 20 µmol/L in 7.5% of the patients. LA was positive in 12.2% of patients. CRP levels were elevated more than 3 mg/L in 71% of patients.

The common provoking and non-provoking risk factors associated with VTE were surgery (4.8%), immobilization (2.7%), long distance travel (2%), cancer (2%), pregnancy and postpartum period (2%), trauma (2%), and obesity (2.7%). More males than females were affected with VTE at advanced age (50–80 years; ►**Fig. 2G**). Systemic hypertension (23.8%), diabetes mellitus (17.7%), and dyslipidemia (10.2%) were the most common comorbidities associated with VTE.

Additive risk effect was found in patients with combined procoagulant genetic risk factors. Patients with triple genetic risk factors (FVL-MTHFR-PAI-4G; FVL-PT G20030A-PAI-4G; FVL-MTHFR-PAI-4G/5G) had initial episodes of thrombosis at a much younger age (<30 years) and have presented with severe form of thrombosis than patients harboring single genetic risk factor. DVT in these patients manifested in almost all deep veins (iliac veins, superficial femoral vein, popliteal vein, saphenous vein, anterior and posterior tibial vein).

Discussion

Both genetic and environmental risk factors contribute to VTE and these risk factors do not always act in isolation. Several Indian studies have reported a cumulative VTE incidence ranging from around 1 to 2 per 1,000 individuals between

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1996–2005 and 2012–2017, respectively.[15,16] In this study, we have analyzed the causative risk factors of VTE in our patient population from Kerala, India. A low prevalence of *FVL* mutation and a complete absence of *PT* G20210A have been reported earlier in the Indian population.[17,18] In our study, *FVL* mutation was found in around 7% of the patients. *PT* G20210A mutation which was reported to be extremely rare in Indian population was present in 2% of our patients. The *PT* G20030A mutation that results in the replacement of arginine by glutamine at position 553 (R553Q) in the highly conserved Na^+ binding loop of prothrombin and enhances the conversion of prothrombin to thrombin[12,19] was also found in 2% of the patients. Interestingly, all the patients with *PT* G20210A and *PT* G20030A mutations were males. Of note, the primers used for detecting the gain-of-function mutations in the 3′-end of the *PT* gene (exon 13, intron 13, exon 14, and the 3′UTR) would detect the most common mutation G20210A along with other rare mutations including the G20030A, A20207C, C20209T, A20218G, T20219A, and C20221T mutations that have been reported to be associated with thrombosis. However, rare mutations that might have been present elsewhere in the *PT* gene were not explored in this study. *MTHFR* C677T mutation was detected in 15% of our patients which was similar to the observed frequencies from previous studies in other parts of India.[20,21] A high frequency of *PAI-1* 4G/4G and 4G/5G genotypes was associated with DVT in our patients compared with the 5G/5G genotype which is in concordance with the previous reports on the prevalence of *PAI-1* 4G/5G from North Indian, Chinese, and the Caucasian populations.[9,14,22,23] Deficiency of the anticoagulants AT and protein C was very low in our patients which is consistent with the study on the young VTE patients from Western India.[18]

VTE is generally considered as an old-age disease.[24] However, studies have shown that majority of the Indians with VTE were younger than Caucasians.[18] In our study too, 68% of the VTE patients were younger than 50 years. The most common comorbidity associated with VTE in our study was hypertension, followed by diabetes mellitus and dyslipidemia. These data are comparable to previous reports on the VTE population of India.[25] In this study, *PAI-1* 4G/4G and 4G/5G genotypes were found as the most common genetic risk factors associated with VTE. 4G/5G polymorphisms present at 675 bp upstream of promoter region of the *PAI-1* gene prevents the binding of transcription repressor in the mutated *PAI-1* gene (4G) leading to enhanced transcription of *PAI-1* and significantly increased PAI-1 levels. PAI-1, a member of the super family of the serine protease inhibitors, inhibits tissue-type plasminogen activator (t-PA) and urinary-type PA and arrests their fibrinolytic activity resulting in a thrombotic state.[26–29] Binding of CRP to the Fcγ receptors (CD32, CD64) on endothelial cells has been shown to upregulate the Rho/Rho-kinase pathway and contribute to CRP-induced PAI-1 expression and alter the fibrinolytic balance of endothelial cells.[30] Majority of the patients in this study had elevated levels of CRP. However, it should be noted that CRP is a general inflammatory marker and may not be useful per se either in the diagnosis of acute venous thrombosis or in predicting future venous thrombosis.

This is the first study on the hereditary thrombophilic risk factors prevalent among the VTE patients from Kerala, a state on the south-western coast of India with Dravidian ethnicity. The main limitation of the current study is the small sample size. Although the power of this study is limited, the high frequency of *PAI-1* 4G/4G and 4G/5G genotypes observed in the majority of our VTE patients suggests that *PAI-1* 4G/5G polymorphism could be a potential biomarker for assessing VTE risk among the Indian population. Future studies with larger sample size involving multiethnic population that represents the genetic heterogeneity of the Indian population are required to further establish the association between *PAI-1* 4G/5G polymorphisms and VTE risk.

Conflict of Interest

The authors declare that they have no conflict of interest.

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