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Role of matrilin-1 (*MATN1*) polymorphism in class III skeletal malocclusion with mandibular prognathism in Deutero-Malay race: a case-control study

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Abstract

Background: Several studies have identified different genes that control the final dimension and structure of the mandible. Prognathism of the mandible is thought to correlate with these genes; however, no specific gene has been assigned as a risk factor due to various genome-wide scan results in different races. Previous studies that involved the Han ethnic group in China and Korea suggested matrilin-1 (*MATN1*) polymorphism as the contributor for mandibular prognathism. To date, no study has been conducted to understand the role of *MATN1* in Deutero-Malay population. This study aimed to detect *MATN1* gene polymorphism in the promoter and exon 5 regions, which is a proposed risk factor in class III skeletal malocclusion with mandibular prognathism in Deutero-Malay population. This was a case-control study with purposive sampling method that involved 47 class III skeletal malocclusion subjects with mandibular prognathism (case group) and 47 class I skeletal relation subjects (control group) performed in the Molecular Genetics Laboratory of Faculty of Medicine, Universitas Padjadjaran, Indonesia. DNA isolated from buccal mucous epithelia and *MATN1* gene was amplified using the polymerase chain reaction (PCR) and sequencing technique. Data were then analyzed statistically to observe the frequency of allele/genotype *MATN1* in class III skeletal malocclusion and mandibular prognathism patients in comparison with the normal mandibular as well as to identify the risk factor of mandibular prognathism.

Result: The frequency of the 354 T > C(rs20566) CC genotype gene polymorphism in the case group was significantly higher than in the control group. The odd ratio (OR) value of the case group was also higher than in the control group ($\chi^2 = 4.89$; $p = 0.027$; OR = 6.27).

Conclusions: Our results show that the polymorphism of 354 T > C in the exon 5 region of the CC genotype *MATN1* gene is a risk factor for class III skeletal malocclusion with mandible prognathism in Deutero-Malay population.

Keywords: Deutero-Malay race, *MATN1* gene polymorphism, Skeletal malocclusion class III, Mandibular prognathism

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Background

Malocclusion is a term used to represent the lack of growth harmony of dental and facial skeletal structures, especially the growth harmony of the maxilla and mandibular. Skeletal malocclusion is classified into three groups, i.e., class I, class II, and class III malocclusions. Class I skeletal malocclusion describes a normal maxilla and mandible relation with a clinically flat facial profile. Class II skeletal malocclusion is declared when the maxilla is relatively more protruded than the mandible with convex facial profile while the class III facial malocclusion represents a condition when the mandible is relatively more protruded than the maxilla with a relatively concave facial profile. When the mandible overgrows in the sagittal direction resulting in a clinically observed protruded chin, the term mandibular prognathism is used [1–4].

Class III skeletal malocclusion, one of the abnormalities in the craniofacial development that affect the esthetics, is an imbalanced maxilla and mandible relation, indicated by a concave face and prominent chin. The prevalence of this malocclusion, which causes a psychosocial disorder, is around 1-15% worldwide with the Asian population prevalence as the highest and the Caucasian population prevalence as the lowest [1–4]. The prevalence of class III skeletal malocclusion in Indonesian subjects visiting the Oral and Dental Hospital, Universitas Padjadjaran/RSGM UNPAD Bandung, Indonesia, for orthodontic consultation and treatment is around 12.42% [5].

Several studies have shown that the etiology of class III skeletal malocclusion is mostly associated with genetics and racial factors. The difference in the gene cluster that reflects the anteroposterior and vertical dimensions of certain craniofacial structures reflects the involvement of different genes in controlling the final dimension and structure of the mandible; however, the specific genes that are involved in this control is still unclear due to different results in genome-wide scan in different population [6–13].

Xue et al. reported that the Erythrocyte Protein Band 4.1, a main structural element of erythrocyte membrane skeleton in humans encoded by *EPB41*, plays a role in mandibular prognathism occurrence in Asian ethnicity, yet its role remains elusive. Another study demonstrated that 14q24.3-31.2 locus and transforming growth factor β3 (*TGFβ3*) associated with mandibular prognathism were found in the Han population of China. They are deemed to be the mediator hormone of both extracellular and cellular proliferations. Some studies showed that class III skeletal malocclusion is a polygenic disease resulted from the interaction between genes and environmental factors, yet the family tree of individuals with mandibular prognathism showed the possibility of class III skeletal malocclusion as a monogenic dominant phenotype [10, 13–15].

Recently, the *MATN1* gene has been studied for its role in bone development and its related diseases [16–19]. The *MATN1* gene plays a role in the regulation of matrilin-1 synthesis in endochondral skeletal growth. A study by Jang et al. in the Korean population shows that 7987 G > A and 8572 C > T *MATN1* polymorphisms contribute to mandibular prognathism. These findings show an important role of *MATN1* as a biological marker in mandibular prognathism [20]. Matrilin-1, a protein secreted by chondrocytes predominantly expressed in cartilage, is considered to be able to form the filamentous tissue that stabilizes the extracellular matrix. It is responsible for the formation of endochondral bone by inducing long bone growth, which can also become a marker for mandibular prognathism [11, 18, 21, 22].

Studies on the genetics of malocclusion have never been conducted in Indonesia despite the importance of a clear understanding on malocclusion etiology and risk factors to support its diagnosis and prognosis to provide a more effective and efficient treatment. This study is expected to give information on whether the *MATN1* gene polymorphism is a risk factor of class III skeletal malocclusion with mandibular prognathism, which will be invaluable information for orthodontic treatment.

Methods

This was a case-control study with a purposive sampling method. The population in this study were patients of Deutero-Malay origin with class III skeletal malocclusion and mandibular prognathism and those with class I skeletal relation who visited orthodontist private practices, orthodontic specialist's clinics, and dental hospitals for orthodontic treatment in Bandung City from 2009 to 2014. Subjects with class III skeletal malocclusion with mandibular prognathism were included in the case group while subjects with class I skeletal relation were assigned to the control group. The inclusion criteria for the case group were Deutero-Malay individual with class III skeletal malocclusion and mandibular prognathism over the age of 16 while the inclusion criteria for the control group were Deutero-Malay individual with class I skeletal relation without mandibular prognathism or family history of mandibular prognathism and over the age of 16. Patients with trauma, systematic diseases, and congenital or acquired growth and development problem affecting the maxillofacial region were excluded from the study.

Subjects were physically measured for the overall dental condition, first molar relation, and facial profile. Cephalograms of subjects were assessed with Steiner analysis for tracing and angular measurement. The reference points used for Steiner analysis were S (sella) in the

middle of sella turcica; Na (nasion) in the outmost anterior spot of frontonasal suture; A (subspinale) that represents the inmost spot of alveolar curvature between the anterior nasal spine and prosthion; and B (supramental) that represents the inmost spot on the anterior contour from the mandibular symphysis between interdental and pogonion. For the Steiner analysis, the SNA, SNB, and ANB on Deutero-Malay subjects were decided by defining an ANB angle of 2 ± 2° as the normal angle or class I skeletal relation and that an angle of more than 4° and below 0° were classified as class II skeletal malocclusion and class III skeletal malocclusion, respectively. An SNA angle of the maxilla of 82 ± 4° was considered normal and the maxillary prognathism was determined when the angle exceeded 86°. An SNB angle of the mandible of 80 ± 4° was considered normal while mandibular prognathism was determined when the value exceeded 84° (Fig. 1).

MATN1 polymorphism detection

DNA was isolated from buccal mucous epithelia and soaked in PBS with pH 7.2. The detection of matrilin-1 (*MATN1*) polymorphism in exon 5 region was performed with polymerase chain reaction (PCR). A specific primer was used to amplify the DNA (Homo sapiens, source: HGCN Symbol; Acc 6907. Gene ID: ENSG00000162510). Information and identification of SNPs were obtained from Ensembl (www.ensembl.org).

The polymorphism of *MATN1* observed in exon 5 were 354 T > C(rs20566), 1136G > A (rs181457111), 1150 T > C(rs376020917), 1156C > T(rs201283860), and 1157C > T(rs371564845). Primers used in this study were F. 5′ TCCTACATGGAGAAGGGCAC 3′; R. 5′ GTGAAGACACAATGCCCCACCTT 3′. The PCR profile included pre-denaturation at 95 °C for 4 min; denaturation at 95 °C for 30 s; annealing at 60 °C for 30 s; elongation at 72 °C for 30 s; and past extension at 72 °C for 10 min in 30 cycles. In the first cycle, the denaturation was extended to 5 min while in the end cycle the extension was extended to 3 min.

The PCR products were diluted in buffer solution containing 0.25% bromophenol blue and 40% b/v which was electrophoresed through agarose 2% at 100 V for 1 h. DNA fragments were then stained with gel red, visualized with

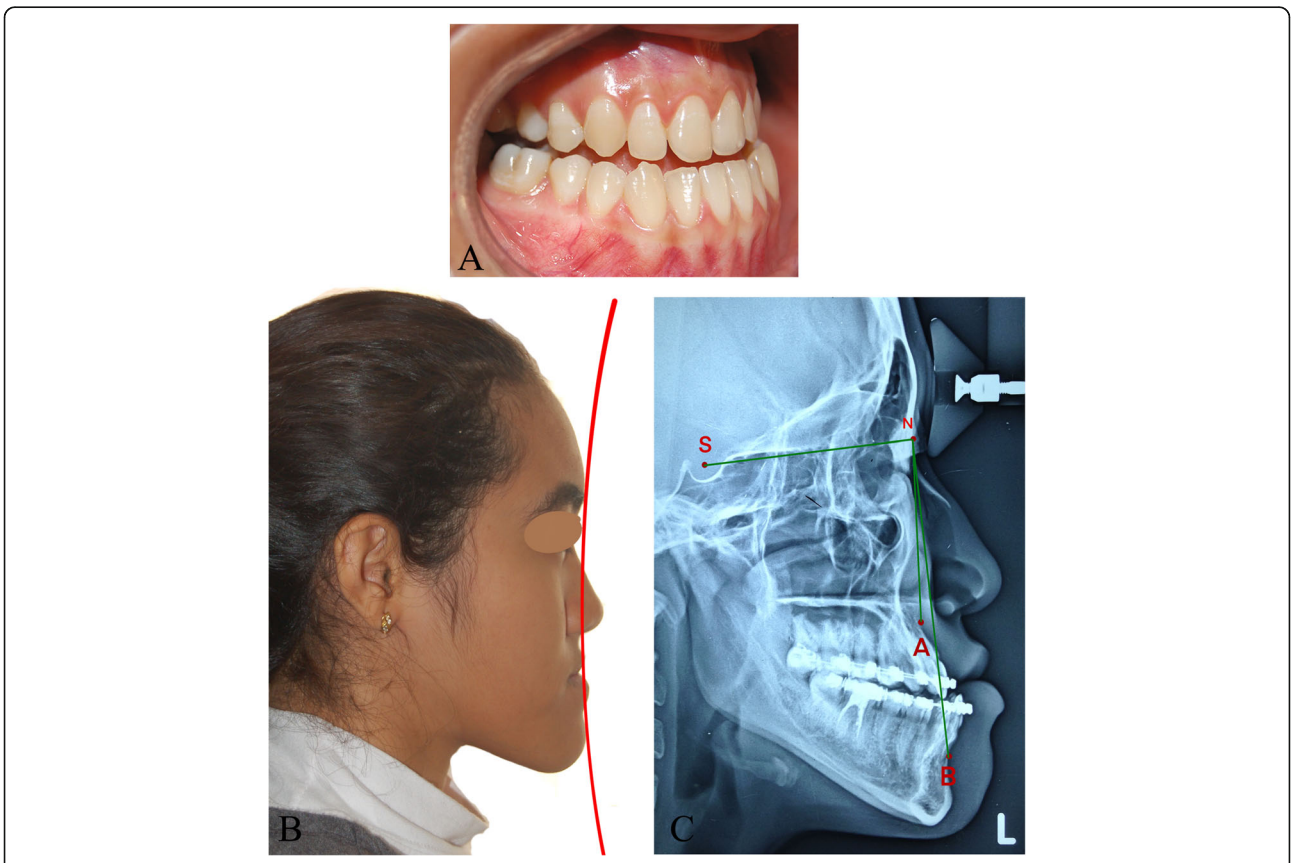

Fig. 1 Class III skeletal malocclusion with mandibular prognathism. **a** Intraoral side, where crossbite anterior is observed and the mandible is more protruded than the maxilla. **b** The facial profile is concave, with a protruded chin caused by mandibular overgrowth. **c** Cephalometric analysis showing an SNB angle that is larger than 82° and an ANB angle that is less than 0°

UV transilluminator, and captured with a special polaroid. The DNA fragment was then sequenced with an Automatic DNA Sequencer. Results were then compared to the human nucleotide in the DNA Bank using BIOEDIT.

Data analysis

Statistical analysis was conducted to observe the frequency of allele/genotype of the *MATN1* gene in class III skeletal malocclusion and mandibular prognathism patients compared to normal to explore the possibility that it may be a risk factor of mandibular prognathism. Data were analyzed using the latest version of SPSS.

Ethical clearance

Written informed consents were obtained from all subjects. The ethical review boards of the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran Indonesia, approved this study.

Results

This study involved 47 subjects, 10 males and 37 females, with class III skeletal malocclusion with mandibular prognathism in the case group. The average age of subjects in this group was 23.33 ± 10.29 years old. The control group consisted of 47 subjects, 5 males and 42 females, with class I skeletal relation with an average age of 21.07 ± 3.95 years old. There were no significant differences in age and sex between the case and control groups. Figure 2 presents the result of the PCR electrophoresis of the exon 5 region of the *MATN1* gene, showing a single band of 130 base pairs under the 200 bp mark. The process was then followed by DNA sequencing of the PCR products. Based on the sequence, genetic variation was found in the exon 5 region of the *MATN1* gene which was 354 T > C(rs20566).

DNA sequence and genetic variations were detected with Sequence Alignment Editor tools in BioEdit (Fig. 3). The genetic variation of heterozygous GA or its counterpart, CT, is depicted in Fig. 3. The genetic variation was indicated by circled letters and overlapping black and green curves (Fig. 3a) with the genetic variation of GG or CC indicated by black curves (Fig. 3b). As shown in Fig. 2c, the AA or TT was in normal condition as indicated by single green curves.

Based on Table 1, a significant difference was identified between the frequency of 354 T > C(rs20566) CC genotype gene polymorphism in the case group (48.9%) and in the control group (26.2%) ($p = 0.027$). This result indicated a higher prevalence of CC genotype polymorphism in the case group compared to the control group. Thus, CC genotype was determined as the risk factor of mandibular prognathism in class III skeletal malocclusion. The odd ratio (OR) value showed that the polymorphism of 354 T > C *MATN1* gene CC genotype was 6.27-fold higher in the case group than in the control group.

There was no significant difference between the frequency of 354 T > C(rs20566) CT genotype gene polymorphism in the case group (46.8%) and control group (59%) ($p > 0.05$). This means that the CT genotype gene polymorphism occurred equally in both groups. The OR value of 2.64 reflected that the CT genotype polymorphism in the case group was 2.64-fold higher than that in the control group, yet it was not a risk factor for mandibular prognathism in class III skeletal malocclusion ($p > 0.05$).

There was a significant difference between the frequency of C allele in the case group (72.3%) when

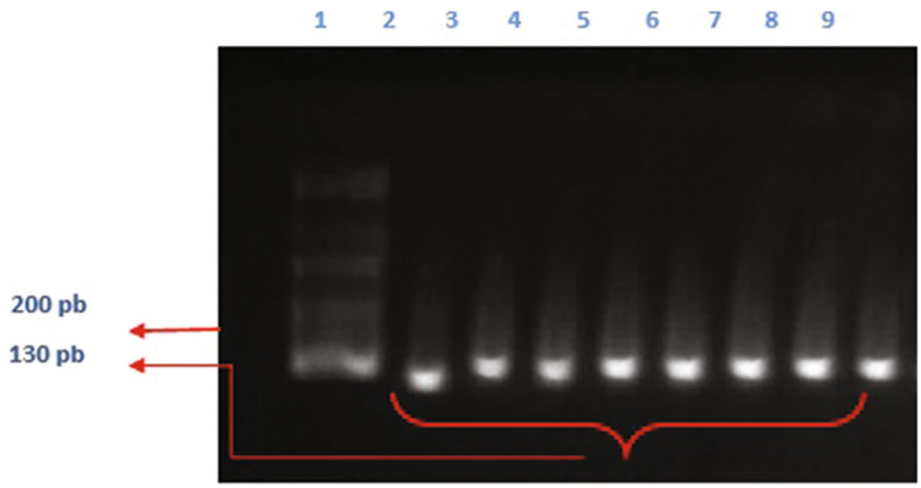

Fig. 2 Electropherogram of PCR exon 5 regions of the *MATN1* gene. The result of PCR optimation in exon 5 region of *MATN1* is a PCR product with a singular ribbon containing 130 base pairs (bp). Line 1 demonstrates the ladder 100 pattern while line 2-9 present the PCR products of samples

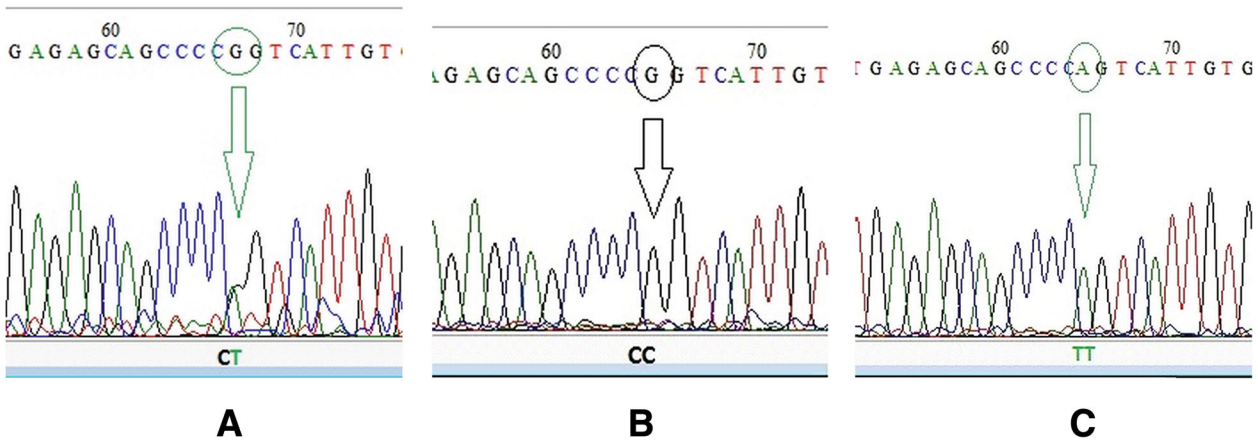

Fig. 3 Genetic variations of SNPs −354 T > C (20566). **a** heterozygous GA or its counterpart CT, **b** homozygous GG or CC in the same position as CT, **c** homozygous AA or TT in normal condition

compared to the control group (55.9%) which indicated that the prevalence of the C allele polymorphism was higher in the case group than in the control group ($p < 0.05$; $p = 0.022$). There was no genetic variation on 1136G > A (rs181457111), 1150 T > C(rs376020917), 1156C > T(rs201283860), and 1157C > T(rs371564845).

Discussion

Class III skeletal malocclusion is known as one of the complex malocclusion types by orthodontists. The number of failures in growth modification with relapsing skeletal malocclusion class III due to the lack of attention to genetic etiology. Treatment that involves genetic factors through early detection using an appropriate marker is therefore needed, including the one that uses gene polymorphism. Studies on heredity factors as the etiology of mandibular prognathism and development of genetics emphasizes on finding gene candidates for mandibular prognathism [12, 13, 23–26].

Several gene candidates have been reported in previous studies as the genetic factors in skeletal malocclusion class III and mandibular prognathism. Referring to studies on various ethnicities, the genes that are suggested to correlate with mandibular prognathism are located in different loci. One of the loci commonly found in Asian is the *MATN1* gene locus 1p35 [12, 13, 15, 21, 25]. No study on genetic factors in the etiology of skeletal malocclusion class III mandibular prognathism has been done in Indonesian subjects; hence, the involvement of heredity factors in this disorder remains unknown.

Genetic variation detected in this study was single nucleotide polymorphisms (SNPs), which is a DNA sequence that undergo alteration on a single nucleotide (A, G, T, and C) in the genome. Polymorphism of exon 5 regions of the *MATN1* gene, 354 T > C(rs20566) CC genotype, is the risk factor of mandibular prognathism in the Deutero-Malay race in Indonesian subjects. No CC genotype was identified in the control group. These findings support the finding in a previous study on Korean subjects, showing that rs20566 can be a marker in mandibular prognathism in Korean subjects. If 354 T > C(rs20566) is indeed a risk factor in mandibular prognathism, it can then be used as a biomarker for the Deutero-Malay race. Several studies reported similarities of a locus involved in mandibular prognathism in some Asian ethnicities. These studies explain the correlation between mandibular prognathism in Deutero-Malay and the Korean races [20, 27–29].

This study is the preliminary study on the role of *MATN1* polymorphism of several SNPs in exon 5 region on skeletal malocclusion class III mandibular prognathism in the Deutero-Malay race in Bandung, Indonesia. Gene polymorphism often varies among ethnicities,

Table 1 Frequency of genotype/allele and polymorphism of *MATN1* gene 354 T > C(rs20566) as a risk factor of malocclusion skeletal class III mandibular prognathism in case ($n = 47$) and control groups ($n = 47$)

	Case Sum (%)	Control Sum (%)	χ^2	[a]*p* value	OR	CI 95%[b]
354 T > C genotype						
TT	2 (4.3%)	6 (14.3%)				
CC	23 (48.9%)	11 (26.2%)	4.89	**0.027**	**6.27**	1.08-36.24
CT	22 (46.8%)	25 (59%)	1.32	0.25	2.64	0.48-14.45
Allele						
T	26 (27.7%)	37 (44.1%)				
C	68 (72.3%)	47 (55.9%)	5.21	**0.022**		

OR odd ratio
[a]Based on *p* value of < 0.05
[b]Confidence interval 95%

which requires further study to observe such events in other races. Moreover, it is also important to confirm the correlation between polymorphism of the *MATN1* gene in another exon in mandibular prognathism.

Conclusion

Polymorphism of 354 T > C, exon 5 region *MATN1* of CC genotype is a risk factor of skeletal malocclusion class III with mandibular prognathism in Deutero-Malay race in Bandung, Indonesia, and can be used as the biomarker for this condition. This makes *MATN1* a potential gene for mandibular overgrowth disorder detection.

Abbreviations

A: Adenine; ANB: A point-nasion-B point; bp: Base pair; C: Citosin; CI: Confidence interval; DNA: Deoxyribonucleic acid; *EPB41*: Erythrocyte Protein Band 4.1; G: Guanine; HGCN: HUGO Gene Nomenclature Committee; ID: Identity; *MATN1*: Matrilin-1; OR: Odd ratio; PBS: Phosphate-buffered saline; PCR: Polymerase chain reaction; SNA: Sella turcica-nasion-A point; SNB: Sella turcica-nasion-B point; SNPs: Single nucleotide polymorphisms; SPSS: Statistical Package for the Social Sciences; T: Thymine; *TGFβ3*: Transforming growth factor β3; UV: Ultraviolet; V: Volt

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Authors' contributions

AL, AM, EM, and BT conceived and planned the experiments. AL, AM, EM, and LP carried out the experiments. AL, AM, EM, LP, and BT planned and carried out the simulations. AL and EM contributed to sample preparations. AL, AM, and EM contributed to the interpretation of the results. AL, AM, EM, BT, and ADZ wrote the manuscript and provided critical feedbacks which helped shaped the research. All authors have read and approved the manuscript.

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Availability of data and materials

The data that support the findings of this study are not available for sharing. The data are not publicly available due to restrictions from the funding organization who owns all the collected data based on the agreement of the Risbin Iptekdok Project grant.

Ethics approval and consent to participate

Ethics committee approval was received for this study from the Health Research Ethics Committee, Faculty of Medicine Universitas Padjadjaran, and Dr. Hasan Sadikin Hospital, Indonesia, with ethical clearance number 314/UN6.C2.1.2/KEPK/PN/2013. Informed consent was obtained for this study. Subjects were given verbal information containing brief explanation about the general outline of the study. The detailed information was given through the written informed consent form. Subjects then signed the statement of willingness part of the written informed consent form.

Consent for publication

Not applicable. The manuscript does not include details, images, or videos relating to an individual person or a group of people which may identify said persons.

Competing interests

The authors declare no potential conflicts of interest concerning the authorship and/or publication of this article.

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