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Lack of association between *PAX6/SOSTDC1/FAM20B* gene polymorphisms and mesiodens

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Abstract

Background: The purpose of this study was to analyze the association between the genetic polymorphism of genes (*PAX6*, *SOSTDC1*and *FAM20B*) and the susceptibility to mesiodens.

Methods: This study was carried out on 50 patients with mesiodens and 50 controls. The family history of each patient with mesiodens were recorded. Genomic DNA was extracted from saliva samples, and single nucleotide polymorphisms were detected in all exons and exon/intron boundaries of *PAX6*, *SOSTDC1* and *FAM20B* using Sanger sequencing. The data were analyzed using pearson chi-square test with theoretical frequency ≥ 5. For theoretical frequency less than 5 but at least 1 (≤20% cell), the data were analyzed by continuity correction. For the rest, Fisher's Exact test was used. A *P*-value< 0.05 was considered statistically significant. The Odds ratio (OR) and confidence intervals (CI) were recorded.

Results: Three polymorphisms were detected in *PAX6*. Two polymorphisms were detected in *SOSTDC1*. Twenty-nine polymorphisms were detected in *FAM20B*. Although, the T allele of *FAM20B* (rs3766626) appears to be associated with mesiodens ($P = 0.051$), there were no significant differences of *PAX6/SOSTDC1/FAM20B* gene polymorphisms between the two groups. The T allele of *FAM20B* (rs3766626) was associated with susceptibility to two mesiodens ($P < 0.001$; OR = 8.333; CI = 2.516–27.600).

Conclusions: Lack of association between *PAX6/SOSTDC1/FAM20B* gene polymorphisms and mesiodens in the population studied was detected. Further studies with large samples on T allele of *FAM20B* (rs3766626) are needed.

Keywords: Mesiodens, *PAX6*, *SOSTDC1*, *FAM20B*, Genetic polymorphism

Background

Mesiodens is the most common supernumerary teeth located in the central position of the upper or lower jaw [1]. Mesiodens can be either erupted or impacted in alveolar bone placed and oriented vertically, horizontally or in an inverted manner [2, 3]. The prevalence of mesiodens in the population ranges from 0.09 to 2.2%, according to previous studies [4–6]. A series of clinical complications can be caused by mesiodens, including malposition or delayed eruption of the permanent incisors or the formation of a dentigerous cyst [7–9]. However, the etiology of mesiodens is still unclear.

An increasing number of studies indicate that genetic polymorphisms are associated with oral diseases. For instance, in Polish children, the prevalence of the AG genotype of the Enamelin (*ENAM*) gene (rs12640848) was higher in subjects with dental caries compared to that in controls [10]. The polymorphism of COX2 -765G/C had significant influence on periodontitis risk [11]. The genetic polymorphism of axin 2 (*AXIN2*) and Gremiln-2 (*GREM2*, also called *PRDC*) were related with tooth agenesis [12, 13].

Studies have shown that several genes can result in the formation of mesiodens. The Paired box gene 6 (*PAX6*) mutant in rats can result in the formation of a supernumerary upper incisor [14]. The inactivation of Family with sequence similarity member 20-B (*FAM20B*) in the

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Table 1 Amplification and sequencing primers

ID	Primer sequences	Amplicon size (bp)	Sequencing size (bp)
PAX6 exon-1 F	CAAACGGACCAATTGCACCA	432	432
PAX6 exon-1 R	GGTTGGTGTGTGAGAGCAATTCTC		
PAX6 exon-2 F	CAGAGGTCAGGCTTCGCTAA	449	449
PAX6 exon-2 R	TCGCTGGAAGTAGAAAGTTTGG		
PAX6 exon-3 F	TGACTGAGCCCTAGATGCATGTG	466	466
PAX6 exon-3 R	TCCCCAATCTGTTTCCCCTACAT		
PAX6 exon-4 F	GAACGGAGATTCTCCTGTCCTA	364	364
PAX6 exon-4 R	CAGTATCGAGAAGAGCCAAGC		
PAX6 exon-5 F	AGGATGCATTGTGGTTGTCTCCTC	405	405
PAX6 exon-5 R	TGGGGGGGTCCATAATTAGCA		
PAX6 exon-6 F	TCCAAGTGCTGGACAATCAA	707	707
PAX6 exon-6 R	AGAGGACACAGACTAAGAGACA		
PAX6 exon-7 F	GGTGTATCTGCAAATCCACCCA	470	470
PAX6 exon-7 R	CAATGTGGTCGATGTGTCCCA		
PAX6 exon-8 F	AAGGCTGACAGTTACCTTGGGAA	398	398
PAX6 exon-8 R	TCTTCTATGCAAAGGGCCCTG		
PAX6 exon-9 F	TTGGTTGGAGGTAATGGGAGTG	334	334
PAX6 exon-9 R	TGGCAGCAGAGCATTTAGCAG		
PAX6 exon 10–11 F	CCTAGAGACAGAGGTGCTTGTA	614	614
PAX6 exon 10–11 R	GCAGACACAGCCAATGAGG		
PAX6 exon-12 F	AGCTCGAGGCCCAATCTTAGAT	436	436
PAX6 exon-12 R	AGGGACAAGGAAAGCAAGGAGT		
PAX6 exon-13 F1	CTTTTCCTTTGGATTGGGGTG	654	–
PAX6 exon-13 R1	CACAGATCAAACATCCATCCAGTC		
PAX6 exon-13 F2	CCTATAAATTTGTATTCCATGTC	Only used for sequencing	149
PAX6 exon-13 R2	CTTGGCCAGTATTGAGACATATC		
SOSTDC1 exon-1 F	ACAAGTGATGAAGTCCAACTCT	550	550
SOSTDC1 exon-1 R	TGTGAGCTAATGCTACCAGAA		
SOSTDC1 exon-2 F1	TGAAAGTGTCCCTATACTATCC	842	842
SOSTDC1 exon-2 R1	AACTACAGGATACGTGGAAT		
SOSTDC1 exon-2 F2	AAATTCCACGTATCCTGTAG	800	800
SOSTDC1 exon-2 R2	CATGTTAGAGGCAACAACA		
FAM20B exon-1 F	GTCCTGCTGCTTGGCTGCCTACCTAC	832	832
FAM20B exon-1 R	CCTTCAGCCGCGACCGCACA		
FAM20B exon-2 F	ACTGCTGCCATCATTAGGTCC	949	949
FAM20B exon-2 R	CAGTGGGTTACCAGGTGTTCT		
FAM20B exon-3 F	AATCAGGCTTGCTAATGGGTG	417	417
FAM20B exon-3 R	AGGCCAGAAATGAAATGACCTA		
FAM20B exon-4 F	TTAATTTGCTCTGTGGGCTTAG	825	825
FAM20B exon-4 R	CACCTGCTTTCACCATCACTA		
FAM20B exon 5–6 F	AGAGTGAGACTGGGTAGAAAGGA	1130	1130
FAM20B exon 5–6 R	TAGCCAAGAAAGAACGATGTAG		
FAM20B exon −7 F	AAGTTCTCCCTTTGGTCTGTG	561	561
FAM20B exon-7 R	TTTGGGTTATCTGCCTTCAC		

Table 1 Amplification and sequencing primers *(Continued)*

ID	Primer sequences	Amplicon size (bp)	Sequencing size (bp)
FAM20B exon-8 F1	CCATAATTTAACTATTTCCCAGTCG	862	862
FAM20B exon-8 R1	CCAATCCCAGTATTCATCTATCC		
FAM20B exon-8 F2	TGGTGACGGGACAGAGTGGC	795	795
FAM20B exon-8 R2	CAGTTTGCTTTGTTAATTTGGGAAG		
FAM20B exon-8 F3	AATTTCCACCTCTGCCTTTAA	793	793
FAM20B exon-8 R3	AGATGAGTGGGCACATCAGG		
FAM20B exon-8 F4	TGACTTTGCACCTAAGTAAATTCTG	735	735
FAM20B exon-8 R4	GGTGGCTCATGCCTGTAATC		
FAM20B exon-8 F5	CTGAACCCATGATGTTGTATTA	666	666
FAM20B exon-8 R5	TCTTCCTATTGTCTCCTCCC		
FAM20B exon-8 F6	TTTTAAGGCTACTCAGTGTTGTG	842	842
FAM20B exon-8 R6	CTCCTGGATTCAAGTGATTCTCC		
FAM20B exon-8 F7	AGGCAAATCTTGGAGAAAAC	764	764
FAM20B exon-8 R7	TCTTGAATAATACTCTGAGCAAA		
FAM20B exon-8 F8	ATTTCCTGCCCTCCTCCAAC	879	879
FAM20B exon-8 R8	CTACCTTGTCACCACCCAGA		
FAM20B exon-8 F9	TAGTGTAAGGCTGCATTGTGG	765	765
FAM20B exon-8 R9	CTTGAGGAATTGAAGGGAAA		
FAM20B exon-8 F10	CAGCGAATAACTACTGAGCAA	514	514
FAM20B exon-8 R10	AAGGGAACTGAAATAGGAACCA		

dental epithelium in mice results in supernumerary maxillary and mandibular incisors [15]. The deletion of Sclerostin domain-containing 1 (*SOSTDC 1*, also known as *Wise*, Ectodin, or *USAG-1*) in mice leads to the development of extra molar and incisors [16, 17]. However, research regarding the association between genetic polymorphism and mesiodens formation has been reported less often. Therefore, the purpose of the current study is to analyze the association between mesiodens formation and the genetic polymorphisms of genes related to this process, identifying the importance of genetic polymorphisms in mesiodens formation-related genes.

Methods

Study participants

One hundred patients (50 mesiodens group, 50 unrelated controls) were recruited in this study in Bengbu, China. The diagnosis of mesiodens was based on oral examination combined with periapical radiograph, panoramic radiograph, and/ or cone-beam computed tomography. The characteristics including gender, crown direction, the number of mesiodens, and the eruption status of mesiodens were recorded. All patients had no abnormalities in their head, ears, eyes, nose, throat, thyroid, trunk, or extremities and were without cleft lip or palate, congenital absence of teeth or tooth malformation. The family history was recorded.

Saliva collection and genomic DNA extraction

A total of 2 mL of unstimulated saliva sample for each recruited participant was collected and stored using Oragene DNA Self-Collection kits (Lang Fu, Shanghai, China). Genomic DNA was extracted using the MagBeads Saliva & Swab DNA Extraction Kit (Regular & Pre-loading Version, Enriching Biotechnology LTD, Shanghai, China) according to the manufacturer's protocol. The Genomic DNA samples were stored at − 20 °C until further analysis.

Sanger sequencing of selected mesiodens formation related genes

We were particularly interested in *PAX6*, *SOSTDC1*, and *FAM20B*, which were reported to result in the formation of mesiodens. All exons and exon/intron boundaries of these three genes in 100 samples were amplified using a GC-rich PCR Kit (Sangon Biotech, Shanghai, China) combined with Champagne Taq DNA Polymerase (Vazyme, Nanjing, China). The PCR products were purified using a MagBeads Gel DNA Extraction Kit (Enriching Biotechnology LTD, Shanghai, China) according to the manufacturer's instructions. The PCR reaction mixture (50 μL) included 3 μL of template, 5 μL of buffer, 4 μL of dNTP, 1 μL of each of the specific forward and reverse primers for these three genes, 0.25 μL rTaq enzyme, and RNase-free water. The PCR was performed with the

following temperature procedures: denaturation at 94 °C for 5 min, 35 cycles of 30 s at 94 °C, 30 s at 55 °C, and 30 s at 72 °C, with a 10-min extension step at 72 °C. The purified products were used for Sanger sequenced using the ABI Prism 3730 platform (Applied Biosystems™, USA). The primers used for amplification and sequencing are listed in Table 1. The primers of *PAX6* were selected according to previous study [18]. The amplification sequences were detailed in Additional file 1 and Additional file 2.

Statistics

The association between susceptibility to mesiodens and the genetic polymorphism of *PAX6*, *SOSTDC1*and *FAM20B* were assessed using IBM SPSS 20.0 software (IBM, Armonk, NY, USA). The data were analyzed using pearson chi-square test with theoretical frequency ≥ 5. For theoretical frequency less than 5 but at least 1 (≤20% cell), the data were analyzed by continuity correction. For the rest, Fisher's Exact test was used. A *P*-value< 0.05 was considered statistically significant. The relationships between the characteristics of mesiodens and the polymorphisms with *P* value less than 0.05 were further analyzed using the same method described previously.

Results

Basic characteristics of patients with mesiodens

Four of the 50 patients with mesiodens (8%) patients had a family history of mesiodens. The basic characterizes of mesiodens are listed in Table 2.

Table 2 Characteristic of patients with mesiodens, mean ± SD, or n (%)

Numbers	50
Age (years)	11.8 ± 9.3
Gender	
Females	16 (32.00)
Males	34 (68.00)
Number of mesiodens per patient	
1	35 (70.00)
2	15 (30.00)
Growth status	
1 erupted	13 (26.00)
1 impacted	22 (44.00)
1 erupted and 1 impacted	8 (16.00)
2 erupted	2 (4.00)
2 impacted	5 (10.00)
Crown direction	
1 vertical	13 (26.00)
1 horizontal	4 (8.00)
1 inverted	17 (34.00)
1 inverted and 1 vertical	6 (12.00)
1 horizontal and 1 vertical	4 (8.00)
2 vertical	4 (8.00)
1 horizontal and 1 inverted	1 (2.00)
2 inverted	1 (2.00)
Family history	4 (8.00)
Located in maxilla	49 (98.00)
Located in mandible	1 (2.00)

Associations between mesiodens formation and genetic polymorphisms

Considering the specific role of family history in mesiodens is still unknown, hence, careful family history is record in our study and excluded when we analyzed the association between mesiodens formation and gene polymorphisms. Removing patients with family history, three polymorphisms (rs750093295, rs667773 and rs3026393) were detected in *PAX6*. Two polymorphisms (rs6945425 and rs12699799) were detected in *SOSTDC1*. Twenty-nine polymorphisms (chr1:179025841, rs193196190, rs72707294, rs1024965514, rs745360443, rs778968805, rs2025584, rs140751029, rs9726948, rs16853612, rs9725887, rs9725888, rs4652352, rs147003645, rs72709441, rs4652353, rs4652354, rs56006430, rs3766625, rs3766626, rs775951319, rs16853619, rs2018786, rs16853621, rs188554154, rs530920451, rs9249, rs117216397, rs1220) were detected in FAM20B. Although, the T allele of *FAM20B* (rs3766626) appears to be associated with mesiodens after removing unqualified sequencing results ($P = 0.051$). There were no significant differences of *PAX6*/*SOSTDC1*/*FAM20B* gene polymorphisms between the two groups (Table 3). The distribution on genotype of these markers according to gender, the number of mesiodens, crown direction, and the eruption status are listed in Tables 4 and 5. The T allele of *FAM20B* (rs3766626) was associated with susceptibility to two mesiodens ($P < 0.001$; OR = 8.333; CI = 2.516–27.600).

Discussion

A total of 8% of patients have a family history of mesiodens, which may indicate that the occurrence of mesiodens is partially determined by genetics. The patients with mesiodens were mostly concentrated in the northern and southern regions of Bengbu. The occurrence of mesiodens might have regional distribution characteristics.

PAX6 is an important gene involved in a series of diseases including eye diseases, diabetes, autism spectrum disorder and mesiodens [14, 19–21]. Variants of *PAX6* are correlated with eye diseases and the insulin response [22–24]. Lei HH et al. identified that variants of rs667773 and rs3026393, and showed that the GG

Table 3 The gene polymorphisms in patients with mesiodens and controls

Marker	Gene polymorphism	Mesiodens	Controls	*P* value
rs2025584 (*FAM20B*)	AA/AG/GG	4/23/16	10/24/15	0.326
	A/G	31/55	44/54	0.223
rs140751029 (*FAM20B*)	CC/CT	40/4	43/4	1.000
	C/T	84/4	90/4	1.000
rs9726948 (*FAM20B*)	GG/GT	41/2	41/6	0.270
	G/T	84/2	88/6	0.282
rs16853612 (*FAM20B*)	AA/AG/GG	23/12/8	28/16/3	0.206
	A/G	58/28	72/22	0.171
rs9725887 (*FAM20B*)	CC/CT/TT	15/22/6	14/19/15	0.146
	C/T	52/34	47/49	0.120
rs9725888 (*FAM20B*)	CT/TT	2/41	6/42	0.273
	C/T	2/84	6/90	0.284
rs4652352 (*FAM20B*)	AA/AC/CC	5/15/23	6/12/30	0.584
	A/C	25/61	24/72	0.537
rs147003645 (*FAM20B*)	GG/AG	43/0	47/1	1.000
	G/A	86/0	95/1	1.000
rs72709441 (*FAM20B*)	CC/TT/CT	22/6/15	28/3/17	0.477
	C/T	59/27	73/23	0.262
rs4652353 (*FAM20B*)	GG/GT/TT	6/14/23	6/12/30	0.668
	G/T	26/60	24/72	0.430
rs4652354 (*FAM20B*)	CC/CT/TT	19/22/1	18/23/7	0.146
	C/T	60/24	59/37	0.159
rs56006430 (*FAM20B*)	CC/CG/GG	7/15/21	3/17/29	0.269
	C/G	29/57	23/75	0.123
rs3766626 (*FAM20B*)	GG/GT/TT	16/21/4	14/19/14	0.067
	G/T	53/29	47/47	0.051
rs3766625 (*FAM20B*)	AA/AG/GG/CC	6/15/20/0	2/17/27/1	0.277
	A/G/C	27/55/0	21/71/2	0.131
rs16853619 (*FAM20B*)	AG/GG	2/39	6/41	0.276
	A/G	2/80	6/88	0.287
rs72707294 (*FAM20B*)	GG/GC/CC	8/18/22	3/18/27	0.249
	G/C	34/62	24/72	0.116
rs2018786 (*FAM20B*)	AA/AG/GG	7/14/23	1/18/30	0.061
	A/G	28/60	20/78	0.076
rs16853621 (*FAM20B*)	AA/AG/GG	36/4/1	40/8/0	0.361
	A/G	76/6	88/8	0.802
rs188554154 (*FAM20B*)	GG/GT	43/0	47/1	1.000
	G/T	86/0	95/1	1.000
rs530920451 (*FAM20B*)	AA/AG	43/1	47/1	1.000
	A/G	87/1	95/1	1.000
rs775951319 (*FAM20B*)	CC	41	47	–
rs778968805 (*FAM20B*)	CC/CT	46/0	46/1	1.000
	C/T	92/0	93/1	1.000
rs745360443 (*FAM20B*)	GG/AG	47/1	49/0	0.495
	G/A	95/1	98/0	0.495
rs1024965514 (*FAM20B*)	CT/CC	1/47	0/48	1.000
	C/T	95/1	96/0	1.000
chr1:179025841 (*FAM20B*)	AA/AG	45/1	42/0	1.000
	A/G	91/1	84/0	1.000
rs193196190 (*FAM20B*)	GG	40	38	–
rs9249 (*FAM20B*)	AA/AG/GG	5/16/23	3/17/28	0.666
	A/G	26/62	23/73	0.392
rs117216397 (*FAM20B*)	AA/AG	42/2	48/0	0.226
	A/G	86/2	96/0	0.227
rs1220 (*FAM20B*)	AA/AC/CC/GG	20/19/4/1	17/23/8/0	0.428
	A/C/G	59/27/2	57/39/0	0.126
rs667773 (*PAX6*)	CC/CT/TT	27/13/2	36/10/1	0.451
	C/T	67/17	82/12	0.178
rs750093295 (*PAX6*)	CC/GG/CT	41/1/0	45/0/1	0.730
	C/T/G	82/0/2	91/1/0	0.226
rs3026393 (*PAX6*)	GG/GT/TT	6/26/10	17/20/10	0.056
	G/T	38/46	54/40	0.104
rs6945425 (*SOSTDC1*)	AG/GG	6/36	8/38	0.691
	A/G	6/78	8/84	0.704
rs12699799 (*SOSTDC1*)	AA/AG/GG	6/23/13	8/17/22	0.199
	A/G	35/49	33/61	0.369

genotype of rs302693 was less prevalent in 20 patients with mesiodens than in 31 controls [18]. These results were further supported by our study. Polymorphisms in rs667773 and rs3026393 of *PAX6* were detected in the current study, and the mesiodens group might have fewer genotypes of GG (rs3026393) than do the controls. Polymorphisms related to other diseases were not detected in this study; however, this may be because the patients with mesiodens did not have any other diseases.

Mesiodens is the most common type among supernumerary teeth, and the development of supernumerary teeth is closely associated with bone morphogenetic protein (*BMP*) and Wnt signaling pathways [25]. *BMP* is

Table 4 The distribution of AA genotype of FAM20B (rs2018786) according to eruption status

genotype	1 erupted	1 impacted	1 erupted + 1 impacted	2 erupted	2 impacted
AA	1	3	0	0	3
others	8	17	8	2	2

Table 5 The distribution of AA genotype of FAM20B (rs2018786) according to crown direction

genotype	1 vertical	1 horizontal	1 inverted	1 inverted + 1 vertical	1 horizontal + 1 vertical	2 vertical	1 horizontal+ 1 inverted	2 inverted
AA	2	0	2	0	2	0	1	0
others	8	3	14	5	2	4	0	1

required for *SHH* expression during early tooth development and postnatal root development [26]. However, *SOSTDC1* is an inhibitor of *BMP*, and the deletion of *SOSTDC1* in mice induces the formation of mesiodens [15]. *Wnt*, another signaling pathway, can be inhibited by *SOSTDC1*, located in the upstream of Sonic hedgehog (Shh), and induces the expression of Shh, followed by the induction of high *SOSTDC1* expression. Insufficient *SOSTDC1* enhances WNT signaling, which increases proliferation and continuous development of vestigial tooth buds and results in the formation of supernumerary teeth [27, 28]. In our study, two polymorphisms (rs6945425 and rs12699799) were detected in *SOSTDC1*, but none of them were found related to susceptibility to mesiodens.

FAM20B is a member of Family with sequence similarity 20 (Fam20) proteins containing FAM20A, FAM20B, and FAM20C in the human genome [29]. *FAM20A* knockout mice have biomineralization defects, and mutations in *FAM20A* have been found to be associated with amelogenesis imperfecta subsequently [30–32]. *FAM20B* null mice showed mesiodens [15]; however, the relationship between variants of *FAM20B* and mesiodens has not yet been reported. Our results suggest for the first time that individuals with T allele of *FAM20B* (rs3766626) appear to have a low risk of mesiodens, which was located in the 3′ untranslated region (3′ UTR) of corresponding gene. Although it isn't translated into protein, previous and recent studies showed that variant in 3′ UTR region could impact the expression of mRNA [33, 34].

The current study provides information on the association between genetic polymorphisms and the occurrence of mesiodens; however, there are some limitations. The sample size (mainly the control size) and the number of genes analyzed in this study were limitations. The mechanism by which these polymorphism affect mesiodens is unknown. Further studies including more samples, more genes, and the mechanism of these polymorphism on mesiodens are needed.

Conclusions

There were no significant differences of *PAX6*/*SOSTDC1*/*FAM20B* gene polymorphisms between the two groups. Further studies with large samples on T allele of *FAM20B* (rs3766626) are needed.

Additional files

Additional file 1: The amplification sequences of *FAM20B*. (DOCX 22 kb)
Additional file 2: The amplification sequences of *SOSTDC1*. (DOCX 13 kb)

Abbreviations

AXIN2: Axin 2; BMP: Bone morphogenetic protein; ENAM: Enamelin; Fam20: Family with sequence similarity member 20; GREM2: Gremiln-2; PAX6: Paired box gene 6; SOSTDC 1: Sclerostin domain-containing 1; UTR: Untranslated region

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Not applicable

Authors' contributions

KZ and SSL conceived and designed the experiments; JCL and JCX contributed to the data acquisition; SKL, YFC, RXZ and RXT analyzed the data; SSL wrote the manuscript; KZ revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data and materials of the present study were available from the corresponding author.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of [2017] KY010 by the First Affiliated Hospital of Bengbu Medical College. Informed consents were written before recruitment. Written informed consent for participation under 16 years old in the study was obtained from their parent or guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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