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Original Article

XPC codon 939 polymorphism is associated with susceptibility to DNA damage induced by aflatoxin B1 exposure

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Abstract: Aflatoxin B1 (AFB1), resulting in the formation of AFB1-DNA adducts, is a known human carcinogen. AFB1-exposure individuals with inherited susceptible carcinogen-repairing genotypes may experience an increased risk of genotoxicity. This study was aimed to investigate whether DNA repair gene xerodermapigmentosum complementation group C codon 939 polymorphism (rs2228001) affected the levels of AFB1-DNA adducts in Guangxi Population (n = 2558), from an AFB1-exposure area. AFB1-DNA adducts were measured by ELISA, and XPC codon 939 genotypes were identified by TaqMan-PCR. We found that longer AFB1-exposure years significantly increased XPC genotypes with codon 939 Gln alleles (namely, XPC-LG and -GG, odds ratios [95% confidence intervals] were 1.37 (1.15-1.63) and 1.99 (1.55-2.55), respectively) was significantly associated with higher levels of AFB1-DNA adducts. Furthermore, there was a positive joint effect between XPC genotypes and long-year AFB1 exposure in the formation of AFB1-DNA adducts. These results suggest that individuals with susceptible genotypes XPC-LG and -GG may experience an increased risk of DNA damage elicited by AFB1 exposure.

Keywords: AFB1, AFB1-DNA adducts, XPC, polymorphism

Introduction

Aflatoxin B1 (AFB1) is an important toxin produced by Aspergillus fungi. This toxin is mainly metabolized by cytochrome P450 into the genotoxic metabolic 8,9-epoxide-AFB1 (AFBO). AFBO can bind to DNA, and cause the formation of AFB1-DNA adducts that may be removed or repaired by DNA repair enzymes [1, 2]. While xerodermapigmentosum complementation group C (XPC) is required for the efficient repair of this DNA adducts [3-5]. The XPC codon 939 polymorphic locus (rs2228001) has been of particular interest in molecular epidemiology studies [6-11]. Increasing evidence has shown this polymorphism may be associated with decreased DNA repair capacity and increased tumor risk [5-8, 12-21]. This suggests that reduced DNA repair capacity may result in the high risk of AFB1-DNA adducts [9, 10]. Therefore, we specifically conducted a study to examine whether XPC codon 939 polymorphism influences the levels of AFB1-DNA adducts among Guangxi population from an AFB1 exposure area.

Materials and methods

Study subjects

A total of 2558 healthy adults (27-78 yrs of age) population who were residence of Guangxi Zhuang Autonomous Regionwere enrolled from affiliated hospitals of Youjiang Medical College for Nationalities and Guangxi Medical University between January 2002 and December 2009. All study subjects, including 1600 individuals previously studied [11], were without any clinical evidence of liver diseases. The characteristic information of all study subjects, including sex, age, ethnicity, hepatitis B virus (HBV) infection, and HCV infection were ascertained as described previously [22]. These having hepatitis B surface antigen (HBsAg)-positive or anti-

Table 1. Characteristics of study population

Characteristics	
Age, yr	
Mean ± SD	49.29 ± 11.34
Range	27-78
Sex	
Male n (%)	1930 (75.4)
Female n (%)	628 (24.6)
Ethnicity	
Han n (%)	1175 (45.9)
Minority n (%)	1383 (54.1)
Years of AFB1 exposure, yr	
Mean ± SD	40.23 ± 11.51
Range	5-76
HBV infection	
HBsAg (-) n (%)	712 (27.8)
HBsAg (+) n (%)	1846 (72.2)
HCV infection	
Anti-HCV (-) n (%)	2092 (81.8)
Anti-HCV (+) n (%)	466 (18.2)

HCV-positive in their peripheral serum were defined as groups infected HBV and HCV, respectively. Additionally, after informed consent was obtained, each subject donated 4 mL of peripheral blood for AFB1-DNA adducts and XPC codon 939 genotypes analysis. One hundred percent of people asked to participate in this study who did enroll agreed to participate in the investigative study, and no one dropped out. The protocol of this study was approved by the Ethic Committees of the hospitals involved in the study.

DNA isolation

Leukocytes from peripheral venous blood samples were isolated by standard procedures. DNA was then extracted from leukocyte samples by standard phenol-chloroform extraction and ethanol precipitation. DNA was stored at -20°C until additional analysis.

AFB1-exposure years assay

AFB1-exposure years was ascertained by our previously published methods [22]. To analyze, AFB1-exposure years were divided into two groups: short-AFB1 exposure (< 40 yrs) and long-AFB1 exposure (≥ 40 yrs), according to the value of AFB1-exposure years, with one cutoff points of 40 yrs, the average AFB1-exposure time.

AFB1-DNA adducts assay

AFB1-DNA adducts levels of DNA samples from leucocytes were measured by competitive enzyme-linked immunosorbent assay (ELISA) using monoclonal antibody 6A10 and 50 μg of DNA as described by Hsieh LL, *et al* [23]. The quality control for adduct assays was administered by blank and positive controls. To analyze, AFB1-DNA adduct levels were divided into two groups: low level (≤ 1.00 μmol/mol DNA) and high level (≥ 1.01 μmol/mol DNA), according to the value of AFB1-DNA adduct levels, with one cutoff points of 1.00 μmol/mol DNA, the average adducts levels among study subjects.

XPC genotype analysis

Gene polymorphism analysis of XPC codon 939 was detected by using a previously published TaqMan-PCR [11]. Briefly, PCR reactions were run in a 25 μL final volume containing 1 × Premix Ex Taq™ (TaKaRa, catalog # DRR039A), 0.2 μM of each probe, 0.2 μM of each primer, and 50-100 ng of genomic DNA. Cycling conditions were 95°C for 2 min, and 45 cycles of 95°C for 10 s, 60°C for 1 min and 72°C 10 s. Controls were included in each run and repeated genotyping of a random 10% subset yielded 100% identical genotypes. Data analysis for allele discrimination was performed with the iCycleriQ software. The quality control for genotypic assays was administered by blank and positive controls.

Statistical analysis

The association between XPC codon 939 genotypes and the levels of AFB1-DNA adducts was analyzed using *t* test. Logistic regression with an adjustment for age, sex, ethnicity, HBsAg, and anti-HCV was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) for the XPC codon 939 genotypes. In this analysis, genotype variable was treated as an ordinal variable (XPC-LL coded as 1, XPC-LG as 2, and as 3), and the corresponding risk value was calculated using the additive model. Additionally, the combinative analysis of risk genotypes (XPC-LG + XPC-GG, also called XPC-LG/GG) was accomplished compared with XPC-LL in dominant model. The interactions between XPC

Table 2. Years of AFB1 exposure and the levels of AFB1-DNA adducts

Exposure years	Low-level adducts (n = 1537)		High-level adducts (n = 1021)		OR (95% CI)[a]	P
	n	%	n	%		
Short	871	56.7	488	47.8	Reference	
Long	666	43.3	533	52.2	1.45 (1.23-1.70)	7.00×10^{-7}

[a]Adjusted for age, sex, ethnicity, HBsAg, and anti-HCV.

codon 939 genotypes and modified factors (including race, sex, HBV and HCV infection, and AFB1-exposure years) on the levels of AFB1-DNA adducts were also estimated and tested on a multiplicative scale by combining genotypes and adding a multiplicative term in the logistic regression model. The statistical significance of the term interaction of genotype-modified factors was evaluated through Likelihood ratio test. All tests were two-tailed. A *P*-value of < 0.05 was considered statistically significant in this study. All the analysis was performed by the statistical package for social science (SPSS) version 18.0 (SPSS Institute, Chicago, IL).

Results

Demographic characteristics for subjects

Table 1 showed the demographic data of all study subjects. The mean age study subjects were 49.29 years. While HBV and HCV infective rates were 72.2% and 18.2%, respectively. These results were in accord with our previously published data [11, 22, 24].

AFB1-exposure years increased AFB1-DNA adducts levels

The average AFB1-exposure years were 40.23 (**Table 1**). We also found those individuals featuring long-AFB1 exposure time were likely to have higher levels of AFB1-DNA adducts in their peripheral blood white blood cells (adjusted OR = 1.45, P < 0.01, **Table 2** and **Figure 1A**).

XPC codon 939 polymorphism increased AFB1-DNA adducts levels

To investigate whether the XPC codon 939 polymorphisms were associated with difference in detoxification and DNA repair, which might be reflected in levels of genotoxic damage, we compared this polymorphism with levels of AFB1-DNA adducts (**Figure 1B** and **Table 3**). The data exhibited that the adjusted OR for those individuals carrying the heterozygotes for Lys and Gln allele of XPC codon 939 (XPC-LG) compared with those exhibiting the homozygote for Lys alleles (XPC-LL) was 1.37 (95% CI, 1.15-1.63), and the corresponding OR for those featuring the homozygote for Gln alleles (XPC-GG) was 1.99 (95% CI, 1.55-2.55), which showed the risk of high AFB1-DNA adduct levels was related with the number of codon 939 Gln alleles. The genotype distributions of XPC codon 939 polymorphisms in the subjects were consistent with Hardy-Weinberg equilibrium.

The XPC codon 939 genotype distribution stratified by age, race, gender, HBV infection, and HCV infection was shown in **Table 4**. The results demonstrated similar risk estimates of around 1.5-fold increased high-level AFB1-DNA adducts risk with XPC genotypes with codon 939 Gln alleles (XPC-LG/GG, $P_{interaction} > 0.05$). Interestedly, we found those individuals featuring HBV- or HCV-infection history and carrying XPC-GG had higher risk of increasing AFB1-DNA adducts levels compared to those having XPC-LL (OR = 2.45 for positive-HBsAg status and 2.39 for positive-anti-HCV status). The hepatitis virus infection-gene interactive analysis, however, did not show statistically significant effects on the levels of AFB1-DNA adducts ($P_{interaction} > 0.05$).

Joint effects of AFB1-exposure years and XPC codon 939 polymorphism on AFB1-DNA adducts levels

We next analyzed the combination effects of AFB1-exposure years and XPC codon 939 polymorphism on the levels of AFB1-DNA adducts (**Table 5**). In this analysis, we used reference the lowest risk group: those who had short AFB1-exposure years and XPC-LL. The results showed those with long AFB1-exposure years and XPC-GG were more likely to have AFB1-DNA adducts in their peripheral blood white blood cells. Additionally, we also evaluated the multiplicatively interactive effects between genotypes and AFB1-exposure years according to the following formula: $OR_{eg} > OR_{eg'} \times OR_{e'g}$[25]. Some evidence of multiplicatively interaction was observed (2.13 > 1.30 × 1.37).

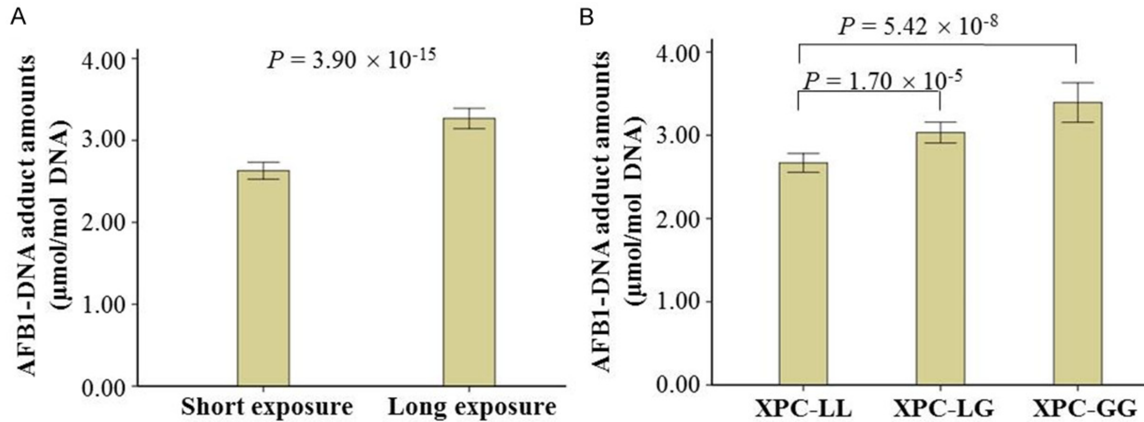

Figure 1. The effects of AFB1-exposure years and XPC codon 939 polymorphism on AFB1-DNA adduct levels. In this study, AFB1-DNA adducts levels in the peripheral blood leukocytes were evaluated using ELISA. Longer AFB1-exposure years (A) and risk genotypes of XPC codon 939 (B) increased AFB1-DNA adduct amounts. Data were analyzed using *t* test and shown as means ± S.E.

Table 3. XPC genotypes and the levels of AFB1-DNA adducts

XPC genotype	Low-level adducts (n = 1537)		High-level adducts (n = 1021)		OR (95% CI)[a]	*P*
	n	%	n	%		
LL	700	45.5	369	36.1	1	
LG	699	43.5	478	46.8	1.37 (1.15-1.63)	3.74×10^{-4}
GG	168	10.9	174	17.0	1.99 (1.55-2.55)	5.62×10^{-8}
LG/GG	837	54.5	654	63.9	1.49 (1.27-1.76)	1.00×10^{-6}

[a]Adjusted for age, sex, ethnicity, HBsAg, and anti-HCV. Abbreviations: LL, XPC genotype with codon 939 Lys alleles; LG, XPC genotype with codon 939 Lys and Gln alleles; GG, XPC genotype with codon 939 Gln alleles; LG/GG, the combination of LG and GG genotypes.

Discussion

To the best our knowledge, no studies have investigated the role of DNA-repair gene XPC codon 939 polymorphisms in the risk of the levels of AFB1-DNA adducts, especially from AFB1-exposure areas. In this study, we analyzed the association between this polymorphism and the levels of AFB1-DNA adducts among Guangxi population, from an high AFB1-exposure area. The results showed that XPC genotypes with codon 939 Gln alleles were related with higher levels of AFB1-DNA adducts (OR = 1.49, 95% CI = 1.27-1.76). These results may suggest that XPC codon 939 polymorphism may have functional significance in the AFB1-induced DNA damage.

AFB1, an important chemical carcinogen, is mainly metabolized by cytochrome P450 into the genotoxic metabolic AFBO which can bind to DNA and cause the formation of AFB1-guanine adducts. This kind of AFB1-DNA adducts, including 8,9-dihydro-8-(N^7-guanyl)-9-hydroxy AFB1-DNA (AFB1-N7-Gua-DNA) adduct, and formamidopyridine-AFB1-DNA (AFB1-FAPy-DNA) adduct [2], if not repaired, might induce DNA damage such as base damage and oxidative DNA damage [2, 26, 27].

While XPC gene spans 33kb on chromosome 3p25, and consists of 16 exons and 15 introns. This gene encodes a 940-amino acid protein, an important DNA damage recognition molecule which plays an important role in NER pathway. XPC protein binds tightly with another important NER protein HR23B to form a stable XPC-HR23B complex, the first protein component that recognizes and binds to the DNA damage sites. XPC-HR23B complex can recognize a variety of DNA adducts formed by exogenous carcinogens such as AFB1 and binds to the DNA damage sites. Therefore, it may play a role in the formation process of AFB1-DNA adducts [3-5].

More than one hundred polymorphisms in the XPC gene have been identified and more and more evidence has expressed that the polymorphisms of this gene are associated with the

Table 4. XPC polymorphism and associated OR in relation to ethnicity, sex, HBsAg and anti-HCV

		Low-level adducts		High-level adducts		OR (95% CI)	*P*
		n	%	n	%		
Ethnicity[a]	XPC						
Han	LL	319	45.6	174	36.6	Reference	
	LG	296	42.3	218	45.8	1.35 (1.05-1.74)[b]	0.02
	GG	84	12.0	84	17.6	1.84 (1.29-2.63)[b]	7.70×10^{-4}
	LG/GG	380	54.4	302	63.4	1.46 (1.15-1.85)[b]	2.04×10^{-3}
Minority	LL	381	45.5	195	35.8	Reference	
	LG	373	44.5	260	47.7	1.41 (1.11-1.79)[b]	4.86×10^{-3}
	GG	84	10.0	90	16.5	2.10 (1.48-2.97)[b]	3.40×10^{-5}
	LG/GG	457	54.5	350	64.2	1.54 (1.23-1.93)[b]	1.94×10^{-4}
Age (yrs)[c]	XPC						
≤ 49	LL	366	44.5	194	35.7	Reference	
	LG	369	44.9	254	46.8	1.34 (1.05-1.70)[d]	0.02
	GG	87	10.6	95	17.5	2.12 (1.51-2.99)[d]	1.70×10^{-5}
	LG/GG	456	55.5	349	64.3	1.49 (1.16-1.86)[d]	5.93×10^{-4}
≥ 50	LL	334	46.7	175	36.6	Reference	
	LG	300	42.0	224	46.9	1.41 (1.10-1.83)[d]	0.01
	GG	81	11.3	79	16.5	1.90 (1.32-2.74)[d]	6.30×10^{-4}
	LG/GG	381	53.3	303	63.4	1.51 (1.19-1.93)[d]	7.40×10^{-4}
Sex[e]	XPC						
Male	LL	167	43.4	94	25.5	Reference	
	LG	178	46.2	111	30.1	1.07 (0.75-1.53)[f]	0.70
	GG	40	10.4	38	10.3	1.69 (1.01-2.85)[f]	0.04
	LG/GG	218	56.6	275	74.5	1.52 (1.20-1.93)[f]	7.40×10^{-4}
Female	LL	533	46.3	275	35.3	Reference	
	LG	491	42.6	367	47.2	1.46 (1.20-1.78)[f]	2.10×10^{-4}
	GG	128	11.1	136	17.5	2.10 (1.58-2.79)[f]	3.03×10^{-7}
	LG/GG	619	53.7	503	64.7	1.59 (1.32-1.92)[f]	1.00×10^{-6}
HBsAg[g]	XPC						
Positive	LL	196	42.9	96	37.6	Reference	
	LG	195	42.7	120	47.1	1.41 (1.15-1.72)[h]	9.72×10^{-4}
	GG	66	14.4	39	15.3	2.45 (1.82-3.30)[h]	3.56×10^{-9}
	LG/GG	261	57.1	159	62.4	1.59 (1.32-1.93)[h]	2.00×10^{-6}
Negative	LL	504	46.7	273	35.6	Reference	
	LG	474	43.9	358	46.7	1.32 (0.94-1.86)[h]	0.11
	GG	102	9.4	135	17.6	1.13 (0.70-1.83)[h]	0.62
	LG/GG	576	53.3	493	64.4	1.27 (0.92-1.76)[h]	0.15
Anti-HCV[i]	XPC						
Positive	LL	562	44.2	296	36.1	Reference	
	LG	567	44.6	382	46.5	1.82 (1.20-2.74)[j]	4.42×10^{-3}
	GG	143	11.2	143	17.4	2.39 (1.29-4.43)[j]	5.67×10^{-3}
	LG/GG	710	55.8	525	63.9	1.93 (1.31-2.85)[j]	8.87×10^{-4}
Negative	LL	138	52.1	73	36.3	Reference	
	LG	102	38.5	96	47.8	1.28 (1.05-1.55)[j]	0.01
	GG	25	9.4	32	15.9	1.91 (1.45-2.51)[j]	4.00×10^{-4}
	LG/GG	127	47.9	128	63.7	1.40 (1.17-1.68)[j]	2.53×10^{-4}

[a]Likelihood ration test for interaction of the stratified variable (Han and Minority) and XPC genotype was calculated as test for the heterogeneity of ORs across strata ($P_{interaction}$ = 0.876). [a]Adjusted for age, sex, HBsAg, anti-HCV, and years of AFB1 exposure. [c]Likelihood ration test for interaction of the stratified variable (Age) and XPC genotype was calculated as test for the heterogeneity of ORs across strata ($P_{interaction}$ = 0.695). [d]Adjusted for race, sex, HBsAg, anti-HCV, and years of AFB1 exposure. [e]Likelihood ration test for interaction of the stratified variable (Male and Female) and XPC genotype was calculated as test for the heterogeneity of ORs across strata ($P_{interaction}$ = 0.168). [f]Adjusted for age, ethnicity, HBsAg, anti-HCV, and years of AFB1 exposure. [g]Likelihood ration test for interaction of the stratified variable (HBsAg-positive and negative) and XPC genotype was calculated as test for the heterogeneity of ORs across strata ($P_{interaction}$ = 0.192). [h]Adjusted for age, sex, ethnicity, anti-HCV, and years of AFB1 exposure. [i]Likelihood ration test for interaction of the stratified variable (Anti-HCV-positive and negative) and XPC genotype was calculated as test for the heterogeneity of ORs across strata ($P_{interaction}$ = 0.241). [j]Adjusted for age, sex, ethnicity, HBsAg, and years of AFB1 exposure. Abbreviations: LL, XPC genotype with codon 939 Lys alleles; LG, XPC genotype with codon 939 Lys and Gln alleles; GG, XPC genotype with codon 939 Gln alleles; LG/GG, the combination of LG and GG genotypes.

Table 5. Joint effects of XPC polymorphism and AFB1-exposure years on AFB1-DNA adducts

AFB1-exposure years	XPC genotype	Low-level adducts		High-level adducts		OR (95% CI)[a]	P
		n	%	n	%		
Short	LL	387	25.2	180	17.6	Reference	
	LG	388	25.2	228	22.3	1.26 (0.99-1.61)	0.06
	GG	96	6.2	80	7.8	1.81 (1.28-2.56)	7.89×10^{-4}
	LG/GG	484	31.5	308	30.2	1.37 (1.09-1.72)	6.59×10^{-3}
Long	LL	313	20.4	189	18.5	1.30 (1.01-1.68)	0.04
	LG	281	18.3	250	24.5	1.94 (1.52-2.49)	1.29×10^{-7}
	GG	72	4.7	94	9.2	2.87 (2.01-4.09)	6.64×10^{-9}
	LG/GG	353	23.0	344	33.7	2.13 (1.69-2.69)	1.69×10^{-10}

[a]Adjusted for age, sex, HBsAg, anti-HCV, and race. Abbreviations: LL, XPC genotype with codon 939 Lys alleles; LG, XPC genotype with codon 939 Lys and Gln alleles; GG, XPC genotype with codon 939 Gln alleles; LG/GG, the combination of LG and GG genotypes.

function of DNA repair capacity [6, 7, 11]. In this study, we only analyzed XPC codon 939 polymorphism because this polymorphism changes the amino acids coded, which may be associated with decreased DNA repair capacity [7, 8, 13-18, 20, 21, 28], increased frequency of p53 mutations [29, 30], and increased tumor risk [6, 11, 15]. Recent some studies have shown that low DNA repair capacity resulting from the genetic mutation of XPC codon 939 polymorphism can progress AFB1-induced HCC [31-33], suggesting that XPC codon 939 polymorphism may be important in the repair of AFB1-DNA adducts. Our present data not only supported this hypothesis, but also we found that this polymorphism would be able to interact with AFB1-exposure years, especially long-year AFB1 exposure, in the formation of AFB1-DNA adducts. Possibly, differences in the AFB1-exposure years reflect differences in cumulative exposure information. In tissues and cells with longer-years AFB1 exposure, AFB1-DNA adducts are cumulated because of the deficiency of DNA repair ability.

Although some clues of the interactive effects between either HBV or HCV infection and XPC codon 939 genotypes on the levels of AFB1-DNA adducts were found in this study, the effect seems to be greatest at the genotype of XPC-GG under the conditions of positive infection history. This may be because of low detoxification capacity resulting from chronic liver diseases history, and low DNA repair ability, which results in the formation of AFB1-DNA adducts.

Conclusion

To the best of our knowledge, this is the first report to investigation associations between the polymorphism at the codon 939 of XPC and the levels of AFB1-DNA adducts. We found evidence to suggest that the XPC codon 939 Gln alleles are associated with increased levels of DNA damage that may be due to reduced detoxification and DNA repair function. However, Selection bias might have occurred through the selection of hospital-based subjects. Furthermore, liver disease (resulting from virus infection) itself may affect the metabolism of aflatoxin and modify the levels of aflatoxin-DNA adducts. Additionally, other polymorphisms (such as the polymorphisms of XRCC4)

might be able to further modify the effect of XPC polymorphism on AFB1-DNA adducts. Therefore, future studies need to characterize the role of the XPC codon 939 Gln alleles in functional detoxification and DNA repair assays and to test to see whether they affect the levels of other biomarkers of DNA damage. Given that high AFB1-DNA adducts positively associates with liver cancer risk, the finding of a genetic susceptibility (if confirmed) may have implications for cancer screening and prevention.

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Disclosure of conflict of interest

None.

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