

## RESEARCH ARTICLE

# ***XPC 939A>C and 499C>T Polymorphisms and Skin Cancer Risk: a Meta-analysis***

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### **Abstract**

The xeroderma pigmentosum complementation group C gene (*XPC*) has been identified as important for repairing UV-related DNA damage. Some subtle changes in this gene may impair repair efficiency and influence susceptibility to human cancers, including skin cancer. Two polymorphisms in *XPC*, 939A>C (rs2228001) and 499C>T (rs2228000), are considered to have possible associations with the risk of skin cancer, but the reported results have been inconsistent. Here we performed a meta-analysis of the available evidence regarding the relationship between these two polymorphisms and the risk of skin cancer. All relevant studies were searched using PubMed, Embase and Web of Science before February 2012. A total of 8 case-control studies were included in this analysis, and no convincing associations between the two polymorphisms and risk of skin cancer were observed in any of the genetic models. Stratified analyses by skin cancer type also did not detect significant associations in any subgroup. This meta-analysis suggested that the *XPC 939A>C* and *499C>T* polymorphisms may have little involvement in susceptibility to skin cancer.

**Keywords:** *XPC* - polymorphism - skin cancer - meta-analysis

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### **Introduction**

Skin cancer is the most frequent cancer in humans, especially in the Western world (Leiter et al., 2008; Gordon, 2009). There are several subtypes of skin cancer: melanoma and nonmelanoma which including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) (Mueller et al., 2008). BCC and SCC are the most common types of skin cancer, and melanoma accounts for the most skin cancer deaths. Skin cancer has a complex etiology resulting from the interaction of inherited and environmental factors. For example, ultraviolet radiation which causes DNA damage, is considered as a major contributor to the development of skin cancer (Young, 2009). In addition, genetic polymorphisms also modulate the susceptibility to skin cancer (Meyer, 2009).

DNA repair systems play a critical role in protecting the genome from the insults of cancer-causing agents. In humans, there are four major DNA repair pathways, one of which called nucleotide excision repair (NER) is thought to be most important in correcting UV-related DNA damage (Moriwaki et al., 2008). *XPC* is a key member in NER and can form *XPC-HR23B* complex that identifies target lesions in this pathway (Sugasawa et al., 1998). The *XPC* gene is located on chromosome 3p25 and encodes *XPC* protein which consists of 940 amino acids (Lehmann, 2003). Some subtle changes in the *XPC* gene product may

impair NER efficiency and influence susceptibility to UV induced malignancy. Khan et al. (Khan et al., 2002; Hu et al., 2005) described that two nonsynonymous single nucleotide polymorphisms (SNPs) of the *XPC* gene may alter NER capacity and modulate cancer risk: 939A>C (A33512C, rs2228001) in exon 15 and 499C>T (C21151T, rs2228000) in exon 8.

Even with a number of reports examining the associations between these two polymorphisms of *XPC* and susceptibility to skin cancer in diverse populations, the results remain conflicting rather than consistent [Table 1, ref: (Festa et al., 2005; Blankenburg et al., 2005; Blankenburg et al., 2005; Thirumaran et al., 2006; Li et al., 2006; Figl et al., 2010; Goncalves et al., 2011; Ibarrola-Villava et al., 2011)]. Studies with relative small sample sizes may lack precision. Thus, a quantitative synthesis may help to obtain summary risk estimation of the associations between specific polymorphisms in *XPC* and risk of skin cancer and quantify the potential between-study heterogeneity. In this study, we conducted a meta-analysis containing 8 published case-control studies with a total of 3,892 cancer cases and 4,287 controls.

### **Materials and Methods**

#### *Identification and eligibility of relevant studies*

We included all case-control studies published to date

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on the association between these two polymorphisms (939A>C and 499C>T) of *XPC* and skin cancer risk. Eligible studies were identified by searching PubMed, Embase and Web of Science databases for relevant reports (last search update Feb. 2012), using the search terms “(skin neoplasms OR skin cancer) AND “DNA repair gene” AND (polymorphism OR variant OR mutation)”. The additional studies were identified by searching references from original papers and review articles on this topic. Data were extracted separately by the two investigators (Y. Lin and G. Ji) in order to ensure homogeneity of data collection and rule out the effect of subjectivity in data gathering and entry. Disagreements were resolved by iteration, discussion and consensus. Studies included in our meta-analysis had to meet all of the following criteria: (1) published in English, (2) study on human beings, (3) in case-control study design or had a part of case-control design in the overall study, (4) had available genotype frequency of cases and controls or can be calculated from the articles, (5) only the study with a larger sample size was selected if studies had partly overlapped subjects. In the current study, data for meta-analysis were available from 8 studies, including 3,598 skin cancer cases and 3,914 controls for 939A>C (7 studies), and 2,679 skin cancer cases and 2,629 controls for 499C>T (4 studies), respectively.

#### Data extraction

The two investigators (Y. Lin and G. Ji) independently extracted data and reached consensus on all of the items. First author's name, year of publication, country of origin, ethnicity, skin cancer types, number of cases and controls, and minor allele frequency (MAF) in controls were described. Different ethnicities were categorized as Caucasian and others. In addition, for stratified analyses, we categorized cancer types into melanoma and nonmelanoma (BCC and SCC), and also categorized sample size into small (case plus control < 1000) and large

(case plus control  $\geq$  1000).

#### Statistical analysis

The strength of the associations between skin cancer risk and two polymorphisms of *XPC* gene was assessed for each study by odds ratio (OR) together with its 95% confidence intervals (95% CI), respectively. A chi-square based Q statistic test was performed to assess the between-study heterogeneity (Lau et al., 1997), and  $P \leq 0.05$  was considered significant. A fixed-effect model using the Mantel-Haenszel method and a random-effects model using the Der Simonian and Laird method were performed, respectively, to pool results of studies (Petitti, 1994). Random-effects model was used when heterogeneity between studies exists, that is,  $P$  value for heterogeneity test is less than 0.05; otherwise, fixed-effect model was used. We firstly estimated the risks of the heterozygote and variant homozygote, compared with the wild-type homozygote, respectively (codominant model), and then evaluated the risks of combined variant homozygote and heterozygote versus wild-type homozygote, and variant homozygote versus combined heterozygote and wild-type homozygote, respectively (dominant and recessive models). Stratification analyses were performed by cancer types [melanoma and nonmelanoma (BCC and SCC)] and sample size (case plus control < 1000 and case plus control  $\geq$  1000). Hardy-Weinberg equilibrium (HWE) was tested by chi-square test for goodness of fit. Sensitivity analyses were performed by deleting one study each time to reflect the influence of the individual data set on the pooled ORs. Egger's test and inverted funnel plots were utilized to assess the publication bias of the literature. The funnel plot was a group of simple scatterplots for the effects estimated from individual studies (horizontal axis) against a measure of study size (vertical axis), and the plot would resemble a symmetrical inverted funnel in the absence of bias (Egger, 1997). The Egger's test was used to evaluate the asymmetry of funnel plot by determining

**Table 1. Characteristics of Literature Included in the Meta-analysis**

Author	Year	Country	Ethnicity	Type of cancer	Cases	Controls	HWE <sup>a</sup>	MAF <sup>b</sup>		Power <sup>†</sup>	
								In controls (%)	1.2	1.5	
939A>C											
rs2228001											
Fernanda TG	2011	Brazil	unknown	cutaneous melanoma	202	210	0.31	0.6	11.3	44.71	
Maidier IV	2011	Spanish	Caucasian	malignant melanoma	684	406	0.4	0.1	25.37	84.98	
Adina F	2010	Mannheim, Germany, Valencia, Spain	Caucasian	cutaneous melanoma	1368	736	0.4	0.35	58.97	99.86	
Chunying L	2006	USA	Caucasian	cutaneous melanoma	605	603	0.42	0.14	32.66	93.16	
Ranjit KT	2006	Hungary, Romania, Slovakia	Caucasian	basal cell carcinoma	529	533	0.42	0.82	29.8	89.84	
Fabiola F	2005	Sweden and Finland	Caucasian	basal cell carcinoma	241	260	0.31	0.69	15.93	62.01	
Sandra B	2005	Germany	Caucasian	cutaneous melanoma	294	375	0.37	0.69	18.48	69.95	
499C>T											
rs2228000											
Maidier IV	2011	Spanish	Caucasian	malignant melanoma	684	406	0.27	0.25	21.48	79.14	
Adina F	2010	Mannheim, Germany, Valencia, Spain	Caucasian	cutaneous melanoma	1368	736	0.27	0.4	51.27	99.59	
Chunying L	2006	USA	Caucasian	cutaneous melanoma	605	603	0.27	0.21	27.66	89.07	
Sandra B	2005	Germany	Caucasian	cutaneous melanoma	294	375	0.22	0.003	14.64	58.94	

<sup>†</sup>Power was calculated by the DSTPLAN 4.2 software with MAF in controls as the frequency of risk factor and OR was selected with 1.2 and 1.5 as the relative risk respectively; <sup>a</sup>Hardy-Weinberg equilibrium (HWE); <sup>b</sup>Minor allele frequency (MAF)

**Table 2. Summary ORs of the XPC Polymorphisms and Skin Cancer Risk by Cancer Type**

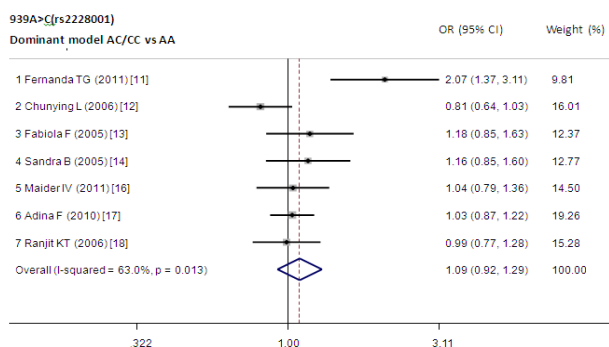
SNP	Type of cancer	Studies	Ht versus WT Ho			VR Ho versus WT Ho			Dominant model			Recessive model		
			OR (95%CI)	P*	P**	OR (95%CI)	P*	P**	OR (95%CI)	P*	P**	OR (95%CI)	P*	P**
939A>C	Total skin cancer	7	1.05(0.90, 1.23) †	0.049		1.19(0.93, 1.52)†	0.015		1.09(0.92, 1.29)†	0.013		1.11(0.98, 1.26)	0.072	
	Melanoma	5	1.04(0.85, 1.29) †	0.023		1.30(0.94, 1.81)†	0.005		1.01(0.88, 1.40)†	0.004		1.25(0.98, 1.60)†	0.038	
	Nonmelanoma (BCC and SCC)	2	1.07(0.87, 1.33)	0.307	0.62	0.98(0.72, 1.33)	0.848	0.371	1.06(0.86, 1.29)	0.409	0.936	0.97(0.73, 1.27)	0.585	0.285
499C>T	Total skin cancer	4	0.90(0.80, 1.01)	0.409		1.16(0.93, 1.46)	0.395		0.93(0.84, 1.04)	0.726		1.21(0.97, 1.51)	0.242	

Ht, heterozygote; WT Ho, wide-type homozygote; VR Ho, variant homozygote; \* Test for heterogeneity; \*\* Test for heterogeneity between groups; †Random-effects model was used when P value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

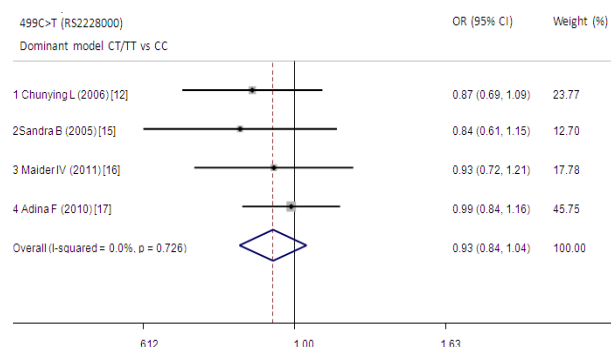
**Table 3. ORs of the XPC Polymorphism and All Skin Cancer by Sample Size**

SNP	Type of cancer	Studies	Ht versus WT Ho			VR Ho versus WT Ho			Dominant model			Recessive model		
			OR (95%CI)	P*	P**	OR (95%CI)	P*	P**	OR (95%CI)	P*	P**	OR (95%CI)	P*	P**
939A>C	<1000	4	1.15(0.98, 1.37)	0.088	0.087	1.49(1.17, 1.89)	0.056	0.005	1.27(0.98, 1.66) †	0.048	0.018	1.40(1.12, 1.74)	0.142	0.014
	≥1000	3	0.96(0.85, 1.09)	0.203		0.97(0.82, 1.15)	0.828		0.96(0.85, 1.08)	0.265		0.99(0.85, 1.16)	0.973	
499C>T	<1000	2	0.83(0.68, 1.03)	0.533	0.398	1.47(0.94, 2.32)	0.382	0.237	0.89(0.73, 1.09)	0.597	0.628	1.57(1.00, 2.44)	0.334	0.185
	≥1000	2	0.93(0.81, 1.06)	0.182		1.07(0.83, 1.39)	0.367		0.95(0.83, 1.08)	0.371		1.11(0.86, 1.43)	0.222	

Ht, heterozygote; WT Ho, wide-type homozygote; VR Ho, variant homozygote; \* Test for heterogeneity; \*\* Test for heterogeneity between groups; †Random-effects model was used when P value for heterogeneity test < 0.05; otherwise, fixed-effect model was used



**Figure 1. Forest Plot of the XPC 939A>C Polymorphism and All Skin Cancer Risk in Dominant Model**



**Figure 2. Forest Plot of the XPC 499C>T Polymorphism and All Skin Cancer Risk in Dominant Model**

whether the intercept deviates significantly from zero in a linear regression of the standardized effect estimates against their precision (Niu et al., 2011). All analyses were performed by using the software Stata version 11 (Stata Corporation, College Station, TX, USA). All statistical evaluations were made assuming a two-sided test with the significance level of 0.05, if not specially stated otherwise.

## Results

### Characteristics of the published studies

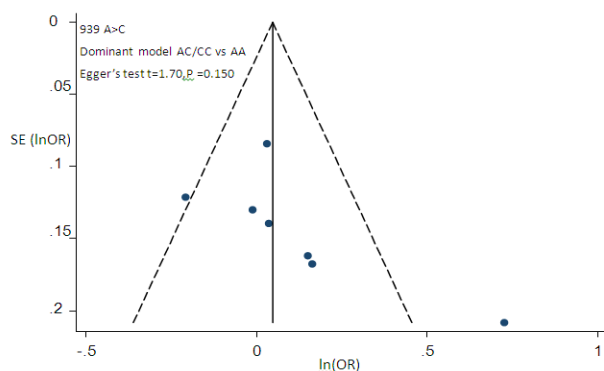
The characteristics of the selected studies were listed in Table 1. Overall, six studies presented results for melanoma, two for BCC. All studies presented results for Caucasian populations, except for one study performed in Brazil (Goncalves et al., 2011). The distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium for all selected studies. When we assumed that the OR for an allelic genetic association was 1.2, no study achieved a statistical power of greater than 80%. One study (Blankenburg et al., 2005) only had recessive genotype frequency, we calculated the frequency of heterozygote genotype and wild-type homozygote genotype according to the MAF of case and control.

### Quantitative synthesis

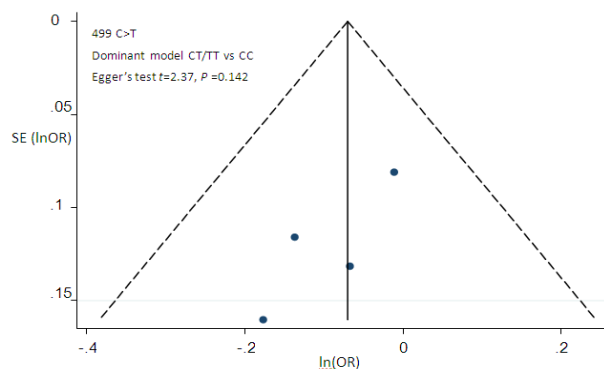
The evaluation of the associations between these two polymorphisms and skin cancer risk was presented in Table 2, Figure 1 and Figure 2. Overall, the variant C allele

of *XPC 939A>C* did not significantly increase the risk of all skin cancer in any of the genetic models (dominant model: OR, 1.09; 95% CI, 0.92-1.29,  $P = 0.013$  for heterogeneity test; recessive model: OR, 1.11; 95% CI, 0.98-1.26,  $P = 0.072$  for heterogeneity test). Similarly, for *XPC 499C>T*, no significant association between the polymorphism and risk of all skin cancer was observed (dominant model: OR, 0.93; 95% CI, 0.84-1.04,  $P = 0.726$  for heterogeneity test; recessive model: OR, 1.21; 95% CI, 0.97-1.51,  $P = 0.242$  for heterogeneity test).

We then investigated the effect of these two *XPC* polymorphisms on the susceptibility to subtypes of skin cancer. All studies about 499C>T and skin cancer susceptibility involved in this meta-analysis were performed in melanoma but not in other skin cancer subtypes, so they could not be stratified. As shown in Table 2, for *XPC 939A>C*, we still did not observe significant association between this polymorphism and risk of melanoma or nonmelanoma (BCC and SCC) in any of the genetic models. In order to obtain the exact consequence of the relationship between these two polymorphisms and skin cancer susceptibility, stratified analyses by sample size of studies were performed, as shown in Table 3. For 939A>C, the C allele was shown to significantly increase the risk of skin cancer in codominant model (CC versus AA: OR, 1.49; 95% CI, 1.17-1.89,  $P = 0.056$  for heterogeneity test) and recessive model (CC versus AA/AC: OR, 1.40; 95% CI, 1.12-1.74,  $P = 0.142$  for heterogeneity test) in the subgroup with small sample size



**Figure 3. Funnel Plot of the *XPC* 939A>C Polymorphism and All Skin Cancer Risk in Dominant Model**



**Figure 4. Funnel Plot of the *XPC* 499C>T Polymorphism and All Skin Cancer Risk in Dominant Model**

(case plus control < 1000), and the *P* values for between-group heterogeneity test in these two models were 0.005 and 0.014, respectively. For 499C>T, the T allele was shown to increase the skin cancer risk in recessive model (TT versus CC/CT: OR, 1.57; 95% CI, 1.00-2.44, *P* = 0.334 for heterogeneity test) in subgroup with small sample size, and the between-group heterogeneity test was not significant (*P* = 0.185). We did not find any significant association in large sample size subgroup.

#### Sensitivity analyses

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs, and all of the corresponding pooled ORs were not materially altered (data not shown).

#### Publication bias

We used Funnel plot and Egger's test to address potential publication bias in the available literature. As shown in Figure 3 and Figure 4, for 939A>C and 499C>T, the shape of the funnel plots seemed symmetrical in dominant model in all skin cancer, suggesting the absence of publication bias. Then, Egger's tests were used to provide statistical evidence for funnel plot symmetry, which were more pronounced when the larger of the intercept deviated from zero in linear regression analysis. No obvious evidence of publication bias was found (*P* value for 939A>C and 499C>T were 0.150 and 0.142, respectively).

## Discussion

The nucleotide excision repair (NER) pathway is one

of the versatile DNA repair systems, which deals with the main types of UV-induced DNA damage. Specifically, NER genes remove bulky DNA lesions caused by UV light, bulky adducts induced by chemical carcinogens, and other helix-distorting DNA lesions (Wood et al., 2005). As one of the important member of NER pathway, *XPC* gene encodes a protein that plays a pivotal role in the recognition of distorted DNA structures caused by DNA lesions and contributes to recruiting the other proteins of the NER complex (i.e., XPA, RPA, TFIIH) (Moriwaki et al., 2008). Variation of *XPC* is suggested to change DNA repair capacity and alter cancer susceptibility. Since the identification of the *XPC* 939A>C and 499C>T polymorphisms, a number of studies have investigated the genetic effects of these two polymorphisms on skin cancer susceptibility, but results were conflicting.

*XPC* 939A>C on exon 15 is assessed in an allele-specific post-UV host cell reactivation assay and resulting in an amino acid change from Lys to Gln (Gozukara et al., 2001). In silico, evidence suggests that 939A>C can possibly damage the protein. It is important to consider that even though the computational analysis suggests a possible damage, this prediction may be not always correct, for the reason that protein-protein interactions may minimize amino-acid substitution-dependent conformation changes (Francisco et al., 2008). Again, if this is correct, the observed effects will be either cell or tissue specific. *XPC* 499C>T also locates on the exon region which suggests to be involved in critical interactions with DNA and repair proteins (Hu et al., 2005). However, the influence of this variant of *XPC* on irradiation-specific DNA-damage repair capacity in in-vitro assays does not corroborate the presumed effect (Vodicka et al., 2004; Vodicka et al., 2007).

In our present pooled analysis of 8 published studies encompassing 3,892 cancer cases and 4,287 controls, no evidence of significant association was found between the two polymorphisms and the risk of any type of skin cancer. The results of stratified analysis by sample size showed that these two polymorphisms could not affect the susceptibility to skin cancer in subgroup with large sample size, which also supported the conclusion above. For this result, one possibility is that the mechanism of repair and the role of *XPC* may differ based on the type of lesions. The UV irradiation directly causes two major photoproducts in DNA: cyclobutane pyrimidine dimers (CPDs) as well as (6-4) photoproducts (6-4PPs) which have been suggested to result in carcinogenesis of the skin (Moriwaki et al., 2008). The *XPC*-HR23B protein complex recognizes helix-distorting lesions as part of the global genome NER repair pathway (Sugasawa et al., 1998). This complex has a strong binding affinity for 6-4PPs, and a rather weak affinity for CPDs (Batty et al., 2000; Kusumoto et al., 2001). It has been postulated that it is the persistent CPD lesions that are more likely to promote cancer induction (Hemminki et al., 2002), and *XPC* is not primarily involved in their repair. Our results of no elevated risk for skin cancer with the *XPC* 939A>C and 499C>T polymorphisms were consistent with this model. Another reasonable explanation for the overall no associations of these two polymorphisms and skin cancer



risk is that, when examining the role of polymorphisms in DNA repair genes in cancer susceptibility, it is important to consider the importance of 'gene-environment' interactions, which are crucial to low-penetrance genes (Lohmueller et al., 2003). For skin cancer, the main risk factor seems to be the exposure to ultraviolet radiation which leads to DNA damage. This damage can be partially repaired by the NER pathway, where *XPC* acts in the initial recognition process of the DNA lesion. Some subtle changes in this gene may impair repair efficiency. Therefore, interactions of the variant genotype of *XPC* and UV exposure may lead to an increased risk of skin cancer, as previously reported (Begg et al., 2006; Cust et al., 2009). Regardless of environment influence, *XPC* may have little influence on skin cancer.

In the eight included studies, one suggested that the variant C allele of *XPC* 939A>C can significantly increase risk of melanoma (Goncalves et al., 2011), which might be biased by some reasons. In clarifying an association between genetic polymorphisms and cancer risk, the quality of study design is of great importance. However, some of the analyzed studies had methodological shortcomings. For instance, control population selected from hospital-based cancer-free patients in Fernanda's and Maider's study (Goncalves et al., 2011; Ibarrola-Villava et al., 2011) could not represent whole population, which could lead to possible biases. In addition, some of the studies had a very small sample size (Blankenburg et al., 2005; Goncalves et al., 2011) and had no adequate power to obtain convincing results. The results from stratified analysis by sample size showed that 939A>C polymorphism could only increase the risk of skin cancer when the sample size was small, which also indicated that the observed significant ORs in these studies may be false associations.

When interpreting our results, compared with individual studies, the current meta-analysis had some key advantages. First, a substantial number of cases and controls were pooled from several studies, which significantly increased the statistical power of the analysis. Second, publication bias was not observed, which indicated that the pooled results should be more credible.

On the other hand, several limitations need to be noted. Firstly, although the funnel plot and Egger's test did not show any publication bias, selection bias might have occurred because only studies published in English were included in this study. Secondly, due to the restriction of the original information, potential gene-gene and gene-environment interactions were not evaluated in this study.

In summary, this meta-analysis provided further evidence that the variant genotypes of *XPC* 939A>C and 499C>T polymorphisms may not increase the risk of any kind of skin cancer. More future studies were suggested to perform to access the associations between polymorphisms and skin cancer.

## Acknowledgements

The author(s) declare that they have no competing interests.

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