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ARTICLE

Haplotype analysis of the 185delAG *BRCA1* mutation in ethnically diverse populations

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The 185delAG* *BRCA1* mutation is encountered primarily in Jewish Ashkenazi and Iraqi individuals, and sporadically in non-Jews. Previous studies estimated that this is a founder mutation in Jewish mutation carriers that arose before the dispersion of Jews in the Diaspora ~2500 years ago. The aim of this study was to assess the haplotype in ethnically diverse 185delAG* *BRCA1* mutation carriers, and to estimate the age at which the mutation arose. Ethnically diverse Jewish and non-Jewish 185delAGBRCA1* mutation carriers and their relatives were genotyped using 15 microsatellite markers and three SNPs spanning 12.5 MB, encompassing the *BRCA1* gene locus. Estimation of mutation age was based on a subset of 11 markers spanning a region of ~5 MB, using a previously developed algorithm applying the maximum likelihood method. Overall, 188 participants (154 carriers and 34 noncarriers) from 115 families were included: Ashkenazi, Iraq, Kuchin-Indians, Syria, Turkey, Iran, Tunisia, Bulgaria, non-Jewish English, non-Jewish Malaysian, and Hispanics. Haplotype analysis indicated that the 185delAG mutation arose 750–1500 years ago. In Ashkenazim, it is a founder mutation that arose 61 generations ago, and with a small group of founder mutations was introduced into the Hispanic population (conversos) ~650 years ago, and into the Iraqi–Jewish community ~450 years ago. The 185delAG mutation in the non-Jewish populations in Malaysia and the UK arose at least twice independently. We conclude that the 185delAG* *BRCA1* mutation resides on a common haplotype among Ashkenazi Jews, and arose about 61 generations ago and arose independently at least twice in non-Jews.**
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INTRODUCTION

More than 3000 pathogenic mutations and sequence alterations have been reported within the *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 600185) since they were identified in the mid 1990s (http://research.nhgri.nih.gov/bic/). In several populations, the spectrum of mutations is rather limited, reflecting a single or a limited number of 'founder mutation(s)': the Dutch,[1] Icelandic,[2] the Polish,[3] Russian,[4] and the Norwegian[5] populations. Notably, among Ashkenazi Jews (ie, Jews of east European ancestry), three mutations in *BRCA1* (185delAG, 5382InsC) and *BRCA2* (6174delT) occur frequently.[6] One of these mutations (185delAG* *BRCA1*) is also reported among non-Ashkenazi (primarily Iraqi origin) Jews,[7] and sporadically among non-Jewish populations (http://research.nhgri.nih.gov/bic/).[8–16] The occurrence of an identical mutation in ethnically diverse populations may stem from either a founder effect or may reflect a so-called mutational hotspot. Earlier studies conducted in a Jewish 185delAG **BRCA1* mutation carrier showed that in Ashkenazim this is a seemingly founder mutation that shares a common haplotype,[7,16–18] but in Indian[12] and Pakistani[13] non-Jewish mutation carriers the haplotype was reportedly different, suggesting that this mutation arose independently in these populations. As the majority of these earlier studies were based on data generated from a few intragenic markers, obtained from a single-genotyped individual from a carrier family, phasing and estimation of the age when the mutation arose were suboptimal. The aim of the present study was to overcome these caveats by using multiple polymorphic markers on multiple family members to allow defining the shared haplotype, phasing, and comparing the haplotype in ethnically diverse 185delAG**BRCA1* mutation carriers.

MATERIALS AND METHODS

Participant identification and recruitment

Israel. The study population was recruited from among individuals counseled and tested at one of three oncogenetics services located at the Sheba Medical Center, Tel-Hashomer, the Rambam Medical Center, Haifa, or the Rivkah Ziv Medical center in Zefat, since 1 January 2000. Participants recruited were either diagnosed with breast cancer or ovarian cancer, or in the minority of cases were asymptomatic individuals from 'high-risk breast/ovarian cancer families

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based on well-accepted criteria.[19] The study was approved by the local IRBs, and each patient gave informed consent.

USA. Hispanics in New Mexico (all of Colonial New Mexico Hispanic ancestry)[20,21] and California (primarily of Mexican ancestry) with a personal or family history of breast and/or ovarian cancer were enrolled in an IRB-approved registry after informed consent and underwent genetic counseling and BRCA testing within the City of Hope Clinical Cancer Genetics Community Research Network (CCGCRN). The CCGCRN is a consortium of 14 US cancer center and community-based clinics that provide GCRA to individuals with a personal or a family history of cancer.[22] A blood sample, demographic data, and four- to five-generation pedigrees were obtained, including reported ethnicity and country/state of origin, for each grandparental lineage. Clinical details (eg, age at diagnosis, pathology report, and/or death certificate when possible) were obtained for relatives affected with breast and/or ovarian cancer. A bilingual cancer risk counselor conducted GCRA sessions for Spanish-speaking patients, or translation services were provided, with adapted counseling aides and Spanish consent forms.[22,23]

Malaysia. Patients were recruited as part of a study into the genetic factors of breast cancer in Malaysia's multiethnic population, using previously described identification and recruitment schemes that were ethically approved.[24]

England. Breast and ovarian cancer families have been tested for *BRCA1/2* mutations since 1996 in the Manchester region of North-West England. The region covers a population of ~4.5 million people. Women who attend the specialist genetic clinics in the region with a family history of breast or ovarian cancer have a detailed family tree elicited with all first-, second-, and, if possible, third-degree relatives recorded. If a *BRCA1* or *BRCA2* mutation is identified, further attempts are made to ensure that all individuals at risk of inheriting the family mutation are represented on the pedigree.[25] Once a family-specific pathogenic *BRCA1/2* mutation is identified, predictive testing is offered to all blood relatives. Where possible, all affected women with breast or ovarian cancer are tested to establish the true extent of *BRCA1/2* involvement in the family.

DNA extraction-Peripheral blood leukocyte DNA was extracted using the PUREgene kit (Gentra Inc., Minneapolis, MN, USA) using the manufacturer's recommended protocol.

Analysis for the 185delAG BRCA1 mutation

Israel. Analysis for the *BRCA1* 185delAG mutation was carried out using a PCR-directed mutagenesis assay to introduce a restriction site that distinguishes between the wild-type and the mutant allele, as previously described and used by us.[6,26] Confirmation of any suspect sample was done using sequencing of the same amplicon.

USA. *BRCA* testing was performed at Myriad Genetic Laboratories (MGL), Inc. (Salt Lake City, UT, USA), including full sequencing of exons and flanking intronic segments.

Malaysia. Full sequencing of exons and intron–exon boundaries, and MLPA analysis were performed as previously described.[24]

England. Mutation screening involves a whole-gene sequencing of exons and intron–exon boundaries, and MLPA analysis for large deletions.[27] Among 335 non-Jewish families with pathogenic *BRCA1* mutations, 5 (1.5%) harbored the 185delAG**BRCA1* mutation.

Allelotyping for the BRCA1 locus

To determine the haplotype structure of the BRCA1*185delAG mutation, the following markers were used: three intragenic short-tandem repeats, D17S855, D17S1322, and D17S1323, and 12 flanking perigenic markers, D17S1147, D2171801, D17S1299, D17S1814, D17S1818, and D17S1867 upstream to BRCA1. D17S951, D17S1789, D17S1861, D17S931, D17S1827, and D17S1795 were downstream to BRCA1. All markers were dinucleotide STRs, except for D17S1299 (tetranucleotide) and D17S1322 (tri-nucleotide). It is noteworthy that the three intragenic markers were also used by

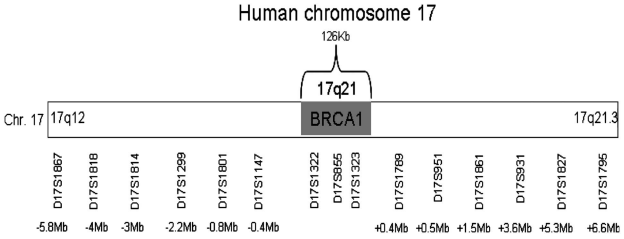

Figure 1 Intra- and peri-*BRCA1* markers used and their locations. A map of chromosome 17 showing the *BRCA1* region and the intragenic and flanking markers used for the haplotype reconstruction. The location of each marker is noted as the distance from the *BRCA1* gene.

Neuhausen *et al*.[18] The primer sequences for all markers were retrieved from the Genome DataBase online database (www.gdb.org). All markers span approximately 12.5 Mbp around the *BRCA1* locus (Figure 1). Genomic DNA from each subject was amplified by PCR for each marker. The forward primers of each pair of primers were labeled with FAM for the analysis of the Amplicons. A volume of 2 μl of each PCR product was mixed with 0.5 μl of the TAMRA 500 internal size standard (Applied Biosystems Inc., Foster City, CA, USA) and 12 μl of formamide. Samples were read on the ABI Prism 3100 using the GeneScan Software (Applied Biosystems). The GeneScan raw data were analyzed using the Genotyper software (Foster City, CA, USA) to obtain the allele repeat in base pairs.

Haplotype construction and age of the mutation

Age Estimates using the maximum likelihood method. To estimate the age of the mutation (or, more precisely, the number of generations as the most recent common ancestor (MRCA) of the 185delAG carriers), we used the method that was first used to estimate the age of several *BRCA1* mutations, including the mutation that is the focus of the present study, 185delAG* *BRCA1*,[18] and then extended and applied to *BRCA2* mutations,[28] and which has been used in several other similar studies, most recently in an analysis of the mutation *BRCA1**c.5266dupC (5382insC).[29] This method uses maximum likelihood and allows for both recombination and mutational events at the marker loci as means of altering a presumed ancestral haplotype. Phased haplotypes were used if these could be inferred from available family data; otherwise, all possible haplotypes were constructed from multi locus genotype data and weighted according to their probability. For each value of G (the number of generations since the MRCA), the relative likelihood that each haplotype is descended from the ancestral haplotype via mutation and recombination is calculated compared with the likelihood that it is a totally independent haplotype (ie, an independent recurrent 185delAG mutation on a different haplotype background). The value of G that maximizes this likelihood is obtained through iterative search. Ninty-five percent support intervals were constructed by identifying those points, GL and GU, where the likelihood differed from the maximum by 0.86 (corresponding to a chi-squared likelihood ratio statistic of 3.84, eg, $P = 0.05$). To examine the likely genetic history of the 185delAG mutation, we analyzed separately each of several defined subgroups in which a sufficient number of samples were available for analysis. These subgroups were Ashkenazi Jewish, Iraqi, and Hispanic. In the case of the Ashkenazi and Iraqi subgroups, there were a few samples of mixed origins (eg, Iraqi–Turkish). We ran the analyses by both including them and excluding them from the relevant group. For these, the reference haplotype was determined by choosing the two most frequent alleles at each marker, and found the reference haplotype and the number of generations that provided the best fit to the data. Haplotypes/multilocus genotypes for all 115 families analyzed in this study are given in Supplementary Table 1.

Assumed genetic map

The recombination rates between markers were assumed to be those estimated in Kong *et al*.[30] Physical positions of the STRs and SNPs were those from the Human Reference sequence, build 3.7. For markers present on the deCODE map, we used the genetic positions in centimorgans as reported there, whereas

for those not on the deCODE map we estimated the genetic position from the proportion of physical distance between the known markers and then translated this to the genetic scale. This has the effect of using locally defined relationships between physical and genetic distance, and thus can accommodate the reported recombination suppression in this region.[31] As our method uses marker allele frequencies in the calculation of the likelihood, we estimated these frequencies from the unlinked allele (not on the assumed haplotype bearing the 185delAG mutation) of the chromosomes in the sample. Marker positions and assumed allele frequencies are given in Supplementary Table 2.

Marker mutation rates

As a baseline, we used the rates for the nine dinucleotide and two tri/tetranucleotide microsatellite markers as estimated from CEPH data by Weber and Wong[32] of 0.0006 and 0.002, respectively, for a mutation of a single-repeat unit. We assumed that the probability of changes of n repeat units in a given meiosis was (0.0006 or 0.002)n for $n=2$, 3, 4 and that for more than four repeats was taken to be equal to that for four repeat units. Because of the imprecision of these rates (and model), we introduced another parameter into the likelihood and jointly estimated the number of generations and a multiplier of the assumed marker mutation rates described above. Thus, to a certain extent, we let the data inform the proper marker mutation rates. In addition to the true underlying marker mutation rates, this also allows for potential genotyping errors to be accounted for in the model. We found that the best fit to our data was when the recombination rate was 1.25x that of Weber and Wong.[32]

Cluster analysis of 185delAG haplotpyes

To graphically present all 115 haplotypes, we performed hierarchical clustering analysis. To measure (in some sense) the similarity of haplotypes, we used a variation of the likelihood method described above, and calculated the likelihood of each haplotype paired with every other haplotype, assuming that the first was the 'reference haplotype' and assuming $G=1$. From these pairwise likelihoods, we calculated $Dij = -(Lij + Lji - Lii - Ljj)$, where Lij is the log likelihood derived from the comparison of haplotype i with haplotype j, as a measure of the distance between haplotypes i and j. Note that because of the assumption that one of the two haplotypes is the reference and the other is derived from that reference, $Lij \neq Lji$. The distance matrix composed of the (Dij) has the properties of being symmetric, positive, and $Dii = 0$. This distance matrix was then used as an input to a hierarchical cluster analysis using the Ward measure of inter-cluster similarity, as implemented in STATA v.11.0 (StataCorp., Austin, TX, USA).

RESULTS

Participants' characteristics

Overall, there were 188 participants in the study (Table 1): 54 Ashkenazim (from 38 families- of whom 46 were carriers and 8 noncarriers from 5 families). Ninety-seven non-Ashkenazi Jews were from the following origins: Iraq, Kuchin India, Syria, Turkey, Iran, Lebanon, and Bulgaria. In 18 non-Ashkenazi families, 24 noncarriers were also genotyped with the *BRCA1*-associated markers. In addition, 24 Hispanics, from 17 families of self-declared Mexican origin all 185delAG* *BRCA1* mutation carriers from the San Luis Valley, CO, USA, Arizona or California, were genotyped, as were three Malaysian non-Jewish individuals from three independent families, and 10 individuals from five families recruited in the UK. Of the 188 participants, 16 were men. There were 64 women diagnosed with breast cancer (mean age at diagnosis being ($\pm$ SD) 42.7 $\pm$ 10.15 years), and an additional four women had bilateral breast cancer. Twenty women were diagnosed with ovarian or peritoneal cancer (mean age at diagnosis was 49.9 $\pm$ 7.5 years) and the remainder ($n=88$) were asymptomatic carriers, with a mean age at counseling (data available for the Israeli patients only, $n=78$) being 42.3 $\pm$ 8.6 years.

Table 1 Number of families and individuals genotyped in the study by country and origin

Country of origin	*Ancestry*	*No. of individuals*	*No. of families*	*No. of carriers*	*Noncarriers*
Israel	Ashkenazi	54	38	46	8 (5 families)
	Non-Ashkenazi	97	18	73	24
USA	Hispanics Mexican	24	17	24	—
England	English	10	5	7	3 (2 families)
Malaysia	Malaysians	3	3	3	—

Estimation of the age of 185delAG

Of the markers genotyped, analysis was restricted to 11 markers, as the four most distant ones (D17S1867, D17S18181, D17S1827, D17S795) were too distant and only added noise to the analysis. For the whole sample consisting of 115 haplotypes/unphased multilocus genotypes, the maximum likelihood estimate of the time to the MRCA of the haplotypes was 59 generations (95% confidence interval (CI), 51–69 generations). It is more informative, however, to look at the results for specific subpopulations rather than the whole data set. In this case, the Ashkenazi Jewish set showed the greatest degree of haplotype diversity with an estimated time to MRCA of 61 generations (95% CI, 47–77 generations), compared with 31 (95% CI, 19–47 genrations) for the Hispanic 185delAG carriers and 23 generations (95% CI, 17–33 generations) in the Iraqi population. Figure 2 shows the results of the cluster analysis as a dendrogram. The heights of the vertical lines are proportional to the distance at which the clusters joined. One can see immediately that, for example, the three Malaysian haplotypes are similar to each other but quite different from the rest of the haplotypes in the data set, indicating that in this group the 185delAG mutation arose independently on a different haplotypic background. The English haplotypes tended to fall into two groups, one a separate haplotype, which has previously been indicated[18] and appears to be relatively common in the north of England (Yorkshire haplotype). However, two of the English haplotypes fit very well within the Ashkenazi Jewish haplotype, and most likely represent members of the Jewish community in Manchester that is of Ashkenazi origin. The Hispanic haplotypes seem to fall into two major groups, although both seem to cluster with a mix of Ashkenazi and Iraqi haplotypes.

DISCUSSION

The results of the present study suggest that the 185delAG**BRCA1* mutation is indeed a founder mutation in Jewish mutation carriers that arose about 1200 years ago in Ashkenazi Jews, and that through the migration of a small subset of founder mutation carriers was introduced into the Hispanic population about 650 years ago, and to the Jewish–Iraqi community about 450 years ago. These numbers are based on calculating 20 years/generation.[33] Using a 30 year/generation and using the upper limits of the estimated the MRCA the estimated ages are 2300, 1400, and 1000 years ago for the Ashkenazi, Hispanics, and the Iraqis, respectively.

These results are somewhat unexpected, as the prevailing notion that was based both on historical events of the Jewish people and the finding of a similar haplotype in Ashkenazi and non-Ashkenazi

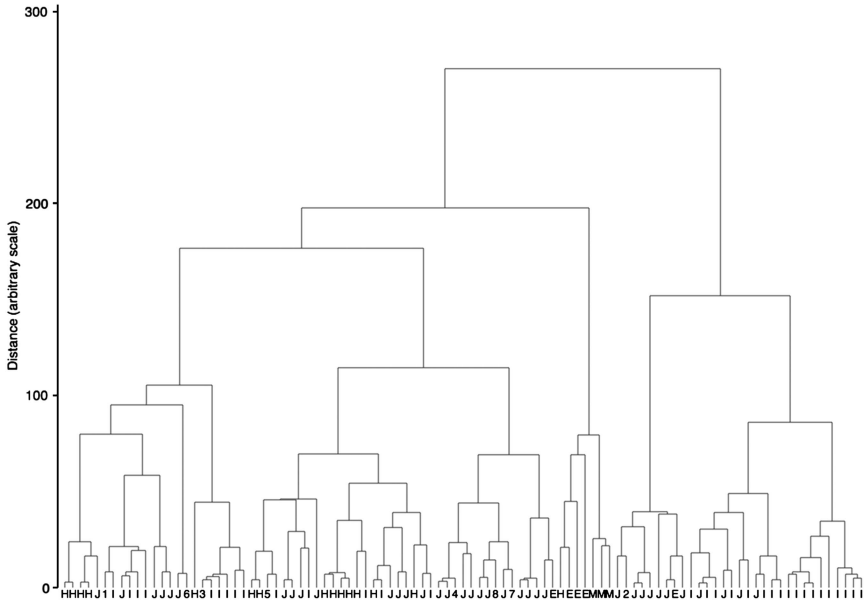

Figure 2 Cluster analysis of the 185delAG* *BRCA1* mutation carriers. The Letter beneath each node describes the origin of the sample: J: Ashkenazi Jews; I: Iraqi Jews; H: US Hispanics; M: Malaysians: E: English. 1–8 refer to other Jewish singleton samples as follows: 1: Sephardic; 2: Ashkenazi/Iran; 3: Kuchin, India; 4: Iran; 5: Syria/Turkey; 6: Turkey/Iran; 7: Lebanese/Bulgarian; 8: non-Ashkenazi. Some similar haplotypes of the same group have already been combined at the first step and could not be individually displayed on the diagram.

(primarily Iraqi) mutation carriers prompted the tentative conclusion that the 185delAG**BRCA1* mutation is an ancient Jewish mutation that arose before the dispersion of the Jews in the Diaspora about 2500 years ago.[34,35] Thus, the finding of a later age at which the mutation arose in Ashkenazim and that the date it was introduced into the Iraqi–Jewish community was significantly later in history is somewhat puzzling, and unaccounted for by historical events. Specifically, there are no records of any major influx of Ashkenazi populations from Europe back to the region of Modern-day Iraq. However, given the central role that Iraq and the area played in trade, the traditional involvement of Jewish Ashkenazim in trade, it is plausible that a few Jewish Ashkenazi individuals (including one or few founders) immigrated to Iraq as individuals and not as part of a big migration wave. Such a small and genealogically insignificant migration would not be captured by most historians.

Yet the results pertaining to the existence of the 185delAG**BRCA1* mutation and the date when it arose in Hispanics are in line with Jewish historical events. In 1492, the Jews in Spain were given the option by the Inquisition of either becoming Christians or be expelled from Spain. A subset of Jews elected to stay in Spain, and while openly converting to Christianity secretly maintained their Jewish way of life.[36] Some of these individuals, called Conversos, later immigrated to the New World. The estimated contribution of Jewish linage in the current-day inhabitants of the Iberian Peninsula is estimated at 20%,[37] and the contribution and existence of Sephardic Jews is also noted in South American communities.[38] The age at which the mutation arose in the Hispanics, and the shared haplotype with Ashkenazim, is in line with these historic events, as well as with the specific history of the establishment of the New Mexico Colony in 1598 and descendants to the San Luis Valley in 1850.[20,35]

The Jewish Ashkenazi 185delAG**BRCA1* mutation carriers all share a common haplotype, supporting the founder mutation theory. These data are consistent with our own previously published data,[7] and those of others reporting on multi locus allelotyping of Jewish Ashkenazi mutation carriers.[16,18] The use of families and saturating the region for polymorphic markers facilitated an accurate evaluation of the age at which the mutation arose. Thus, the age at which the 185delAG**BRCA1* mutation arose in the Ashkenazi population reported herein (61 generations ago $\sim$1200 years ago) is consistent with the age estimated by Neuhausen *et al*,[18] who estimated that the mutation arose around 1235 CE (90% CI ranging from 396 to 1536 CE) based on the 500-kb conserved region centromeric to the mutation. It is noteworthy that Im *et al*[39] reported that 50% of 316 Ashkenazi 185delAG**BRCA1* mutation carriers share a common ancient 2.1-Mb haplotype at the same locus, making this a more recent mutation. On the basis of a much smaller number of cases, Pereira *et al*[40] reported that there is a single common Ashkenazi 185delAG-bearing haplotype present in 15% of all Ashkenazi individuals.

In the present study, three Malaysian non-Jewish 185delAG**BRCA1* mutation carriers were also genotyped. Their haplotype seemed to cluster in a small genomic segment, suggesting that it arose independently from that of the Ashkenazi and other Jewish individuals. Yet, the small number of analyzed individuals precludes the ability to assess the precise age of the mutation. The so-called Yorkshire haplotype[18] also seems to have arisen independently of the Jewish mutation carriers. These data may be interpreted to indicate that this is a mutational hotspot, but this notion remains speculative and should be stated cautiously. Yet some British mutation carriers have a haplotype indistinguishable from that of the Ashkenazi one. Indeed, Jewish presence in the British Isles is well documented since 1070, with earlier presence presumably dating even to Roman times. Jewish migration from Europe into current-day England, was ongoing until the expulsion of Jews from England in 1290 by King Edward I.[41] Thus, it seems plausible that similar to the occurrence of the 185delAG* *BRCA1* mutation in the Jewish–Iraqi population a few founders also migrated into the UK. Earlier studies reported the existence of the 185delAG **BRCA1* mutation in non-Jewish

individuals of diverse ethnicities: Chilean,[8] Spanish,[9] Spanish Gypsies,[10] Indian,[11,12] Pakistani,[13] Egyptians,[14] East Europeans,[15] and other populations in Europe.[1] In all cases where the haplotype of non-Jewish mutation carrying individuals was determined,[8–10,15] the haplotype was reportedly identical with that of Ashkenazim except for a few British families[18] the Indian,[12] and Pakistani[13] mutation carriers. These latter families shared an identical haplotype, distinct from that of Ashkenazim. It is possible that these individuals share the same haplotype with the Malaysian non-Jews genotyped in the current study. However, without actual haplotyping of more families from that area, this remains speculative.

In conclusion, the 185delAG**BRCA1* mutation arose in the Ashkenazi population about 61 generations ago and was later introduced into the Sephardic and Iraqi–Jewish populations, and in non-Jewish individuals it has a different origin and may have arisen at least twice independent of the Jewish origin mutation.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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