

Distribution of *IFITM3* polymorphism (dbSNP: rs12252) in mestizo populations in four states of Mexico

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Summary

Interferon-inducible transmembrane protein 3 (IFITM3) participates in the defense against viral infections. This study identified and compared the frequency of the IFITM3 rs12252 polymorphism in 410 individuals in western Mexico. The western Mexican allelic frequencies (frequency of the “C” allele = 0.18) differ from some American, East Asian and European populations.

KEYWORDS

disease susceptibility, gene frequency, immunity, innate, interferon

1 | INTRODUCTION

The innate immune response against viral infection is important and mediated through different restriction factors. The first line of defense in viral infections is the interferon system, wherein interferon-inducible transmembrane proteins (IFITM) are involved (Takaoka & Yanai, 2006). In humans, there are four interferon genes located on chromosome 11 (*IFITM* 1, 2, 3 and 5), and several studies, including a functional genomic screen, have shown that IFITM 1, 2 and 3 mediate cellular resistance [demonstrated in vitro (Brass et al., 2009) and in vivo (Everitt et al., 2012)] in a wide variety of pathogenic viruses, including influenza, West Nile, dengue, HIV-1, filovirus and SARS coronavirus, indicating a differential antiviral role (Brass et al., 2009; Feeley et al., 2011; Huang et al., 2011; Jiang et al., 2010; Lu et al., 2011; Weidner et al., 2010). Interestingly, all IFITM proteins block viral replication and thereby mediate cellular resistance to viruses; nevertheless, it has been documented that IFITM3 protein shows greater restrictive capacity (Brass et al., 2009; Feeley et al., 2011; Huang et al., 2011; Lu et al., 2011; Weidner et al., 2010). Recently, Savidis et al. (2016) showed the inhibitory capacity of IFITMs, particularly IFITM3, in Zika virus (ZIKV) replication (Savidis et al., 2016). Over the last decade, compared with other emergent outbreaks due to viruses, ZIKV has rapidly emerged as a public health emergency according to the World Health Organization (Savidis et al., 2016). In a murine model (*Ifitm3*^{-/-}) of chikungunya virus infection, *Ifitm3* exhibited

an antiviral role, controlling the infection of multiple alphaviruses (Poddar, Hyde, Gorman, Farzan, & Diamond, 2016). Currently, the mechanism of cellular resistance to viruses mediated through IFITM family proteins is not fully understood. Thus far, diverse approaches have provided evidence that IFITM proteins inhibit viral fusion with the cellular membrane and do not function at steps of receptor binding or conformational changes in pH-dependent virus proteins required for membrane fusion (Brass et al., 2009; Feeley et al., 2011; Li et al., 2013). In 2013, Li et al. showed that IFITM proteins block hemifusion through changes in the topology of the cellular membrane and protect against virus infections at early stages (Feeley et al., 2011; Li et al., 2013).

Mexico suffered from a pandemic caused by influenza A (H1N1) pdm09 virus (Echevarría-Zuno et al., 2009), and cases of chikungunya (Díaz-Quinonez et al., 2016; Macías-Hernández, López-Magaña, Fletes-Rayas, & Cambero-González, 2014) and ZIKV infections have recently been reported (Jimenez Corona et al., 2016). The severity of infections reflects a combination of host and viral genetic components. Therefore, it is important to investigate the molecular aspects of IFITM proteins. The human *IFITM3* gene has two exons, and multiple genetic variants have been identified in the coding region (Everitt et al., 2012). One of these variants, rs12252 (T/C substitution mutation), is an SNP that generates a splice acceptor site, resulting in an isoform (Δ 2IFITM3) characterized by the absence of the first N-terminal 21 amino acids (Everitt et al., 2012). The frequency of the “C” allele for SNP rs12252 is

heterogeneous and varies between different human populations: the "C" allele is rare in European populations (C allele frequency = 0.041) and some American countries, and it is particularly rare in Colombia and Puerto Rico (C allele frequency = 0.074 and 0.111, respectively) (1000 Genomes Project Consortium et al., 2015).

A recent meta-analysis concluded that SNP rs12252 is associated with severe influenza susceptibility (Yang et al., 2015). Notwithstanding, studies with larger patient sample sizes and various ethnicities are necessary because Asian and European populations have primarily been analysed, wherein the extremes of the frequencies are represented: on the one hand, the C/C genotype is rare in Europe (markedly in Northern Europe), while on the other hand, this genotype is common in Asiatic populations (Mills et al., 2014; Yang et al., 2015; Zhang et al., 2013). Currently, there are no reports concerning the frequency of the rs12252 polymorphism in mestizos born and raised in Mexico, and western regions of Mexico are similar in proportions between native Mexican components (pre-Columbian diversity) and European ancestries, with a minor African component, according to Moreno-Estrada et al. (2014). The main objective of this study was to identify the frequency of the rs12252 polymorphism in four mestizo populations of western Mexico and compare the results with those previously reported in all populations analysed in the "1000 Genomes Project Consortium phase 3" (1000 Genomes Project Consortium et al., 2015).

2 | MATERIALS AND METHODS

2.1 | Study population

A total of 410 samples from healthy urban volunteer donors who attended western Mexico hospitals (blood banks) were studied by convenience, generating a DNA library comprising the following states: Nayarit ($n = 100$), Jalisco ($n = 135$), Colima ($n = 84$) and Michoacan ($n = 91$). For descriptive studies, sample size was calculated using "Epi Info™ StatCalc" software, considering a 3% true prevalence of genotype C/C in North American populations with Mexican ancestry established in the 1000 Genomes Project phase 3 (342 subjects were calculated as a sufficient sample, assuming a confidence level of 97%). The subjects were between 18 and 50 years of age. Demographic and hereditary information was obtained from all recruited individuals confirmed as unrelated up to the previous two generations. None of the included individuals had a genetic condition diagnosed at the onset of the study.

2.2 | Molecular analysis

The SNP rs12252 was analysed based on PCR-RFLP. Blood samples were collected from all subjects in EDTA-Na₂ tubes, and genomic DNA was purified from peripheral blood leucocytes according to a standard method (Gustincich, Manfioletti, Del Sal, Schneider, & Carninci, 1991). The selected markers were genotyped using a previously described method (Mills et al., 2014) with the modified primers, ACTGTTGAGAAACCGAACTACTGG (F) and

CTATAGGGAGAACTGCTCTGGGCT (R) for yield optimization. MscI (New England Biolabs, Ipswich, MA, USA) was used to digest the PCR product in the presence of the T allele (wild). Fragments with lengths of 624, 490 and/or 134 base pairs were observed. The genotypes were identified using polyacrylamide gel electrophoresis (29:1, 6%) and stained with silver nitrate. Additionally, two PCR products (homozygote CC and heterozygote CT) were sequenced using the same primers with the Sanger method (CEQ™ 8000 Genetic Analysis System, Beckman Coulter) to confirm the genotype (Figure 1). The samples were genotyped at CIBO, IMSS (Guadalajara, Mexico).

2.3 | Statistical analysis

Nonparametric statistical analysis for all comparisons (Fisher's exact test) was performed using SPSS v.22 (Crosstabs) for Windows (IBM, Armonk, NY, USA), and statistical significance was considered when $p < .05$. Allele frequencies were directly obtained through gene counting, and conformance to the Hardy-Weinberg equilibrium (HWE) was analysed using the Fisher's exact test, comparing the observed genotype frequencies with the expected genotype frequencies.

3 | RESULTS

The results of frequency analyses within the western population (410 subjects) are highlighted in Table 1, wherein rs12252 polymorphism frequencies did not show differences between the four states using Fisher's exact test ($p > .17$). Nonetheless, by ordering from the highest to lowest allelic frequency, the state that showed the highest frequency of the C allele was Michoacan, Nayarit, Jalisco and Colima showed the lowest frequency, without exhibiting a clear geographical trend. In this study, the C allele frequency in Nayarit and Jalisco (northern states in the western region) was similarly contrasted with the total frequency of the western population (Table 1). Mendelian segregation analyses of the rs12252-polymorphism in the western Mexican population revealed that genotype frequencies were in HWE agreement. The findings obtained from western Mexico are summarized in Table 1.

Regarding population genetics, the rs12252 frequencies were contrasted among 26 populations belonging to five super-populations (admixed American, East Asian, South Asian, European and African populations) considered in the 1000 Genomes Project phase 3 (1000 Genomes Project Consortium et al., 2015). The results of the inter super-population analyses are summarized in Table 2. Intracontinental (four admixed American populations) analyses showed differences ($p > .03$) in genotypic and allelic frequencies of rs12252 between western Mexico and populations of Colombia, Peru and Puerto Rico. The 1000 Genomes Project phase 3 includes a small sample of Mexican US residents ($n = 64$) (1000 Genomes Project Consortium et al., 2015), with frequencies similar to those in the western Mexico population (present study) according to Fisher's exact test (Table 2). Concerning the presence of C alleles in the remaining super-populations (East

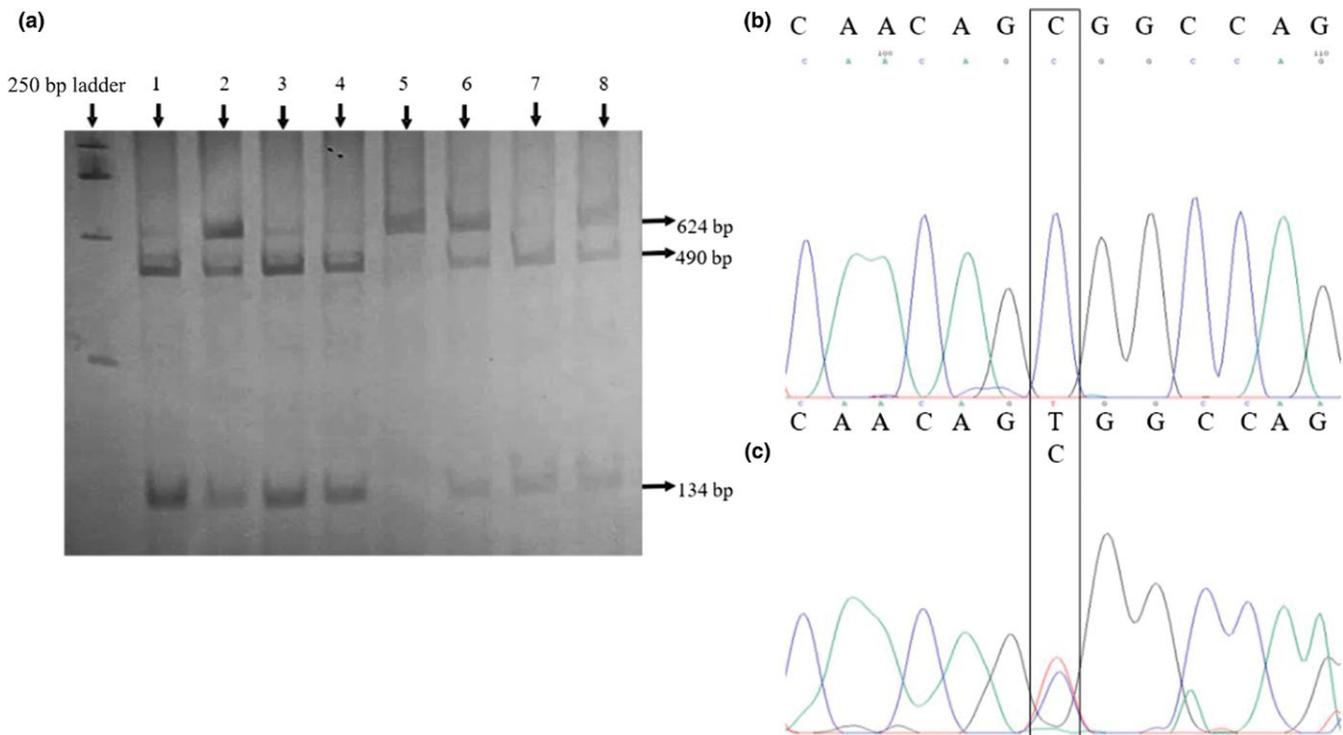


FIGURE 1 Electrophoresis and electropherograms of SNP rs12252-C. (a) PCR products digested. Allelic systems: Wild homozygous individuals (TT), lanes 1, 3, 4 and 7 (490/134-bp fragments); Heterozygous individuals (CT), lanes 2, 6 and 8 (624/490 and 134-bp fragments); Homozygous mutants (CC), lane 5 (624-bp fragment). (b and c) Electropherograms of mutant homozygous (CC) and heterozygous (CT) individuals, respectively. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Genotypic and allelic frequencies of rs12252 in healthy urban individuals belonging to different western Mexico states and Hardy-Weinberg equilibrium

Group (n)	Genotypic frequencies, (n)			Allelic frequencies, (n)			p value
	T/T	T/C	C/C	T	C		
Nayarit (100)	0.63 (63)	0.36 (36)	0.01 (1)	0.81 (162)	0.19 (38)	>.18 ^a	
Jalisco (135)	0.69 (93)	0.28 (38)	0.03 (4)	0.83 (224)	0.17 (46)	>.17 ^b	
Colima (84)	0.74 (62)	0.25 (21)	0.01 (1)	0.86 (145)	0.14 (23)		
Michoacán (91)	0.62 (56)	0.32 (29)	0.06 (6)	0.78 (141)	0.22 (41)		
Western (410)	0.67 (274)	0.30 (124)	0.03 (12)	0.82 (672)	0.18 (148)		
Hardy-Weinberg equilibrium							
Western (n = 410)	Genotypic frequencies Observed		Genotypic frequencies Expected	p value			
T/T	274		275.4	>.65 ^a			
T/C	124		121.3				
C/C	12		13.4				

^aComparison of genotypic frequencies by Fisher's exact test.

^bComparison of Allelic frequencies by Fisher's exact test.

Asian, South Asian, European and African) and the statistical comparison to the genotypes and allele frequencies revealed in this study, four populations belonging to Africa (total = seven) and four populations belonging to South Asia (total = five) did not show statistically significant differences ($p > .05$) (Table 2).

Nevertheless, the genotypic and allelic distribution in western Mexico differed ($p < 10^{-3}$) among all (five) East Asian populations and all European ancestry populations (five), all of which are presented in the 1000 Genomes Project phase 3 (1000 Genomes Project Consortium et al., 2015).

TABLE 2 Genotypic and allelic frequencies of rs12252 in Western Mexico states and other populations belonging to the 1000 Genomes Project Consortium phase 3 (2015)

Group (n)	Genotypic frequencies, (n)			Allelic frequencies, (n)		p value	
	T/T	T/C	C/C	T	C	Gen*	Alle**
Western of Mexico ^{a,c} (410)	0.67 (274)	0.3 (124)	0.03 (12)	0.820 (672)	0.180 (148)	–	–
MXL ^{b,c} (64)	0.6 (38)	0.37 (24)	0.03 (2)	0.781 (100)	0.219 (28)	.470	.320
Medellin, Colombia ^c (94)	0.85 (80)	0.15 (14)	0	0.926 (174)	0.074 (14)	.001	
Lima, Peru ^c (85)	0.42 (36)	0.47 (40)	0.11 (9)	0.659 (112)	0.341 (58)	<10⁻³	
Puerto Rico ^c (104)	0.78 (81)	0.22 (23)	0	0.889 (185)	0.111 (23)	.037	.016
All ^c (347)	0.68 (235)	0.29 (101)	0.03 (11)	0.823 (571)	0.177 (123)	.920	.890
Xishuangbanna, China ^d (93)	0.26 (24)	0.53 (49)	0.21 (20)	0.522 (97)	0.478 (89)	<10⁻³	
Han in Beijing, China ^d (103)	0.18 (19)	0.56 (57)	0.26 (27)	0.461 (95)	0.539 (111)		
Southern Han, China ^d (105)	0.27 (28)	0.46 (48)	0.27 (29)	0.495 (104)	0.505 (106)		
Tokyo, Japan ^d (104)	0.18 (19)	0.36 (37)	0.46 (48)	0.361 (75)	0.639 (133)		
Ho Chi Minh, Vietnam ^d (99)	0.33 (33)	0.40 (39)	0.27 (27)	0.530 (105)	0.470 (93)		
All ^d (504)	0.24 (123)	0.46 (230)	0.30 (151)	0.472 (476)	0.528 (532)		
Bengal, Bangladesh ^e (86)	0.71 (61)	0.26 (22)	0.03 (3)	0.837 (144)	0.163 (28)	.690	.661
Gujarati Indians in Houston, US ^e (103)	0.71 (73)	0.25 (26)	0.04 (4)	0.835 (172)	0.165 (34)	.554	.683
Indian Telugu in UK ^e (102)	0.80 (82)	0.19 (19)	0.01 (1)	0.897 (183)	0.103 (21)	.024	.008
Punjabi in Lahore, Pakistan ^e (96)	0.70 (67)	0.25 (24)	0.05 (5)	0.823 (158)	0.177 (34)	.332	1.00
Sri Lankan Tamil in the UK ^e (102)	0.76 (77)	0.22 (23)	0.02 (2)	0.868 (177)	0.132 (27)	.263	.119
All ^e (489)	0.74 (360)	0.23 (114)	0.03 (15)	0.853 (834)	0.147 (144)	.061	.063
Utah, US ^{f,h} (99)	0.91 (90)	0.09 (9)	0	0.955 (189)	0.045 (9)	<10⁻³	
Finland ^f (99)	0.84 (83)	0.16 (16)	0	0.919 (182)	0.081 (16)	.020	<10⁻³
England and Scotland ^f (91)	0.98 (89)	0.02 (2)	0	0.989 (180)	0.011 (2)	<10⁻³	
Spain peninsular ^f (107)	0.93 (100)	0.07 (7)	0	0.967 (207)	0.033 (7)		
Tuscany, Italy ^f (107)	0.93 (100)	0.07 (7)	0	0.967 (207)	0.033 (7)		
All ^f (503)	0.92 (462)	0.08 (41)	0	0.959 (965)	0.041 (41)		
Caribbean in Barbados ^g (96)	0.59 (57)	0.37 (35)	0.04 (4)	0.776 (149)	0.224 (43)	.303	.183
Southwest US ^{g,i} (61)	0.46 (28)	0.47 (29)	0.07 (4)	0.697 (85)	0.303 (37)	.004	.002
Esan, Nigeria ^g (99)	0.65 (64)	0.28 (28)	0.07 (7)	0.788 (156)	0.212 (42)	.162	.310
Webuye, Kenya ^g (99)	0.49 (48)	0.43 (43)	0.08 (8)	0.702 (139)	0.298 (59)	.001	<10⁻³
Mandinka, Gambia ^g (113)	0.63 (72)	0.30 (33)	0.07 (8)	0.783 (177)	0.217 (49)	.144	.213
Mende, Sierra Leone ^g (85)	0.56 (48)	0.38 (32)	0.06 (5)	0.753 (128)	0.247 (42)	.105	.054
Ibadan, Nigeria ^g (108)	0.43 (46)	0.48 (52)	0.09 (10)	0.667 (144)	0.333 (72)	<10⁻³	
All ^g (661)	0.55 (363)	0.38 (252)	0.07 (46)	0.740 (978)	0.260 (344)		

Bold values indicate statistically significant ($p < .05$).

*Genotypic p value by Fisher's exact test.

**Allelic p value by Fisher's exact test.

^aOur study. Populations: ^bMexican (from California), ^cadmixed American, ^dEast Asian, ^eSouth Asian, ^fEuropean and ^gAfrican, ^hUtah residents with Northern and Western European ancestry. ⁱPeople with African Ancestry in Southwest United States.

4 | DISCUSSION

IFITM3 proteins are the first line of defense to protect against viral infections, including viruses that cause influenza, West Nile fever, dengue, chikungunya and Zika (Brass et al., 2009; Feeley et al., 2011; Jiang et al., 2010; Poddar et al., 2016; Savidis et al., 2016).

The T/C substitution (rs12252) in the gene encoding IFITM3 protein is an important host mutation associated with severe influenza susceptibility (Yang et al., 2015). The frequency of the "C" allele for SNP rs12252 is heterogeneous in different admixed American populations (Table 2). In the present study, we selected four states of western Mexico, as pre-Columbian diversity currently remains a

genetic legacy throughout Mexico. The cosmopolitan Mexican mestizos of the northern states show the highest average proportion of European components, whereas significantly decreased proportions of European components have been observed in southern states, particularly in Guerrero, Oaxaca, and Campeche (Moreno-Estrada et al., 2014).

In the present study, the *IFITM3*-C allele was detected in the four states of western Mexico, and the highest prevalence of the C allele was identified in Michoacan state (0.225) (Table 1). 1000 Genomes Project Consortium et al. (2015) reported an SNP rs12252 frequency in Mexicans from California in a small sample ($n = 64$), and this allele showed an equal frequency in the present study at 0.22 vs. 0.18 ($p > .3$). In Mexico, Moreno-Estrada et al. (2014) used a fine-scale ancestry patterns approach, revealing that a majority of Mexicans are admixed individuals with a large amount of Native and European ancestry and <5% of African ancestry (notably, these authors only analysed those three ancestries). Interestingly, Mexican-Americans in Los Angeles (MXL) did not exhibit a homogeneous pattern, consistent with the diverse origins of these individuals within Mexico (Moreno-Estrada et al., 2014). The frequency differences in rs12252 in western Mexicans compared with other populations sharing the same continent (Medellin, Colombia, Lima, Peru and Puerto Rico) were remarkable. Nevertheless, ancestry proportions of the three American admixed populations were analysed in the 1000 Genomes Project in 2012, wherein Mexico had a minor European ancestry, followed by Colombia and Puerto Rico with the highest proportion of European ancestry (1000 Genomes Project Consortium et al., 2012). In addition, Mexico has the largest proportion of Native American components, followed by Colombia; Puerto Rico has the lowest Native American ancestry (1000 Genomes Project Consortium et al., 2012), suggesting that although these populations share the same continent, there is a differential genetic structure between them. In addition, a comparison of population differentiation measured by Wright's fixation index (F_{st}) of native and resident Mexican populations in US with populations sharing the same continent showed that Colombia has a minor genetic differentiation, followed by Peru and Puerto Rico with F_{st} values = 0.0093, 0.0174 and 0.0189, respectively (1000 Genomes Project Consortium et al., 2015). However, there is striking genetic stratification among indigenous populations within Mexico depending on the geographical area (Gorodezky et al., 2001; Moreno-Estrada et al., 2014; Rubi-Castellanos et al., 2009).

Regarding interancestry comparisons (1000 Genomes Project Consortium phase 3 data), we observed differences primarily in East Asian and European ancestries ($p < 10^{-3}$), while the remaining ancestries showed differences only in select groups (African [African Ancestry in Southwest US and Webuye, Kenya] and South Asian [Indian Telugu in the UK]). Interestingly, populations of African and South Asian ancestry residing in the United States and UK, respectively, did not show homogeneous genetic patterns, reflecting their diverse origins, as previously described by Moreno-Estrada et al. (2014) for Mexican-Americans in Los Angeles (Table 2). The average F_{st} values calculated from the 1000 Genomes Project Consortium phase 3 data revealed

that the admixed American population has a higher F_{st} value compared with the other ancestries (South Asian = 0.00331, European = 0.00494, African = 0.00661, East Asia = 0.00726 and admixed American = 0.02445), reflecting the differences in the observed frequencies. Nevertheless, a high degree of fine-scale genomic structure across Mexico, shaped by pre-Columbian population dynamics (Moreno-Estrada et al., 2014; Rubi-Castellanos et al., 2009), has been reported and could represent a limitation of the present study, as the western Mexican population does not represent the total population of Mexico, reflecting marked European ancestry differences between cosmopolitan Mexican mestizo populations throughout Mexico and showing a clear north-south decline (Moreno-Estrada et al., 2014). As previously described, the frequency of the rs12252 polymorphism in mestizos of Mexican nationality primarily differs from the frequency of European ancestries. Thus, it will be important to characterize the frequency of the rs12252 marker in the remaining regions of Mexico.

In conclusion, this study is the first report of rs12252 polymorphism among Mexican mestizo populations born and raised in Mexico. In Mexican mestizo populations, the allelic frequency of the rs12252 polymorphism makes it a potentially useful and informative genetic biomarker for future association studies. The major prevalence of the "C" allele was identified in the Michoacan population. An understanding of the frequency distribution of marker rs12252 in Mexico in conjunction with other genetic and environmental factors is necessary for personalized medicine and could provide support to delineate therapeutic schemes in viral diseases currently identified as a public health emergency in Mexico.

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ETHICS STATEMENT

Written informed consent was obtained from all subjects for the use of their DNA samples in the present study. The procedures were performed in accordance with the principles of the Helsinki Declaration, and the protocol was approved by the Institutional Scientific and Ethics Committee (registration number 2000-03-02-033).

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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