

# Distribution and genotype frequency of the C1431T and pro12ala polymorphisms of the peroxisome proliferator activator receptor gamma gene in an Iranian population

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**BACKGROUND:** Peroxisome proliferator activator receptor gamma (PPAR $\gamma$ ) is a nuclear transcription factor regulating multiple genes involved in cell growth, differentiation, carbohydrate and lipid metabolism and energy production. Several genetic variations in the PPAR $\gamma$  gene have been identified to be associated with diabetes, obesity, dyslipidemia, insulin resistance, metabolic syndrome and coronary artery disease. The present study was designed to explore the distribution of two common single nucleotide polymorphisms of the PPAR $\gamma$  gene (C1431T and Pro12Ala) in an Iranian population.

**MATERIALS AND METHODS:** Genotype frequencies for these two polymorphisms were compared for 160 healthy Iranian individuals with reports from other populations. The Genotyping was performed using real-time polymerase chain reaction.

**RESULTS:** The genotype distribution of the C1431T PPAR $\gamma$  polymorphism was 0.869 for the CC genotype, 0.119 for the CT genotype and 0.013 for uncommon TT genotype. Allelic frequencies were 0.93 for C and 0.07 for T allele respectively. For the Pro12Ala polymorphism of PPAR $\gamma$  gene, genotypic distributions and allelic frequencies were, 0.813 for CC, 0.181 for CG and 0.06 for GG and 0.903 for C and 0.097 for G respectively. Allelic and genotypic frequencies for both polymorphisms of PPAR $\gamma$  gene were in Hardy-Weinberg equilibrium.

**CONCLUSIONS:** Iran is a country with an ethnically diverse population and a comparison of allelic and

genotypic frequencies of PPAR $\gamma$  C1431T and Pro12Ala polymorphisms between our population and others showed significant differences.

**Key words:** Iranian population, PPAR $\gamma$  gene, single nucleotide polymorphism

## Introduction

Peroxisome proliferator activator receptor gamma (PPAR $\gamma$ ) is a member of the nuclear receptor superfamily and is a ligand-activated transcription factor that regulates genes responsible for some very important biological functions including: Cell growth, differentiation and metabolism and acts as dietary lipid sensor.<sup>[1]</sup>

The PPAR $\gamma$  gene is located on the human chromosome 3p25-24 and consists of nine exons and as a result of alternative splicing and promoter usage produces four isoforms; PPAR $\gamma$ 1, PPAR $\gamma$ 2, PPAR $\gamma$ 3 and PPAR $\gamma$ 4. PPAR $\gamma$ 1 is expressed by most tissues.<sup>[2]</sup> PPAR $\gamma$ 2 is predominantly expressed in adipose tissue and regulates adipocyte differentiation.<sup>[3]</sup> PPAR $\gamma$ 3 expression appears to be confined to macrophages, adipose tissue and the colon.<sup>[4]</sup> Primer extension studies have confirmed that PPAR $\gamma$ 4 mRNA is present in adipose tissue suggesting that the PPAR $\gamma$ 4 isoform has a role in adipocyte biology.<sup>[5]</sup>

PPAR $\gamma$  plays critical roles in regulating lipid and carbohydrate metabolism (energy balance), adipocyte

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differentiation, proliferation and insulin sensitivity and create a relationship between environmental factors and metabolic processes of the organism.<sup>[6]</sup> PPAR $\gamma$  also plays roles in macrophages by enhancing foam cell formation and suppressing inflammatory cytokine production. It may also participate in controlling systemic glucose and lipid metabolism in the liver.<sup>[7,8]</sup> PPAR $\gamma$  may therefore affect processes involved in atherosclerosis.<sup>[9]</sup>

Since PPAR $\gamma$  is a nuclear transcription factor regulating multiple genes involved in energy production, glucose and lipid metabolism it may be a promising candidate gene for several major common diseases including cardiovascular disease, cancer, diabetes, inflammation and polymorphisms in this receptor may influence the pathology of these diseases. The PPAR $\gamma$  gene has been reported to be associated with various metabolic disorders including diabetes,<sup>[10]</sup> obesity,<sup>[11]</sup> dyslipidemia, insulin resistance, metabolic syndrome<sup>[12]</sup> and coronary artery disease (CAD).<sup>[13]</sup>

Several PPAR $\gamma$ 2 gene single nucleotide polymorphisms (SNPs) have been reported to be associated with diabetes, obesity, dyslipidemia, insulin resistance, metabolic syndrome and CAD. Several genetic variations of the PPAR gene have been found in the activation function domain 1, deoxyribonucleic acid binding domain and ligand binding domain (LBD) of the receptor and confer some conformational changes in protein structure that may affect transcriptional activity.<sup>[14]</sup>

Among several genetic variants of the PPAR $\gamma$  gene, two polymorphisms Pro12Ala of the exon B (rs1801282) and the C1431T silent substitution (rs3856806) in the 6<sup>th</sup> exon are the most frequently occurring SNPs and have been associated with various diseases and extensive studies have been undertaken to assess the effects of these polymorphisms on many aspects of human physiology. The C1431T polymorphism is also known as the C161T or His477His was identified in 1998 by Meirhaeghe *et al.*,<sup>[15]</sup> and has been studied in relation to bone metabolism, metabolic syndrome, CAD, obesity and glucose intolerance. The Pro12Ala protein polymorphism is due to a CCA-to-GCA missense mutation and was identified by Yen *et al.*<sup>[16]</sup> It is associated with type-2 diabetes mellitus, insulin resistance, obesity and metabolic disorders. In addition, numerous studies have

demonstrated rare alleles of these two common variants play a role in the complex pathogenetic mechanism of major diseases supposed to be useful markers to evaluate the connection between PPAR $\gamma$  and metabolic derived disorders.

Given the pivotal roles of PPAR $\gamma$  in regulating metabolism several studies in various ethnic populations including, Caucasians,<sup>[17]</sup> Mexican-Americans,<sup>[18]</sup> African-Americans,<sup>[19,13]</sup> Asian,<sup>[20]</sup> Eastern Asian,<sup>[12]</sup> European,<sup>[10]</sup> Hispanic and non-Hispanic<sup>[21]</sup> have been conducted to determine allelic frequencies and genotypic distribution. There have been no studies of the distribution of C1431T polymorphism in an Iranian population and there is some controversy about the frequency of Pro12Ala polymorphism. Therefore, the present study was designed to explore the distribution of these two common variants of PPAR gene in Iranian population and compare the finding with other populations. A number of 160 healthy individuals were analyzed to evaluate the frequency of PPAR $\gamma$  alleles and genotypes in a healthy Iranian population.

## Materials and Methods

A total of 160 healthy volunteer subjects comprised of 70 males and 90 females, mainly people of Iranian descent (primarily Persian), were selected randomly from all parts of Mashhad as a second largest city in Iran and enrolled in this study. A health questionnaire, including questions such as name, ethnicity, family history, age, sex and dietary habits, was provided to each participant. Blood was taken in accordance with the World Health Organization protocol for blood donation and the healthy state of the all the participants was determined by medical history, physical examination and blood chemistry tests. Subjects were excluded from the study if they had a history of congestive heart disease, liver and/or renal disease, endocrinological abnormalities and alcohol consumption or were under medications that altered blood pressure, glucose or lipid metabolism. The clinical and biochemical characteristics of the all the individuals enrolled into the study were normal at baseline. The protocol was approved by the Ethics Committee of the Mashhad University of Medical

Science and Informed consent was obtained from all participants.

Genomic deoxyribonucleic acid (DNA) was extracted from whole blood using the FlexiGene DNA isolation Kit (Qiagen). C1431T and Pro12Ala polymorphisms of the PPAR $\gamma$  gene were determined by a predesigned TaqMan SNP genotyping assay (Applied Biosystems). Oligonucleotides used for allelic discrimination assays for Pro12Ala and C1431T were as follows:

- Context sequences for Pro/12Ala ([VIC/FAM]) (Applied Biosystems ID: C\_1129864\_10):
  - AACTCTGGGAGATTCTCCTATTGAC[C/G]  
CAGAAAGCGATTCTTCACTGATAC
  - Pro12 Probe (Vic labeled): C\_1129864\_10-C
  - Ala12 Probe (Fam labeled): C\_1129864\_10-G.
- Context sequences for C1431T ([VIC/FAM]) (Applied Biosystems ID: C\_11922961\_30):
  - ACCTCAGACAGATTGTCACGGAACA[C/T]  
GTGCAGCTACTGCAGGTGATCAAGA
  - C1431 Probe (Vic labeled): C\_11922961\_30-C
  - T1431 Probe (Fam labeled): C\_11922961\_30-T.

The reaction was performed in 25  $\mu$ l final volume with real-time polymerase chain reaction (PCR) using 96-well plates on an ABI 7500 real time PCR system (Applied Biosystems). The PCR conditions were 95°C for 10 min and 40 cycles of 92°C for 15 s and 60°C for 1 min. Individual genotypes identification was analyzed by SDS software version 1.3 (Applied Biosystems). For genotyping quality control, duplicate samples and negative controls were included to ensure the accuracy.

Allele frequencies of two SNPs were computed using genotype data obtained from these healthy controls and were compared with those reported in other populations. Each SNP was tested for Hardy-Weinberg equilibrium (HWE) conformity. The statistical significance

of the differences between genotypic distributions in populations was tested by the Chi-square ( $\chi^2$ ) or Fisher's exact test using the SPSS 16.0 statistical package. (SPSS Inc., Chicago, IL)  $P < 0.05$  was considered to be significant.

## Results

The genotype characteristics of studied individuals are shown in Table 1. Allelic and genotypic frequencies for both polymorphisms of PPAR $\gamma$  gene were in HWE ( $P \geq 0.05$ ) [Table 1]. The genotypic distribution of the C1431T PPAR $\gamma$  polymorphism were 0.869 for CC, 0.119 for CT and 0.013 for TT and allelic frequencies were 0.93 for C and 0.07 for T respectively [Table 1]. For another Pro12Ala variant of PPAR $\gamma$ , genotypic distributions and allelic frequencies were, 0.813 for CC, 0.181 for CG and 0.06 for GG and 0.903 for C and 0.097 for G respectively [Table 1]. Differences in allelic frequencies and genotype distribution of the polymorphisms between Iranian population and those reported for other populations are shown in Tables 2 and 3 respectively.

## Discussion

The present study represents the examination of the PPAR $\gamma$  gene C1431T and Pro12Ala polymorphisms distribution in Iranian healthy population and comparison with other populations. Several studies have demonstrated these two common polymorphisms of PPAR $\gamma$  gene have a relationship with some major diseases. This current study is part of another study dealing with patients with metabolic syndrome and CADs (unpublished data); many studies have showed these two common variants of PPAR $\gamma$  are associated with decreased risk of CAD and MS in various

**Table 1: Allelic and genotypes frequency of studied population**

Gene	Allelic frequencies n (%)		Genotypic frequencies n (%)			HWE
	C	T	CC	CT	TT	
PPAR $\gamma$	297 (93.00)	23 (7.00)	139 (86.9)	19 (11.9)	2 (1.3)	$P > 0.05$ , NS
	<b>C (Pro)</b> 289 (90.3)	<b>G (Ala)</b> 31 (9.7)	<b>CC (Pro/Pro)</b> 130 (81.3)	<b>CG (Pro/Ala)</b> 29 (18.1)	<b>GG (Ala/Ala)</b> 1 (0.6)	$P > 0.05$ , NS

HWE: Hardy-Weinberg equilibrium, NS: Non-significant, PPAR $\gamma$ : Peroxisome proliferator activator receptor gamma

**Table 2: Comparison of allelic and genotypic frequencies of PPAR $\gamma$  C1431T variant between our population and others**

Population	N	Allele frequencies		Genotype frequencies			P (A)	P (G)	HWE	Reference
		C (%)	T (%)	CC (%)	CT (%)	TT (%)				
Iranian (this study)	160	297 (93.0)	23 (7.0)	139 (86.9)	19 (11.9)	2 (1.3)			Yes	
Chinese	1008	1531 (75.9)	485 (24.1)	595 (59.0)	341 (33.8)	72 (7.1)	0.000	0.000	Yes	[22]
Chinese	89	140 (78.7)	38 (21.30)	55 (61.8)	30 (33.7)	4 (4.5)	0.000	0.000	Yes	[23]
Chinese	181	248 (68.5)	114 (31.5)	89 (49.2)	70 (38.7)	22 (12.2)	0.000	0.000	Yes	[24]
Chinese	461	1254 (79.2)	330 (20.8)	287 (62.3)	154 (33.4)	20 (4.3)	0.000	0.000	Yes	[25]
Indians	568	944 (83.1)	192 (16.9)	396 (69.7)	152 (26.8)	20 (3.5)	0.000	0.001	Yes	[20]
Chinese	2730	4082 (74.8)	1378 (25.2)	1521 (55.7)	1040 (38.1)	169 (6.2)	0.000	0.000	Yes	[20]
Japanese	404	688 (85.1)	120 (14.9)	291 (72.1)	106 (26.2)	7 (1.7)	0.003	0.004	Yes	[26]
Japanese	716	1188 (83.0)	244 (17.0)	496 (69.3)	196 (27.4)	24 (3.4)	0.000	0.000	Yes	[27]
Indian	291	508 (87.3)	74 (12.71)	221 (75.9)	66 (22.7)	4 (1.4)	0.027	NS	Yes	[28]
Korean	253	407 (80.4)	99 (19.7)	164 (64.8)	79 (31.2)	10 (3.9)	0.000	0.000	Yes	[12]
Malays	740	1480 (78.0)	326 (22.0)	459 (62.0)	236 (31.9)	45 (6.1)	0.000	0.000	Yes	[20]
Australian	133	211 (79.3)	55 (33.1)	79 (59.4)	53 (39.8)	1 (0.8)	0.000	0.000	Yes	[29]
Turkish	105	152 (72.4)	58 (27.61)	52 (49.5)	48 (45.7)	5 (4.8)	0.000	0.000	Yes	[13]
Denmark	779	1327 (85.2)	231 (14.8)	561 (72.0)	205 (26.3)	13 (1.7)	0.003	0.003	Yes	[30]
Danish Caucasian	171	311 (90.9)	31 (9.1)	142 (83.0)	27 (15.8)	2 (1.2)	NS	NS	Yes	[31]
Scotland	983	1686 (85.8)	280 (14.2)	725 (73.8)	236 (24.0)	22 (2.2)	0.004	0.011	Yes	[10]
Northern France	703	1212 (86.2)	194 (13.8)	520 (73.9)	172 (24.5)	11 (1.6)	0.007	0.011	Yes	[15]
European	482	863 (89.5)	101 (10.5)	383 (79.5)	97 (20.1)	2 (0.04)	NS	NS	Yes	[32]
Finnish	141	230 (81.6)	52 (18.4)	98 (69.5)	34 (24.1)	9 (6.4)	0.000	0.003	Yes	[11]
Italian	100	187 (93.5)	13 (6.5)	88 (88.00)	11 (11.00)	1 (1.00)	NS	NS	Yes	[33]
German	138	231 (83.7)	45 (16.3)	93 (67.4)	45 (32.6)	0 (0.00)	0.002	0.000	≤0.05	[34]
African American	48	86 (89.6)	10 (10.4)	38 (79.2)	10 (20.8)	0 (0.00)	NS	NS	NM	[35]
African American	124	238 (96.0)	10 (4.0)	114 (91.9)	10 (8.1)	0 (0.00)	NS	NS	NM	[35]
Hispanics	282	497 (88.1)	67 (11.9)	218 (77.3)	61 (21.6)	3 (1.06)	0.054	NS	Yes	[21]
Non-Hispanics	417	707 (84.8)	127 (15.2)	301 (72.2)	105 (25.17)	11 (2.63)	0.002	0.007	Yes	[21]
German	353	619 (87.7)	87 (12.3)	273 (77.3)	73 (20.7)	7 (2.0)	0.035	NS	Yes	[17]
Caucasian	435	743 (85.4)	127 (14.6)	316 (72.6)	111 (25.5)	8 (1.8)	0.004	0.007	Yes	[17]
Sub-Saharan African	120	232 (96.7)	8 (3.3)	112 (93.3)	8 (6.7)	0 (0.00)	NS	NS	NM	[35]

HWE: Hardy-Weinberg equilibrium, PPAR $\gamma$ : Peroxisome proliferator activator receptor gamma, P (A): P value of  $\chi^2$  test between allele frequencies, P (G): P value of  $\chi^2$  test between genotypic frequencies, HWE: Hardy-Weinberg equilibrium, NM: Not mentioned, NS: Non-significant ( $P \geq 0.05$ )

**Table 3: Comparison of allelic and genotypic frequencies of PPAR $\gamma$  Pro12Ala variant between our population and others**

Population	N	Allele frequencies		Genotype frequencies			P (A)	P (G)	HWE	References
		C (%)	G (%)	CC (%)	CG (%)	GG (%)				
Iranian (this study)	160	289 (90.3)	31 (9.7)	130 (81.3)	29 (18.1)	1 (0.6)			Yes	
Chinese	137	264 (96.4)	10 (3.6)	131 (95.6)	2 (1.5)	4 (2.9)	0.006	0.000	Yes	[36]
Chinese	2730	5258 (96.3)	202 (3.7)	2533 (92.8)	192 (7.0)	5 (0.18)	0.00	0.000	Yes	[20]
Malays	740	1432 (96.8)	48 (3.2)	693 (93.6)	46 (6.2)	1 (0.14)	0.00	0.000	Yes	[20]
Indians	568	1001 (88.1)	135 (11.9)	443 (78.0)	115 (20.2)	10 (1.8)	NS	NS	Yes	[20]
Hans	102	193 (94.6)	11 (5.4)	91 (89.2)	11 (10.8)	0 (0.0)	NS	NS	Yes	[37]
Indians	291	517 (88.8)	65 (11.2)	230 (79.0)	57 (19.6)	4 (1.4)	NS	NS	Yes	[28]
Korean	253	479 (94.7)	27 (5.3)	226 (89.0)	27 (11.0)	0 (0.0)	0.028	0.041	Yes	[12]
Kazaks	80	146 (91.3)	14 (8.7)	66 (82.5)	14 (17.5)	0 (0.0)	NS	NS	Yes	[37]
Uygurs	111	197 (88.7)	25 (11.3)	86 (77.0)	25 (23.0)	0 (0.0)	NS	NS	Yes	[37]
Denmark	779	1315 (84.4)	243 (15.6)	549 (70.5)	217 (27.9)	13 (1.7)	0.026	NS	Yes	[30]
Scotland	1060	1817 (85.7)	303 (14.3)	777 (73.3)	263 (24.8)	20 (1.9)	NS	NS	Yes	[10]
Italian	100	195 (97.5)	5 (2.5)	95 (95.0)	5 (5.0)	0 (0.0)	0.002	0.003	Yes	[33]
Ukrainians	46	73 (79.3)	19 (20.7)	29 (63.0)	15 (32.6)	2 (4.4)	0.01	0.028	Yes	[38]
French	1149	2035 (88.6)	263 (11.4)	905 (78.8)	225 (19.6)	19 (1.7)	NS	NS	Yes	[15]
French	107	169 (79.0)	45 (21.0)	62 (57.9)	45 (42.1)	0 (0.0)	0.001	0.000	Yes	[11]
German	432	750 (86.8)	114 (13.2)	324 (75.0)	102 (23.6)	6 (1.4)	NS	NS	Yes	[17]
Finnish	141	242 (85.8)	40 (14.2)	107 (75.8)	28 (19.9)	6 (4.3)	NS	NS	Yes	[11]
Slovenia	657	1079 (82.1)	235 (17.9)	450 (68.5)	179 (27.2)	28 (4.3)	0.003	0.017	Yes	[39]
Czechs	118	184 (78.0)	52 (22.0)	74 (62.8)	36 (30.1)	8 (6.7)	0.000	0.004	Yes	[38]
Caucasian	577	923 (80.0)	231 (20.0)	436 (75.5)	133 (23.0)	9 (1.5)	0.000	NS	Yes	[38]
Hispanics	293	518 (88.4)	68 (11.6)	229 (78.2)	60 (20.4)	4 (1.4)	NS	NS	Yes	[21]
Non-Hispanics	414	730 (88.2)	98 (11.8)	322 (77.8)	86 (20.8)	6 (1.4)	NS	NS	Yes	[21]
African-American	1005	1964 (97.7)	46 (2.3)	959 (95.4)	46 (4.6)	0 (0.0)	0.000	0.000	Yes	[40]
African American	48	92 (95.8)	4 (4.2)	44 (91.7)	4 (8.3)	0 (0.0)	NS	NS	NM	[35]

P (A): P value of  $\chi^2$  test between allele frequencies, P (G): P value of  $\chi^2$  test between genotypic frequencies, HWE: Hardy-Weinberg equilibrium, NM: Not mentioned, NS: non-significant ( $P \geq 0.05$ ), PPAR $\gamma$ : Peroxisome proliferator activator receptor gamma

populations. On the other hand, C1431T polymorphism is why we selected these two common variants to has not been studied in our population before, so this evaluate in our population.



Allelic and genotypic frequencies of PPAR $\gamma$  C1431T polymorphism in our population showed significant differences from other populations listed in Table 2 except for two reports from European,<sup>[31,32]</sup> one from Italy,<sup>[33]</sup> two in African-American,<sup>[35]</sup> and one from sub-Saharan African population.<sup>[35]</sup> Allelic but not genotypic frequencies in one report from European,<sup>[32]</sup> one from Caucasian,<sup>[17]</sup> one from Hispanic<sup>[21]</sup> and one from Indian<sup>[28]</sup> showed significant differences from what we found in our Iranian population. In all the populations the frequency of rare allele homozygote's (TT) was low (0-7%), but there was one exception for a Chinese population that showed more than 12% frequency that it might be due to small sample size.<sup>[24]</sup> In general, Chinese and other Asian populations showed a higher frequency than others. In this case, our data was different from those of Asian populations and was similar to those in Australian, European and Caucasian.

With respect to Pro12Ala polymorphism, comparison of allelic and genotypic frequencies between our data and other studies listed in Table 3 shows no significant differences with most of them. However there were some significant differences with two reports from China ( $P = 0.00$ ),<sup>[20,36]</sup> one from Korea ( $P = 0.041$ ),<sup>[12]</sup> one from Asia ( $P = 0.00$ ),<sup>[20]</sup> and a few reports from Europe including, Italy ( $P = 0.003$ ), Slovenia ( $P = 0.017$ ),<sup>[39]</sup> The Czech Republic ( $P = 0.004$ ),<sup>[38]</sup> France ( $P = 0.00$ )<sup>[11]</sup> and in an African-American population ( $P = 0.00$ )<sup>[40]</sup> as well. One report from Europe and one within a Caucasian population showed significance differences in allelic but not genotypic frequencies with our results.<sup>[38,30]</sup> As shown in Table 3, the CC ((Pro/Pro) genotype was the predominant form in all populations. Data are presented in Table 3 shows some inconsistency among different studies in the distribution of the G (12Ala) allele that might be due to the difference in racial and ethnic groups. The highest distribution of the G (12Ala) allele belongs to European and Caucasian populations and the least is relate to Chinese and African-American populations.

Most of the population in Iran is genetically close to Caucasian and their ancestors were the Aryans who had migrated from Central Asia to Iran. The main reason for the significant differences between our data and

other populations results from Iran as a country with an ethnically diverse population including Pars, Turk, Kurd, Tajik, Turkmen, Baloch and special religious such as Muslims, Zoroastrians, Jews, Christians and Assyrians. However, Iran is located along the ancient Silk Road and connected Asia to Europe and during the course of history, Iranian population has encountered foreigners including Macedonians, Arabs, Turks and Mongols on various occasion. Therefore, the population living in this country might be mixed due to contacting with others and the immigration of some people from neighboring nations.<sup>[41]</sup>

Several studies have been undertaken on the association between the Pro12Ala and C1431T mutations with numerous diseases such as cardiovascular disease, cancer, diabetes, inflammation on various populations and the results showed controversy. The controversial findings related to these polymorphisms may be attributable to genetically differences in populations. Therefore, it is necessary to study in different populations to reach a general consensus in this field.

An important limitation in our study is the relatively small sample size. Further association study with a larger population base is needed to confirm our results and may be useful in understanding these SNPs roles in pathology of the main disease in the future.

## Conclusion

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Statistical differences in the distribution of two common polymorphisms of PPAR $\gamma$  gene between Iranian population and others showed the importance of studying these SNPs in relation to some major diseases. Regards to Iranian different genetic with some other populations in Asia and other continents, it seems that our study confirms this difference concerning the two common PPAR $\gamma$  polymorphisms.

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