Original Article

Prevalence Rates of ADIPOQ Polymorphisms in Indian Population and a Comparison with Other Populations

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Abstract

Introduction: The adiponectin gene, *ADIPOQ*, encodes an adipocytokine, known as adiponectin hormone. This hormone is known to be associated with insulin sensitization, fat metabolism, immunity, and inflammatory response. Polymorphisms in *ADIPOQ* gene lower the adiponectin levels, increasing the risk for diabetes and cardiovascular diseases. **Aims:** The study aimed to calculate the prevalence rates of ADIPOQ polymorphisms in Indian population and to compare those prevalence rates with that of other populations. **Subjects and Methods:** Microarray-based genotypic data of 14 ADIPOQ polymorphisms from 703 individuals of Indian origin were used. **Statistical Analysis Used:** Frequency estimation, identity-by-descent, Hardy–Weinberg equilibrium, Chi-square test of significance were used for statistical analysis. **Results:** Allelic and genotypic frequencies of ADIPOQ polymorphisms, Chi-square tests of significance for allelic and genotypic frequencies across various populations. **Conclusions:** East Asians are very different from Indians in terms of allelic and genotypic frequencies of ADIPOQ polymorphisms. Europeans have similar genotypic and allelic patterns with Indians. Admixture Americans and Africans also showed significant differences with polymorphisms of the Indian population.

Keywords: *ADIPOQ*, adiponectin, fat metabolism

Introduction

The *ADIPOQ* gene, present on the long arm of chromosome 3, was first discovered by isolation from adipocyte cell lines.[1] DNA sequence of this gene contains three exons and two introns and encodes adiponectin hormone. Adiponectin hormone is a 244 amino acid long protein, which undergoes several posttranslational modifications before its secretion into the bloodstream. The parent molecule is a monomeric protein which forms trimeric complexes known as low-molecular-weight adiponectin and multimeric complexes known as high-molecular-weight (HMW) adiponectin. The latter form of the protein is found in highest concentrations, in circulation. Hence, it has been deduced that HMW adiponectin is required for specific functions. Plasma adiponectin is an important chemical entity for various physiological functions and overall wellness.

Differential regulation of nitric oxide and superoxide anion formation is one of the mechanisms through which adiponectin exhibits strong antioxidant action.[2] It also reduces insulin resistance, a major development in diabetic patients. Studies have shown that adiponectin level is inversely proportional to the level of cytokines such as tumor necrosis factor-alpha, highlighting its role in inflammatory pathways, sepsis, and immune function.[3] Apart from fat metabolizing enzymes, good cholesterol, and lipid profile, regulation of adiponectin levels is essential for cardiovascular health. A deficiency in adiponectin promotes atherosclerosis and can result in coronary heart disease, myocardial infarction, or cardiac hypertrophy.[4,5] The role of adiponectin in cancer protection has also been widely studied.[6] Promotion of angiogenesis (production of new blood vessels) by stimulation of epithelial progenitor cells is supposedly regulated by adiponectin although some experts say that further evidence is warranted.

Genetic polymorphisms in *ADIPOQ* gene affect the adiponectin levels and increase the risk for obesity, type 2

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diabetes, several cancers, and cardiovascular diseases. Various single-nucleotide polymorphisms (SNPs) have been identified in ADIPOQ gene, and the prevalence of these polymorphisms varies across the populations.[7] However, very little information is known about the prevalence of ADIPOQ polymorphisms in Indian population. In the present study, we have analyzed 703 samples, spread across India, to understand the frequencies of 14 SNPs of ADIPOQ gene present on Illumina Human Core Exome chips. We compared the frequencies with that of 1000 genomes databases to evaluate the significant differences between Indian population and other populations.

Subjects and Methods

Genotype data used in the present study were obtained from SNPmart, an integrated SNP genotype database at Mapmygenome India Limited. SNPmart contains more than 2000 samples taken across India, with various disease phenotypes. Blood or saliva samples were collected after taking written informed consent from the individuals. From each sample, DNA was extracted after internal quality control procedures to ensure adequate yield. Extracted DNA was hybridized onto Illumina Human Core Exome chips (version 1.0 and 1.1). Genotypes were obtained using Illumina's GenomeStudio software (version 1.9.4).

A total of 931 samples from the individuals of Indian origin, who had given consent to use their sample for the research, were considered in the present study. Samples were checked for interrelations, and only unrelated samples were used. In the case of parent–child samples, only parent samples were considered. Further, samples with > 20% missing call rates were removed. Identity-by-descent estimates were obtained using PLINK,[8] and from sample pairs with PI_HAT ≥ 0.5, one sample was removed from the study. Finally, 703 samples were used in calculating genotype and allele frequencies for 14 SNPs of ADIPOQ gene that were present across all Illumina chip versions.

Genotype and allele frequencies for various other populations were obtained from Phase 3 call set of 1000 genomes project. Table 1 gives information on populations considered in the study and their super population category. Chi-square tests of significance were calculated to understand the significant differences between frequencies of ADIPOQ polymorphisms in Indian population and other populations. Data retrieval, frequency estimations, and significant analyses were done by writing scripts in Linux and R programming languages.

Table 1: Populations considered in the comparisons with Indian population (Source: http://www.internationalgenome.org/)

Super population	Populations considered in sampling	Sample size
SAS	Bengali from Bangladesh (BEB); Gujarati Indian from Houston, Texas (GIH); Indian Telugu from the UK (ITU); Punjabi from Lahore, Pakistan (PJL); Sri Lankan Tamil from the UK (STU)	489
EAS	Chinese Dai in Xishuangbanna, China (CDX); Han Chinese in Beijing, China (CHB); Southern Han Chinese (CHS); Japanese in Tokyo, Japan (JPT); Kinh in Ho Chi Minh City, Vietnam (KHV)	504
EUR	Utah Residents (CEPH) with North and Western European ancestry (CEU); Finnish in Finland (FIN); British in England and Scotland (GBR); Iberian Population in Spain (IBS); Toscani in Italia (TSI)	503
AMR	Colombians from Medellin, Colombia (CLM); Mexican Ancestry from Los Angeles, USA (MXL); Peruvians from Lima, Peru (PEL); Puerto Ricans from Puerto Rico (PUR)	347
AFR	African Caribbean in Barbados (ACB); Americans of African Ancestry in SW USA (ASW); Esan in Nigeria (ESN); Gambian in Western Divisions in the Gambia (GWD); Luhya in Webuye, Kenya (LWK); Mende in Sierra Leone (MSL); Yoruba in Ibadan, Nigeria (YRI)	661

SAS: South Asian, EAS: East Asian, EUR: European, AMR: Admixed American, AFR: African

Results

A total of 703 samples were used to understand the prevalence of ADIPOQ polymorphisms in Indian population. Table 2 gives genotypic and allelic frequencies of 14 polymorphisms considered in the study. Table 2 also gives information on *P* values obtained for Hardy–Weinberg equilibrium. Six polymorphisms that have minor allele frequency (MAF) <5% were removed from further calculations. Tables 3 and 4 give information on the comparison of allelic frequencies and comparison of genotypic frequencies of remaining SNPs in Indian population with that of other populations, respectively.

Discussion

The adiponectin gene, *ADIPOQ*, has been found to be associated with fat metabolism, type 2 diabetes, cardiovascular diseases, and inflammatory responses, through regulating the adiponectin hormone. As diabetes and obesity are fast-reaching epidemic proportions in India, it is important to understand the polymorphisms of *ADIPOQ* gene in Indian population. The present study investigates the prevalence rates of *ADIPOQ* gene polymorphisms in Indian population and compares those prevalence rates with that of other populations in the world. Fourteen SNPs that were present on Illumina microarrays were considered in the study. Among the selected SNPs, six SNPs have MAF < 5% or equal to zero, indicating the low prevalence of alternate allele. Those SNPs were found to have a similar pattern in all the populations considered in the study and were removed from the comparisons.

As expected, genotypic and allele frequencies are not significantly different in Indian and South Asian (SAS) populations, indicating the close similarity among the people living in this subcontinent.

Table 2: Genotypic and allelic frequencies of 14 ADIPOQ polymorphisms considered in the study

SNP name	Chromosome	Position	REF	ALT	Allele frequencies		Genotype frequencies			HWE (*P*)
					REF (%)	ALT (%)	Ref-Hom (%)	Het (%)	Alt-hom (%)	
rs182052	3	186560782	G	A	909 (64.65)	497 (35.35)	295 (41.96)	319 (45.38)	89 (12.66)	0.4436
rs822396	3	186566877	G	A	268 (19.06)	1138 (80.94)	29 (4.13)	210 (29.87)	464 (66)	0.4578
rs17366568	3	186570453	G	A	1199 (85.4)	205 (14.6)	509 (72.51)	181 (25.78)	12 (1.71)	0.4436
rs114155159	3	186570873	T	A	1406 (100)	0	703 (100)	0	0	NA
rs144448520	3	186570960	G	A	1391 (99.93)	1 (0.07)	695 (99.86)	1 (0.14)	0	0
rs138227502	3	186571010	C	T	1395 (99.93)	1 (0.07)	697 (99.86)	1 (0.14)	0	0
rs1501299	3	186571123	G	T	1085 (77.39)	317 (22.61)	426 (60.77)	233 (33.24)	42 (5.99)	0.2145
rs3821799	3	186571486	T	C	643 (45.8)	761 (54.2)	160 (22.79)	323 (46.01)	219 (31.2)	0.0597
rs3774262	3	186571814	G	A	1222 (87.16)	180 (12.84)	534 (76.18)	154 (21.97)	13 (1.85)	0.7341
rs62625753	3	186572026	G	A	1402 (99.72)	4 (0.28)	699 (99.43)	4 (0.57)	0	5.46E-11
rs17366743	3	186572089	T	C	1384 (99.14)	12 (0.86)	686 (98.28)	12 (1.72)	0	0.0479
rs138773406	3	186572419	C	A	1406 (100)	0	703 (100)	0	0	NA
rs141205818	3	186572480	A	C	1406 (100)	0	703 (100)	0	0	NA
rs6773957	3	186573705	A	G	500 (35.56)	906 (64.44)	97 (13.8)	306 (43.53)	300 (42.67)	0.2044

HWE: Hardy-Weinberg equilibrium, SNP: Single-nucleotide polymorphism, REF: Reference allele, ALT: Alternate allele

Table 3: Comparison of allelic frequencies of ADIPOQ polymorphisms in Indian population with that of other populations

SNP name	REF	ALT	Allele	Indian	SAS	EAS	EUR	AMR	AFR
rs182052	G	A	REF (G)	909 (64.65)	620 (63.39)	558 (55.36)	609 (60.54)	405 (58.36)	851 (64.37)
			ALT (A)	497 (35.35)	358 (36.61)	450 (44.64)	397 (39.46)	289 (41.64)	471 (35.63)
P (χ^2)					0.5579	4.88E-06	0.0433	0.0059	0.9105
rs822396	G	A	REF (G)	268 (19.06)	195 (19.94)	122 (12.1)	183 (18.19)	129 (18.59)	241 (18.23)
			ALT (A)	1138 (80.94)	783 (80.06)	886 (87.9)	823 (81.81)	565 (81.41)	1081 (81.77)
P (χ^2)					0.6312	6.05E-06	0.6258	0.8405	0.6116
rs17366568	G	A	REF (G)	1199 (85.4)	827 (84.56)	983 (97.52)	893 (88.77)	656 (94.52)	1309 (99.02)
			ALT (A)	205 (14.6)	151 (15.44)	25 (2.48)	113 (11.23)	38 (5.48)	13 (0.98)
P (χ^2)					0.6127	3.20E-23	0.0188	1.26E-09	8.31E-39
rs1501299	G	T	REF (G)	1085 (77.39)	773 (79.04)	712 (70.63)	725 (72.07)	484 (69.74)	810 (61.27)
			ALT (T)	317 (22.61)	205 (20.96)	296 (29.37)	281 (27.93)	210 (30.26)	512 (38.73)
P (χ^2)					0.3647	0.0002	0.0034	0.0002	9.36E-20
rs3821799	T	C	REF (T)	643 (45.8)	451 (46.11)	617 (61.21)	475 (47.22)	361 (52.02)	809 (61.2)
			ALT (C)	761 (54.2)	527 (53.89)	391 (38.79)	531 (52.78)	333 (47.98)	513 (38.8)
P (χ^2)					0.9117	1.06E-13	0.5174	0.0084	1.11E-15
rs3774262	G	A	REF (G)	1222 (87.16)	830 (84.87)	710 (70.44)	876 (87.08)	566 (81.56)	1275 (96.44)
			ALT (A)	180 (12.84)	148 (15.13)	298 (29.56)	130 (12.92)	128 (18.44)	47 (3.56)
P (χ^2)					0.1243	5.25E-24	1	0.0008	3.55E-18
rs17366743	T	C	REF (T)	1384 (99.14)	966 (98.77)	1008 (100)	968 (96.22)	689 (99.28)	1320 (99.85)
			ALT (C)	12 (0.86)	12 (1.23)	0	38 (3.78)	5 (0.72)	2 (0.15)
P (χ^2)					0.5014	0.0079	1.61E-06	0.9402	0.0209
rs6773957	A	G	REF (A)	500 (35.56)	353 (36.09)	594 (58.93)	412 (40.95)	352 (50.72)	804 (60.82)
			ALT (G)	906 (64.44)	625 (63.91)	414 (41.07)	594 (59.05)	342 (49.28)	518 (39.18)
P (χ^2)					0.8234	9.11E-30	0.0080	3.92E-11	1.51E-39

SNP: Single-nucleotide polymorphism, Indian: Study population. SAS: South Asian, EAS: East Asian, EUR: European, AMR: Admixed American, AFR: African, REF: Reference allele, ALT: Alternate allele

However, there are marked differences in Indian and East Asian (EAS) populations. All the SNPs showed significant differences between Indian and EAS populations. At 1% level of significance, admixture Americans and Africans (AFRs) were different from Indian population for five SNPs, at genotypic level.

rs6773957 and rs3821799 showed high prevalence of alternate allele in Indian, SAS, and European (EUR) populations, compared to other populations. Allele G at rs6773957, known to be associated with low adiponectin levels and high body weight,[9-11] is more prevalent in Indian, SAS, and EUR populations. EAS and AFR have high prevalence of the A allele, and AMR has equal proportions of A and G alleles. This could be one of the factors for thinner body frames of Japan and Korean people. The prevalence rate of C allele of rs3821799, which is

Table 4: Comparison of genotypic frequencies of ADIPOQ polymorphisms in Indian population with that of other populations

SNP name	REF	ALT	Genotype	Indian	SAS	EAS	EUR	AMR	AFR
rs182052	G	A	Ref-Hom (GG)	295 (41.96)	198 (40.49)	162 (32.14)	182 (36.18)	121 (34.87)	276 (41.75)
			Het (AG)	319 (45.38)	224 (45.81)	234 (46.43)	245 (48.71)	163 (46.97)	299 (45.23)
			Alt-hom (AA)	89 (12.66)	67 (13.7)	108 (21.43)	76 (15.11)	63 (18.16)	86 (13.01)
P (χ^2)					0.8180	2.28E-05	0.1076	0.0190	0.9813
rs822396	G	A	Ref-Hom (GG)	29 (4.13)	27 (5.52)	8 (1.59)	15 (2.98)	13 (3.75)	29 (4.39)
			Het (AG)	210 (29.87)	141 (28.83)	106 (21.03)	153 (30.42)	103 (29.68)	183 (27.69)
			Alt-hom (AA)	464 (66)	321 (65.64)	390 (77.38)	335 (66.6)	231 (66.57)	449 (67.93)
P (χ^2)					0.5200	3.90E-05	0.5784	0.9525	0.6673
rs17366568	G	A	Ref-Hom (GG)	509 (72.51)	353 (72.19)	480 (95.24)	393 (78.13)	323 (93.08)	649 (98.18)
			Het (AG)	181 (25.78)	121 (24.74)	23 (4.56)	107 (21.27)	10 (2.88)	11 (1.66)
			Alt-hom (AA)	12 (1.71)	15 (3.07)	1 (0.2)	3 (0.6)	14 (4.03)	1 (0.15)
P (χ^2)					0.2906	4.77E-23	0.0360	4.82E-19	7.11E-39
rs1501299	G	T	Ref-Hom (GG)	426 (60.77)	308 (62.99)	252 (50)	265 (52.68)	165 (47.55)	248 (37.52)
			Het (GT)	233 (33.24)	157 (32.11)	208 (41.27)	195 (38.77)	154 (44.38)	314 (47.5)
			Alt-hom (TT)	42 (5.99)	24 (4.91)	44 (8.73)	43 (8.55)	28 (8.07)	99 (14.98)
P (χ^2)					0.6214	0.0008	0.0138	0.0003	2.65E-18
rs3821799	T	C	Ref-Hom (TT)	160 (22.79)	111 (22.7)	189 (37.5)	119 (23.66)	89 (25.65)	251 (37.97)
			Het (CT)	323 (46.01)	229 (46.83)	239 (47.42)	237 (47.12)	183 (52.74)	307 (46.44)
			Alt-hom (CC)	219 (31.2)	149 (30.47)	76 (15.08)	147 (29.22)	75 (21.61)	103 (15.58)
P (χ^2)					0.9550	2.79E-12	0.7606	0.0050	5.22E-14
rs3774262	G	A	Ref-Hom (GG)	534 (76.18)	354 (72.39)	244 (48.41)	386 (76.74)	231 (66.57)	615 (93.04)
			Het (AG)	154 (21.97)	122 (24.95)	222 (44.05)	104 (20.68)	104 (29.97)	45 (6.81)
			Alt-hom (AA)	13 (1.85)	13 (2.66)	38 (7.54)	13 (2.58)	12 (3.46)	1 (0.15)
P (χ^2)					0.2853	3.89E-23	0.6178	0.0032	6.36E-17
rs17366743	T	C	Ref-Hom (TT)	686 (98.28)	478 (97.75)	504 (100)	466 (92.64)	343 (98.85)	659 (99.7)
			Het (CT)	12 (1.72)	10 (2.04)	0	36 (7.16)	3 (0.86)	2 (0.3)
			Alt-hom (CC)	0	1 (0.2)	0	1 (0.2)	1 (0.29)	0
P (χ^2)					0.4493	NA	6.19E-06	0.2020	NA
rs6773957	A	G	Ref-Hom (AA)	97 (13.8)	71 (14.52)	175 (34.72)	87 (17.3)	85 (24.5)	248 (37.52)
			Het (AG)	306 (43.53)	211 (43.15)	244 (48.41)	238 (47.32)	182 (52.45)	308 (46.6)
			Alt-hom (GG)	300 (42.67)	207 (42.33)	85 (16.87)	178 (35.39)	80 (23.05)	105 (15.89)
P (χ^2)					0.9399	9.34E-27	0.0272	2.75E-10	3.22E-35

SNP: Single-nucleotide polymorphism, Indian: Study population. SAS: South Asian, EAS: East Asian, EUR: European, AMR: Admixed American, AFR: African, REF: Reference allele, ALT: Alternate allele

also associated with increased body weight/body mass index,[10] is also high in Indian population as compared to EAS and AFR populations.

Allele A at rs17366568, which is associated with type 2 diabetes,[12] is highly prevalent in Indian, SAS, and EUR compared to EAS, AMR, and AFR populations. rs1501299, which is associated with cardiovascular diseases and cancers in Chinese and Han Chinese populations,[13-15] has high prevalence of risk allele in EAS, AMR, and AFR populations but less prevalence rates in India, SAS, and EUR populations. Similarly, A allele of rs3774262, which is known to be associated with prostate cancer in Han Chinese population,[16] is highly prevalent in EAS than the Indian group.

To the best of our knowledge, this is the first study to compare ADIPOQ polymorphism frequencies between Indian population and other populations. The only limitation of the study is that it did not consider the differences in North and South Indian populations. It can be concluded that EASs are very different from Indians in terms of ADIPOQ polymorphisms and consequently adiponectin levels and body weights.

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Conflicts of interest

There are no conflicts of interest.

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