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Authors' contributions

This work was carried out in collaboration between all authors. Authors MLM and MGGE conceived and designed the project. Author MLM developed the strategies and supervised the project. Authors MGGE, NVG and DPE obtained samples and collected data. Author MGDC prepared the database and processed samples. Authors MGDC, ATS and ADB performed statistical analyses. Authors MLM, MGDC and ATS wrote the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Maya ancestry populations from Yucatan have exhibited a high prevalence of diabetes and obesity; consequently, the aim of this study was to determine the allelic and genotype frequencies of six polymorphisms associated with diabetes and obesity in two Maya populations.

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Place and Duration of Study: Department of Genetics and Molecular Biology, Centro de Investigación y de Estudios Avanzados del IPN; Laboratorios de Genética y Hematología, Centro de Investigaciones Regionales "Dr. Hideyo Noguchi", Universidad Autónoma de Yucatán between September 2014 and March 2016.
Methodology: Healthy individuals with Maya ancestry were recruited in small rural and urban communities from Yucatan. Six polymorphisms present in five genes (*PPARGC1A*, *NRF1*, *SLC30A8*, *ADRA2A* and *UCP3*) were genotyped using TaqMan assays. Linkage disequilibrium analysis was performed for rs13266634 and rs11558471 (*SLC30A8*).
Results: The observed frequencies in the small rural community (SRC) and Merida were in Hardy Weinberg equilibrium. Frequencies of five polymorphisms (rs8192678, rs1882095, rs13266634, rs11558471 and rs3781907) correlated with 1000 genomes project data, furthermore, statistical analysis did not reveal a significant difference between genotype frequencies of the SRC and Merida populations. Contrary, frequencies from Mexicans living in Los Angeles compared with frequencies obtained in Yucatan (SRC and Merida) indicated significant difference on genotype frequencies in the *ADRA2A* gene (P-value= .017). The polymorphisms rs13266634 and rs11558471 in the *SLC30A8* gene displayed strong linkage disequilibrium (D'= 0.96), displaying frequencies of 0.725, 0.255, and 0.015 for haplotypes *C-A*, *T-G*, and *C-G* respectively.
Conclusion: Distribution of *A* allele in rs553668 (*ADRA2A*) in the Yucatan populations was higher than the frequency reported for Mexicans from LA, Americans, Europeans, and Africans. This finding could be related to blood pressure levels in the Maya populations. Additionally, a high frequency of *C-A* haplotype (rs13266634 and rs11558471) in the *SLC30A8* gene could be associated with an increased risk of diabetes and obesity in these populations.

Keywords: Mexican-Maya; PPARGC1A; NRF1; SLC30A8; ADRA2A; UCP3.

1. INTRODUCTION

The state of Yucatan is known for its Maya heritage, with the ancient Pre-Hispanic cultures having settled in this region more than 3,500 years ago. Past studies have emphasized certain physical and genetic characteristics of Maya descendants, which are thought are playing a major role in their physical constitution and risk of metabolic disease [1-4]. Currently, Yucatan is in the top five states in the nation with the highest rates of diabetes and hypertension. The National Health and Nutrition survey of 2012 registered 7,210 and 7,070 cases of diabetes and hypertension, respectively, in Yucatan [5,6]. Projections for the next 25 years estimate an increase from 44.3 to 60.5 million cases of Type 2 diabetes (T2D) [7]. Reports from 2011 show that the prevalence of T2D in Yucatan is 8.2-9.2% [5]. Despite this modest average, communities in the northeast coast of Yucatan display a higher prevalence of T2D [3,8]. Specifically, there is a case of a small rural community (SRC) with less than 5,000 habitants where the prevalence of T2D rises up to 22% (unpublished data). Additionally, this population exhibits a strong Maya ancestry, as well as a high prevalence of obesity [3,8].

Genetic, environmental factors and ethnicity have been related to the development of diabetes [9-11]. However, genetic polymorphisms found throughout the genome also play a role in susceptibility to T2D, mainly when there are polymorphisms in genes implicated in insulin secretion [12–14], insulin resistance [15–17], β-pancreatic cells impairment [18,19] and/or lipid metabolism [20,21].

1.1 Function of Genes Involved in T2D of this Study

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha encoded by *PPARGC1A* gene is a transcriptional coactivator of nuclear receptors and other transcription factors that regulate metabolic processes, including mitochondrial biogenesis and respiration, and hepatic gluconeogenesis [22,23]. This protein may be also involved in controlling blood pressure, regulating cellular cholesterol homeostasis, and obesity development [24]. The rs8192678 variant has been associated with diabetes related traits such as insulin resistance [25] and insulin secretory response and lipid oxidation [26].

The nuclear respiratory factor-1 encoded by the gene *NRF1* homodimerizes and functions as a transcription factor which activates the expression of some key metabolic genes, regulating cellular growth and nuclear genes

required for respiration, heme groups biosynthesis, and mitochondrial DNA transcription and replication [22,27,28]. It also has been reported that decrease in *PPARGC1A* expression may be responsible for decreased expression of NRF1 dependent genes, leading to insulin resistance and T2D [29]. The variant rs13266634 has been associated to T2D in a Finnish population [30].

The solute carrier family 30 member 8 encoded by the gene *SLC30A8* is a zinc efflux transporter involved in the accumulation of zinc in intracellular vesicles. This gene is expressed at a high level in islets of Langerhans [22,31]. Recently, it has been confirmed the increased risk of developing T2D in Asian, European and African populations with the variant rs13266634 [31]; and the variants rs11558471 and rs13266634 together have been also associated to T2D in a Han Chinese population [32].

Alpha-2-adrenergic receptors are members of the G protein-coupled receptor superfamily [22]. These receptors have a critical role in regulating neurotransmitter release from sympathetic nerves and from adrenergic neurons in the central nervous system [33]. The variant rs553668 located in the 3′ UTR region of the adrenoreceptor alpha 2A encoded by the gene *ADRA2A*, caused its overexpression, which has been associated with impaired insulin secretion in a Scandinavian population [34].

Mitochondrial uncoupling proteins encoded by the *UCP3* gene are members of the larger family of mitochondrial anion carrier proteins (MACP). It is primarily expressed in skeletal muscle [22]. UCPs facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane. Expression levels of this gene increase when fatty acid supplies to mitochondria exceed their oxidation capacity and the protein enables the export of fatty acids from mitochondria. The haplotype that includes the variants rs3781907, rs11235972, and rs1800849 has been associated with high LDL-cholesterol in a Finnish population [35].

The two Maya populations of this study exhibit particular genetic characteristics inherent to Maya ancestry, which makes them unique for distribution studies as an initial approach for research in complex diseases. Therefore, the aim of this study was to describe the distribution of six polymorphisms associated with T2D and obesity in two communities with high prevalence of these pathologies.

2. MATERIALS AND METHODS

2.1 Subjects

Individuals were recruited in the SRC and Merida (Yucatan, Mexico). The study included 181 healthy, contemporary Mexicans with Maya ancestry, between ages of 20 to 90 years. Participants had at least three generations of ancestors born at the place of sampling and their last names were of Maya origin. The study was performed according to the Helsinki Declaration and Institutional Review Board authorizations were obtained from Centro de Investigaciones Regionales “Dr. Hideyo Noguchi”, Universidad Autónoma de Yucatán, and informed consent was obtained from all participants.

2.2 DNA Isolation

DNA was isolated from peripheral blood using either a commercial kit Invisorb® Spin Blood Midi Kit (STRATEC Molecular GmbH, Berlin, Germany), as described in the manual and/or using the automated extraction system Chemagic Prepito® (PerkinElmer Inc., Waltham, MA, USA).

2.3 Genotyping

This procedure was carried out by Real Time PCR using TaqMan® Assays (Applied Biosystems, Foster City, CA, USA) as suggested by the manufacturer in five genes (*PPARGC1A* rs8192678, *NRF1* rs1882095, *SLC30A8* rs13266634, *SLC30A8* rs11558471, *ADRA2A* rs553668 and *UCP3* rs3781907) (Table 1).

2.4 Statistical Analysis

Allelic and genotype frequencies, and Hardy Weinberg equilibrium (HWE) were evaluated with SNPstat software (Barcelona, Spain). Analysis of Fisher’s exact test or the Chi square test were performed with R package version 3.2.3, (Vienna, Austria). Linkage disequilibrium and haplotype frequency in variants located in the *SLC30A8* gene (rs13266634 and rs11558471) were assessed using SNPstat. Haplotype was verified using Haploview version 4.1 (Cambridge, MA, USA), values of D’ and r^2 in both SNPs were determined.

Table 1. Characteristics of variants studied

Gene	Ref A*/RA** MAF***	Pathology	Population	Reference
PPARGC1A rs8192678	C/A 0.2658/1331	Increased risk of non-alcoholic fatty liver disease	Taiwanese	Lin et al. 2013 [36]
		Higher triacylglycerols, suggested increased risk for cardiovascular diseases and/or type 2	Brazilian	Queiroz et al. 2015 [37]
		Sarcoidosis	Slovenia	Maver et al. 2008 [38]
NRF1 rs1882095	T/T 0.4902/2455	Higher risk of type 2 diabetes	Finnish	Gaulton et al. 2008 [30]
SLC30A8 rs13266634	C/C 0.2552/1278	Higher risk of type 2 diabetes	Asian/ European	Cheng et al. 2015 [39]
		Higher risk of type 2 diabetes	French	Sladek et al. 2007 [40]
SLC30A8 rs11558471	A/C 0.2600/1302	Fasting glucose levels	South Asians	Rees et al. 2011 [41]
	A/A 0.2600/1302	Fasting proinsulin levels	Europeans	Strawbridge et al. 2011 [42]
ADRA2A rs553668	A/A 0.3295/1650	Higher risk of type 2 diabetes	Europeans	Chen et al. 2013 [43]
		Obesity	Swedish	Långberg et al. 2013 [44]
UCP3 rs3781907	A/G 0.2855/1430	Serum lipid levels and higher risk of type 2 diabetes	Finnish	Salopuro et al. 2009 [45]

Abbreviations: Ref A= Reference allele, RA**= Risk allele, MAF***= Minor allele frequency*

3. RESULTS

3.1 Genotype and Allelic Frequencies

In this study were included 181 individuals from two different populations, 93 subjects were from Merida and 88 from the SRC. The genotype and allelic frequencies are shown in Fig. 1. Observed frequencies in both the SRC and Merida populations were in HWE. Frequencies of six previously described SNPs were compared with other populations worldwide [African, European, East and South Asian, American and Mexican living in Los Angeles (LA) populations] using data obtained from the 1000 Genomes Project (1000 GP) (Appendix I). Five out of the six variants (rs8192678, rs1882095, rs13266634, rs11558471 and rs3781907) were consistent with the frequencies of the 1000 GP (Figs. 1A, B; C; D; F).

In order to compare frequencies and assess significant differences between data from the SRC versus Merida participants, and Mexicans from LA versus Yucatan individuals (SRC and Merida), the Fisher's exact test or the Chi-square test were estimated. The results did not reveal a significant difference between genotype frequencies of SRC and Merida participants in most cases. Nevertheless, the *ADRA2A* gene showed a significant difference between frequencies (P= .01) when Mexicans in LA were compared to Yucatan individuals (Merida and the SRC) (Fig. 1E).

3.2 Linkage Disequilibrium Analysis

Polymorphisms rs13266634 and rs11558471 in the *SLC30A8* gene showed a strong linkage disequilibrium of D'= 0.96 (Fig. 2), displaying haplotypes *C-A*, *T-G*, and *C-G* with frequencies of 0.725, 0.255 and 0.015, respectively.

4. DISCUSSION

The Maya populations of this study have been very important historically. The two populations are located near each other (with 53 km of distance between them); however, there are notable differences, for example the SRC is an isolated population in a rural community, meanwhile Merida is a cosmopolitan city in an urban area with genetic and ancestry differences that could influence studies of complex diseases [3,46].

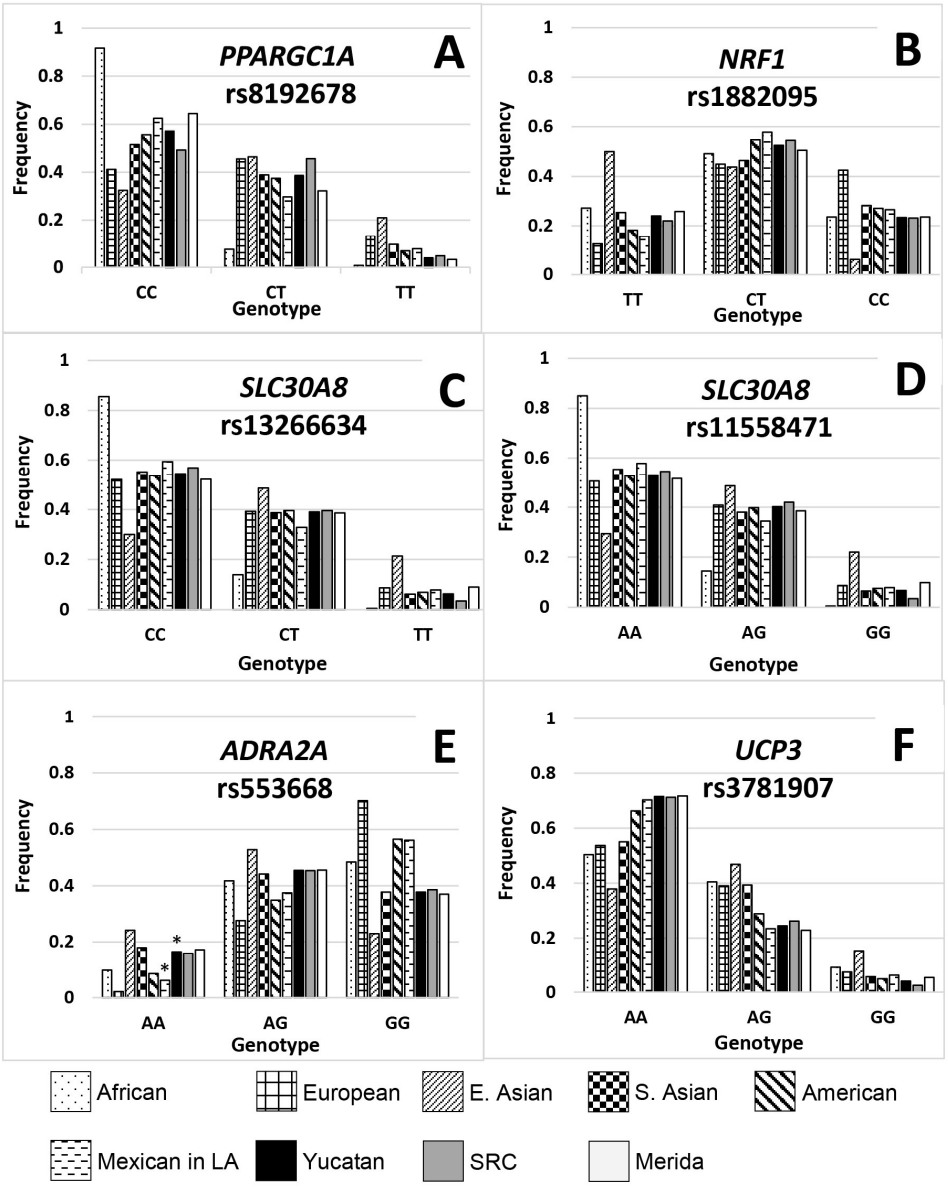

Fig. 1. Distribution of genotype frequencies including SRC and Merida of six SNPs. A. *PPARGC1A* rs8192678; B. *NRF1* rs1882095; C. *SLC30A8* rs13266634; D. *SLC30A8* rs11558471; E. *ADRA2A* rs553668; and F. *UCP3* rs3781907

*Significant difference between Mexicans living in Los Angeles, USA and Mayas from Yucatan, Mexico; P=.017 is displayed by **

Maya populations are often lumped together and treated as a homogeneous population. Consequently, there have been inconsistent findings regarding the heterogeneity of Maya and relationship among individuals in this culture [46]. Physiologically, individuals of Maya populations exhibit different metabolic rates, heart rates, blood pressure, and incidence of hyperthyroidism [47,48], making this population a target of study in the context of its genetic variation and susceptibility for multifactorial diseases, such as obesity and diabetes. Genotype frequency and distribution studies of the *SLC16A11* gene among different Maya populations, for example, could give us insight of how genomic variants may influence the incidence of multifactorial diseases in Mexicans [49,50].

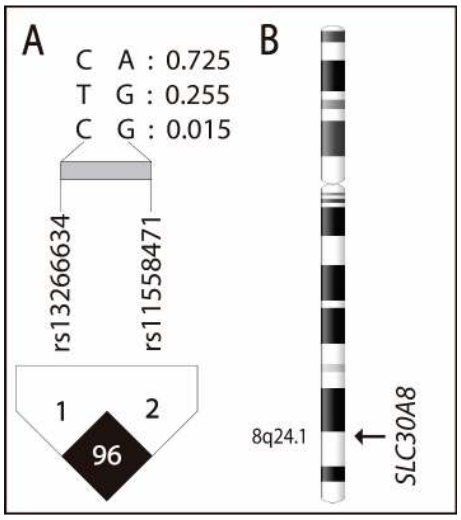

Fig. 2. Linkage disequilibrium structure and locus. A. Haploview figure of *SLC30A8* gene (rs13266634 and rs11558471). Linkage disequilibrium coefficients D' x 100 is shown in coloured black square and was measured using data from all subjects (Yucatan). Three haplotype blocks are shown and the haplotype frequencies are next to each haplotype. B. Locus of *SLC30A* gene is represented in chromosome 8

This is the first study reporting frequencies of five polymorphisms (rs8192678, rs1882095, rs11558471, rs553668 and rs3781907) located in five genes (*PPARGC1A, NRF1, SLC30A8, ADRA2A* and *UCP3*) in two contemporary Maya populations with a history of high prevalence of obesity and diabetes [8,50]. Genotype and allelic frequencies of these communities were analyzed and compared with those of African, European, South and East Asian, American and Mexican living in LA populations reported in the 1000 GP. Mexican populations are genetically shaped by an admixture of different ethnicities; hence, allelic and genotype frequencies cannot be considered the same for Mayas and for Mexican-Americans. Volunteers from LA genotyped on the 1000 GP are considered globally as a representative sample of Mexican-Mestizos, who present a high rate of admixture owing to their Spanish and Native-American genetic background and, to a minor extent, to Asian and African genetic background [51]. According to the International HapMap Project, Mexicans that are from Los Angeles have 45%, 49, and 5% of Native American, European, and African ancestry respectively (http://hapmap.org); however, evaluation of ancestry in Mexico City using trios, estimated proportions were 65%, 31%, and 3% in Native American, European and African respectively, that is different to HapMap analysis [52].

The frequencies obtained from *PPARGC1A, SLC30A8,* and *UCP3* are in agreement to those reported by the 1000 GP in Mexican-Mestizos from LA, unlike the frequencies of *NRF1* and *ADRA2A,* with 5.7% and 14.3%, respectively. The results of *NRF1* frequencies are similar to those reported in African and South Asians, despite their evolutionary distance. Furthermore, in contrast with data reported from individuals living in LA with Mexican ancestry, whose frequencies are used as a reference of Mexican-Mestizos, a high frequency of the *A* allele of *ADRA2A* was found in the populations from the SRC and Merida. In a previous study, Kurnik et al. [53] associated homozygous individuals containing *A* allele with a greater hypotensive response to Dexmedetomidine (agonist of alpha receptors 2). The variant rs553668 has been also associated to overexpression of *ADRA2A* which contributes to T2D [34] and may be favoring a low blood pressure and increase risk to T2D.

The Maya, African and South Asian populations have high risk to T2D including migrants from South Asia [54,55] and Africa [56–58] living in other countries, however our study showed that the frequencies of rs1882095 (*NRF1*) in the Maya, Asian, and African populations are similar. Nevertheless, there were no significant differences with the 1000 GP. Consequently, it will be important to increase the sample size in future studies to determine if the difference in frequency of rs1882095 in Maya populations are statistically significant.

As we mentioned most of the SNPs frequencies were similar, even though the SRC may have a different genetic background due to a poor rate of migration inducing less genetic admixture with other communities. In addition, the analyzed frequencies of variants rs1155847 and rs13266634 located in the *SLC30A8* gene displayed similar frequencies compared to those reported for Maya populations living in communities of Yucatan [50]. Furthermore, linkage disequilibrium of these SNPs resulted in a D'=0.96 indicating a high linkage disequilibrium; the fact that these SNPs are 950 bp apart from each other on chromosome 8q24.1 explains this D' value. The analysis also showed high haplotype frequency with 72.5% of *C-A* haplotype, 25.5% of *T-G* haplotype and 1.5% of

C-G. This is important because the *C* allele (rs13266634) and *A* allele (rs1155847) from *C-A* haplotype have been reported as risk alleles in other populations [39,40,42].

In previous reports haplotype *C-G* in rs13266634 and rs1995222 were associated with a higher risk of T2D in all ethnicities (OR = 1.67, $P = 8.6 \times 10^{-5}$) and in Indian subjects (OR = 1.93, P = .001) [59]. Moreover, rs11558471, rs2466295 and rs4876703 exhibited the *A-C-A* haplotype, which was associated with a high risk of T2D development in a Chinese Han population [60]. These results are remarkable because frequencies in SNP rs13266634 in Africans are quite contrasting. In this African population, the homozygous *T* allele shows a frequency of 0.5%, meanwhile the frequency of the same SNP in Mexicans in LA, SRC and Merida, present frequencies of 7.8%, 3.4% and 9%, respectively, without having a significant difference among them.

Results obtained in this work could help researchers around the world in selecting variants to develop and replicate T2D case-control studies in Mexican populations including Maya. Furthermore, the high difference of 14.3% for *ADRA2A* in the Maya populations of this study may explain the risk to T2D in Mexicans and also might help in determine susceptibility to this disease in the future.

5. CONCLUSION

The distribution of rs553668 (*ADRA2A* gene) has a higher frequency in our samples compared to European, Asian and African populations, which could be related to other studies that report lower blood pressures in populations living in the Yucatan Peninsula. Additionally, according to our significant findings regarding *ADRA2A*, we suggest to take into consideration the *C-A* (rs13266634 and rs11558471) haplotype for future case-control diabetes studies, and related traits.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. García-Escalante MG, Suárez-Solís VM, López-Avila MT de J, Pinto-Escalante D del C, Laviada-Molina H. Effect of the Gly972Arg, SNP43 and Prol2Ala polymorphisms of the genes IRS1, CAPN10 and PPARG2 on secondary failure to sulphonylurea and metformin in patients with type 2 diabetes in Yucatán, México. Invest. Clin. 2009;50(1):65–76.
2. Hernandez-Escalante VM, Nava-Gonzalez EJ, Voruganti VS, Kent JW, Haack K, Laviada-Molina HA, et al. Replication of obesity and diabetes-related SNP associations in individuals from Yucatán, México. Front. Genet. 2014;5:380.
3. Vargas-Ancona L. Epidemiología de la diabetes mellitus, intolerancia a la glucosa y factores de riesgo aterogénico en Yucatán, México. Rev Biomed. 1994;5(3): 151–159.
4. Pinto Escalante D, Ceballos Quintal J. Estudio comparativo de consanguinidad entre una poblacion suburbana y una urbana de yucatan, México. Rev Biomed. 1994;5(2):70–76.
5. Gutiérrez J, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L, et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. 1st ed. Cuernavaca, México: Instituto Nacional de Salud Pública; 2012. Available:http://ensanut.insp.mx/informes/ENSANUT2012ResultadosNacionales.pdf
6. Barquera S, Campos-Nonato I, Hernández-Barrera L, Pedroza-Tobías A, Rivera-Dommarco JA. Prevalencia de obesidad en adultos mexicanos, ENSANUT 2012. Salud Publica Mex. 2013;55(supl 2):S151–S160.
7. International Diabetes Federation. IDF Diabetes Atlas, 7th Edn; 2015. Available:http://www.diabetesatlas.org

8. Bastarrachea-sosa R, Laviada-molina H, Vargas-ancona L. Nutrición en Yucatán. Rev. Endocrinoly Nutr. 2001;9(2):73–76.
9. Chen R, Corona E, Sikora M, Dudley JT, Morgan AA, Moreno-Estrada A, et al. Type 2 diabetes risk alleles demonstrate extreme directional differentiation among human populations, compared to other diseases. PLoS Genet. 2012;8(4): e1002621.
10. Mao J, Ai J, Zhou X, Shenwu M, Ong M, Blue M, et al. Transcriptomic profiles of peripheral white blood cells in type II diabetes and racial differences in expression profiles. BMC Genomics. 2011; 12(Suppl 5):S12.
11. Waters KM, Stram DO, Hassanein MT, Le Marchand L, Wilkens LR, Maskarinec G, et al. Consistent association of type 2 diabetes risk variants found in Europeans in diverse racial and ethnic groups. PLoS Genet. 2010;6(8):e1001078.
12. Rosengren AH, Braun M, Mahdi T, Andersson SA, Travers ME, Shigeto M, et al. Reduced insulin exocytosis in human pancreatic β-cells with gene variants linked to type 2 diabetes. Diabetes. 2012;61(7): 1726–33.
13. Scott RA, Fall T, Pasko D, Barker A, Sharp SJ, Arriola L, et al. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independent of obesity. Diabetes. 2014;63(12):4378–4387.
14. Talmud PJ, Cooper JA, Gaunt T, Holmes MV, Shah S, Palmen J, et al. Variants of ADRA2A are associated with fasting glucose, blood pressure, body mass index and type 2 diabetes risk: meta-analysis of four prospective studies. Diabetologia. 2011;54(7):1710–1719.
15. Mercader JM, Puiggros M, Segrè AV, Planet E, Sorianello E, Sebastian D, et al. Identification of novel type 2 diabetes candidate genes involved in the crosstalk between the mitochondrial and the insulin signaling systems. PLoS Genet. 2012; 8(12):e1003046.
16. Chen G, Bentley A, Adeyemo A, Shriner D, Zhou J, Doumatey A, et al. Genome-wide association study identifies novel loci association with fasting insulin and insulin resistance in African Americans. Hum. Mol. Genet. 2012;21(20):4530–4536.
17. Manning AK, Hivert M-F, Scott RA, Grimsby JL, Bouatia-Naji N, Chen H, et al. A genome-wide approach accounting for body mass index identifies genetic variants influencing fasting glycemic traits and insulin resistance. Nat. Genet. 2012;44(6): 659–669.
18. Mitchell RK, Mondragon A, Chen L, Mcginty JA, French PM, Ferrer J, et al. Selective disruption of Tcf7l2 in the pancreatic β cell impairs secretory function and lowers β cell mass. Hum. Mol. Genet. 2015;24(5):1390–1399.
19. Steneberg P, Bernardo L, Edfalk S, Lundberg L, Backlund F, Ostenson C-G, et al. The type 2 diabetes-associated gene ide is required for insulin secretion and suppression of α-synuclein levels in β-cells. Diabetes. 2013;62(6):2004–2014.
20. Zhong H, Beaulaurier J, Lum PY, Molony C, Yang X, Macneil DJ, et al. Liver and adipose expression associated SNPs are enriched for association to type 2 diabetes. PLoS Genet. 2010;6(5):e1000932.
21. Kong X, Zhang X, Xing X, Zhang B, Hong J, Yang W. The association of type 2 diabetes loci identified in genome-wide association studies with metabolic syndrome and its components in a chinese population with type 2 diabetes. PLoS One. 2015;10(11):e0143607.
22. Medicine M-NI of G. Online Mendelian Inheritance in Man. Johns Hopkins Univ; 2016.
23. Lin J, Wu PH, Tarr PT, Lindenberg KS, St-Pierre J, Zhang CY, et al. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1? Null mice. Cell. 2004;119(1):121-135.
24. National Center for Biotechnology Information. PPARGC1A PPARG Coactivator 1 Alpha [Homo Sapiens (Human)]. Report; 2016. Available:http://www.ncbi.nlm.nih.gov/gene/10891
25. Hara K, Tobe K, Okada T, Kadowaki H, Akanuma Y, Ito C, et al. A genetic variation in the PGC-1 gene could confer insulin resistance and susceptibility to type II diabetes. Diabetologia. 2002;45(5):740–3.
26. Muller YL, Bogardus C, Pedersen O, Baier L. A Gly482Ser missense mutation in the peroxisome proliferator-activated receptor gamma coactivator-1 is associated with altered lipid oxidation and early insulin secretion in Pima Indians. Diabetes. 2003; 52(3):895–8.
27. Gopalakrishnan L, Scarpulla RC. Structure, expression, and chromosomal assignment of the human gene encoding

nuclear respiratory factor 1. J. Biol. Chem. 1995;270(30):18019-25.

28. National Center for Biotechnology Information. NRF1 Nuclear Respiratory Factor 1 [Homo Sapiens (Human)]. Report; 2016. Available:http://www.ncbi.nlm.nih.gov/gene/4899
29. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. Proc. Natl. Acad. Sci. U. S. A. 2003; 100:8466–8471.
30. Gaulton KJ, Willer CJ, Li Y, Scott LJ, Conneely KN, Jackson AU, et al. Comprehensive association study of type 2 diabetes and related quantitative traits with 222 candidate genes. Diabetes. 2008; 57(November):3136–3144.
31. Chimienti F, Devergnas S, Favier A, Seve M. Identification and cloning of a beta-cell-specific zinc transporter, ZnT-8, localized into insulin secretory granules. Diabetes. 2004;53(9):2330-2337.
32. Fan M, Li W, Wang L, Gu S, Dong S, Chen M, et al. Association of SLC30A8 gene polymorphism with type 2 diabetes, evidence from 46 studies: A meta-analysis. Endocrine. 2016;53(2):381–94.
33. National Center for Biotechnology Information. ADRA2A Adrenoceptor Alpha 2A [Homo sapiens (human)]. Report; 2016. Available:http://www.ncbi.nlm.nih.gov/gene/150
34. Rosengren AH, Jokubka R, Tojjar D, Granhall C, Hansson O, Li D-Q, et al. Overexpression of alpha2A-adrenergic receptors contributes to type 2 diabetes. Science. 2010;327:217-220.
35. Salopuro T, Pulkkinen L, Lindström J, Kolehmainen M, Tolppanen A-M, Eriksson JG, et al. Variation in the UCP2 and UCP3 genes associates with abdominal obesity and serum lipids: The finnish diabetes prevention study. BMC Med. Genet. 2009; 10:94.
36. Lin Y-C, Chang P-F, Chang M-H, Ni Y-H. A common variant in the peroxisome proliferator-activated receptor-γ coactivator -1α gene is associated with nonalcoholic fatty liver disease in obese children. Am. J. Clin. Nutr. 2013;97(2):326–331.
37. Queiroz EM, Cândido APC, Castro IM, Bastos AQA, Machado-Coelho GLL, Freitas RN. IGF2, LEPR, POMC, PPARG, and PPARGC1 gene variants are associated with obesity-related risk phenotypes in Brazilian children and adolescents. Brazilian J. Med. Biol. Res. 2015;48(7):595–602.
38. Maver A, Medica I, Salobir B, Tercelj-Zorman M, Sabovic M, Petrovic D, et al. Peroxisome proliferator-activated receptor gamma/Pro12Ala polymorphism and peroxisome proliferator-activated receptor gamma coactivator-1 alpha/Gly482Ser polymorphism in patients with sarcoidosis. Sarcoidosis Vasc. Diffuse Lung Dis. 2008; 25(1):29-35.
39. Cheng L, Zhang D, Zhou L, Zhao J, Chen B. Association between SLC30A8 rs13266634 polymorphism and type 2 diabetes risk: A meta-analysis. Med. Sci. Monit. 2015;21:2178–2189.
40. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 2007; 445(7130):881–885.
41. Rees SD, Hydrie MZI, O'Hare JP, Kumar S, Shera AS, Basit A, et al. Effects of 16 genetic variants on fasting glucose and type 2 diabetes in South Asians: ADCY5 and GLIS3 variants may predispose to type 2 diabetes. PLoS One. 2011;6(9): e24710.
42. Strawbridge RJ, Dupuis J, Prokopenko I, Barker A, Ahlqvist E, Rybin D, et al. Genome-wide association identifies nine common variants associated with fasting proinsulin levels and provides new insights into the pathophysiology of type 2 diabetes. Diabetes. 2011;60(10):2624–2634.
43. Chen X, Liu L, He W, Lu Y, Ma D, Du T, et al. Association of the ADRA2A polymorphisms with the risk of type 2 diabetes: A meta-analysis. Clin. Biochem. 2013;46(9):722–726.
44. Långberg E-C, Seed Ahmed M, Efendic S, Gu HF, Östenson C-G. Genetic association of adrenergic receptor alpha 2A with obesity and type 2 diabetes. Obesity. 2013;21(8):1720–1725.
45. Salopuro T, Pulkkinen L, Lindström J, Kolehmainen M, Tolppanen A-M, Eriksson JG, et al. Variation in the UCP2 and UCP3 genes associates with abdominal obesity and serum lipids: The finnish diabetes prevention study. BMC Med. Genet. 2009; 10:94.

46. Justice AE. Genetic structure of the maya in Guatemala. Perspectives of the population history of the maya using mtDNA and Y-chromosome markers; 2011.
47. D.F. R, M.T. N. No Title. Austin: University of Texas Press; 1970.
48. Arroyo P, Fernández V, Loría A, Pardío J, Laviada H, Vargas-Ancona L, et al. Obesidad, morfología corporal y presión arterial en grupos urbanos y rurales de Yucatán. Salud Publica Mex. 2007;49(4): 274–285.
49. Williams AL, Jacobs SBR, Moreno-Macías H, Huerta-Chagoya A, Churchhouse C, Márquez-Luna C, et al. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. Nature. 2014; 506(7486):97–101.
50. Lara-Riegos JC, Ortiz-López MG, Peña-Espinoza BI, Montúfar-Robles I, Peña-Rico MA, Sánchez-Pozos K, et al. Diabetes susceptibility in mayas: Evidence for the involvement of polymorphisms in HHEX, HNF4α, KCNJ11, PPARγ, CDKN2A/2B, SLC30A8, CDC123/CAMK1D, TCF7L2, ABCA1 and SLC16A11 genes. Gene. 2015;565(1):68–75.
51. Silva-Zolezzi I, Hidalgo-Miranda A, Estrada-Gil J, Fernandez-Lopez JC, Uribe-Figueroa L, Contreras A, et al. Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico. Proc. Natl. Acad. Sci. U. S. A. 2009;106:8611–8616.
52. Johnson NA, Coram MA, Shriver MD, Romieu I, Barsh GS, London SJ, et al. Ancestral components of admixed genomes in a Mexican Cohort. PLoS Genet. 2011;7(12):e1002410.
53. Kurnik D, Muszkat M, Li C, Sofowora GG, Friedman EA, Scheinin M, et al. Genetic variations in the α(2A)-adrenoreceptor are associated with blood pressure response to the agonist dexmedetomidine. Circ. Cardiovasc. Genet. 2011;4(2):179–87.
54. Gupta LS, Wu CC, Young S, Perlman SE. Prevalence of diabetes in New York City, 2002-2008: Comparing foreign-born South Asians and other Asians with U.S.-born whites, blacks, and Hispanics. Diabetes Care. 2011;34(8):1791–3.
55. Zimmet P, Taylor R, Ram P, King H, Sloman G, Raper LR, et al. Prevalence of diabetes and impaired glucose tolerance in the biracial (Melanesian and Indian) population of Fiji: A rural-urban comparison. Am. J. Epidemiol. 1983; 118(5):673–88.
56. Azevedo M, Alla S. Diabetes in Sub-Saharan Africa: Kenya, Mali, Mozambique, Nigeria, South Africa and Zambia. Int. J. Diabetes Dev. Ctries. 2008;28(4):101–8.
57. Savitz DA, Janevic TM, Engel SM, Kaufman JS, Herring AH. Ethnicity and gestational diabetes in New York City, 1995-2003. BJOG. 2008;115(8):969–78.
58. Rulifson IC, Karnik SK, Heiser PW, Ten Berge D, Chen H, Gu X, et al. Wnt signaling regulates pancreatic beta cell proliferation. Proc. Natl. Acad. Sci. U. S. A. 2007;104(15):6247–52.
59. Salem SD, Saif-Ali R, Ismail IS, Al-Hamodi Z, Muniandy S. Contribution of SLC30A8 variants to the risk of type 2 diabetes in a multi-ethnic population: A case control study. BMC Endocr. Disord. 2014;14:2.
60. Xu J, Wang J, Chen B. SLC30A8 (ZnT8) variations and type 2 diabetes in the Chinese Han Population. Genet. Mol. Res. 2012;11(2):1592–1598.

APPENDIX I

Allelic and genotype frequency distribution of worldwide populations.

Gene/SNP	Population*	Allele frequency		Genotype frequency		
***PPARGC1A* rs8192678**	ALL	*C: 0.734 (3677)*	*T: 0.266 (1331)*	*C|C: 0.568 (1422)*	*C|T: 0.333 (833)*	*T|T: 0.099 (249)*
	AFRICAN	*C: 0.955 (1262)*	*T: 0.045 (60)*	*C|C: 0.917 (606)*	*C|T: 0.076 (50)*	*T|T: 0.008 (5)*
	EUROPEAN	*C: 0.639 (643)*	*T: 0.361 (363)*	*C|C: 0.412 (207)*	*C|T: 0.455 (229)*	*T|T: 0.133 (67)*
	EAST ASIAN	*C: 0.558 (562)*	*T: 0.442 (446)*	*C|C: 0.325 (164)*	*C|T: 0.464 (234)*	*T|T: 0.210 (106)*
	SOUTH ASIAN	*C: 0.710 (694)*	*T: 0.290 (284)*	*C|C: 0.515 (252)*	*C|T: 0.389 (190)*	*T|T: 0.096 (47)*
	AMERICAN	*C: 0.744 (516)*	*T: 0.256 (178)*	*C|C: 0.556 (193)*	*C|T: 0.375 (130)*	*T|T: 0.069 (24)*
	MEXICAN IN LA	*C: 0.773 (99)*	*T: 0.227 (29)*	*C|C: 0.625 (40)*	*C|T: 0.297 (19)*	*T|T: 0.078 (5)*
	SRC MEX	*C: 0.722 (120)*	*T: 0.277 (46)*	*C|C: 0.493 (41)*	*C|T: 0.457 (38)*	*T|T: 0.048 (4)*
	MERIDA MEX	*C: 0.805 (145)*	*T: 0.194 (35)*	*C|C: 0.644 (58)*	*C|T: 0.322 (29)*	*T|T: 0.033 (3)*
	YUCATAN MEX	*C: 0.765 (265)*	*T: 0.234 (81)*	*C|C: 0.572 (99)*	*C|T: 0.387 (67)*	*T|T: 0.040 (7)*
***NRF1* rs1882095**	ALL	*T: 0.510 (2553)*	*C: 0.490 (2455)*	*T|T: 0.272 (682)*	*C|T: 0.475 (1189)*	*C|C: 0.253 (633)*
	AFRICAN	*T: 0.518 (685)*	*C: 0.482 (637)*	*T|T: 0.272 (180)*	*C|T: 0.492 (325)*	*C|C: 0.236 (156)*
	EUROPEAN	*T: 0.350 (352)*	*C: 0.650 (654)*	*T|T: 0.125 (63)*	*C|T: 0.449 (226*	*C|C: 0.425 (214)*
	EAST ASIAN	*T: 0.719 (725)*	*C: 0.281 (283)*	*T|T: 0.500 (252)*	*C|T: 0.438 (221)*	*C|C: 0.062 (31)*
	SOUTH ASIAN	*T: 0.486 (475)*	*C: 0.514 (503)*	*T|T: 0.254 (124)*	*C|T: 0.464 (227)*	*C|C: 0.282 (138)*
	AMERICAN	*T: 0.455 (316)*	*C: 0.545 (378)*	*T|T: 0.182 (63)*	*C|T: 0.548 (190)*	*C|C: 0.271 (94)*
	MEXICAN IN LA	*T: 0.445 (57)*	*C: 0.555 (71)*	*T|T: 0.156 (10)*	*C|T: 0.578 (37)*	*C|C: 0.266 (17)*
	SRC MEX	*T: 0.494 (85)*	*C: 0.505 (87)*	*T|T: 0.220 (19)*	*C|T: 0.546 (47)*	*C|C: 0.232 (20)*
	MERIDA MEX	*T: 0.510 (95)*	*C: 0.489 (91)*	*T|T: 0.258 (24)*	*C|T: 0.505 (47)*	*C|C: 0.236 (22)*
	YUCATAN MEX	*T: 0.502 (180)*	*C: 0.497 (178)*	*T|T: 0.240 (43)*	*C|T: 0.525 (94)*	*C|C: 0.234 (42)*
***SLC30A8* rs11558471**	ALL	*A: 0.740 (3706)*	*G: 0.260 (1302)*	*A|A: 0.566 (1418)*	*A|G: 0.347 (870)*	*G|G: 0.086 (216)*
	AFRICAN	*A: 0.923 (1220)*	*G: 0.077 (102)*	*A|A: 0.850 (562)*	*A|G: 0.145 (96)*	*G|G: 0.005 (3)*
	EUROPEAN	*A: 0.709 (713)*	*G: 0.291 (293)*	*A|A: 0.505 (254)*	*A|G: 0.408 (205)*	*G|G: 0.087 (44)*
	EAST ASIAN	*A: 0.537 (541)*	*G: 0.463 (467)*	*A|A: 0.294 (148)*	*A|G: 0.486 (245)*	*G|G: 0.220 (111)*
	SOUTH ASIAN	*A: 0.744 (728)*	*G: 0.256 (250)*	*A|A: 0.554 (271)*	*A|G: 0.380 (186)*	*G|G: 0.065 (32)*
	AMERICAN	*A: 0.726 (504)*	*G: 0.274 (190)*	*A|A: 0.527 (183)*	*A|G: 0.398 (138)*	*G|G: 0.075 (26)*
	MEXICAN IN LA	*A: 0.750 (96)*	*G: 0.250 (32)*	*A|A: 0.578 (37)*	*A|G: 0.344 (22)*	*G|G: 0.078 (5)*
	SRC MEX	*A: 0.755 (133)*	*G: 0.244 (43)*	*A|A: 0.545 (48)*	*A|G: 0.420 (37)*	*G|G: 0.034 (3)*
	MERIDA MEX	*A: 0.708 (129)*	*G: 0.291 (53)*	*A|A: 0.516 (47)*	*A|G: 0.384 (35)*	*G|G: 0.098 (9)*
	YUCATAN MEX	*A: 0.731 (262)*	*G: 0.268 (96)*	*A|A: 0.530 (95)*	*A|G: 0.402 (72)*	*G|G: 0.067 (12)*
***SLC30A8* rs13266634**	ALL	*C: 0.745 (3730)*	*T: 0.255 (1278)*	*C|C: 0.573 (1435)*	*C|T: 0.343 (860)*	*T|T: 0.083 (209)*
	AFRICAN	*C: 0.926 (1224)*	*T: 0.074 (98)*	*C|C: 0.856 (566)*	*C|T: 0.139 (92)*	*T|T: 0.005 (3)*
	EUROPEAN	*C: 0.717 (721)*	*T: 0.283 (285)*	*C|C: 0.521 (262)*	*C|T: 0.392 (197)*	*T|T: 0.087 (44)*

Gene/SNP	Population*	Allele frequency		Genotype frequency		
	EAST ASIAN	*C: 0.543 (547)*	*T: 0.457 (461)*	*C|C: 0.300 (151)*	*C|T: 0.486 (245)*	*T|T: 0.214 (108)*
	SOUTH ASIAN	*C: 0.745 (729)*	*T: 0.255 (249)*	*C|C: 0.552 (270)*	*C|T: 0.387 (189)*	*T|T: 0.061 (30)*
	AMERICAN	*C: 0.733 (509)*	*T: 0.267 (185)*	*C|C: 0.536 (186)*	*C|T: 0.395 (137)*	*T|T: 0.069 (24)*
	MEXICAN IN LA	*C: 0.758 (97)*	*T: 0.242 (31)*	*C|C: 0.594 (38)*	*C|T: 0.328 (21)*	*T|T: 0.078 (5)*
	SRC MEX	*C: 0.767 (132)*	*T: 0.232 (40)*	*C|C: 0.569 (49)*	*C|T: 0.395 (34)*	*T|T: 0.034 (3)*
	MERIDA MEX	*C: 0.715 (126)*	*T: 0.284 (50)*	*C|C: 0.522 (46)*	*C|T: 0.386 (34)*	*T|T: 0.090 (8)*
	YUCATAN MEX	*C: 0.741 (258)*	*T: 0.258 (90)*	*C|C: 0.545 (95)*	*C|T: 0.390 (68)*	*T|T: 0.063 (11)*
***ADRA2A* rs553668**	ALL	*A: 0.329 (1650)*	*G: 0.671 (3358)*	*A|A: 0.126 (316)*	*A|G: 0.407 (1018)*	*G|G: 0.467 (1170)*
	AFRICAN	*A: 0.307 (406)*	*G: 0.693 (916)*	*A|A: 0.098 (65)*	*A|G: 0.418 (276)*	*G|G: 0.484 (320)*
	EUROPEAN	*A: 0.160 (161)*	*G: 0.840 (845)*	*A|A: 0.022 (11)*	*A|G: 0.276 (139)*	*G|G: 0.702 (353)*
	EAST ASIAN	*A: 0.506 (510)*	*G: 0.494 (498)*	*A|A: 0.242 (122)*	*A|G: 0.528 (266)*	*G|G: 0.230 (116)*
	SOUTH ASIAN	*A: 0.401 (392)*	*G: 0.599 (586)*	*A|A: 0.180 (88)*	*A|G: 0.442 (216)*	*G|G: 0.378 (185)*
	AMERICAN	*A: 0.261 (181)*	*G: 0.739 (513)*	*A|A: 0.086 (30)*	*A|G: 0.349 (121)*	*G|G: 0.565 (196)*
	MEXICAN IN LA	*A: 0.250 (32)*	*G: 0.750 (96)*	*A|A: 0.062 (4)*	*A|G: 0.375 (24)*	*G|G: 0.562 (36)*
	SRC MEX	*A: 0.386 (68)*	*G: 0.613 (108)*	*A|A: 0.159 (14)*	*A|G: 0.454 (40)*	*G|G: 0.386 (34)*
	MERIDA MEX	*A: 0.401 (65)*	*G: 0.598 (97)*	*A|A: 0.172 (14)*	*A|G: 0.456 (37)*	*G|G: 0.370 (30)*
	YUCATAN MEX	*A: 0.393 (133)*	*G: 0.606 (205)*	*A|A: 0.165 (28)*	*A|G: 0.455 (77)*	*G|G: 0.378 (64)*
***UCP3* rs3781907**	ALL	*A: 0.714 (3578)*	*G: 0.286 (1430)*	*A|A: 0.516 (1293)*	*A|G: 0.396 (992)*	*G|G: 0.087 (219)*
	AFRICAN	*A: 0.707 (934)*	*G: 0.293 (388)*	*A|A: 0.504 (333)*	*A|G: 0.405 (268)*	*G|G: 0.091 (60)*
	EUROPEAN	*A: 0.732 (736)*	*G: 0.268 (270)*	*A|A: 0.537 (270)*	*A|G: 0.390 (196)*	*G|G: 0.074 (37)*
	EAST ASIAN	*A: 0.613 (618)*	*G: 0.387 (390)*	*A|A: 0.379 (191)*	*A|G: 0.468 (236)*	*G|G: 0.153 (77)*
	SOUTH ASIAN	*A: 0.746 (730)*	*G: 0.254 (248)*	*A|A: 0.550 (269)*	*A|G: 0.393 (192)*	*G|G: 0.057 (28)*
	AMERICAN	*A: 0.807 (560)*	*G: 0.193 (134)*	*A|A: 0.663 (230)*	*A|G: 0.288 (100)*	*G|G: 0.049 (17)*
	MEXICAN IN LA	*A: 0.820 (105)*	*G: 0.180 (23)*	*A|A: 0.703 (45)*	*A|G: 0.234 (15)*	*G|G: 0.062 (4)*
	SRC MEX	*A: 0.843 (135)*	*G: 0.156 (25)*	*A|A: 0.712 (57)*	*A|G: 0.262 (21)*	*G|G: 0.025 (2)*
	MERIDA MEX	*A: 0.831 (153)*	*G: 0.168 (31)*	*A|A: 0.717 (66)*	*A|G: 0.228 (21)*	*G|G: 0.054 (5)*
	YUCATAN MEX	*A: 0.837 (288)*	*G: 0.162 (56)*	*A|A: 0.715 (123)*	*A|G: 0.244 (42)*	*G|G: 0.040 (7)*

** Data for African, European, Asian, American and Mexican in Los Angles frequencies were obtained from 1000 genomes project. Results of this study are shown in bold*

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