consumption of animal protein, milk and dairy protein might increase the PCa risk by hormonal changes [17,56].

Milk and dairy products high consumption are a key feature in Puerto Rican nutritional habits [29,55]. Milk contains high concentrations of miRNA-29s rich exosomes, which attack DNA methyltransferases, reducing the methylation of *FTO* CpG islands, stimulating *FTO* expression [17]. Moreover, in animal model's overexpression of FTO increases the expression of the RUNX1T1 transcription factor in embryonic fibroblasts stimulating the number of adipocytes [57]. Knowing that *FTO* expression can modulate obesity onset [19,58] due to its stronger expression during childhood, it is feasible to think that throughout adulthood the high consumption of foods that stimulate *FTO* overexpression would contribute to the high incidence of obesity, and hence PCa risk. Unfortunately, we did not have access to the lifetime health records of our participants, so we are unable to establish the timeline for obesity onset in our cohort.

The heterozygous form (T/A) of *rs9939609* was the most prevalent in our cohort. This would suggest that *rs9939609* "A" allele may be implicated in the phenotype of PCa and the male population in PR could have a more severe PCa if they have the "A" genotype, thus contributing to the high mortality rate from the disease. Our results prompt us to inquire if patients with high grade PCa at an early age and the FTO mutated *rs9939609* will also have high triglycerides levels, given that in a previous work our group found that age and high triglycerides levels are related to high grade PCa [34]. This premise remains unclear in the literature. Authors like De Luis et al. have related high triglycerides levels to the FTO *rs9939609* homozygous form (*T/T*) in Spanish obese men [59], while others like Grunnet et al. report an association to the FTO *rs9939609* heterozygous form (*A/T*) [60]. We faced the limitation that we did not have access to the serum lipid levels of all our patients at the diagnosis.

We propose that *FTO* could be another gene that may be implicated in the early onset of PCa in this Hispanic population and that this gene is impacting PCa by its effect on overweight.

Conclusion

Notwithstanding our limitations, we found a definite association between the presence of *rs9939609* with the risk of having PCa in this cohort of Puerto Rican men and the early onset of disease in a relatively young group of Puerto Rican men. To our better knowledge, no other study has characterized the Puerto Rican population with respect to the *FTO rs9930506* or *rs9939609* SNPs and their association with PCa. The alleles and genotypes frequency for both SNPs agreed with those published in 1000 genomes and these findings contribute to advance in the direction of having a genomic database of the Puerto Rican population for PCa. Further studies are needed to understand the mechanisms that may be involved in this early onset of PCa in this population. These results provide additional information to the complex nature of PCa in this population.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Minority Health and Health Disparities or the National Institutes of Health.

Supplementary Table Puerto Rico's geographical region distribution of municipalities.

Metro	North	West	South	East
San Juan	Arecibo	Aguadilla	Adjuntas	Aguas Buenas
Guaynabo	Barceloneta	Aguada	Aibonito	Canovanas
Caguas	Camuy	Anasco	Arroyo	Carolina
Bayamon	Catano	Cabo Rojo	Barranquitas	Ceiba
	Ciales	Guanica	Cayey	Culebra
	Corozal	Hormigueros	Cidra	Fajardo

	Dorado	Isabela	Coamo	Gurabo
	Florida	Lajas	Comerio	Humacao
	Hatillo	Lares	Guayama	Juncos
	Manati	Las Marias	Guayanilla	Las Piedras
	Morovis	Maricao	Jayuya	Loiza
	Naranjito	Mayaguez	Juana Diaz	Luquillo
	Orocovis	Moca	Patillas	Maunabo
	Quebradillas	Rincon	Penuela	Naguabo
	Toa Alta	Sabana Grande	Ponce	Rio Grande
	Toa Baja	San German	Salinas	San Lorenzo
	Trujillo Alto	San Sebastian	Santa Isabel	Vieques
	Vega Alta	Yauco	Utuado	Yabucoa
	Vega Baja		Villalba	

References

1. Zavala ZD, Tortolero LG, Torres CCR, Alvarado OM, Traverso OM, et al. (2015) Cancer in Puerto Rico, 2008-2012. Puerto Rico Central Cancer Registry: San Juan, PR 125-126.
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, et al. (2016) SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD.
3. Allott EH, Masko EM, Freedland SJ (2013) Obesity and prostate cancer: Weighing the evidence. Eur Urol 63: 800-809.
4. Bassett JK, Severi G, Baglietto L, MacInnis RJ, Hoang HN, et al. (2012) Weight change and prostate cancer incidence and mortality. Int J Cancer 131: 1711-1719.
5. Bhaskaran K, Douglas I, Forbes H, Dos-Santos-Silva I, Leon DA, et al. (2014) Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5· 24 million UK adults. The Lancet 384: 755-765.
6. Chamie K, Oberfoell S, Kwan L, Labo J, Wei JT, et al. (2013) Body mass index and prostate cancer severity: Do obese men harbor more aggressive disease on prostate biopsy?. Urology 81: 949-955.
7. Häggström C, Stocks T, Ulmert D, Bjørge T, Ulmer H, et al. (2012) Prospective study on metabolic factors and risk of prostate cancer. Cancer 118: 6199-6206.
8. Tewari R, Rajender S, Natu SM, Dalela D, Goel A, et al. (2012) Diet, obesity, and prostate health: are we missing the link?. J Androl 33: 763-776.
9. Fawcett KA, Barroso I (2010) The genetics of obesity: FTO leads the way. Trends Genet 26: 266-274.
10. Blanco S, Frye M (2014) Role of RNA methyltransferases in tissue renewal and pathology. Curr Opin Cell Biol 31: 1-7.
11. Gulati P, Avezov E, Ma M, Antrobus R, Lehner P, et al. (2014) Fat mass and obesity-related (FTO) shuttles between the nucleus and cytoplasm. Biosci Rep 34: e00144.
12. Gulati P, Yeo GS (2013) The biology of FTO: From nucleic acid demethylase to amino acid sensor. Diabetologia 56: 2113-2121.
13. Klungland A, Dahl JA (2014) Dynamic RNA modifications in disease. Curr Opin Genet Dev 26: 47-52.
14. Larder R, Cheung MM, Tung YL, Yeo GS, Coll AP (2011) Where to go with FTO?. Trends in Endocrinology & Metabolism 22: 53-59.
15. Hess ME, Brüning JC (2014) The fat mass and obesity-associated (FTO) gene: Obesity and beyond?. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1842: 2039-2047.
16. Tang H, Dong X, Hassan MM, Abbruzzese JL, Li D (2011) Body mass index and obesity-and diabetes-associated genes and risk for pancreatic cancer. Cancer Epidemiol Biomarkers Prev 20 : 779-792.
17. Melnik BC (25015) Milk: An epigenetic amplifier of FTO-mediated transcription? Implications for Western diseases. J Transl Med 13: 385.
18. Tung YL, Yeo GS, O'Rahilly S, Coll AP (2014) Obesity and FTO: Changing focus at a complex locus. Cell Metab 20: 710-718.
19. Ursu RI, Badiu C, Cucu N, Ursu GF, Craciunescu I, et al. (2015) The study of the rs9939609 FTO gene polymorphism in association with obesity and the management of obesity in a Romanian cohort. J Med Life 8: 232.
20. Xia Q, Grant SF (2013) The genetics of human obesity. Ann NY Acad Sci 1281: 178-190.
21. Yang J, Loos RJ, Powell JE, Medland SE, Speliotes EK, et al. (2012) FTO genotype is associated with phenotypic variability of body mass index. Nature 490: 267.
22. Yeo GS (2014) The role of the FTO (Fat Mass and Obesity Related) locus in regulating body size and composition. Mol Cell Endocrinol 397: 34-41.
23. Li G, Chen Q, Wang L, Ke D, Yuan Z (2012) Association between FTO gene polymorphism and cancer risk: evidence from 16,277 cases and 31,153 controls. Tumor Biol 33: 1237-1243.
24. Hinney A, Nguyen TT, Scherag A, Friedel S, Brönner G, et al. (2007) Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS one 2: e1361.