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RESEARCH ARTICLE

Genomic of Prostate Cancer in Senegal: Perspectives in the Era of Genome Wide Association Studies

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Abstract

Introduction: Prostate cancer is the second most commonly diagnosed cancer in men from Sub Saharan Africa including Senegal and a major cancer related cause of death. Carcinogenesis involves both environmental and genetic factors. The aim of this study was to describe the advances of prostate cancer genomic in Senegal. **Materials and Methods:** This study summarized and discussed the available publications on genetic data of prostate cancer prostate cancer in Senegal. The type and methods of genetic studies are presented and discussed in the context of the transition from candidate genetic variants to genome wide associations studies. **Results :** The earlier results on the candidate genes CYP3A4 and SRD5A2, associated with prostate cancer in Senegal indicates a high frequency of alleles associated with a higher risk of prostate cancer (CYP3A4*1B) and lower frequency of alleles associated with a lower risk of prostate cancer (SRD5A2 V89L). The was also an association between SRD5A2 rs523349 CG genotype and T stage. PCa tissue studies indicatesNAM tumors exhibited the enrichment of pro-inflammatory pathways including cytokine, interleukins, inflammatory response, and NFκB signaling. More recently, the customized array for African men has allowed genome wide associations studies that shows a large heterogeneity in Polygenic risk score among African men with a lower predicted risk of PCa in Senegalese compared to other West African and South Africa.

Conclusion: Genomic of prostate cancer in Senegalese is at its early phase of investigation. There are several traits consistent with genetic factors of higher incidence and more aggressive features of prostate cancer in black male. WAS are suggestive of specific features of Senegalese men compared to other African and non-African men.

Key words: Genomic of Prostate Cancer, GWAS, African descent, Senegal.

1. Introduction

Prostate cancer is an important public health problem in Sub Saharan Africa (SSA). Based on Globocan 2020 estimates, prostate cancer (PCa) is the second most commonly diagnosed cancer in men from SSA (1)and the fifth highest in mortality. Prostate cancer etiology is a combination of genetic and environmental factors(2). Such interactions are widely illustrated by the mutual influence between lipids compounds and pollutants and Cytochrome P450 whichcontribute to the carcinogenesis(3).

Cytochrome P450 is involved in the metabolism of these compounds and the latter can alter the expression of Cytochrome P450. Several genetic changes are

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involved in PCa carcinogenesis (4) including allelic loss in the short arm of chromosome 8 and the long arm of chromosome16. The impacted regions involve tumor suppressor genes in the form of deletion and inactivation of Rb and P53 genes and another suppressor gene in chromosome 17p (4).

Beside candidate genes associated with PCa risk, many susceptibility and risk variants are now identified by population-based genome-wide association studies (GWAS) (5). Those genetic predispositions vary widely across race, ethnic and geographic regions with significantly more scant data in SSA (6).

In fact, most available data are from developed countries. Understanding molecular signatures of PCa is important in the effort to provide personalized cancer care (7). The aim of this review was to describe the existing data on PCa susceptibility alleles onPCaand the initial findings on the ongoingGWAS studies among Senegalese men.

Prostate Cancer Susceptibility Alleles in Testosterone Metabolism Among Senegalese

Ziegler-Johnson et al.compared the frequency of PCa susceptibility alleles at CYP3A4A and SRD5A2 between Senegalese, Ghanaian, African American and Caucasian American men (8).CYP3A4 is the largest of the human Cytochrome P450 CYP34A that also includes CYP3A5 and CYP3A7.

It is located in chromosome 7q21 and is involved in the metabolism of many compounds likecholesterol (9), testosterone (10) and dehydroepiandrosterone (DHEA) (11). Of the 3 major hydroxylated metabolites of testosterone, 6β-hydroxytestosterone is of great interest (Figure 1).

More broadly, CYP3A4 variant was found to be associated with higher risk and more aggressive PCa among African American men (12-13).Germline mutation of CYP3A4 is involved in prostate cancer risk (14). Germline refers to stem cells and sex cells. Those cells pass on their genetic material to the progeny. In comparison, somatic cells are diploid, containing 1 set of chromosomes inherited from each parent.

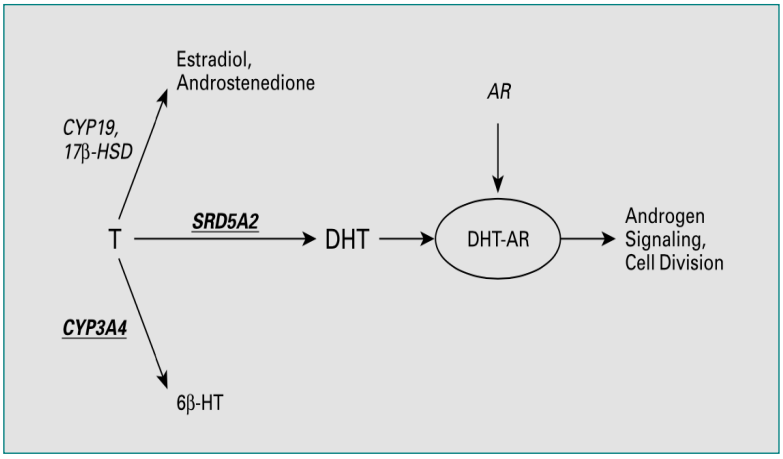

Figure 1. *Testosterone metabolism pathways with prostate cancer candidate genes (8)*

HSD = Hydroxysteroid dehydrogenase; T = testos- terone; HT = hydroxytestosterone.

SRD5A2 is implicated in converting testosterone in its active form, dihydrotestosterone (DHT) in prostate cells (15-16). It promotes cell proliferation in benign prostate hyperplasia and is involved in prostate carcinogenesis.

SRD5A2 counts 2 high-activity allele variants: A49T and V89L which are associated with a higher risk of PCa(17).

The V89L polymorphism on the SRD5A2 seems to decrease the conversion of testosterone to DHT (18) while this conversion is increased by A49T (18). The mechanism of action of these androgens is the fixation of DHT to androgen receptors, resulting in androgen signaling and cell division and proliferation (Figure 2).

The 1st study of CYP3A4 involving Senegalese, comprised 178 Senegalese, 129 Ghanaians, 147 African Americans and 410 Caucasian-Americans, they were all cancer-free (8). All participants provided a mouth cheek swab used for DNA extraction on the Qiagen robot with the QIAamp 96 DNA Buccal Swab Biorobot Kit to estimate the allele/genotype frequencies of autosomally inherited genes. Analyses were undertaken to compare the frequencies of the SRD5A2 and CYP3A4 genotypes by ethnicity.

For SRD5A2 V89L, the study noted an allele frequency of 0.301 for Caucasians, 0.274 for African-Americans, 0.194 for Ghanaians, and 0.183 for Senegalese (Table I).

When comparing the study group with other ethnic groups like Asian and Latinos there were differences in L alleles distribution. Asians were most likely to carry the L variant (allele frequency of 0.548) and Africans were least likely to carry the L variant (allele frequency of 0.188).

Therefore, the lower frequency of L allele is Senegalese population is in favor of a higher conversion of Testosterone to DHT in favor of PCa.

For SRD5A2 A49T, the allele frequency distribution was not different between the African and American of the study cohort.

For CYP3A4*1B, there was a higher frequency of 0.786 among Senegalese and a lower frequency of 0.079 among Caucasian (Table II). It appeared that the variant CYP3A4*1B, associated with increased risk of PCa in more frequent among Senegalese and Ghanaian compared to Caucasian.

Cleary the study showed a higher frequency of variants associated with increased PCa in the Senegalese population of this study and a lower proportion of variants associated with a lower risk of PCa.

However, this study has significant limitations. The first one is the fact that the population studied was free from PCa. The second is that autosomal variants that are not inherited. The third limitation is the fact that the role of candidate genes in prostate carcinogenesis is questionable because the many studies addressing this relationship often used inappropriate sampling designs and lacked power to detect relevant effects (6).

Table 1. *Comparison of genotype and variant frequencies by control group: V89L (8)*

Ethnicity (location)	Sample size	Genotype frequencies			L allele frequency	95% CI of L allele frequency	Reference
		VV	VL	LL			
US Caucasians (PA)	326	0.485	0.429	0.086	0.301	0.267–0.337	present study
US Caucasians (CA, HI)	49	0.571	0.388	0.041	0.235	0.162–0.328	Makridakis, 1997
US Caucasians (NC, hospital)	148	0.410	0.500	0.085	0.338	0.286–0.394	Lunn, 1999
US Caucasians (NC, community)	176	0.415	0.500	0.085	0.335	0.288–0.386	Lunn,1999
US Caucasians (various states)	799	0.489	0.413	0.098	0.304	0.282–0.327	Febbo, 1999
Italian (Italy)	116	0.578	0.345	0.078	0.250	0.199–0.310	Margiotti, 2000
Pooled Caucasian	1,614	0.482	0.428	0.090	0.304	0.288–0.320	–
African-American (PA)	106	0.528	0.396	0.076	0.274	0.218–0.337	present study
African-American (CA, HI)	95	0.589	0.379	0.032	0.221	0.168–0.285	Makridakis, 1997
African-American (NC, hospital)	8	0.250	0.625	0.125	0.438	0.231–0.668	Lunn, 1999
African-American (NC, community)	118	0.653	0.322	0.025	0.186	0.142–0.241	Lunn,1999
Pooled African-American	327	0.584	0.370	0.046	0.231	0.200–0.265	–
Ghanaian (Accra)	108	0.639	0.333	0.028	0.194	0.147–0.252	present study
Akan	53	0.660	0.302	0.038	0.189	0.126–0.274	present study
Ewe	22	0.591	0.409	0	0.205	0.112–0.345	present study
Ga-Adangbe	20	0.650	0.300	0.050	0.200	0.105–0.348	present study
Other	13	0.615	0.385	0	0.192	0.085–0.379	present study
Senegalese (Dakar)	137	0.681	0.275	0.044	0.183	0.141–0.233	present study
Wolof	50	0.680	0.300	0.020	0.170	0.109–0.256	present study
Pulaar	36	0.583	0.278	0.139	0.278	0.188–0.391	present study
Sereer	22	0.636	0.364	0	0.182	0.095–0.320	present study
Mandingues	16	0.938	0.063	0	0.031[a]	0.006–0.157	present study
Diola	10	0.700	0.300	0	0.150	0.052–0.360	present study
Other	3	0.667	0.333	0	0.167[a]	0.030–0.564	present study
Pooled African	245	0.661	0.302	0.037	0.188	0.156–0.225	present study
Latino (CA, HI)	40	0.475	0.375	0.150	0.337	0.244–0.446	Makridakis, 1997
Mexicans (Mexico City)	100	0.450	0.500	0.050	0.300[a]	0.241–0.367	Vilchis, 1997
Pooled Latino/Hispanic	140	0.457	0.464	0.079	0.311	0.259–0.367	–
US and Singapore Asians	102	0.294	0.490	0.216	0.461	0.394–0.529	Makridakis, 1997
Taiwanese (Taiwan)	108	0.149	0.574	0.278	0.565	0.498–0.629	Lunn, 1999
Chinese (Shanghai)	303	0.205	0.449	0.347	0.571	0.531–0.610	Hsing, 2001
Pooled Asian	513	0.211	0.483	0.306	0.548	0.517–0.578	–

[a] Hardy-Weinberg proportions p value <0.05.

A second study compared the distribution of CYP3A4, CYP3A5 and SRD5A2 variants between Senegalese and South African men (19).The study population included South African White (120 cases; 134 controls), South African Mixed Ancestry (207 cases; 167 controls), and South African Black (25 cases; 20 controls) men, as well as Senegalese men (86 cases; 300 controls). The CYP3A4 rs2740574 polymorphism was associated with PCa risk and tumor aggressiveness in South African men after correction for population stratification, and the SRD5A2 rs523349 CG genotype was inversely associated with high-stage disease in Senegalese men (Table III).

Despite the limitations related to candidate genes mentioned above, the results of this study indicate some particularities of Senegalese population in respect to Cytochrome P450 and SRD5A2. Moreover, these initial findings pave the way for further studies to elucidate molecular characteristics of PCa in Senegal.

Table 2. *comparison of genotype and variant frequencies by control group: CYP3A4 (8)*

Group	n	*1A/*1A	*1A/*1B	*1B/*1B	Frequency (*1B)	95% CI	Reference
US Caucasian (PA)	340	0.882	0.077	0.041	0.079[a]	0.061–0.102	present study
US Caucasian (CA)	117	0.930	0.060	0.010	0.039	0.020–0.072	Paris, 1999
Scottish Caucasian (UK)	101	0.890	0.110	0	0.055	0.031–0.095	Tayeb, 2000
US Caucasian	15	100.0	0	0	0[b]	––	Wandel, 2000
Pooled Caucasian	573	0.897	0.077	0.026	0.065[a]	0.052–0.080	–
African-American (PA)	130	0.208	0.400	0.392	0.592	0.532–0.650	present study
African-American (CA)	116	0.190	0.530	0.276	0.543	0.479–0.606	Paris, 1999
African-American	15	0.067	0.267	0.667	0.800	0.627–0.905	Wandel, 2000
Pooled African-American	261	0.115	0.364	0.770	0.582	0.540-0.624	–
Ghanaian (Accra)	100	0.130	0.360	0.510	0.690	0.623–0.750	Tayeb, 2000
Ghanaian (Accra)	118	0.059	0.271	0.670	0.805	0.750–0.851	present study
Akan	59	0.085	0.237	0.678	0.797	0.715–0.859	present study
Ewe	25	0	0.280	0.720	0.860	0.738–0.931	present study
Ga-Adangbe	21	0.048	0.429	0.524	0.738	0.589–0.847	present study
Other	13	0.125	0.125	0.750	0.846	0.665–0.939	present study
Senegalese (Dakar)	173	0.080	0.269	0.651	0.783[a]	0.737–0.823	present study
Wolof	64	0.094	0.281	0.625	0.766	0.685–0.831	present study
Pulaar	45	0.178	0.289	0.533	0.678[a]	0.576–0.765	present study
Sereer	26	0	0.231	0.769	0.885	0.770–0.946	present study
Mandingues	20	0	0.200	0.800	0.900	0.770–0.960	present study
Diola	14	0	0.429	0.571	0.786	0.601–0.898	present study
Other	4	0	0	1.000	1.000[b]	–	present study
Pooled African	391	0.087	0.294	0.622	0.766[a]	0.735–0.794	–
Latino (CA)	121	0.800	0.180	0.020	0.107	0.074–0.153	Paris, 1999
Taiwanese (Taiwan)	130	1.000	0	0	0[b]	–	Walker 1998
US Asian (CA)	80	1.000	0	0	0[b]	–	Paris, 1999
Pooled Asian	210	1.000	0	0	0[b]	–	–
Saudi (Saudi Arabia)	101	0.830	0.160	0.010	0.089	0.057–0.136	Tayeb, 2000

[a] Hardy-Weinberg proportions p value < 0.05.
[b] Hardy-Weinberg proportions p value could not be estimated due to small sample size or low variant allele frequency.

Prostate Cancer Tissue Study in Senegalese Men

PCa is diagnosed by biopsy and study of formalin-fixed paraffin-embedded (FFPE) prostate tissues. However, the need to better characterize PCa aggressiveness and support personalized medicine has taken advantage on the recent developments in domains like proteomics, RNA and DNA microarrays and immunohistochemical (IHC) staining (20). FFPE tissue is therefore a good alternative to fresh frozen tissue to conduct genomic and proteomic studies, pending the availability of fewer protein, nucleic acides and metabolites (21). Table IV describes the different proteins of PCa biomarkers in FFPE and their prognostic role(22).

Recognizing the critical role of good quality FFPE prostate tissue, many researchers interested in PCa in men of African descent in collaboration with the NCI sought to investigate the feasibility of using FFPE biospecimens acquired from various international sites for utility in next-generation sequencing (23). This study collected 976 FFPE blocks from six international sites in Africa and the Caribbean. Genomic DNA was checked for quality and quantity. Differences in mean quality control (QC) for pre-and-post pathology training were assessed using t-test(23). The Senegalese FFPE prostate tissues included in this study passed the DNA quantity and quality control with an improvement of 36.4% each between 2002 and 2017. In fact, the FFPE passed the quality and quantity control at 100% each in 2017. These performances were both higher than those of the other African countries (Nigeria, Kenya) of the study and the difference was statistically significant for both controls. These findings indicate a great potential of Senegalese FFPE to contribute to tissue genomic studies in PCa.

FFPE prostate tissue was used by Yamoah K et al. (24)to attempt to uncover biological pathways that are enriched in men of African origin. The contribution of participating populations is described by Figue 2.Immunohistochemistry analysis on selected biomarkers showed a consistent association between ERG status and race with 83% of native African men (NAM) exhibiting tumors that lacked TMPRSS2-ERG translocation ($ERG^{negative}$) as compared to African American men (AAM) (71%) and European American men (EAM) (52%). NAM tumors had more pronounced pro-inflammatory pathways including cytokine, interleukins, inflammatory response, and NFκB signaling(24).

Table 3. *Frequency of genotypes among South African and Senegalese prostate cancer cases and controls (19).*

Genotypes	White		South Africa						Senegal	
			Mixed		Black		Combined		Senegalese	
Genes	Controls (n = 134)	Cases (n = 120)	Controls (n = 167)	Cases (n = 207)	Controls (n = 20)	Cases (n = 25)	Controls (n = 321)	Cases (n = 352)	‡Controls (n = 300)	‡Cases (n = 86)
CYP3A4 (rs2740574)										
AA	122 (91.0%)	84 (70.0%)	117 (70.1%)	82 (39.6%)	2 (10.0%)	9 (36.0%)	241 (75.1%)	175 (49.7%)	21 (7.5%)	6 (7.1%)
AG	12 (9.0%)	34 (28.3%)	49 (29.3%)	111 (53.6%)	15 (75.0%)	16 (64.0%)	76 (23.7%)	161 (45.7%)	91 (32.3%)	40 (47.6%)
GG	0 (0%)	2 (1.7%)	1 (0.6%)	14 (6.8%)	3 (15.0%)	0 (0%)	4 (1.2%)	16 (4.6%)	170 (60.3%)	38 (45.2%)
CYP3A5 (rs776746)										
GG	113 (84.3%)	95 (79.2%)	58 (34.7%)	58 (28.0%)	1 (5.0%)	1 (4.0%)	172 (53.6%)	154 (43.8%)	14 (5.3%)	4 (5.1%)
AG	18 (13.4%)	22 (18.3%)	72 (43.1%)	106 (51.2%)	5 (25.0%)	5 (20.0%)	95 (29.6%)	133 (37.8%)	66 (25.1%)	20 (25.3%)
AA	3 (2.3%)	3 (2.5%)	37 (22.2%)	43 (20.8%)	14 (70.0%)	19 (76.0%)	54 (16.8%)	65 (18.4%)	183 (69.6%)	55 (69.6%)
SRD5A2 V89L (rs523349)										
GG	56 (41.8%)	61 (50.8%)	96 (57.5%)	131 (63.3%)	5 (25.0%)	16 (64.0%)	157 (48.9%)	208 (59.1%)	26 (12.2%)	10 (14.1%)
CG	70 (52.2%)	51 (42.5%)	65 (38.9%)	71 (34.3%)	7 (35.0%)	7 (28.0%)	142 (44.2%)	129 (36.6%)	61 (28.5%)	10 (14.1%)
CC	8 (6.0%)	8 (6.7%)	6 (3.6%)	5 (2.4%)	8 (40.0%)	2 (8.0%)	22 (6.9%)	15 (4.3%)	127 (59.4%)	51 (71.8%)
SRD5A2 A49T (rs9282858)										
GG	107 (79.8%)	90 (75.0%)	127 (76.0%)	120 (58.0%)	10 (50.0%)	17 (68.0%)	244 (76.0%)	227 (64.5%)	278 (100.0%)	75 (100.0%)
GA	27 (20.2%)	30 (25.0%)	40 (24.0%)	87 (42.0%)	10 (50.0%)	8 (32.0%)	77 (24.0%)	125 (35.5%)	0 (0%)	0 (0.0%)

$P < 0.001$, for each polymorphism when comparing across each of the respective population groups for cases or for controls.
‡Some participants had missing genotype data. The numbers and percentages shown are for the available information.

Table 4. *miRNAs as PCa biomarkers in FFPE tissue (22)*

miRNA	Clinical significance	References
Let-7 family	Diagnosis, prognosis (↓)	[45, 52]
miR-17	Diagnosis, prognosis (↓)	[154, 155]
miR-19a	Diagnosis	[156]
miR-20a/b	Diagnosis	[154]
miR-21	Prognosis (↑), treatment outcome	[157]
miR-25	Diagnosis	[156]
miR-26a	Diagnosis (↓)	[21]
miR-29a	Diagnosis (↓)	[21, 158]
miR-29b	Diagnosis (↓)	[159]
miR-31-5p	Diagnosis (↓)	[66]
miR-30d	Diagnosis (↑)	[21]
miR-34a	Diagnosis (↓)	[21, 160]
miR-34c-5p	Diagnosis (↓)	[66]
miR-93	Diagnosis	[154]
miR-101	Diagnosis	[154]
miR-106a	Diagnosis	[154]
miR-125b	Diagnosis (↑)	[25]
miR-126	Diagnosis (↓)	[21]
miR-132	Prognosis (↓), treatment outcome	[161]
miR-141	Diagnosis	[154]
miR-143	Diagnosis, prognosis (↓)	[43, 51, 156]
miR-145	Diagnosis, prognosis (↓)	[43, 49–51, 154, 162]
miR-146a/b-5p	Diagnosis, prognosis (↓)	[163]
miR-183-96-182 cluster	Diagnosis, prognosis	[56, 59, 66, 154, 164]
miR-187	Diagnosis	[156]
miR-195	Diagnosis (↓)	[21]
miR-200a	Treatment outcome	[56]
miR-203	Diagnosis, prognosis (↓)	[164]
miR-214	Diagnosis	[154]
miR-221	Diagnosis, prognosis (↓), treatment outcome	[55, 154]
miR-222	Diagnosis	[154]
miR-342-3p	Diagnosis (↑)	[21]
miR-375	Diagnosis (↑)	[43, 154]
miR-519d	Prognosis (↑), treatment outcome	[67]
miR-616	Diagnosis (↑)	[165]
miR-622	Diagnosis (↑)	[21]
miR-647	Prognosis (↓), treatment outcome	[67]
miR-720	Diagnosis	[154]
miR-768-3p	Diagnosis	[154]
miR-1256	Diagnosis (↓)	[158]

Arrows indicate the sense of deregulation: (↑): upregulation; (↓): downregulation in PCa versus normal tissues or low risk versus high risk PCa.

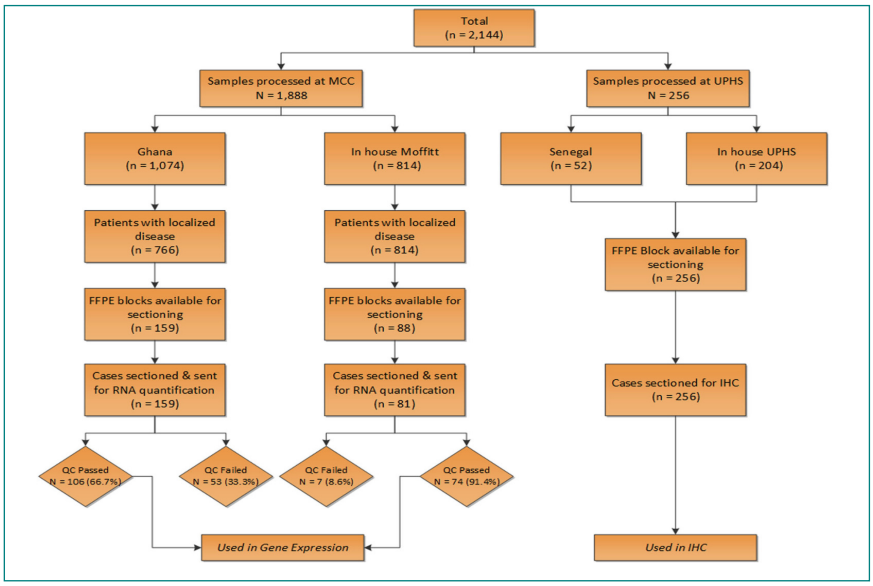

Figure 2. *Consort diagram for the samples used in the study (24)*

Customized Genotyping Arrays for Senegalese and Other African Population

Association between black rare and increased PCa risk(25) and aggressiveness(26) is widely documented. But most data contributing to these documented disparities are from candidate alleles (6). In the past decades, it has been common to study the entire genome at the level of base pairs (27). Genomic of native African is important to study as genetic variants existing across human populations occurred in early human in Africa before a dissemination to the rest of the world(8).

Therefore, understanding PCa genomic in native African will help addressing PCa in black men worldwide but will also bring diversity in the world PCa genetic epidemiology. The possibility of studying all genes simultaneously has the potential to improve risk prediction by Polygenic risk score. Generally, the existing disease associations are studied in Caucasian men and the used genotyping arrays,like OncoArrays(29), do not capture well the genetic variants of men from SSA.

For instance, in 2016, the European Ancestry was addressed by 81% of Genome Wide Association Studies (GWAS) samples, while Eastern Asian ancestry was addressed by 14% of GWAS samples (30). That is why the Men of African Descent Carcinoma of the Prostate (MADCaP) consortium(31) has developed a customized MADCAaP Array, a genotyping array optimized for fine-mapping and detecting novel associations with PCa in African populations (32). The MADCaP Array tags over 94% of common genetic variants and 63 to 97% or rare genetic variants in African populations. In addition, 131,469 markersare shared between the MADCaP Array and the OncoArray, and 398,460 markers are shared between the MADCaP Array and the H3Africa Array(32).

This array also has a high density of markers in genomic regions associated with cancer susceptibility, including 8q24. The effectiveness of the MADCaP Array was tested in samples from Ghana and Nigeria clustered together and samples from Senegal and South Africa yielded distinct ancestry clusters. Using the MADCaP array, the authors identified cancer-associated loci that have large allele frequency differences across African populations(32).

While showing a large heterogeneity in Polygenic risk score, this study reported a lower predicted risk of PCa in Senegalese compared to other West African and South Africa. This pilot study found that the allele at rs3817963 associated with increased lung cancer risk, has an allele frequency of 33.9% in Senegal, 12.9% in Ghana, 10.4% in Nigeria, and 8.4% in South Africa (p-value<0.0001 for pairwise comparisons between Senegal and other countries, two sample Z-test). Another cancer associated variant was also identified with allele frequency differences between African populations is rs2294008, located at 8q24.3.

This study has the importance of being the first genotyping array adapted to Senegalese population and will allow for subsequent GWAS studies among Senegalese and other African populations.

In support of the need for more studies in SSA, Conti et al. (33)previously reported novel susceptibility loci for PCa in men of African descent. This studycombined genetic association results from the African Ancestry

Prostate Cancer GWAS Consortium, the Ghana Prostate Study, the Kaiser/ProHealth Prostate Cancer Study and the ELLIPSE/PRACTICAL OncoArray Consortium. The 2 loci are located in chromosomes 13q34 and 22q12 with a risk-associated alleles found only in men of African ancestry.

Existing Data and Perspectives in Gwas for Prostate Cancer in Senegal

The MADCaP resources were used to test the generalizability of ancestry-specific polygenic risk scores to predict prostate cancer in sub-Saharan Africa(34). This study included 136 Senegalese cases of prostate cancer and 145 controls. Figure 3 identifies for each center the cases in blue and the controls in red and shows that cases and controls clusters together by country.

West African individuals are found on the left of each multi-dimensional scaling plot, and South African individuals are found on the bottom right of each plot. In figure 3b, Senegalese individuals have a different mix of ancestries than Ghanaian, Nigerian, and South African individuals(34).

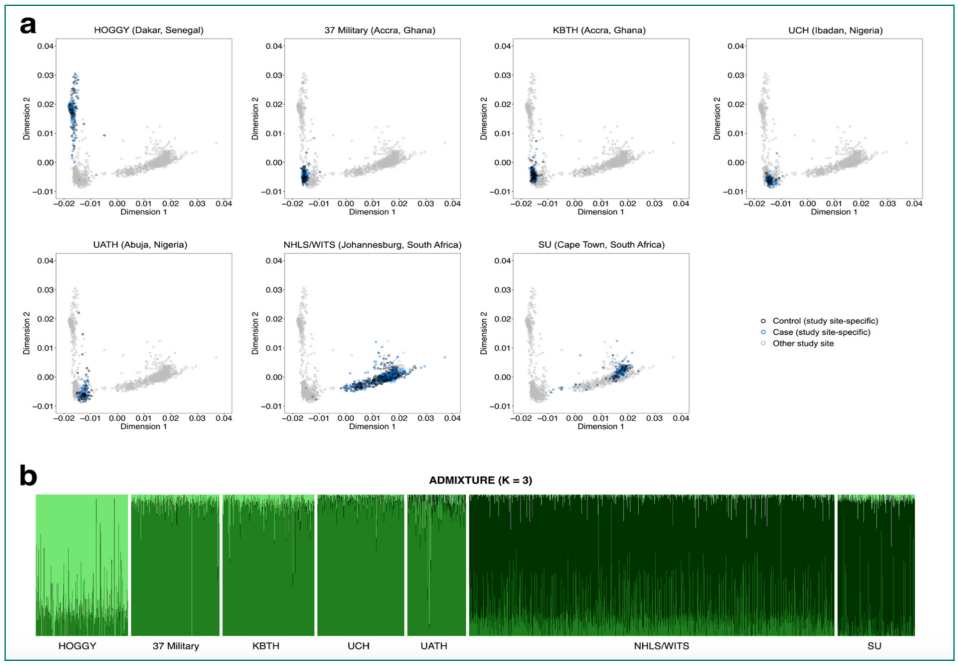

Figure 3. *Population structure of MADCaP Network samples reveals shared genetic ancestries among urban and suburban African study sites. a Two-dimensional MDS plots of 2631 MADCaP individuals. Subpanels focus on specific study sites, with controls colored black, CaP cases colored blue, and samples from other study sites colored grey. b ADMIXTURE plot of 2631 MADCaP individuals(34).*

In evolutionary genetics of CaP-associated loci, the study showed large differences between Caucasian and African, where the 1000 genome was predictive of PCa risk only for Caucasian. The study then tested PCa risk prediction between case and controls using different scoring systems and again the models were more suitable for Caucasian. The multi-ancestry weights from the Conti PRS yielded an OR of 5.29 for individuals from the UKBiobank and an OR of 1.86 for individuals from the MADCaP Network(34).

When considering ancestry-matched polygenic predictions of PCa risk, the combination of MADCaP data from Senegalese, Ghanaian, and Nigerian study sites yielded an AUC of 0.611 for the African weights from the Conti PRS. By contrast, South African study sites yielded an AUC of 0.560 for the Conti PRS with African weights. These findings indicates that genetic predictions of PCa risk perform better for West African men than South African men (p-value = 0.021, DeLong's test)(34).Finally, this study indicates that polygenic predictors do not inform the histopathology of PCa in African men as it does not predict Gleason score.

The lack of performance of the Predictors reported Kim et al. (34) in African men are improved by the validation of a multi-ancestry polygenic risk score and age-specific risks of PCa(35). In that study (34) a PRS was evaluated in men from European (22,049 cases, 414,249 controls), African (8794 cases, 55,657 controls), and Hispanic (1082 cases, 20,601 controls). The association of PRS with PCa risk was evaluated separately in each case–control study and then combined in a fixed-effects inverse-variance-weighted meta-analysis. Comparing men in the top decile (90–100% of the PRS) to the average 40–60% PRS category, the PCa odds ratio (OR) was 3.8-fold

in European ancestry men (95% CI = 3.62–3.96), 2.8-fold in African ancestry men (95% CI = 2.59–3.03), and 3.2-fold in Hispanic men (95% CI = 2.64–3.92). The PRS did not discriminate risk of aggressive versus nonaggressive PCa.

To further investigate prostate cancer risk variants relevant to men of African Ancestry, Chen et al. (35)conducted the largest genetic analysis to date combining GWAS results from ten consortia and biobanks. The study tested 27,753,840 genotyped and imputed single- nucleotide variants and small insertion/deletion variants with a minor allele frequency (MAF) of ≥≥1% in African populations for an association with PCa risk.

Nine novel susceptibility loci for PCa were identified, of which seven were only found or substantially more common in men of African ancestry. Multi-ancestry polygenic risk score was effective in stratifying PCa risk, and was able to differentiate risk of aggressive and nonaggressive disease. While this latter study did not include Senegalese men, it remains a great progress toward better characterizing PCa in Senegal and more broadly in SSA.

2. Conclusion

Genomic of prostate cancer in Senegalese is at its early phase of investigation. There are several traits consistent with genetic factors of higher incidence and more aggressive features of prostate cancer in black male. These traits are mostly candidate alleles variants although recent data from GWAS are suggestive of specific features of Senegalese men compared to other African and non-African men. More research is needed to better describe molecular epidemiology of prostate cancer in Senegal.

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