Associations of genetic polymorphisms in SLCO transporters with clinical aggressiveness of prostate cancer in the North Carolina-Louisiana Prostate Cancer Project (PCaP)

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Background

- African-American men (AAs), compared to European-American men (EAs), are more likely to present with more aggressive phenotypes of prostate cancer, characterized by earlier onset and higher rates of progression.
- Both socio-economic and biological factors may contribute to the racial disparity in prostate cancer.
- Androgen-stimulated androgen receptor signaling is crucial to proliferation and survival of prostate cancer cells, in which availability of androgen to cancer cells may play an important role in prostate cancer development.
- The potential androgen transporters, the solute carrier family of the organic anion transporting peptides (SLCO), are highly polymorphic with differed genetic structure between AAs and EAs.
- It is hypothesized that genetic variations in SLCO transporters may alter availability of androgen to prostate cancer cells and contribute to racial differences in prostate cancer aggressiveness.

Material and Method

- ***Study population:*** Blood DNA samples and relevant clinical and epidemiological data were requested from the North Carolina-Louisiana Prostate Cancer Project (PCaP), a multidisciplinary population-based, case-only study of racial/ethnic differences in prostate cancer aggressiveness.
- ***SNP selection and genotyping:*** For all 11 members of SLCO family, tag single nucleotide polymorphisms (SNPs) were selected based on HapMap data for AAs and EAs, requiring $r^2 \geq 0.8$ with minor allele frequency ≥ 5%. The panel of SNPs also included potential functional SNPs selected from the literature and 128 ancestry informative markers for population structure analysis. Genotyping was performed using Illumina GoldenGate.
- ***Sample size:*** After removing individual samples (n=65) and SNPs (n=107) with call rate <95%, a total of 1045 SNPs in 2050 research subjects (993 AAs and 1057 EAs) were examined in the analysis.
- ***Statistical method:*** Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) separately in AAs and EAs, adjusting for age, study site, family history of prostate cancer and African ancestry proportion.
- ***SLCO expression:*** Fifty pairs of prostate cancer and adjacent benign tissues (96% EAs) were requested from Pathology Resource Network at Roswell Park and subjected to qRT-PCR examination. *In situ* expression was determined using RNA-Scope.

Table 1. Prostate cancer characteristics by SLCO genotypes in AAs and EAs

Gene	SNP	Genotype	European American # high vs low	European American OR (95% CI)[a]	European American p_adj[b]	African American # high vs low	African American OR (95% CI)[a]	African American p_adj[b]	p_interaction[c]
Aggressiveness High vs. Low/Intermediate[d]									
SLCO2A1	rs9917636	AA	33/231	1.00		62/150	1.00	0.03	0.004
		AG	88/417	1.52 (0.98-2.36)		93/367	0.59 (0.41-0.86)		
		GG	34/222	1.04 (0.62-1.74)		44/233	0.45 (0.29-0.71)		
		AG/GG	122/639	1.35 (0.89-2.05)		137/600	0.54 (0.38-0.77)		
SLCO2A1	rs3811662	GG	150/861	1.00		160/519	1.00	0.04	0.004
		GA	5/10	3.77 (1.22-11.64)		38/210	0.58 (0.39-0.86)		
		AA	0/0			1/20	0.16 (0.02-1.2)		
		GA/AA				39/230	0.54 (0.37-0.8)		
Sum Gleason Score ≥ 8 vs. < 8									
SLCO2A1	rs3811662	GG	114/922	1.00		108/603	1.00	0.05	0.218
		GA	2/13	1.55 (0.33-7.23)		22/235	0.52 (0.32-0.84)		
		AA	0/0			0/22			
		GA/AA				22/257	0.47 (0.29-0.77)		
SLCO2A1	rs9874493	AA	84/671	1.00		94/518	1.00	0.05	0.352
		AG	30/243	1.04 (0.66-1.62)		36/294	0.66 (0.44-1)		
		GG	2/22	0.88 (0.2-3.85)		0/48			
		AG/GG	32/265	1.02 (0.66-1.59)		36/342	0.56 (0.37-0.85)		
Stage 3/4 vs. 1/2									
SLCO5A1	rs16919172	AA	11/914	1.00	0.039	15/729	1.00		0.028
		AG	7/101	6.24 (2.32-16.8)		3/199	0.78 (0.22-2.75)		
		GG	0/3			0/12			
		AG/GG	7/104	5.98 (2.23-16.08)		3/211	0.74 (0.21-2.64)		
SLCO5A1	rs4370538	AA	10/901	1.00	0.035	6/468	1.00		0.25
		AG	8/113	6.95 (2.64-18.27)		10/414	2.22 (0.77-6.36)		
		GG	0/3			2/64	2.85 (0.54-14.94)		
		AG/GG	8/116	6.67 (2.54-17.52)		12/478	2.31 (0.83-6.39)		
SLCO5A1	rs4377973	GG	11/908	1.00	0.039	6/447	1.00		0.383
		GC	7/108	5.93 (2.21-15.95)		11/422	2.28 (0.81-6.44)		
		CC	0/3			1/77	1.08 (0.13-9.32)		
		GC/CC	7/111	5.68 (2.12-15.26)		12/499	2.09 (0.75-5.77)		
SLCO5A1	rs10096246	AA	11/911	1.00	0.039	10/572	1.00		0.078
		AG	7/105	6.04 (2.24-16.26)		7/336	1.29 (0.48-3.47)		
		GG	0/3			1/37	1.69 (0.2-14.02)		
		AG/GG	7/108	5.79 (2.15-15.57)		8/373	1.33 (0.51-3.45)		

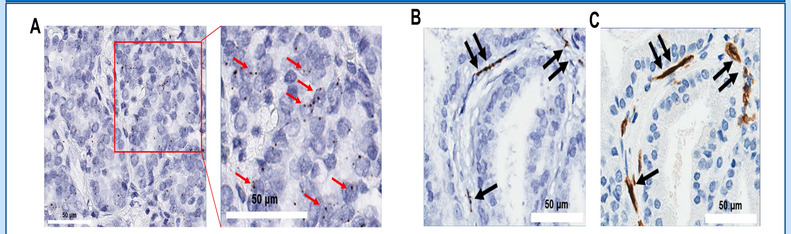
a: ORs and 95% CIs were estimated from co-dominant and dominant models adjusting for age at diagnosis, study site (NC or LA), first degree family history of prostate cancer (yes/no), African ancestry component.
b: p_adj was estimated from genetic dose response according to the number of variant alleles and adjusted for multiple comparison by False Discovery Rate.
c: p_interaction was for the differences in ORs between AA and EA men.
d: Aggressiveness was defined in 3 categories: high (Gleason sum ≥ 8, or PSA > 20 ng/mL, or Gleason sum = 7 and clinical stage T3-T4); low (Gleason sum < 7 and stage cT1-cT2 and PSA < 10 ng/mL); and intermediate (all other cases).

Table 2. SLCO expression in human prostate cancer and benign tissues.

Gene	Mean (range) Cancer (%)	Mean (range) Benign (%)	p-value*
SLCO1A2	2.0 (0-26.3)	0.4 (0-2.7)	0.02
SLCO1B1	0 (0-0.4)	0 (0-0.1)	0.07
SLCO1B3	1.8 (0-31.6)	0.3 (0-3.2)	0.003
SLCO1C1	0 (0-0.1)	0 (0-0.1)	0.16
SLCO2A1	27.1 (4.6-57.7)	36.1 (0-84.4)	0.005
SLCO2B1	1.9 (0-38.6)	1.4 (0-38.0)	0.62
SLCO3A1	5.0 (0.6-58.9)	5.6 (0-15.6)	0.01
SLCO4A1	3.1 (0.1-41.4)	3.3 (0-23.2)	0.01
SLCO4C1	0.4 (0-6.2)	0.4 (0-2.9)	0.1
SLCO5A1	58.7 (5.6-93.6)	50.3 (0-93.9)	0.008
SLCO6A1	0 (0-0.1)	ND	N/A
Total	**2.2 (0.3-12.8)**	**4.0 (0-64.9)**	**0.001**

* p-values were calculated by Wilcoxon signed-rank test for paired samples. ND, undetectable; N/A, not available.

Figure 1. Expression of SLCO at mRNA levels in human prostate cancer.



SLCO5A1 in prostate epithelial cells **SLCO2A1 in CD31-positive endothelial cells**

Summary

- At genomic level, SNPs in *SLCO2A1* were associated with reduced prostate cancer aggressiveness and low Gleason Scores in AAs; while, SNPs in *SLCO5A1* were associated with advanced clinical stages in EAs.
- At tissue level, *SLCO2A1* and *SLCO5A1* were the most expressed SLCO transporters in the prostate with mRNA level significantly differed between malignant and adjacent benign prostate tissues.
- At cell level, SLCO2A1 is primarily expressed in endothelial cells; while, SLCO5A1 is primarily expressed in epithelial cells.
- In conclusion, among 11 SLCO family members, 2A1 and 5A1 may play an important role in prostate cancer. Genetic variations in SLCO2A1 and 5A1 may contribute differently to prostate cancer aggressiveness in AAs and EAs.

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