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Mutational Profile of Aggressive, Localised Prostate Cancer from African Caribbean Men Versus European Ancestry Men

Laurie Tonon, Gaëlle Fromont, Sandrine Boyault, Emilie Thomas, Anthony Ferrari, Anne-Sophie Sertier, Janice Kielbassa, Vincent Le Texier, Aurélie Kamoun, Nabila Elarouci, Jacques Irani, Luc Multigner, Ivo Glynne Gut, Marta Gut, Pascal Blanchet, Aurélien De Reynies, Géraldine Cancel-Tassin, Alain Viari, Olivier Cussenot

Abstract

Causes of high mortality of prostate cancer in men of African ancestry living in the French West Indies are still debated, between suspicions of environmental factors and genetic susceptibility. We report an integrated genomic study of 25 tumour tissues from radical prostatectomy of aggressive (defined by International Society of Urological Pathology ≥3) prostate cancer patients (10 African Caribbean and 15 French Caucasian) using single nucleotide polymorphism arrays, whole-genome sequencing, and RNA sequencing. The results show that African Caribbean tumours are characterised by a more frequent deletion at 1q41–43 encompassing the DNA repair gene PARP1, and a higher proportion of intrachromosomal rearrangements including duplications associated with CDK12 truncating mutations. Transcriptome analyses show an overexpression of genes related to androgen receptor activity in African Caribbean tumours, and of PVT1, a long non-coding RNA located at 8q24 that confirms the strong involvement of this region in prostate tumours from men of African ancestry.

Patient summary: Mortality of prostate cancer is higher in African Caribbean men than in French Caucasian men. Specificities of the former could be explained by genomic events linked with key genes such as DNA damage pathway genes PARP1, CDK12, and the oncogenic long non-coding RNA gene PVT1 at the 8q24 prostate cancer susceptibility locus.

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Prostate Cancer (PCa) is a major cause of morbidity and mortality in men worldwide, causing an estimated 307,000 deaths per year. However, ethnic disparities are widely recognised with higher incidence and cancer death rates in black men than in non-Hispanic white men. Similarly, in Guadeloupe (French West Indies, FWI) where 90% of the population is of African ancestry, the standardised incidence and mortality were approximately twice that observed in metropolitan France (mostly Caucasian population) [1].

Higher PCa incidence in men of African ancestry is largely explained by genetic factors as they display a higher prevalence of PCa risk variants [2]. However, the relationship with the highest mortality observed in black population remains debated, with involvement of not only genetic, environmental, and biological factors but also sociocultural factors. Indeed, an increased risk of PCa was associated with exposure to agricultural pesticides in epidemiological studies, including some performed in FWI [3,4]. Ethnic differences in the frequency of some genomic alterations, such as TMPRSS2 gene fusions, SPINK1 overexpression, PTEN loss or SPOP mutation, have been reported [5], suggesting some variability in carcinogenic pathways according to the genetic background.

To provide new insights on the differences observed in molecular alterations between PCa from men of African and Caucasian ancestry, we report here the whole-genome sequencing (WGS) and RNA sequencing (RNAseq) of 25 aggressive PCa (10 from African Caribbean [AC] and 15 from French Caucasian [FC] patients) defined by International Society of Urological Pathology ≥3 (Supplementary Table 1), as well as a pooled analysis of their copy number variation (CNV) profiles with an additional dataset of 132 tumour tissues from radical both aggressive and nonaggressive prostatectomy specimens [6] (Supplementary methods).

Copy number analysis of 157 tumours (56 AC + 101 FC) showed that the main somatic CNV events were amplifications at locus 8q24.21 (18%) encompassing concomitantly PCAT1, MYC, and NCOA2 genes, and deletions at loci 8p21 encompassing NKX3.1 (39%), 13q14 encompassing RB1 (30%), 6q14 encompassing ZNF292 (24%), 8p11 encompassing FGER1 (23%), and 16q23 encompassing BCA1 (22%; Fig. 1A). Notably, homozygous deletion of 10q24 (PTEN) was observed with a frequency of 7% only. Significant correlations were found between the deletion at 8p21 (NKX3.1) and the gain at 8q24.21 (PCAT1) \( p = 2.6 \times 10^{-4} \), Fisher exact test, Benjamini-Hochberg corrected), deletions at 10q24 (PTEN) and 17p13 (TP53) \( p = 9.5 \times 10^{-7} \), Fisher exact test, Benjamini-Hochberg corrected), and deletions at 5q21 (NIP7P3) and 6q22 (CHD1) \( p = 5.31 \times 10^{-4} \), Fisher exact test, Benjamini-Hochberg corrected; Supplementary Fig. 1). We also observed the recurrent deletions/losses at SPOP and PCDH9 loci recently reported in PCa from Chinese men (10%/13% for AC and 10%/21% for FC, respectively) [7].

Interestingly, a deletion at 1q42-43, encompassing PARP1, was significantly more frequent in AC patients (12/56 AC vs 4/101 FC; \( p = 3.8 \times 10^{-4} \), Fisher exact test; Fig. 1B).

Using RNAseq on 25 tumours, we observed that this haploinsufficiency was related to decreased expression of genes located between PARP1 and TOMM20 (Supplementary Fig. 2). This molecular event could be linked to the specific exposure to organochlorine pesticides used for banana cultivation in FWI [3]. Indeed, the SNP rs7679673, located near the gene TET2, was shown to be associated with a higher PCa risk in men who were exposed to higher dose of the organochlorine aldrin [4]. Moreover, TET2 and PARP1 are both implicated in early-stage epigenetic modification at pluripotency loci during somatic cell reprogramming [8] and in androgen regulation in PCa [9]. This lower expression of PARP1 suggests that the patients harbouring this deletion would not benefit from treatment with PARP inhibitors and should rather be explored with therapies based on homologous recombination deficiency inhibitors such as mTor inhibitors.

Based on WGS data, we identified a mean number of 4972 somatic single-base mutations (range: 1788–12,576) and 603 somatic insertion/deletion (range 318–1491) mutations per sample without any significant difference between FC and AC tumours (Supplementary Figs. 3 and 4). We observed that CDK12 truncating mutations were more frequent in AC than in FC tumours (4/10 vs 1/15; Fig. 2). Regions of localised hypermutations, namely kataegis, were identified in 10 tumours (four AC and six FC) for 37 events but without any recurrent event (Supplementary Fig. 5).

Two germline mutations of the BRCA2 gene (AC patients) and one from PALB2 (FC patient) were observed (Fig. 2). Notably, the tumour with a germline frameshift mutation and a somatic homozygous deletion of BRCA2 had the highest chromosomal instability (large-scale state transitions) score among all samples (Supplementary Fig. 6). The higher frequency of germline DNA repair gene mutations found in this cohort of AC patients (20% vs 6.7% in FC) could be compared to the higher frequency of those mutations observed in metastatic than in localised PCa, and suggested that some of these patients could benefit from PARP inhibitors or platinum-based chemotherapy.

Using RNAseq data, we found that expression level of the long non-coding RNA (IncRNA) PVT1, located at 8q24.21 near FOXA1 binding sites, was significantly higher in tumours from AC patients (\( p = 1 \times 10^{-3} \), Mann-Whitney test; Fig. 2). Concordantly, Yang et al. [10] reported recently that higher levels of this IncRNA were associated with poorer overall survival and disease-free survival. Moreover, they showed that PVT1 knockdown by small interfering RNA transfection significantly inhibited PCa growth in vivo and in vitro and promoted cell apoptosis, suggesting that PVT1 played an oncogenic role in PCa. PVT1 expression positively correlated with the androgen activity (Spearman \( \rho = 0.6 \), \( p = 4 \times 10^{-3} \)) and EZH2 expression (Spearman \( \rho = 0.6 \), \( p = 4 \times 10^{-3} \); Supplementary Fig. 7).

Only three samples harboured the TMPRSS2-ERG fusion, whereas four others had a previously described fusion involving genes ETV1, ETV4, or SKIL, all from FC patients (Fig. 2). These fusions were correlated with high expression of the corresponding genes (Fig. 2). We also looked for large chromosomal rearrangements in tumours and found 5093 intra- and 424 interchromosomal events. The ratio...
Fig. 1 – Cumulative copy number variations on 157 tumour samples for the two ancestries. Along the (A) genome and (B) chromosome 1, is represented the percentage of samples in the cohort with a copy number variation at each position (the upper part represents the gains and the lower part the losses). Events statistically more present in the African Caribbean samples are coloured in orange, whereas the ones more frequent in the Caucasian samples are coloured in blue.

AC = African Caribbean; FC = French Caucasian.
of intra- to interchromosomal rearrangements was significantly higher in AC than in FC population ($p = 4 \times 10^{-2}$, Mann-Whitney test; Supplementary Figs. 8 and 9). In addition, almost half of the AC samples (40%) showed a high proportion of duplications versus only one (6.7%) of the FC samples, and this duplicator phenotype was associated with CDK12 truncating mutations (Fig. 2; Supplementary Fig. 10). Similarly, Wu et al. [11] found recently that CDK12 biallelic loss is enriched in metastatic castration-resistant PCa and that this loss is associated with focal tandem duplications.

![Fig. 2 – Summary of biological features and genomic alterations of 25 prostate tumours. Small somatic mutations (substitutions [SSMs] and small indels [SIMs]) and copy number variations observed in selected genes. Top rows: summary of biological features: ancestry, racial mixing score, Gleason score, relapse, and DNA mismatch repair germline mutations. Bottom rows: summary of other genomic alterations: total number of SSMs and SIMs, presence of kataegis in the sample, ratio of intra- versus inter-chromosomal structural variants, ETS gene fusion transcripts, expression values of ERG, ETV1, ETV4, SKIL, PARP1, EZH2, and PVT1 represented by quartiles, AR activity signature score and proliferation signature score, represented by quartiles. AC = African Caribbean; FC = French Caucasian.](https://doi.org/10.1016/j.eururo.2018.08.026)
Moreover, they showed that the CDK12 mutations are associated with an increased level of gene fusion-induced neoantigens and high immune infiltration, suggesting that patients with these mutations could benefit from immune checkpoint immunotherapy.

The structural rearrangements more frequently observed in AC tumours, such as tandem duplications or PARP1 haploinsufficiency, as well as the higher frequency of germline DNA repair mutations suggest that further investigations dedicated to this population with specific therapeutic protocols using checkpoint inhibitor immunotherapy, DNA-damaging therapies, or kinase-inhibiting agents are needed.

Author contributions: Olivier Cussenot had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cussenot.
Acquisition of data: Tonon, Fromont, Boyault, Kamoun, Irani, Multigner, I.G. Gut, M. Gut, Blanchet, De Reynies, Cancel-Tassin, Viari.
Analysis and interpretation of data: Tonon, Thomas, Ferrari, Sertier, Kielbassa, Kamoun, Cancel-Tassin, Viari, Cussenot.
Drafting of the manuscript: Tonon, Thomas, Kamoun, Irani, Multigner, I.G. Gut, M. Gut, Blanchet, Cancel-Tassin, Viari, Cussenot.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.08.026.

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