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DNA repair genes and pathways involved in lethal prostate cancer in European and African American men

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Conclusion

Using a comprehensive panel of DNA repair genes, we observed high carrier frequencies of pathogenic variants within DNA repair pathways among men with lethal prostate cancer of European and African American ancestry. In African Americans, alterations in non-BRCA DNA repair genes appear to be of particular importance for prostate cancer aggressiveness.

Background

Prior work has identified rare genetic variation in DNA repair genes as risk factors for aggressive prostate cancer in men of European ancestry. We sought to determine the DNA repair genes and pathways associated with lethal disease in European and African American men with prostate cancer.

Methods

We included 767 men with lethal (metastatic disease and/or prostate cancer-specific death) or non-lethal Gleason score 6 prostate cancer from four US hospitals. We obtained blood (98%) or buccal swab tissue samples from all men and sequenced 306 pre-selected DNA repair genes. We calculated and compared carrier frequencies of pathogenic or likely pathogenic variants summarized by gene and by DNA repair pathway in lethal cases and non-lethal controls.

Figure 1. Carrier frequencies for pathogenic or likely pathogenic variants in lethal cases and non-lethal controls summarized by DNA repair pathway. * P-value < 0.05 for the comparison between lethal cases and non-lethal controls.

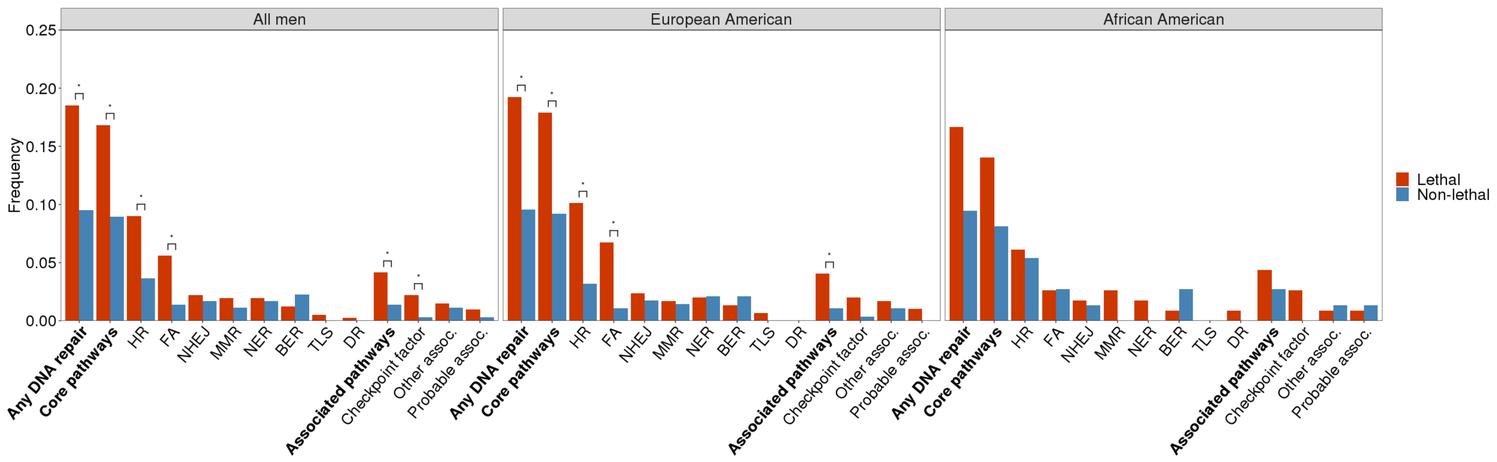

Table 1. DNA repair genes with pathogenic variants in men with lethal and non-lethal prostate cancer. The colors refer to pathogenic variants potentially enriched in men with lethal disease of both ancestries (**bold**), European Americans only (green) and African Americans only (orange).

Core DNA repair pathways								Associated DNA repair pathways		
HR	FA	NHEJ	MMR	NER	BER	TLS	DR	Checkpoint factor	Other associated	Probable associated
BLM	*BARD1*	*APTX*	*EXO1*	*DDB2*	*APTX*	*POLH*	*ASCC1*	***ATM***	***ATM***	*CCNO*
BRCA2	*BLM*	***ATM***	*MLH1*	***ERCC2***	*MUTYH*			*ATR*	*BLM*	*POLG*
MRE11	***BRCA2***	*DCLRE1C*	*MLH3*	*ERCC3*	*NTHL1*			*PER2*	*MRE11*	*VCP*
NBN	*BRIP1*	*MRE11*	***MSH2***	*ERCC5*	*PNKP*			*RAD50*	*NBN*	
RAD50	*FANCA*	*NBN*	*MSH6*	*ERCC8*	*POLE*			*RBBP8*	*RAD50*	
RAD51	*FANCI*	*PNKP*	*PMS2*	*POLE*	*POLH*				*TP53*	
RAD51C	*RAD51*	*RAD50*		*XPA*	*UNG*					
RAD54B	*RAD51C*	*XRCC1*		*XRCC1*	*XRCC1*					
RAD54L		*XRCC4*								
RECQL4										
SLX4										
UIMC1										

Results

Of the 306 analyzed genes, pathogenic or likely pathogenic variants were found in 47 genes (**Table 1**). In European Americans, 19.3% of lethal cases and 9.5% of indolent controls (P-value = 9.2e-04) carried at least one pathogenic variant in a DNA repair gene. In African Americans, the corresponding frequency was 16.7% among lethal cases and 9.5% among indolent controls (P-value = 0.2). Individual gene analysis revealed pathogenic variants within *BRCA2* in 5.1% (European American) and 0.9% (African American) of lethal cases. Several pathways were associated with lethal prostate cancer in European Americans, including FA, HR and DNA repair associated pathways (**Figure 1**). In African Americans, the strongest associations, though not statistically significant, were observed for the MMR and the checkpoint factor pathways.

Abbreviations: homologous recombination (HR), Fanconi anemia (FA), non-homologous end joining (NHEJ), mismatch repair (MMR), nucleotide excision repair (NER), base excision repair (BER), translesion synthesis (TLS), and direct repair (DR).

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