***CDK12* is a prostate cancer predisposition gene**

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Background: Germline variants in genes involved in DNA damage response are associated with increased risk of prostate cancer and the development of aggressive disease, but the full spectrum of relevant genes is unknown. *CDK12* mutations are found in 2-7% of metastatic prostate cancers (mPCa) and were previously thought to be exclusively somatic. Here, we investigated whether *CDK12* pathogenic variants are present in the germline DNA of patients with aggressive prostate cancer.

Methods: This study applied targeted sequencing across coding exons of *CDK12* to leukocyte DNA from patients with aggressive PCa in a discovery cohort (n=2869, 100% mPCa) and an independent validation cohort (n=1621, ~80% mPCa). *CDK12* variants were classified by prediction to gene truncation or kinase activity disruption. Tumours were then evaluated for confirmatory evidence of somatic *CDK12* second allele inactivation and the characteristic *CDK12*-associated tandem duplication phenotype.

Results: In the discovery cohort we identified two patients with germline CDK12 truncating variants. Both were diagnosed with de novo mPCa at a young age (44 and 61) and had multiple independent CDK12-driven tumours characterised by unique secondary somatic CDK12 mutations and associated tandem duplication phenotypes in tumour tissue. Germline CDK12 truncating variants were enriched in mPCa compared to gnomAD non-cancer controls (odds ratio 18.7, 95%CI 1.8-114.7). In the validation cohort, we identified two additional patients with germline variants predicted to truncate CDK12. Similar to the discovery cohort, both patients were diagnosed at a young age (48 and 61) with de novo mPCa and had confirmed secondary somatic CDK12 mutations and tandem duplication phenotypes in the tumours. Family history of cancer was assessed in all identified patients and revealed multi-generation PCa diagnoses in two patients and a first-degree relative with ovarian cancer (the other solid cancer associated with somatic CDK12 mutations) in another patient.

Conclusion: Germline variants predicted to truncate the *CDK12* gene are present in ~0.1% of mPCa and associated with *CDK12*-driven disease in affected patients. Our data provides compelling evidence that *CDK12* is a rare mPCa predisposition gene and should be incorporated into clinical genetic testing workflows.

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