Association of *HOXB13* p.G84E with prostate cancer among 592,158 men

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Background: The *HOXB13* c.G251G>A:p.G84E variant was identified as a prostate cancer (PCa) risk allele in individuals of European descent approximately ten years ago. Several studies from high-risk cohorts have demonstrated a 3-5-fold increased risk of developing PCa with this variant. However, whether this variant confers risk of more aggressive PCa remain controversial. We report age-specific PCa risks and clinical pathological associations in a population-based *HOXB13* p.G84E cohort of heterozygous individuals (n=1660) from the VA Million Veterans Program.

Methods: *HOXB13* p.G84E heterozygotes were identified by SNP genotyping in patients from the Million Veterans Program (MVP). Cox proportional hazard models were used to determine the association of the variant with patient outcomes. Multivariable logistic regression models were used to determine the association of the variant with risk of PCa diagnosis on first biopsy in a sub-cohort of Veterans diagnosed with PCa in the VA.

Results: This MVP study included a total of 592,158 males with 1,660 (0.28%) *HOXB13* p.G84E heterozygous individuals. There was a significant increase in overall incidence of PCa in *HOXB13* p.G84E heterozygous individuals (31.3% (n=519) vs 12.1% (n=71,500), p<0.001) compared to homozygous wild-type individuals. Additionally, *HOXB13* p.G84E heterozygotes were more likely to be diagnosed with PCa at a younger age group (p=0.001). In a Cox proportional hazards model, *HOXB13* p.G84E heterozygous individuals had a significantly increased risk of any PCa (HR 3.23, 95% CI 2.97-3.53, p<2.0E-16), metastatic PCa (HR 2.96, 95%CI 2.30-3.81, p<2.0E-16), and PCa related death (HR 2.65, 95% CI 1.67-4.21, p=3.8E-05). At age 60, the fraction of heterozygotes with any PCa (8.5%) and metastatic PCa (0.7%) was higher than that of wild-type individuals (any PCa: 2.8%, metastatic PCa: 0.1%). At age 90, a larger fraction of heterozygotes had any (59.5%) or metastatic PCa (12.4%) compared to wild-type individuals (any PCa: 26.9%, metastatic PCa: 5.0%). The fraction of *HOXB13* p.G84E heterozygotes who died of PCa at age 80 and 90 was 1.2% and 7.5% respectively, compared to 0.6% and 2.2% of wild-type individuals. To validate our results, we analyzed 36,321 males genotyped in MVP who underwent first prostate biopsy in the VA, among whom 202 (0.56%) were *HOXB13* p.G84E heterozygous individuals. *HOXB13* p.G84E heterozygotes were more likely to be diagnosed with PCa on first biopsy (83.2% (n=168) vs 62.7% (n=22,639), p<0.001) and had higher risk of PCa diagnosis on first biopsy (OR 2.60, 95%CI 1.94-3.52, p<0.001) compared to homozygous wild-type individuals.

Conclusions: We report on the largest cohort of heterozygotes with the *HOXB13* p.G84E variant to date and that this variant confers an increased risk of any and aggressive PCa. Further work is needed to determine if initiation of early PCa screening in *HOXB13* p.G84E heterozygous individuals would improve patient outcomes.

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