HOXB13 G84E mutation and prostate cancer risk: kin-cohort analysis using data from the UK Genetic Prostate Cancer Study

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G84E missense mutations in *HOXB13* are associated with prostate cancer. However, a wide range of risk estimates has been reported. Based on case-control studies, reported OR range from 2 to 20, often with wide confidence intervals because mutations are rare in the population. To obtain more precise risk estimates, we used a kin-cohort study design and modified segregation analysis, using family data on 11,988 PCa index-cases (4509 consecutive cases, 870 and 6609 cases recruited based on family history and young age at diagnosis, respectively) enrolled in the UK Genetic Prostate Cancer Study, who had been genotyped for G84E. Among index-cases, 182 carried at least one copy of G84E. PCa incidence was assumed to follow a mixed Cox regression model of the form $\lambda(t) = \lambda_0(t) \times \exp(G + P)$, where G is a fixed effect which depends on G84E, $P \in N(0, \sigma_P^2)$ a residual polygenic random effect, and $\lambda_0(t)$ is the baseline incidence for non-carriers to age *t*. Using maximum likelihood, after adjusting for ascertainment, we estimated the frequency and RR (i.e. penetrance) for G84E under different genetic models, and σ_P. Preliminary results suggest that under the best fitting model, the data are consistent with a multiplicative model where each copy of G84E confers RR for PCa of 2.6 (95%CI 1.7-4.2), and a significant σ_P of 1.8 (95%CI 1.7-1.9), indicating that family history increases risk above that resulting from being a mutation carrier. Ongoing work will evaluate effect-modification of RR and/or σ_P by age, birth cohort, and mutation status, and estimate absolute risks for reference family structures.