Background: The p.G84E alteration in HOXB13 has been associated with an increased risk for prostate cancer in male carriers. While the phenotypic spectrum in carriers unselected for personal or family history of prostate cancer has not been well studied, predisposition to breast or ovarian cancers in females has been suggested. Here we aim to evaluate the role of p.G84E in predisposition to breast and ovarian cancer using a clinical laboratory cohort.

Methods: De-identified molecular results and clinical histories were retrospectively reviewed for 33146 individuals who had multigene panel testing (MGPT) that included analysis of the HOXB13 p.G84E locus. The frequency of HOXB13 p.G84E was compared between non-Finnish European (NFE) MGPT cases and NFE controls from the Exome Aggregation Consortium (ExAC).

Results: Eighty-nine individuals were HOXB13 p.G84E carriers (0.27% of 33146), including nine with a mutation in a second gene. The most common cancers reported in p.G84E carriers were female breast (42 of 70; 60%), ovarian (3 of 70; 4.3%), and prostate (2 of 10; 20%). The frequency of p.G84E was significantly higher in NFE prostate probands than the ExAC NFE controls (1.35%; OR 4.4 p=0.03), but not in NFE female breast (0.35%; OR 1.1 p=0.5) or ovarian (0.16%; OR 0.5 p=0.4) probands. Individuals with family history of prostate cancer were more likely to carry p.G84E than those without (OR 2.43 p=5.06e-05) and the effect was strengthened in individuals with two or more family members with prostate cancer compared to those with no family history (OR 3.2 p=0.002). In contrast, individuals with family history of breast or ovarian cancer were not more likely to carry p.G84E than those without family history of these cancers.

Conclusions: Although breast and ovarian cancer were among the most common cancers in p.G84E carriers, the mutation rate in these probands was not increased compared to the general population. Therefore, the preponderance of breast and ovarian cancer likely reflects the nature of this laboratory cohort rather than a risk association. The impact of prostate cancer family history on HOXB13 mutation frequency highlights the importance of including prostate cancer when collecting family history regardless of the primary cancer indication for testing. The results of this study reinforce the association between HOXB13 and prostate cancer; however, more data is needed to determine if female carriers are at increased risk to develop cancer.