Succinate dehydrogenase pathogenic variants are not associated with non-canonical cancers

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289/300

Background: Germline *succinate dehydrogenase (SDHx)* pathogenic variants (PVs) are associated with pheochromocytoma (PCC) and paraganglioma (PGL), gastrointestinal stromal cell tumors, and renal cell carcinomas. Associations with other cancers have not been studied systematically. The goal of this study was to determine associations between *SDHx* PVs and cancer in a cohort of patients undergoing testing for cancer predisposition genes.

Methods: Subjects who underwent multigene panel testing of cancer predisposition genes between 2013 and 2016 (Ambry Genetics) were included. Demographic data and histories were obtained from clinical documentation. Logistic regression was used to assess the association between *SDHx* (*SDHA, SDHB, SDHC, SDHD,* and *SDHAF2*) PVs and 11 common cancer types. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Results: Of 8510 unrelated individuals undergoing testing of *SDHx* genes, 5% had germline *SDHx* PVs. The mean age at testing was 48 yo (SD: 15.3). The majority of subjects were female (79%). 77% of the study cohort had a personal history of cancer, most commonly breast cancer (n=2746), followed by kidney cancer (n=1629) and PCC/PGL (n=894). By gene subunit, *SDHB* was associated with the highest risk of PCC, while *SDHD* had the highest risk of PGL. In subjects tested for all *SDHx* genes, the presence of any *SDHx* PV was significantly associated with a personal history of cancer (OR:2.3, 95% CI:1.2-4.0). When evaluated by cancer type, *SDHx* PVs correlated with risk of PCC (OR:17.7, 95% CI:7.4-37.4) and PGL (OR:75.4, 95% CI:40.4-139.3) but not with breast, colorectal, kidney (all histologies), melanoma, pancreatic, prostate, ovarian, thyroid, or uterine/endometrial cancer, in patients tested for all *SDHx* genes.

Conclusion: *SDHx* PVs were strongly associated with PCC/PGL, but not with increased risk of other canonical human cancers. Future population-based studies are required to confirm these findings.

Figure 1. Cancer risk associated with *SDHx* mutation, by cancer type. *SDHx* mutation is associated with significantly increased risk of PCC and PGL in subjects tested for all *SDHx* genes.