Title: Germline *SDHA*-Related Tumor Risks: A Cohort Of 558 *SDHA* Positive Patients From a Single Reference Laboratory

Authors:

Lauren Lovrien
Morgan Armstrong
Darcy Berry
Cassidy Carraway
Jane Churpek
Marcy Richardson
Amanda Jacquart

SDHA PVs (pathogenic and likely pathogenic variants) have historically been considered high risk for paragangliomas (PGLs), pheochromocytomas (PCCs), renal cell carcinomas (RCCs), and gastrointestinal stromal tumors (GISTs). Prior studies have estimated lifetime penetrance as low as 2%, when utilizing Bayesian analysis and large population data, and as high as 90%, when using tumor registry populations enriched for PGLS and PCCs. Without a more comprehensive understanding *SDHA* penetrance and phenotype, it is difficult to apply testing criteria and management guidelines. Additionally, *SDHA* PVs are frequently identified as incidental findings on multigene panel testing (MGPT). It is important to characterize *SDHA* PVs for the proper identification of at-risk patients and for appropriate long-term management of germline-positive patients.

This study sought to characterize *SDHA* PV tumor burden in a retrospective cohort representative of current cancer genetics patient populations, including those detected on pan-cancer MGPT without personal or family history relevant for *SDHx*. De-identified data from 1,072 individuals with a PV in *SDHA* or *SDHB* who underwent germline testing at a single reference clinical laboratory were reviewed. An additional 12,717 individuals with germline negative testing were reviewed for comparative analysis. All individuals underwent pan-cancer or targeted genetic testing between January 2013 and June 2024. Cases with secondary PVs in

cancer-associated genes were excluded. Five cohorts were developed based on genotype and panel type; *SDHA* pan-cancer (n = 492), *SDHA* targeted (n = 66), *SDHB* pan-cancer (n = 158), *SDHB* targeted (n = 212), and germline negative (n = 12,717). The *SDHA* pan-cancer cohort served as the test cohort. The *SDHA* targeted cohort was largely phenotypically driven, presumed to have a moderate Hereditary Paraganglioma and Pheochromocytoma Syndrome (HPPGL) tumor prevalence. The *SDHB* pan-cancer and targeted cohorts served as comparative high HPPGL prevalence cohorts. In this analysis, HPPGL tumors included PGLs, PCCs, GISTs, neuroblastomas, and renal, pituitary, and thyroid tumors. Kaplan-Meier estimation analyses were used to estimate HPPGL penetrance.

The following lifetime HPPGL penetrances were estimated: *SDHA* pan-cancer = 19.31%, *SDHA* targeted = 96.68%, *SDHB* pan-cancer = 77.98% and *SDHB* targeted = 98.28%. The *SDHA* pan-cancer cohort demonstrated the following individual lifetime (80 yrs) tumor risks: PGL = 7.90%, PCC = 1.47%, GIST = 4.22%, renal = 2.67%, pituitary = 2.40%, and thyroid = 1.35%. Based on these data, the *SDHA* PV patient population is most at risk for PGLs and GISTs. Importantly, the GIST lifetime risk was higher in the *SDHA* pan-cancer and targeted cohorts (4.22%, 18.77%) than in the *SDHB* pan-cancer and targeted cohorts (4.03%, 3.27%).

This is the largest *SDHA* study to date, investigating tumor burden and family histories of more than 500 *SDHA* PV patients. This study demonstrates that *SDHA* PVs tend to have low lifetime penetrance, although this penetrance remains above the general hereditary cancer clinic population average risks for PGLs, PCCs, GISTs, and pituitary tumors. Genetics professionals will need to provide adequate anticipatory guidance and appropriate risk communication to patients with *SDHA* PVs.

Bausch, B., Schiavi, F., Ni, Y., Welander, J., Patocs, A., Ngeow, J., Wellner, U., Malinoc, A., Taschin, E., Barbon, G., Lanza, V., Söderkvist, P., Stenman, A., Larsson, C., Svahn, F., Chen, J.-L., Marquard, J., Fraenkel, M., Walter, M. A., … Neumann, H. P. H. (2017). Clinical Characterization of the Pheochromocytoma and Paraganglioma Susceptibility Genes SDHA, TMEM127, MAX, and SDHAF2 for Gene-Informed Prevention. *JAMA Oncology*, *3*(9), 1204–1212. https://doi.org/10.1001/jamaoncol.2017.0223

Benn, D. E., Zhu, Y., Andrews, K. A., Wilding, M., Duncan, E. L., Dwight, T., Tothill, R. W., Burgess, J., Crook, A., Gill, A. J., Hicks, R. J., Kim, E., Luxford, C., Marfan, H., Richardson, A. L., Robinson, B., Schlosberg, A., Susman, R., Tacon, L., … Clifton-Bligh, R. J. (2018). Bayesian approach to determining penetrance of pathogenic SDH variants. *Journal of Medical Genetics*, *55*(11), 729–734. https://doi.org/10.1136/jmedgenet-2018-105427

Bush, L., Prigmore, B., Sengupta, U., Balcioglu, M., Sha, Y., Nyberg, A. (2024, September 17-21). *Hereditary Paraganglioma-Pheochromocytoma Syndrome Identification in a Primarily Unaffected Patient Cohort Pursuing Multigene Hereditary Cancer Testing* [Poster Abstract]. National Society of Genetics Counselors Annual Conference, New Orleans, LA, United States.

Hall, C. B. M., Watson, E. M., Prasad, T., Myers, C. L., & Mersch, J. A. (2024). Hereditary and clinical insights into paraganglioma and pheochromocytoma. *Endocrine Oncology*, *4*(1). https://doi.org/10.1530/EO-24-0029

Kohlmann, W., Pauley, K., Naumer, A., Greenberg, S., Stevenson, N., Ellis, K., Roberts, A. F., Kawasaki, J., Jump, T., & Sutherland, N. (2023). P083: Incidental findings in FH and SDHA genes: Navigating cancer risk assessment and follow-up recommendations. *Genetics in Medicine Open*, *1*(1). https://doi.org/10.1016/j.gimo.2023.100102

Maniam, P., Zhou, K., Lonergan, M., Berg, J. N., Goudie, D. R., & Newey, P. J. (2018). Pathogenicity and Penetrance of Germline SDHA Variants in Pheochromocytoma and Paraganglioma (PPGL). *Journal of the Endocrine Society*, *2*(7), 806–816. https://doi.org/10.1210/js.2018-00120

van der Tuin, K., Mensenkamp, A. R., Tops, C. M. J., Corssmit, E. P. M., Dinjens, W. N., van de Horst-Schrivers, A. N., Jansen, J. C., de Jong, M. M., Kunst, H. P. M., Kusters, B., Leter, E. M., Morreau, H., van Nesselrooij, B. M. P., Oldenburg, R. A., Spruijt, L., Hes, F. J., & Timmers, H. J. L. M. (2018). Clinical Aspects of SDHA-Related Pheochromocytoma and Paraganglioma: A Nationwide Study. *The Journal of Clinical Endocrinology & Metabolism*, *103*(2), 438–445. https://doi.org/10.1210/jc.2017-01762