

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) has approximately 20-30% penetrance in individuals carrying loss-of-function mutations in *SMARCA4*.

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Introduction: Loss- of -function (LoF) alterations in *SMARCA4* are associated with a rare and highly aggressive type of ovarian cancer, known as small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), typically diagnosed between childhood and early 40s. *SMARCA4* was first reported in association with this phenotype in 2013. With fewer than 1000 patients described in the literature since, penetrance is not well-defined. Here, we aimed to estimate the crude penetrance of SCCOHT.

Methods: From a cohort of individuals undergoing multigene panel testing, we retrospectively curated clinical data reported for carriers of LoF *SMARCA4* alterations and their relatives. We estimated the penetrance of SCCOHT in this cohort by dividing the number of affected female carriers by the number of total female carriers in the cohort

Results: We identified 58 female probands with a LoF alteration in *SMARCA4*. 12 of these individuals were reported to have a clinical history of SCCOHT, diagnosed between the ages of 9 and 39 years of age. An additional 4 patients were diagnosed with ovarian cancers of unspecified subtype between the ages of 15 and 46 years. With a total of 12-16 possible affected individuals, the crude penetrance of SCCOHT in this cohort is approximately 20.7-27.6%. As these individuals are undergoing multigene panel testing for cancer, ascertainment bias may impact this estimate. Of the 42 unaffected female probands, 5 (~11.9%) reported a history of SCCOHT or early-onset ovarian cancer (<40) in a first-degree relative. 9 of the unaffected individuals were under the age of 40, thus are within the age range to still be potentially impacted by this disease.

Conclusions: Based on our data, crude penetrance of *SMARCA4*-associated SCCOHT is 20-30%. This information is critical for the management of these patients and their family members when considering the potential for risk-reducing options and planning.