Role of SMARCA4 Mutations in Ovarian Carcinoma: Preliminary Data from a Laboratory-based Multigene Panel Testing Cohort

Objectives

This study aims to describe the clinical characteristics of SMARCA4 mutation carriers in a multigene panel testing (MGPT) cohort, estimate the mutation frequency in ovarian cancer probands with and without small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), and identify the utility of SMARCA4 testing in ovarian cancer probands ascertained from a MGPT cohort.

Methods

A retrospective data review was conducted of 39,879 consecutive individuals who underwent next generation sequence and deletion/duplication analysis of SMARCA4 as part of MGPT at our diagnostic laboratory since May 2015. Molecular results and clinical histories were reviewed in probands with ovarian cancer and/or a positive or inconclusive SMARCA4 result.

Results

Overall, 0.005% (2/39,879) of individuals tested positive for a SMARCA4 pathogenic mutation/likely pathogenic variant. One individual had SCCOHT diagnosed at age 22 years and another individual had a personal history of colon cancer at age 41 years. Family history was noncontributory for both positive individuals. An additional 1.3% (519/39,879) of individuals were found to carry variants of uncertain significance in SMARCA4. The previously mentioned individual with SCCOHT at age 22 was the only proband who tested positive for a SMARCA4 mutation in the ovarian cancer cohort (1/4391 or 0.02%). No SMARCA4 mutations were detected among 890 individuals for whom epithelial ovarian histology was specified. Among 7 individuals for whom small cell ovarian pathology was specified, one individual (14.3%) was found to carry a SMARCA4 mutation. There is no statistically significant difference in mutation rate for ovarian cancer probands undergoing MGPT when SMARCA4 is excluded or included (15.6% vs. 15.7%; OR 1.002; p-value 0.97).

Conclusions

Results from this study demonstrate that SMARCA4 germline mutations are rare in the absence of SCCOHT and suggest that SMARCA4 mutations do not predispose to epithelial ovarian cancer. While the inclusion of SMARCA4 in MGPT did not significantly improve the diagnostic yield for ovarian cancer patients in this cohort, it should be included in the differential diagnosis for patients with SCCOHT and patients with unknown/questionable ovarian tumor histology diagnosed at a young age. Further investigation in larger ovarian cancer cohorts is necessary to determine the utility of SMARCA4 testing in other types of ovarian cancer.

Learning Objectives

Learners will be able to recognize that including SMARCA4 analysis on MGPT does not appear to add significant value in the evaluation of the majority of patients with ovarian cancer, but it can nevertheless be of value in patients with SCCOHT, and also in rare cases for which ovarian cancer histology is unknown or misclassified.