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.