Genetic heterogeneity of ovarian sex cord-stromal tumors

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Background

- Sertoli-Leydig and granulosa cell tumors (adult and juvenile types) are sex cord-stromal tumors of the ovary
- These tumors primarily occur in young women
- Adult-type granulosa cell tumors (aGCTs) are characterized by pathognomonic somatic *FOXL2* mutations
- 30-60% of Sertoli-Leydig cell tumors (SLCTs) harbor *DICER1* mutations
- A comprehensive assessment of the repertoire of genomic alterations of sex cord-stromal tumors has yet to be performed

Aims

- To determine the repertoire of somatic mutations and copy number alterations in juvenile-type granulosa cell tumors (jGCTs) and Sertoli-Leydig cell tumors (SLCTs).

Methods

- DNA was extracted from primary SLCTs (n=2), jGCTs (n=3) and one primary and matched mixed SLCT/ aGCT recurrence (n=2), and subjected to whole-exome sequencing.
- Somatic mutations, copy number alterations, loss of heterozygosity (LOH) and mutational signatures were defined using validated bioinformatics methods.

Figure 1. Histologic characteristics of sex cord-stromal tumors. A) SLCT, B) aGCT, C) jGCT and D) mixed aGCT/SLCT. Scale bars 20 and 50 μm.

Results

Primary and matched recurrent SLCT/ aGCT

Figure 2. Primary SLCT and matched mixed SLCT-aGCT recurrence. Left) Non-synonymous somatic mutations and cancer cell fractions color-coded according to legend. Right) Copy number log₂ ratios.

Results

Genetic landscape of pure SCLTs and jGCTs

Figure 3. Landscape of somatic mutations in SLCTs and jGCTs. Non-synonymous somatic mutations identified in 2 SLCTs and 3 jGCTs (left) and cancer cell fractions of mutations identified (right), color-coded according to the legend.

Figure 4. CNAs in SLCTs and jGCTs.

- Clonal *FOXL2* p.C134W hotspot mutations were present in the primary and matched recurrent mixed SLCT/ aGCT, and patterns of CNAs were similar.
- Mutations restricted to either the primary or the recurrent SLCT/aGCT were found.
- The median number of non-synonymous mutations identified in the SCLTs and jGCTs studied was 14 (range 7-57).
- SLCT-1 & SLCT-2 harbored pathogenic *DICER1* mutations.
- SERPINB7* mutations were found in SLCT1 and jGCT1.
- Neither the jGCTs nor SLCT-2 harbored *FOXL2* or *DICER1* mutations.
- Subclonal mutations are present in all SCLTs and jGCTs studied.
- No clear driver genetic alterations were identified in jGCTs.
- jGCTs were found to harbor more CNAs, whereas SLCTs were largely devoid of CNAs.

Conclusions

- Sex cord-stromal tumors are a genetically heterogeneous group of rare ovarian neoplasms.
- Few recurrent driver alterations were identified in these lesions.
- Further studies to define driver alterations in jGCTs are warranted.