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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BACKGROUND

- Loss-of-function (LoF) alterations in *SMARCA4* are associated with small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), a rare and highly aggressive type of ovarian cancer with rhabdoid features (Witkowski et al 2013), and have also been recently described in a subset of individuals with neuroblastomas (Witkowski et al 2023).
- SCCOHT primarily affects younger women, with diagnosis typically occurring in females between childhood and early 40s in age.
- Germline *SMARCA4* variants were first described in association with SCCOHT in 2013 (Witkowski *et al* 2013), and since that time, fewer than 1000 cases have been described in the literature.
- Penetrance of SCCOHT appears to be incomplete, however the penetrance of this phenotype has not previously been well defined due to the rarity and relatively recent gene-disease association of this phenotype.
- In this study, we aimed to estimate penetrance of SCCOHT in females who underwent multigene panel testing for cancer and were identified as carrying a LoF variant in *SMARCA4*.

METHODS

- We curated clinical data on personal and family history for female probands identified as carrying a germline LoF variant in *SMARCA4* through multigene panel testing at a clinical diagnostics laboratory.
- LoF variants included nonsense, frameshifting, and canonical splice site alterations predicted to result in premature truncation of the protein or nonsense mediated decay.
- We calculated a crude estimate of penetrance of the SCCOHT phenotype in this cohort by dividing the number of affected females in this group by the total number of females identified as carrying LoF variants in *SMARCA4.*
- "Affected" individuals included those reported to have a clinical history of SCCOHT, as well as those reported to have a history of early-onset ovarian cancer diagnosed before the age of 50.
- "Unaffected" individuals had no personal history of ovarian cancer.

RESULTS

- A total of 58 female probands carried a germline LoF variant in *SMARCA4.* 12 of these reported a clinical history of SCCOHT, and an additional 4 reported diagnosis with ovarian cancers of unspecified subtype between the ages of 15 and 46 years, for a total of 12-16 possibly affected probands.
- Based on this data, penetrance of SCCOHT in this cohort was calculated as approximately 20.7 % (SCCOHT-subtype specific) to 27.6% (including early-onset ovarian cancers as affected)
- The age range of individuals with a clinical diagnosis of SCCOHT or ovarian cancer in this cohort was 9-46 years.
- Of the 42 unaffected probands with a LoF alteration in *SMARCA4*, 6 probands (~14%) reported a clinical history of SCCOHT or early-onset ovarian cancer in a first-degree relative, while approximately 62% of individuals in the total cohort (36/58 female probands) reported no personal or family history of SCCOHT or ovarian cancer diagnosed under age 50.
- 12 individuals in the unaffected cohort were under the age of 50 at the time of screening, therefore are still within the age range to potentially be impacted by this phenotype.

LoF VARIANTS IN *SMARCA4* IDENTIFIED IN FEMALES UNDERGOING MULTIGENE CANCER PANEL TESTING

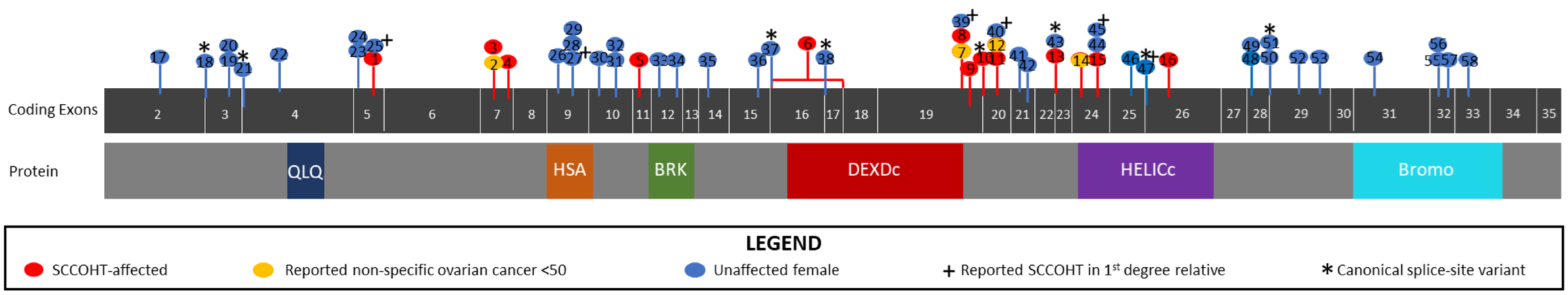

Figure 1: Representation (not to scale) of locations of loss-of-function (LoF) variants identified in *SMARCA4* in female probands undergoing multigene panel testing. Case numbers correspond to samples listed in Tables 1 and 2. LoF variants included nonsense, canonical splice-site, and frameshifting variants predicted to result in premature truncation of the protein or nonsense-mediated mRNA decay. 16 probands reported a clinical history of SCCOHT or early-onset ovarian cancer diagnosed under age 50. 42 probands were unaffected with ovarian cancer at the time of testing, however 6 of these individuals report a family history of SCCOHT in a first-degree relative.

Protein Structure: QLQ: Gln, Leu, Gln motif. HSA: helicase/SANT-associated domain. BRK: Brahma and Kismet domain. DEXDc: DEAD-like helicase superfamily domain. HELICc: helicase superfamily C-terminal domain. Bromo: bromodomain.

DISCUSSION

- We estimated penetrance of SCCOHT to be approximately 20-30% based on data from our cohort of individuals undergoing multigene cancer panel testing, however ascertainment bias may impact this assessment, as these individuals are likely to have a personal or family history of cancer. In contrast, however, 12/42 unaffected individuals (~29% of unaffected) were under the age of 50 at the time of screening, and therefore are still within the range of ages that may still be impacted by SCCOHT, and thus may contribute to under-estimation of risk in this cohort.
- An understanding of penetrance for *SMARCA4* is critical for patient management and risk estimates. Penetrance and age of onset are important factors to consider when considering risk-reducing procedures, such as prophylactic oophorectomy in female patients.
- Of note, 0 of 58 female probands and only 1 of 14 male probands identified to carry a LoF alteration in *SMARCA4* reported a clinical history of neuroblastoma in our internal cohort.

Proband #	Variant	Predicted p.	Phenotype	Age of Dx
1	c.826_827delCC	p.P276Sfs*10	SCCOHT	37
2	c.1141C>T	p.R381*	Non-specific ovarian	31
3	c.1141C>T	p.R381*	SCCOHT	36
4	c.1183delG	p.D395Ifs*16	SCCOHT	23
5	c.1892dupC	p.D632Rfs*19	SCCOHT	22
6	Ex 16_17del	N/A	SCCOHT	25
7	c.2838delC	p.F947Lfs*3	Non-specific ovarian	15
8	c.2838delC	p.F947Lfs*3	SCCOHT	18
9	c.2854_2855delGAinsC	p.E952Qfs*5	SCCOHT	21
10	c.2859+1G>C	N/A	SCCOHT	23
11	c.2935C>T	p.R979*	SCCOHT	9
12	c.2935C>T	p.R979*	Non-specific ovarian	31
13	c.3168+2T>C	N/A	SCCOHT	23
14	c.3229C>T	p.R1077*	Non-specific ovarian	46
15	c.3277C>T	p.R1093*	SCCOHT	39
16	c.3565C>T	p.R1189*	SCCOHT	21

Table 1: LoF variants in *SMARCA4* identified in individuals with SCCOHT or early-onset ovarian cancer. SCCOHT= small-cell carcinoma of the ovary, hypercalcemic type. Non-specific ovarian cancer= ovarian cancer reported, but no subtype was indicated.

Proband #	Variant	Predicted p.	Family Hx of SCCOHT or Ovarian Ca in FDR?	Age at Testing
17	c.102_114dup13	p.A39Lfs*47	No	67
18	c.222+1G>T	N/A	No	44
19	c.300delA	p.G102Afs*201	No	43
20	c.300delA	p.G102Afs*201	No	35
21	c.355+2G>T	N/A	No	47
22	c.478delC	p.Q160Rfs*143	No	62
23	c.788delC	p.P263Qfs*40	No	43
24	c.788delC	p.P263Qfs*40	No	45
25	c.826_827delCC	p.P276Sfs*10	Yes	9
26	c.1472_1473insGCAAA	p.S492Qfs*11	No	46
27	c.1489dupA	p.I497Nfs*37	Yes	Unknown
28	c.1489dupA	p.I497Nfs*37	No	33
29	c.1489dupA	p.I497Nfs*37	No	36
30	c.1645delC	p.R549Afs*64	No	65
31	c.1666C>T	p.Q556*	No	34
32	c.1666C>T	p.Q556*	No	74
33	c.1823delA	p.E608Gfs*5	No	54
34	c.1911dupG	p.Q638Afs*13	No	54
35	c.2032C>T	p.Q678*	No	70
36	c.2236_2239delTCAG	p.S746Rfs*27	No	34
37	c.2275-1G>C	N/A	No	49
38	c.2438+1G>T	N/A	No	25
39	c.2838delC	p.F947Lfs*3	Yes	27
40	c.2935C>T	p.R979*	Yes	42
41	c.3000delG	p.M1000Ifs*19	No	50
42	c.3013C>T	p.R1005*	No	65
43	c.3168+2T>C	N/A	No	42
44	c.3277C>T	p.R1093*	No	52
45	c.3277C>T	p.R1093*	Yes	22
46	c.3533G>A	p.W1178*	No	47
47	c.3546+1G>A	N/A	Yes	54
48	c.3874delG	p.E1292Rfs*14	No	55
49	c.3874delG	p.E1292Rfs*14	No	27
50	c.3951+2T>C	N/A	No	27
51	c.3951+2T>C	N/A	No	60
52	c.4038G>A	p.W1346*	No	62
53	c.4153delG	p.E1385Rfs*110	No	63
54	c.4339C>T	p.R1447*	No	59
55	c.4567C>T	p.R1523*	No	67
56	c.4567C>T	p.R1523*	No	67
57	c.4573G>T	p.E1525*	No	56
58	c.4675A>T	p.K1559*	No	71

Table 2: LoF variants in SMARCA4 identified in unaffected individuals. "Unaffected" = no personal history of ovarian cancer.

TAKE-HOME POINTS

1. In this genotype-first analysis, germline LoF variants in *SMARCA4* are associated with small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT), however are not fully penetrant.
2. Approximately 20-30% of females with LoF variants in our cohort were affected with SCCOHT.
3. There appears to be a window of risk for SCCOHT, most frequently occurring before the age of 40y and exclusively before the age of 50y in this study.
4. These findings have important counseling and risk management implications.

REFERENCES

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