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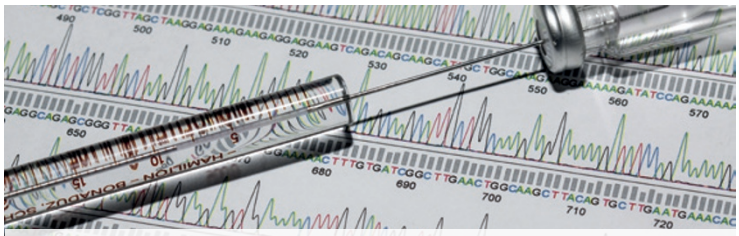

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GENETICS

SMARCA4 mutated in SCCOHT

Small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare—occurring in less than 1% of all ovarian malignancies—but aggressive form of ovarian cancer that primarily affects young women. The mean age at diagnosis is 23 years, and more than 65% of patients die from their disease within 2 years of diagnosis. Although the underlining mechanisms of this malignancy are unknown, three different studies, published in *Nature Genetics*, have now shown that SCCOHT is a monogenic disease caused by mutations in the *SMARCA4* gene.

In the first study, led by William Foulkes, a group of researchers analysed several familial cases of SCCOHT that were characterized by autosomal dominant transmission—a strong indication that mutations in a single gene might cause this disease. The researchers performed whole-exome sequencing on DNA obtained from 24 familial or sporadic cases. As Foulkes highlights, "the most significant finding was that 22 of the 24 cases analysed were due to *SMARCA4* mutations". Furthermore, the researchers suggest that SCCOHT tumours are essentially malignant rhabdoid tumours of the ovary, "they are not always comprised of small cells, are not carcinomas, and only two thirds have hypercalcemia," concludes Foulkes. It is, therefore, possible that chemotherapeutic regimens used to treat rhaboid tumours might help improve the outcome of this disease.

In a second study, Jeff Trent and colleagues performed whole-genome and whole-exome sequencing on a series of tumours and germline samples derived from 12 cases of SCCOHT. Remarkably, the investigators identified germline or somatic mutations in *SMARCA4* in 75% of the cases. Furthermore, they reported a loss of SMARCA4 protein in 82% of the SCCOHT tumours analysed, indicating that the loss of the functional SMARCA4 protein might underline the oncogenic process.

Finally, in the third study led by Douglas Levine, the researchers examined 12 SCCOHT tumours. "We have a novel next-generation sequencing platform ... that allowed us to survey nearly 300 cancer-related genes from archival formalin fixed paraffin-embedded tissues," says Levine. Of note, *SMARCA4* inactivating mutations were identified in all 12 cases.

These studies provide clear evidence of the genetic basis of SCCOHT. Furthermore, as Levine emphasizes, "these findings can be used to help diagnose this disease," and immunohistochemistry can be used to assess the level of SMARCA4 protein to confirm such a diagnosis. All three groups are now planning on developing targeted therapies to test in *SMARCA4* mutated cell lines initially, to ultimately improve the treatment of SCCOHT.

Alessia Errico

Original articles Jelinic, P. *et al*. Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary. *Nat. Genet.* doi:10.1038/ng.2922 | Ramos, P. *et al*. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*. *Nat. Genet.* doi:10.1038/ng.2928 | Witkowski, L. *et al*. Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nat. Genet.* doi:10.1038/ng.2931