Ovary: inv(10)(q11q11) in ovarian germ cell tumors

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Identity

Note
Ovarian germ cell (OGC) tumours arise in the primitive germ cells of the ovary and primarily affect younger women. Struma ovarii are the most common monodermal teratomas arising from OGCs. Struma Ovarii are characterized by a composition of at least 50% mature thyroid tissue. Two reports have shown that oncogenic mutations characteristic of thyroid carcinoma in situ, most notably mutations found in thyroid follicular cells that give rise to papillary thyroid carcinoma (PTC), can be found within the thyroid tissue of Struma Ovarii. These mutations can promote oncogenesis, resulting in initiation of PTC within the teratoma.

Clinics and pathology

Disease
Papillary thyroid carcinoma arising in struma ovarii.

Phenotype / cell stem origin
Struma ovarii originate from ovarian germ cells. Malignant transformation of these monodermal teratomas primarily occurs in follicular-like cells of the thyroid tissue contained within struma ovarii, producing a tumour that resembles papillary thyroid carcinoma.

Treatment
Surgical resection of tumour, $^{131}$I radioablation therapy.

Cytogenetics

Cytogenetics Molecular
inv(10)(q11q11)

Genes involved and proteins

Note
The inv(10)(q11q11) fuses the promoter and 5’ coding regions of NCOA4 to the 3’ kinase domain coding region of RET.

RET

Location
10q11.21

Protein
RET encodes a 175 kDa transmembrane receptor tyrosine kinase that is required for development of the kidney and enteric nervous system. Three isoforms of RET have been identified that arise through 3’ alternative splicing involving exons 19, 20 and 21, and encode proteins of 1072, 1106, and 1114 amino acids.

NCOA4

Location
10q11.23

Protein
NCOA4 is a 70 kDa co-activator protein that serves to enhance transcriptional activity downstream of the androgen receptor, other steroid receptors, and peroxisome proliferator-activated receptor gamma.

Diagrammatic representation of RET and NCOA4 exon locations on Chromosome 10. Introns and exons are to scale within respective genes. Breakpoints within each gene are indicated (BP).
**Result of the chromosomal anomaly**

**Hybrid Gene**
The RET/NCOA4 fusion gene is also referred to as PTC3.

**Description**
The inv(10)(q11q11) results in fusion of exons 1-6 of NCOA4 with exon 12-through to the C-terminus of RET.

**Detection**
RT-PCR, Southern blot, and FISH (see Zu et al., 2006 for detailed methods).

**Fusion Protein**
The RET/NCOA4 fusion protein is also referred to as PTC3. Chimeric protein consisting of the tyrosine kinase domain of RET fused downstream of the homodimerization domain of NCOA4. Constitutive dimerization of fusion proteins results in continuous downstream signalling through canonical cell growth and proliferation pathways, promoting oncogenesis.

**Description**
Fusion protein consists of amino acids 1-238 of NCOA4 and 712-C-terminus of RET. The N-terminal region donated by NCOA4 contains a homodimerization domain that results in constitutive dimerization and activation of the RET kinase domain in the C-terminal region of the molecule. Constitutive activation increases signalling through a number of downstream signalling pathways involved in cell proliferation and survival, promoting oncogenesis.

**Expression / Localisation**
Cytoplasm.

**Oncogenesis**
RET/NCOA4 fusion proteins have been implicated in the oncogenesis of papillary thyroid carcinoma.

**To be noted**
Although RET/NCOA4 fusion proteins are known to play a role in initiating papillary thyroid carcinoma, they can also occur as a late mutational event. As with all tumours, care must be taken in attributing oncogenesis to a single genetic event.

**References**
- Zhu Z, Ciampi R, Nikiforova MN, Gandhi M, Nikiforov YE. Prevalence of RET/PTC rearrangements in thyroid papillary carcinomas: effects of the detection methods and genetic heterogeneity. J Clin Endocrinol Metab. 2006 Sep;91(9):3603-10

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