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Solid Tumour Section

Short Communication

Thyroid: Papillary carcinoma with inv(10)(p12.1q11.2) ACBD5/RET

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Abstract

Mini review on inv(10)(p12.1q11.2) ACBD5/RET in papillary thyroid cancer (PTC).

Keywords

chromosome abnormality; ACBD5; RET; papillary thyroid cancer.

Identity

Intrachromosomal rearrangement

Classification

Papillary Thyroid Carcinoma is a malignant tumor with papillary sturucture derived from thyroid follicular epithelial cells.
The tumor cells show cytological features including overlapping nuclei, nuclear grooves and intranuclear cytoplasmic inclusions.

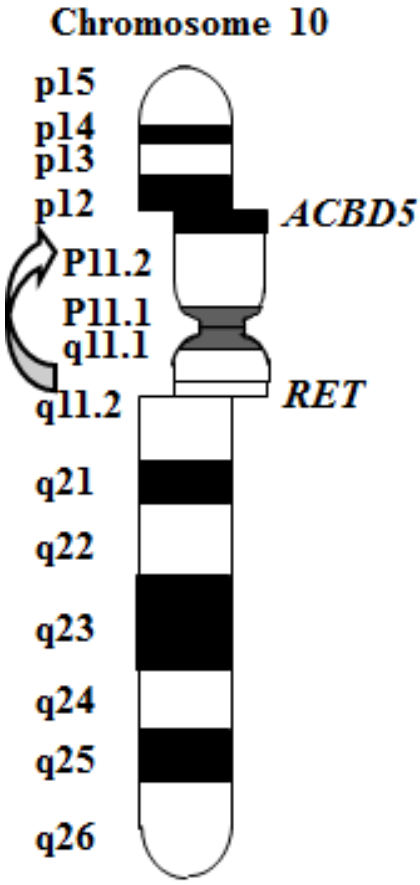
Clinics and pathology

Disease

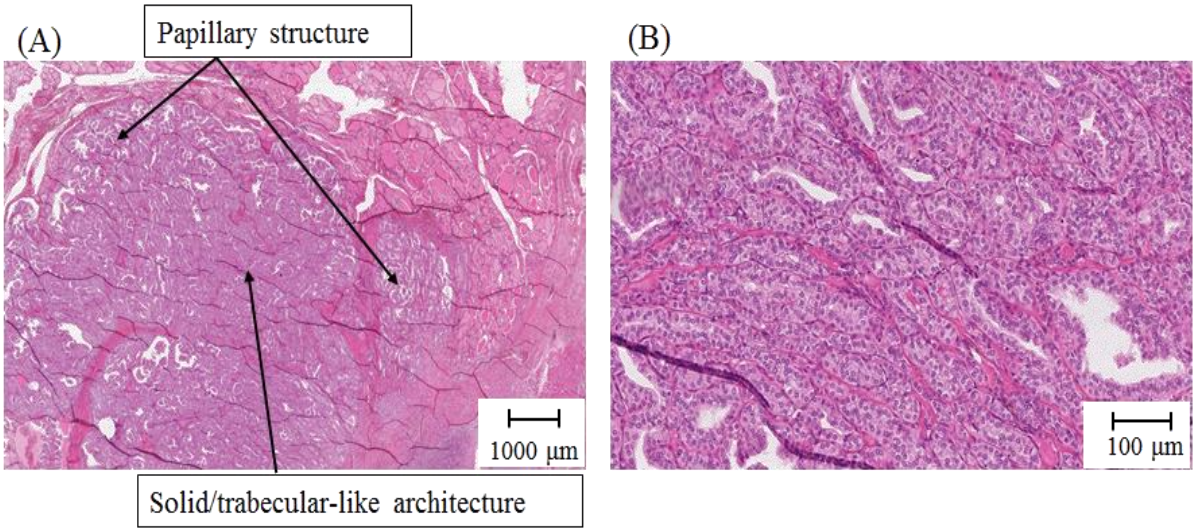
Papillary thyroid carcinoma

Epidemiology

Thyroid cancer is one of the malignancies most closely associated with exposure to ionizing radiation in humans, such as exposure produced by the atomic bombings in Hiroshima and Nagasaki (Imaizumi et al., 2006) and by the Chernobyl nuclear power plant accident (Kazakov et al., 1992; Astakhova et al., 1998).



ACBD5-RET fusion gene is a chimeric gene formed by pericentric inversion of the short and long arms of chromosome 10.



(A)Low magnification of papillary thyroid carcinoma with ACBD5/RET. (B) The larger magnification of solid/trabecular-like region.

RERF's statisticians have recently reported that about 36% of the PTC cases among those exposed as children or adolescents (below 20 years old) were estimated to be attributable to radiation exposure, which was considerably higher than that of 4% for those exposed as adults (above 20 years old) (Furukawa et al., 2013).
Constitutive activation of the mitogen-activated protein kinase (MAPK)-signaling pathway-such as alterations of RET, NTRK1, BRAF, and RAS genes-are frequently found in PTC (Gandhi et al., 2010; Greco et al., 2010; Xing et al., 2010).
These gene alterations can be detected in more than 70% of PTC cases.
In PTC from A-bomb survivors who were exposed to a radiation dose of more than 500 mGy, gene rearangements, including RET, NTRK1 and ALK genes, were frequently detected (Hamatani et al., 2008 and 2012).

Pathology

This PTC case developed from one A-bomb survivor exposed to radiation dose of 1.8 Gy showed moderately or well differentiated papillary structure with solid/trabecular-like architectures in several areas within cancerous regions.

Genes involved and proteins

ACBD5

Location
10p12.1

Protein
ACBD5 (acyl-coenzyme A binding domain containing 5)is a member of the acyl-Coenzyme A binding protein family, known to function in the transport and distribution of long chain acyl-Coenzyme A. This gene may play a role in the differentiation of megakaryocytes and formation of platelets. Seven spliced variants have been reported (RefSeq, July 2014).

RET

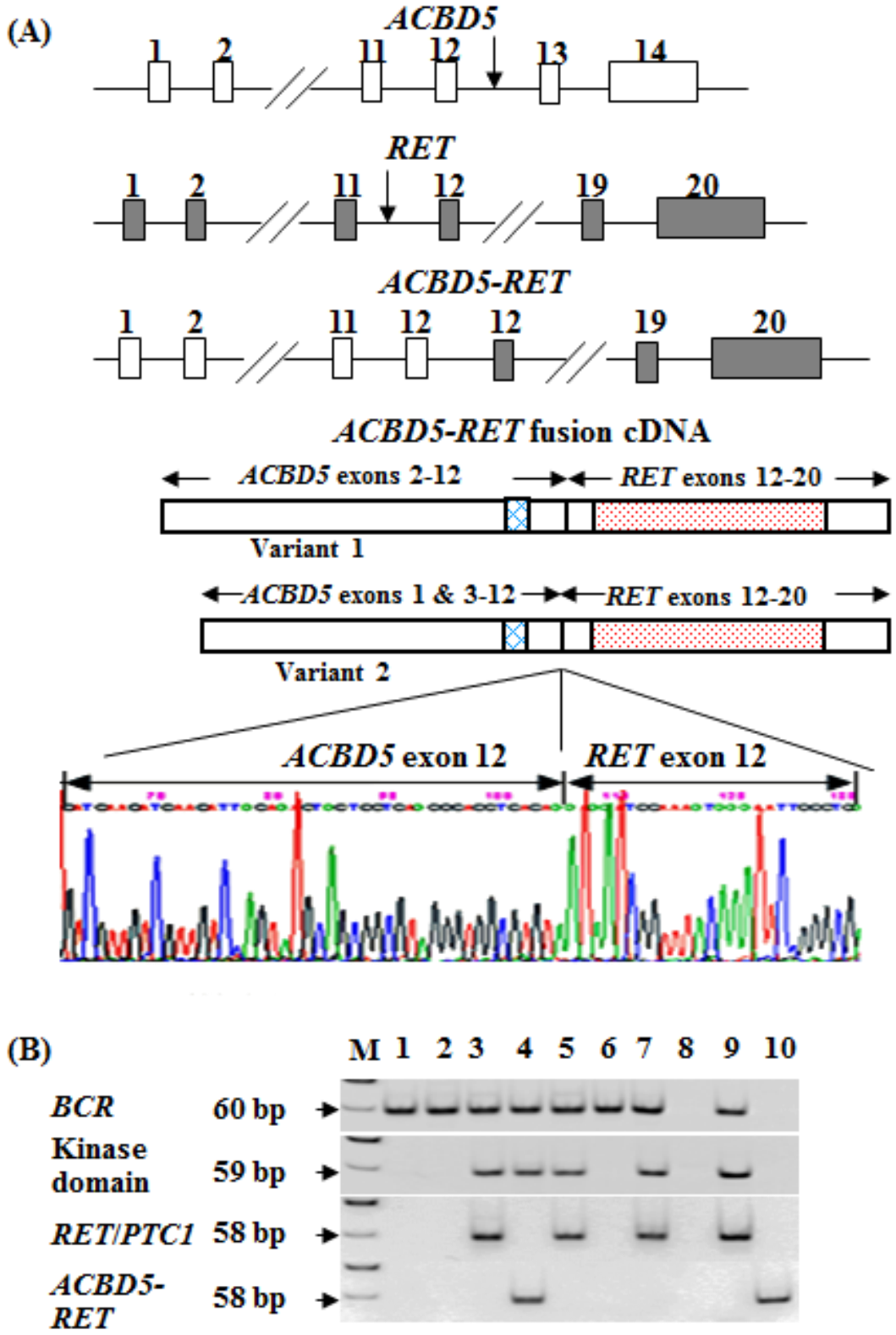
Location
10q11.2

Protein
RET is a tyrosine kinase receptor whose ligands are neurotrophic factors of the glial-cell line derived neurotrophic factor (GDNF) family, including GDNF, neurturin, artemin and persefin.
RET activation is mediated via different glycosyl phosphatidylinositol-linked GRF-receptors (Niccoli-Sire http://documents.irevues.inist.fr/bitstream/handle/2042/38039/10-2003-RETID76.pdf).

Result of the chromosomal anomaly

Hybrid Gene

Transcript
ACBD5-RET fusion traanscript was detected in an exposed PTC case. Exon 1-12 of ACBD5 gene located on 10p12.1 is fused to exon 12-20 of RET gene located 10q11.2 by pericentric inversion of chromosome 10.



A)The scheme of ACBD5, RET and ACBD5-RET gene, and predicted ACBD5-RET fusion cDNA as well as the cDNA sequence around the fusion point.Red and blue dotted boxes indicate tyrosine kinase domain and coiled-coil domain. (B)RT-PCR confirmation of ACBD5-RET fusion. Lanes 1, 2, and 6, PTC cases without rearranged RET; lanes 3, 5, and 7, those with RET/PTC1; lane 4, PTC harboring ACBD5-RET; lane 8, H2O for negative control; lane 9, cell line TPC1 harboring RET/PTC1; lane 10, the synthesized nucleotides for positive control of ACBD5-RET plus genomic DNA; lane M, DNA size marker(pUC19-MspI digest)(Hamatani et al., 2014).

Detection

A 102 bp cDNA fragment of ACBD5-RET containing the fusion point was detected by SMART RACE method with SMART adaptor-specific primer (5'-AAGCAGTGGTAACAACGCAGAGTA-3') and RET gene-specific reverse primer (5'-TCCGAGGGAATTCCCACTTT-3')(Hamatani et al., 2010).

Fusion Protein

Description

This fusion protein contains the tyrosine kinase domain of RET and coiled-coil domain of ACBD5 even if any variant of ACBD5 is fused to RET, since coiled-coil domain of ACBD5 gene is located on exon 10.

Oncogenesis

Tumorigenicity of ACBD5-RET fusion gene was indicated by an in vitro kinase assay and a in vivo tumorigenesis assay with nude mice (Hamatani et al., 2014). The tumorigenesis induced by ACBD5-RET fusion gene products would be due to the constitutive activation of tyrosine kinase of RET gene through the homodimerization of this fusion gene followed by the constitutive activation of MAPK pathway (Hamatani et al., 2014).

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