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Leukaemia Section

Short Communication

t(2;5)(p23;q35) SQSTM1/ALK

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Identity

Note

Not to be confused with the t(2;5)(p23;q35) with NPM1-ALK involvement.

Clinics and pathology

Disease

ALK-positive large B-cell lymphoma (ALK+ LBCL)

Phenotype/cell stem origin

One case to date, a 67-year-old male patient (Takeuchi et al., 2011).

Cytology

Anti-ALK immunohistochemistry showed a diffuse cytoplasmic staining pattern, in contrast with the nuclear and cytoplasmic pattern usually sen in the NPM1-ALK fusion gene/protein.

Prognosis

Complete remission was obtained, but the patient relapsed four months later.

Genes involved and proteins

ALK

Location

2p23

Protein

ALK is composed of an extracellular region (containing two MAM (meprin, A-5 protein, and receptor protein-tyrosine phosphatase mu) and one LDLa (low-density lipoprotein receptor) domains, and one glycin-rich region), a transmembrane domain, and an intracellular region (composed of a tyrosine kinase domain). Membrane receptor tyrosine kinase.

Germinal mutations

In familial neuroblastoma.

Somatic mutations

Fusion proteins in anaplastic large cell lymphoma, some diffuse large B-cell lymphomas, inflammatory myofibroblastic tumours, and some non-small cell lung cancers. Somatic mutations in sporadic neuroblastoma (review in Allouche, 2010).

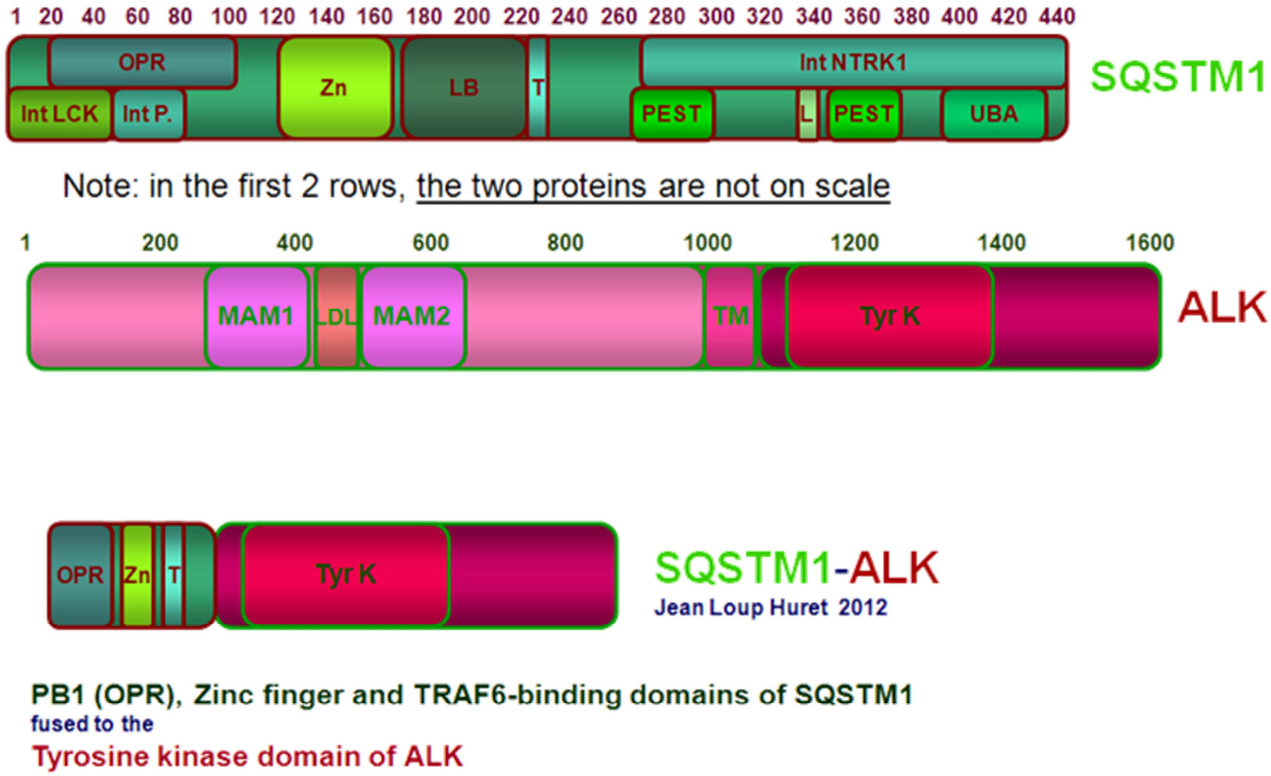
SQSTM1

Location

5q35.3

Protein

SQSTM1 (sequestosome1), also called p62, is a scaffolding protein with several interaction domains; it is composed of an OPR domain (octicosapeptide repeat (PB1 dimerization domain)), a Zn finger, a LIM protein-binding region, a TRAF6-binding motif, a PEST sequence (proline, glutamic acid, serine, and threonine rich), a LIR motif (LC3 interaction region, SGGDDDWTHLSS), a second PEST sequence, a KIR (keap1 interacting region), and an UBA (ubiquitin-associated) domain. Interacts with Caspase-8 and the apoptosis, machinery, MAPK kinases such as MAP2K5 (15q23), LCK (1p34), NBR1 (17q21), PRKCI (3q26), PAWR (12q21), RIPK1 (6p25), TRAF6 (11p12) and NTRK1 (1q23) and the NF-kappaB pathway, KEAP1 (19p13), GABARAPL1 (12p13), MAP1LC3A/LC3 (20q11), and ubiquitin. Mediates the interaction between TRAF6 and CYLD (16q12). Implicated in the activation of the transcription factor NF-kappaB.



Involved in the autophagy-lysosome pathway. Plays a role in the formation of cytoplasmic proteinaceous inclusions in various pathologic situations where autophagy is inactivated (Geetha and Wooten, 2002; Lamark et al., 2009; Moscat and Diaz-Meco, 2009; Moscat et al., 2009; Ichimura and Komatsu, 2010; Komatsu and Ichimura, 2010; Moscat and Diaz-Meco, 2011).

Germinal mutations

Mutated in Paget's disease of bone.

Result of the chromosomal anomaly

Hybrid gene

Description

Exon 5 of SQSTM1 fused to the ALK exon 20.

Fusion protein

Description

Fuses the PB1 dimerization domain of SQSTM1 to the tyrosine kinase domain of ALK, resulting in a constitutive activation of the ALK kinase domain.

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