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Cancer Prone Disease Section

Short Communication

Paget's disease of bone

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Identity

Other names
osteitis deformans

Inheritance
Autosomal dominant; polygenic.

Clinics

Note
A family history is found in approximately 15% of cases. In such families, the disease is inherited as an autosomal dominant trait with about 80-90% penetrance by the age of 70. About 50% of patients with familial PDB have a mutation in the SQSTM1 gene and in others there is linkage to a locus on chromosome 10p13 (Lucas et al., 2008). The gene responsible in this locus remains to be identified. There also may be familial clustering without a clear patten of inheritance consistent with polygenic inheritance. Common genetic variants at seven loci have been identified that predispose to Paget's disease (Albagha et al., 2011; Albagha et al., 2010), but the causal variants have not been identified. Overall relatives of patients with Paget's have 7-fold increase risk of developing the disease as compared with the general population.

Phenotype and clinics

The disease is characterised by focal bone lesions in which there is increased osteoclastic bone resorption coupled with increase and disorganised new bone formation (Ralston, 2013). The axial skeleton is predominantly affected. The most common sites are the pelvis, spine, femurs, skull and tibia. Many patients are asyptomatic and a common mode of presentation is with an abnormal serum alkaline phosphatase picked up on routine blood tests or an abnormal radiograph.
The most common complaint in patients who come to medical attention is bone pain. Other common complications include pathological fractures, bone deformity, deafness (when the base of the skull is involved), secondary osteoarthritis, and nerve compression syndromes (van Staa et al., 2002). Rare complications include hypercalcaemia which can occur if the patient is immobilised and dehydrated and high output cardiac failure due to increased blood flow through affected bone.

Neoplastic risk

The risk of osteosarcoma is increased and it has been estimated to occur in about 0.3% of patients (Mangham et al., 2009).
This represents more than one thousand fold increase in risk as compared with adults in the general population (van Staa et al., 2002). The osteosarcoma arises in affected bones.

Treatment

Paget's disease can be treated with bisphosphonates which supress the elevated bone turnover and can improve pain. Orthopaedic surgery may be required for the treatment of fractures, secondary osteoarthritis and spinal stenosis. Surgical excision and chemotherapy may be required for osteosarcoma.

Prognosis

Bisphosphonates are often effective at helping bone pain but it is uncertain at present if they alter the natural history of Paget's or prevent complications. The prognosis is poor for patients who develop osteosarcoma, even with agressive treatment (Sharma et al., 2005).

Cytogenetics

Note
No cytogenetic abnormalities have been identified in Paget's.

Cytogenetics of cancer

Multiple chromosomal abberations have been described in osteosarcoma, but none are specific for Paget's disease.

Genes involved and proteins

SQSTM1

Location

5q35

DNA/RNA

Note

The human gene contains 8 exons and spans 31.6 Kb of genomic DNA. There are three mRNA transcripts. The predominant transcript is NM_003900 which comprises 2923 bp. Two other transcripts have been identified. One (NM_001142298.1) of 2931 bp differs from NM_003900 in the 5' UTR, lacks a portion of the 5' coding region, and initiates translation from an in-frame downstream start codon compared to another variant 1. This results in an isoform with a shorter N-terminus compared to NM_003900. A third transcript (NM_001142299) of 2848 bp differs from NM_001142298.1 in the 5'UTR, but encodes the same protein isoform.

Protein

Description

The p62 protein contains 440 amino acids and has a mass of 47 Kda. It contains several domains, uncluding a TRAF-6 binding domain, a ubiquitin associated domain and SH2 domains.

Expression

Widely expressed in many cells and tissues.

Function

The p62 protein is an adaptor protein involved in NFkB signalling downstream of the RANK receptor, TNF receptor, IL-1 receptor and NGF receptor. In RANK signaling is responsible for recruiting CYLD to the intracellular receptor complex and this requires a functional UBA domain.

Mutations

Note

More than 25 mutations of SQSTM1 have been described in Patients with Paget's disease and most of these affect the UBA domain (Ralston and Layfield, 2012). Functional analysis indicates that most mutations impair the ability of the UBA domain to bind ubiquitin chains (Goode and Layfield, 2010).

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