

Human genetics of *SOST*

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Van Buchem disease and sclerosteosis

Van Buchem disease is a rare sclerosing bone dysplasia, first described by van Buchem et al. in 1955¹. It is also known under the name hyperostosis corticalis generalisata, and is classified among the craniotubular hyperostoses. Radiographic examination shows a generalized, progressive overgrowth and sclerosis of the skeleton. Typical features are an impressive thickening and sclerosis of the mandible and both the roof and base of the skull, often resulting in facial distortion. Facial nerve palsy, hearing disturbances, visual loss and neurological pain, caused by encroachment of the cranial foramina by hyperostotic bone, are frequently observed clinical complications. The clinical phenotype of sclerosteosis is often more severe and variable expression of congenital hand malformations and raised intracranial pressure, sometimes leading to sudden death, is observed¹.

Both conditions are observed with an equal sex distribution, and the prevalence is very low. Only about 40 cases of van Buchem disease and less than 100 sclerosteosis patients have been reported. The prevalence of sclerosteosis has been estimated at 1 in 75,000 in the South African population, where the incidence is the highest, and at least 1 in every 140 Afrikaners is a carrier of the disease-causing mutation.

Gene localization

Both conditions are inherited in an autosomal recessive mode. We were able to find 11 Van Buchem patients in a small ethnic isolate in The Netherlands allowing gene localization by homozygosity mapping. This led to the assignment

of the disease causing gene to chromosome 17q12-q21². By studying two families with several sclerosteosis patients and also from inbred populations, we were able to show that the gene underlying this condition is located in the same chromosomal region³. This obviously corroborated the hypothesis, based on clinical and radiological similarities, that both conditions are allelic as due to mutations in the same gene.

Gene identification and characterization

As a final result of a large genomic cloning and sequencing effort of the candidate region, a previously unknown gene was identified as the disease causing gene, currently known as the *SOST* gene^{4,5}. *SOST* is a two-exon gene and encodes sclerostin, a 213 amino acid propeptide with a calculated molecular weight of 24 kDa including a signal sequence for secretion and two putative N-glycosylation sites. Based on amino acid sequence similarity, sclerostin belongs to the DAN subfamily of secreted proteins containing a cystein knot motif.

Thus far, five different disease-related sequence variants have been described. Three nonsense mutations, Q23X, W124X and R126X, have been found in respectively South African, Brazilian and American patients with sclerosteosis^{4,5}. The Q23X nonsense mutation present in the South African sclerosteosis patients leads to lack of sclerostin expression in bone. Introduction of this premature stop codon, however, does not result in increased degradation of mRNA. We anticipate that the two other nonsense mutations, W124X and R126X, similarly result in abolition of protein expression. Furthermore, two splice site variants, IVS1+3 A→T and IVS1+1 G→C, were identified in respectively sclerosteosis patient from Senegal^{4,5} and two German siblings diagnosed with the milder van Buchem disease⁶. Both IVS1+3 A→T and IVS1+1 G→C are likely to affect splicing of *SOST*. An *in vitro* splicing assay for the IVS1+3 A→T mutation showed that this variant results in the use of a cryptic splice site located 214 bp downstream of the authentic site introducing an in-frame stop codon and resulting in strongly reduced transcript processing.

However, no mutation was found in the *SOST* gene of the Dutch van Buchem patients but a genomic deletion down-

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stream of *SOST* was found in these patients^{7,8}. This 52-kb deletion contains at least one long-range enhancer specifically regulating gene transcription in bone⁹. Absence of this enhancer results in complete lack of sclerostin protein in bone biopsies of van Buchem patients.

Conclusion

Van Buchem disease and sclerosteosis are confirmed to be allelic disorders as both are shown to be due to loss of function of sclerostin protein albeit by a different molecular mechanism.

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