Mandibuloacral dysplasia (MAD) is a rare autosomal recessive syndrome characterized by mandibular hypoplasia, delayed cranial suture closure, dysplastic clavicals, abbreviated and club-shaped terminal phalanges, acroosteolysis, and atrophy of the skin of the hands and feet, and typical facial changes. The syndrome is also associated with lipodystrophy and clinical features of metabolic syndrome such as insulin resistance, glucose intolerance, diabetes mellitus and hypertriglyceridemia.

About 40 patients have been described in the literature, of which nearly half have abnormalities in body fat distribution. It is however likely that lipodystrophy in patients with mandibuloacral dysplasia is under-reported.

Our team has described two patterns of lipodystrophy in patients with MAD; (i) type A pattern characterized by fat loss from the upper and lower extremities with normal or slight excess in the neck and truncal regions and (ii) type B pattern with more generalized fat loss and it is characterized mainly by a prematurely aged appearance and bone abnormalities. Loss of fat layers under the skin occurs mainly in the extremities, face and trunk in type B.

**Genetic Basis**

Patients with MAD frequently have partial lipodystrophy and insulin resistance, and the disease is caused by mutations in the LMNA gene. The LMNA gene encoding two nuclear envelope proteins (lamin A/C) maps to chromosome 1q21. Mutations in Lamin A/C which is involved in the post-translational proteolytic cleavage of prelamin A to form mature lamin A have been reported in patients with mandibuloacral dysplasia. Patients with MAD and type A (partial) lipodystrophy have mutations in lamin A/C gene. Mutation in the zinc metalloproteinase (ZMPSTE24) mutations which is also involved in the proteolytic cleavage of prelamin A to form mature lamin A have been noted in patients with MAD and type B (generalized) lipodystrophy.
Initially, our lab reported compound heterozygous mutations in ZMPSTE24 gene in a Belgian woman who had severe MAD with type B lipodystrophy. Subsequently, in collaboration with other groups, we have reported 3 other patients with mutations in the same gene. Some patients with MAD due to ZMPSTE24 mutations have been observed to have focal segmental glomerulosclerosis. Complete loss of ZMPSTE24 protein function causes autosomal recessive “Restrictive dermopathy” characterised by intra-uterine growth retardation, tight and rigid skin with prominent superficial vessels, characteristic facial features, generalized joint contractures, enlarged fontanelle, dysplasia of clavicles, respiratory insufficiency and an enlarged placenta with short umbilical cord.

Some patients with mandibuloacral dysplasia have no apparent alterations in either the LMNA or ZMPSTE24 gene, suggesting the existence of other as yet unmapped loci for this disorder.

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