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A Review of the Type-1 Fibrillinopathies: Pathophysiology, Diagnosis and Novel Therapeutic Strategies

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Abstract

Type-1 fibrillinopathies are a family of connective tissue disorders with major clinical manifestations in the skeletal, ocular and cardiovascular systems. The type-1 fibrillinopathies are caused by mutations in the fibrillin-1 gene (FBN1), which encodes fibrillin-1, a large glycoprotein and a major component of the extracellular matrix microfibrils, providing both structural and regulatory support to connective tissues.

The type-1 fibrillinopathies have been associated with over 1800 unique mutations within the FBN1 and demonstrate a wide range of phenotypic variability. This, in conjunction with a number of other factors has impacted on the identification of genotypephenotype correlations, pathogenesis and diagnostic tests for this family of diseases, leaving many open-ended theories. Current standard of care relies heavily on surgical intervention and lifelong use of β-blockers to slow disease progression, with research focused heavily on antagonism of transforming growth factor β, which is known to be dysregulated in patients with FBN1 mutations.

Antisense oligonucleotides present a novel therapeutic strategy for the type-1 fibrillinopathies, by mediating the alteration of exon arrangement of both the normal and disease-causing mRNA transcripts, to re-establish the periodicity of fibrillin-1. The induced proteins, while internally truncated, should be homologous and thus be able to form multimer units. This treatment alone or in association with isoform switching, TGF-β antagonism or enhanced/inhibited protein degradation could facilitate the assembly of fibrillin-1 monomers into multimers and consequently a decrease in phenotypic severity.

This review presents a basic overview of the past and current knowledge about the spectrum of type-1 fibrillinopathies with a particular focus on Marfan syndrome, as well as presenting novel potential therapeutic strategies.

He type-1 fibrillinopathies are a family of heritable connective tissue disorders characterised by skeletal, ocular and cardiovascular abnormalities. Hese diseases are caused by mutations in the fibrillin-1 gene (FBN1) ,with over 1800 unique mutations, spread throughout the FBN1 sequence, described in the universal mutation database (UMD) .He majority of mutations described are missense mutations, however, insertions, deletions and splice site mutations have also been described .FBN1 is one of three distinct genes in the fibrillin family, along with fibrillin-2 and fibrillin-3, all of which share sequence similarities .

FBN1 is a large gene consisting of 66 exons spanning over 200 Kb .While exon 1 of FBN1 does not directly contribute to the translated product, the exon numbering system used in this review is based on the full 66 exon transcript (GenBank reference sequence NM_000138.4). He remaining 65 exons encode a 2871 amino acid preproprotein, which is cleaved, by the protease furin, into the large glycoprotein fibrillin-1 and the protein hormone asprosin .Fibrillin-1 is present in the majority of connective tissues and has both structural and regulatory roles. As a major structural element of microfibrils fibrillin-1 acts as a backbone to which other microfibril associated proteins bind [8,9], while also being essential for the stability of elastic fibres .He assembly of fibrillin into microfibrils is initiated immediately aier synthesis and secretion when fibrillin-1 monomers aggregate into multimer units, bound by disulphide bonds between the first 4 cysteine residues at the Nterminus .Heterodimers between fibrillin-1 and the

other fibrillin monomers have not been observed, suggesting that the proline-rich sequence at the N-terminus, unique to fibrillin-1, provides the specificit\ responsible for this binding

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