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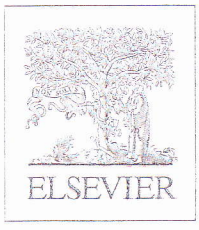

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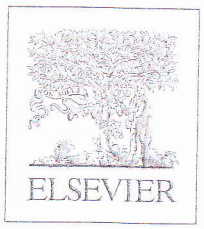

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Chapter 39

Hereditary gelsolin amyloidosis

SARI KIURU-ENARI[1]* AND MATTI HALTIA[2]

[1]*Department of Neurology, Unit for Neuromuscular Diseases, Helsinki University Central Hospital, Helsinki, Finland*

[2]*Department of Pathology, Haartman Institute, University of Helsinki, Helsinki, Finland*

INTRODUCTION

Hereditary gelsolin amyloidosis (HGA) is an autosomal dominantly inherited form of systemic amyloidosis, which was first described in 1969 by the Finnish ophthalmologist Jouko Meretoja (Meretoja, 1969). It is also known under a number of other designations, including Meretoja disease, gelsolin-related amyloidosis, amyloid polyneuropathy IV, familial amyloidosis Finnish (FAF), amyloidosis V (McKusick No. 105120), and corneal lattice dystrophy type II (Kiuru, 1998). HGA differs from the other types of familial amyloid polyneuropathies both clinically, pathologically, and biochemically. In its usual heterozygous form it is clinically characterized by adult onset of slowly progressive neurological, ophthalmological, and dermatological symptoms, most typically corneal lattice dystrophy, cranial neuropathy, and cutis laxa.

In 1990 two independent groups showed that the amyloid fibrils, deposited in the patients tissues, were composed of fragments of gelsolin generating AGel, a previously unknown amyloid protein (Maury et al., 1990a; Haltia et al., 1990b). In the very same year, these groups also discovered the primary cause of HGA, a mutation of the gelsolin gene in the patient's DNA (Levy et al., 1990; Maury et al., 1990b), paving the way for molecular genetic diagnostics (Haltia et al., 1992; Paunio et al., 1992) and a deeper understanding of the pathogenesis. At present, two disease-causing gelsolin gene mutations, namely G654A and G654T, are known in HGA (de la Chapelle et al., 1992b). Gelsolin is a ubiquitous calcium-activated, actin-modulating protein which has been implicated in multiple biological processes (Kwiatkowski, 1999; Bucki et al., 2008). Wild-type gelsolin has been linked to various diseases ranging from Alzheimer's disease, inflammation, and cancer (Spinardi and Witke, 2007) to muscle wasting in chronic conditions (Lee et al., 2010). However, HGA is the first and so-far only known disorder caused by a gelsolin gene defect.

After its original description by Meretoja in 1969, HGA soon turned out to be one of the most common inherited disorders among the Finnish population. New cases, probably mostly caused by independent mutations in various parts of the world, have been gradually reported from many other European countries as well as from North and South America and Asia (Fig. 39.1). HGA is probably still underdiagnosed worldwide, because its very slowly progressive symptoms usually cause marked incapacity first at an advanced age. Correct diagnosis is important because adequate symptomatic treatment decisively improves the quality of life of HGA patients, although specific/curative treatment is not yet available. However, recent identification of AGel generating enzymes (Chen et al., 2001; Page et al., 2005) and development of a murine HGA model (Page et al., 2009) represent important steps toward specific treatment of this slowly progressive but devastating amyloidosis.

EPIDEMIOLOGY

So far the majority of HGA patients have been reported from Finland (Kiuru, 1998). A marked geographical clustering of HGA was noted earlier in Southeastern Finland, especially in the districts of South Häme and Kymenlaakso (Meretoja, 1973a). This may well have resulted from a single ancestral mutation, as suggested by the genetic homogeneity (Kiuru, 1998) and the uniformity of disease-associated haplotypes in some families (de la Chapelle et al., 1992b; Paunio et al., 1995).

*Correspondence to: Sari Kiuru-Enari, Department of Neurology, Unit for Neuromuscular Diseases, Helsinki University Central Hospital, Haartmaninkatu 4, 00290 Helsinki, Finland. Tel: +358-9-471-72327, Fax: +358-9-471-71446, E-mail: sari.kiuru-enari@hus.fi