Hereditary systemic (non-neuropathic) amyloidosis, sometimes known as hereditary renal amyloidosis, first described by Ostertag in 1932, is characterized by extensive visceral amyloidosis which invariably involves the kidneys but, notably, spares the nerves. Clinical presentation is usually with features of renal disease, and the disease is frequently fatal within 10 years of diagnosis, although prognosis may be improved with supportive therapy such as dialysis. Although the disease was originally described more than 60 years ago, its molecular and genetic basis was not characterized until 1991. Since then, five amyloidogenic variants of apolipoprotein AI (apoAI), two variants of lysozyme, and four variants of fibrinogen $\alpha$-chain have been identified as the cause of the disease, which has an autosomal dominant pattern of inheritance. The mutant genes are highly penetrant, although phenotypic expression may vary, even among members of the same kindred. Heterogeneity was also observed in the timing and distribution of amyloid deposits, but the factors determining such variation in phenotypic expression remain unidentified. The molecular, genetic, biochemical, clinical, histological, and scintigraphic characteristics of all 16 kindreds in whom the disease has been fully characterized are reviewed here.

**Key words** Hereditary, Amyloid, Renal, Amyloidosis

**Introduction**

In 1932, Ostertag, a German pathologist, reported the first kindred with hereditary systemic (non-neuropathic) amyloidosis. Post-mortem examination of two brothers who died in their thirties with renal failure revealed extensive amyloid deposits in heart, kidney, spleen, and liver. Since then, several kindreds have been reported to have similar extensive visceral amyloid deposits. The pattern and severity of organ involvement may vary, but these families were identifiable by the invariable involvement of the kidneys and absence of neurological disease, distinguishing them from the more common hereditary neuropathic amyloidoses, subsequently described by Andrade in 1952. Therefore the term hereditary renal amyloidosis (HRA) is sometimes used to describe Ostertag type families with hereditary systemic (non-neuropathic) amyloidosis. The molecular basis of this disease was first characterized only in the 1990s, and since then 11 amyloidogenic variants of three circulating plasma proteins which are not normally amyloidogenic in humans have been described. The clinical, histological, biochemical, scintigraphic, and genetic characteristics of families with HRA in whom the disease has been fully characterized are reviewed here.

**Proteins associated with hereditary renal amyloidosis**

**Variant apolipoprotein AI (apoAI)**

The incidence of electrophoretic variants of apoAI is 1:1000 and although more than 20 amino acid substitutions, together with two frame shift mutations and one inversion, have now been identified, only a few are pathogenic, causing abnormal cholesterol metabolism and premature coronary artery disease (especially in homozygotes in whom apoAI may be completely absent from the plasma compartment) or HRA. In heterozygotes with HRA, the circulating levels of both variant and wild-type apoAI are low and could be due to accelerated catabolism of variant and, to a lesser extent, wild-type apoAI. Interestingly, all three amyloidogenic apoAI point mutations described thus far result in the substitution of a neutral residue by the positively charged arginine, and the more
complex deletion mutations also result in the acquisition of an extra positive charge in variant apoAI, suggesting that this structural change may play an important role in amyloidogenesis.

Kindreds with amyloidogenic apoAI variants typically have an extensive visceral amyloid load affecting heart, adrenals, gut, and, in particular, liver, spleen, and kidneys. Most patients present with hypertension, proteinuria, hematuria, chronic renal failure, and hepatosplenomegaly. The disease has an autosomal pattern of inheritance and penetrance appears to be complete in all patients studied thus far. However, the disease, which may present as early as the third decade, may vary in its course even among members of the same kindred, although it almost always terminates in end-stage renal failure (ESRF), necessitating renal replacement therapy with dialysis or renal transplantation. The clinical features are therefore very similar to those in the original description of the disease by Ostertag in 1932. The exception is the Spanish family with the apoAI deletion mutation in whom affected individuals presented with liver disease, and death was from liver failure, while renal function remained well preserved despite extensive interstitial amyloid.14

Histologically, the variants may be divided into two smaller groups according to the pattern of distribution of renal involvement by amyloid (Figs. 1–3). In kindreds with the Arg26 variant and the Spanish kindred with the deletion mutation (Fig. 1), only the renal interstitium was infiltrated with amyloid; in contrast, with the Arg60 (Fig. 2) and in particular, the Arg50 variants, only the glomeruli were severely affected, similar to the finding reported in the brothers reported by Ostertag. The reasons for localization of deposits to glomeruli or interstitium are not obvious, although it is interesting that other forms of systemic amyloidosis also usually affect only the glomeruli.23,24

Fig. 1. Immunoperoxidase staining of renal tissue of proband with hereditary renal amyloidosis (HRA) with apoAI deletion mutation demonstrating deposits localized to interstitium. ×100. From S.Y. Tan MD thesis51, with permission

Fig. 2. Renal section of a patient with HRA due to apoAI Arg60; stained with Congo red and viewed in polarized light, demonstrating nodular amyloid deposits confined to the glomeruli. ×40. From S.Y. Tan MD thesis51, with permission

Fig. 3. Renal section of a patient with HRA due to lysozyme His67; stained with Congo red and viewed in polarized light, showing widespread and diffuse infiltration of glomeruli and interstitium by amyloid. ×40. From S.Y. Tan MD thesis51, with permission

Variant lysozyme

Lysozyme is a ubiquitous bacteriolytic enzyme present in external secretions and in polymorphs and macrophages,25