

Review article

Inherited amyloidosis

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The amyloidoses are a group of deposition diseases in which the tissue deposits are composed of protein fibrils. These fibrils are the result of aggregation of specific precursor proteins into ordered structures which are resistant to proteolytic digestion and solubilisation. The ordered structure of the fibrils causes the deposits to be birefringent and, when histological sections are stained with Congo red, a characteristic green birefringence is seen by polarisation microscopy.

The amyloidoses can be classified into broad groups on the basis of distribution: (1) localised and (2) systemic (table 1). Both of these broad groups include hereditary and non-hereditary forms of deposition disease. Immunoglobulin (primary) amyloidosis is the most common form of non-hereditary systemic amyloidosis. In this disease the amyloid fibrils are composed of monoclonal immunoglobulin light chain molecules or degradation products of these light chains. Reactive (secondary) amyloidosis is usually seen in association with chronic inflammatory diseases. The amyloid fibrils in this disease contain a degradation product of the acute phase serum protein SAA. Amyloidosis associated with chronic haemodialysis has fibres synthesised from  $\beta_2$ -microglobulin. While this type of amyloidosis is usually restricted to bones and joints, some systemic deposits may occur. The localised forms of non-hereditary amyloidosis include isolated amyloidosis of the genitourinary tract, isolated bronchopulmonary amyloidosis, lichen amyloidosis, most cases of Alzheimer's disease, the hyalinised islets of Langerhans in non-insulin dependent diabetes mellitus, and a number of others.

Familial amyloidotic polyneuropathy (FAP) associated with variants of plasma transthyretin (prealbumin) represents the most frequent form of inherited amyloidosis.<sup>1</sup> In these syndromes the amyloid fibril deposits contain the variant trans-

Table 1 Systemic amyloidoses.

Type	Chemical subunit
Immunoglobulin (AL)/primary	Ig light chains Kappa Lambda
Reactive (AA)/secondary Hereditary (AH)/FAP	Amyloid A Transthyretin Apo A1 Others
$\beta_2$ -microglobulin/dialysis	$\beta_2$ -microglobulin

thyretin and usually some normal transthyretin as well. FAP is not specific for the transthyretin variants, however. Recently it has been shown that FAP can also be caused by a variant form of apolipoprotein A1. The possibility of other protein variants causing FAP must be considered.

Localised forms of inherited amyloidosis can be caused by a number of protein variants. Hereditary cerebral haemorrhage with amyloidosis described as an autosomal dominant condition in Iceland is associated with Congophilic angiopathy in which the amyloid fibril deposits contain a variant of cystatin C ( $\gamma$  trace). Hereditary cerebral haemorrhage with amyloidosis of the Dutch type has now been shown to have Congophilic angiopathy in which the amyloid fibril deposits contain a variant of the Alzheimer  $\beta$  protein. Approximately 10% of Alzheimer's disease patients have an inherited form of the disease, but no definite protein mutations have yet been described. Medullary carcinoma of the thyroid is associated with amyloid deposits containing procalcitonin.

While recent advances in protein chemistry have given us more insight into the pathogenesis of the inherited amyloidoses, perhaps the best clinical approach to these syndromes is from the perspective of the type of neuropathy and related factors such as ethnicity, age of onset, and organ system involvement. The clinician's most frequent contact with inherited amyloidosis will be some form of FAP. While FAP is not a specific term, if the pattern of a patient's polyneuropathy is thoroughly evaluated, it will often lead to the correct diagnosis. Although there is considerable overlap, there are three basic categories of FAP: (1) symmetrical polyneuropathy

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starting in the lower extremities with progression proximally and association with autonomic neuropathy; (2) upper extremity neuropathy related to compression of the median nerve (carpal tunnel syndrome) followed by a more generalised, slowly progressive polyneuropathy with varying degrees of autonomic involvement; (3) little or clinically insignificant degree of sensorimotor neuropathy with varying degrees of autonomic dysfunction.

#### **Familial amyloidotic polyneuropathy type I**

As originally described by Andrade,<sup>2</sup> FAP-I starts in the lower extremities. First there are usually paraesthesiae and, not uncommonly, painful dysaesthesiae before numbness and progressive sensory loss occurs. Occasionally, however, a patient may be asymptomatic until he or she suffers painless injury to the feet or legs. It has been reported that amyloid neuropathy may be associated with dissociation of the sensory modalities such that early lack of discrimination of temperature sensation occurs. This finding, while not specific, may be an early clue to the diagnosis. The neuropathy progresses relatively rapidly to involve motor function with foot drop occurring early. Motor loss is progressive and walking becomes increasingly difficult. Many patients spend their final years in wheelchairs. The upper extremities become involved months to years after the lower extremity involvement starts and has essentially the same progression of paraesthesiae, dysaesthesiae, and motor loss. While fine manipulation suffers considerably, patients are usually able to attend to activities of daily living although often requiring adaptive devices. The upper extremity involvement does limit the use of prosthetic devices (canes, crutches) required to maintain ambulation. Carpal tunnel syndrome occurs in a fair number of patients with FAP type I, but is usually not the presenting feature. If it occurs early in the syndrome, carpal tunnel release may be effective in relieving dysaesthesiae in the hands, but often it occurs after significant infiltrative neuropathy has occurred. At this point median nerve decompression may have minimal effect on alleviating symptoms.

Autonomic nervous system involvement occurs in most patients with FAP type I. Orthostatic hypotension is common. Bowel involvement commonly gives alternating constipation and diarrhoea and can be severe with gastric retention and distension. This often leads to malnutrition and, in patients with minimal cardiac or renal involvement, malnutrition is a major factor in patients' death. Sexual impotence is common and occurs in the majority of males. Impotence occasionally can be the presenting feature in FAP-I and a patient may be referred from the urologist or the psychiatrist. Bladder retention can be another feature of FAP-I.

Rarely, patients with FAP-I may have cranial nerve

involvement with changes in facial features and the scalloped pupil deformity. This latter finding is probably the result of ciliary nerve involvement giving irregular constriction of the iris. It will be missed if the eyes are treated with a cycloplegic before examination. Occasionally, involvement of the laryngeal nerve will give hoarseness.

Anhidrosis can be a feature of FAP and, while not usually a clinically important feature, should be considered when patients are exposed to prolonged raised ambient temperatures.

The peripheral neuropathy of FAP-I often leads to foot ulcers which can give chronic cellulitis and osteomyelitis. When the sensory neuropathy progresses much more rapidly than the motor neuropathy, Charcot joint may occur, especially in the knee. Vitreous deposits of amyloid occur in several types of FAP-I and may be the initial presenting feature. Indeed, some patients may have loss of vision without symptoms of peripheral neuropathy. In the FAP-I Portuguese/Swedish syndrome (methionine 30 transthyretin), vitreous deposits are seen in patients who present at an older age.

FAP-I is usually associated with a variant form of plasma transthyretin (prealbumin). It is an autosomal dominant condition and most patients are heterozygous for the variant transthyretin. Patients homozygous for two different variants (methionine 30 and isoleucine 122) have been reported, but show no clinical features to distinguish them from their heterozygous fellow sufferers. There are now 10 single amino acid variants of plasma transthyretin that have been found to be associated with inherited amyloidosis. The majority of these are associated with neuropathy of the FAP type I. The classical description is the methionine 30 variant which was originally reported in patients in Northern Portugal, but has subsequently been found to be the cause of amyloidosis in Swedish, English, and Japanese families.<sup>2</sup> It has also been described in Greece, Majorca, Cyprus, Turkey, and Brazil. The clinical features in patients with this mutation vary considerably from one family to another, but the peripheral neuropathy is usually of the FAP-I variety. The age of presentation can vary considerably. In Portuguese families the average age at onset is 32 or 33 years. In Sweden the average age of onset is 59 years. In the Portuguese patients progression of disease is over 10 to 15 years. Gastrointestinal, cardiac, and renal symptoms vary, but are the usual cause of death. In the Swedish population vitreous opacities are frequent.

The single patient with the isoleucine 33 transthyretin variant (Jewish) also had FAP-I. Severe gastrointestinal involvement was present. Onset of disease was in the late twenties and vitreous involvement was also a feature of the syndrome. The tyrosine 77 (Illinois/German) type of inherited amyloidosis is usually associated with an FAP-I neuropathy. The

proband of the original kindred had renal involvement, but his family also had members who died with cardiac disease. A French kindred with tyrosine 77 transthyretin amyloidosis has predominantly cardiac disease associated with a typical FAP-I neuropathy.

FAP-I is not always associated with variants of transthyretin. The neuropathy in an Iowa kindred described by Van Allen *et al*<sup>3</sup> in 1969 is typical of the type I variety. At that time, a high association of the syndrome with gastric ulcer led to a separate classification of FAP type III. Recently it has been shown that this syndrome is associated with a variant of apolipoprotein A1.<sup>4</sup> No transthyretin abnormality has been found in this kindred and the apolipoprotein A1 variant (arginine 26) has been shown to be associated with the syndrome over three generations. The amyloid deposits are composed of a truncated portion of the apolipoprotein A1 molecule containing the variant arginine 26 residue. No normal apolipoprotein A1 was present in the amyloid deposits of the one patient that was studied in detail. Renal failure has been the usual cause of death although several patients had perforated gastric ulcers late in the clinical course. Vitreous deposits are not a feature of this disease.

A number of kindreds with typical FAP-I have been described in which variants of transthyretin have not yet been found. There have been reports that normal transthyretin can cause amyloidosis, but this has not been conclusively proven at the gene level.

Two recently described forms of hereditary amyloidosis associated with transthyretin variants would appear to belong in the category of FAP-I neuropathy. These include the asparagine 90 variant and the cysteine 114 variant of transthyretin.<sup>5 6</sup> Both of these have a lower limb neuropathy. The Japanese patient with cysteine 114 was described as having significant autonomic involvement with decreased libido. Vitreous opacities were present in patients with both the asparagine 90 and cysteine 114 amyloidosis.

### Familial amyloidotic polyneuropathy type II

FAP type II was originally described in two separate kindreds of different origin: (1) a large Swiss family from Indiana and (2) a kindred comprising 11 different families of German origin living in the Maryland/Pennsylvania/Virginia area. FAP-II is characterised by the early onset of carpal tunnel syndrome which usually occurs around the age of 40, but may occur as early as the late 20s. Surgical decompression of the median nerve usually gives relief. The flexor retinaculum and surrounding tissues are infiltrated by amyloid deposits. A more generalised peripheral neuropathy starts later and progresses slowly. In the Indiana kindred this gives mild problems with walking in the later stages of the disease. In the Maryland/German families peripheral

neuropathy can give severe, generalised, painful dysaesthesiae as well as motor neuropathy. Bowel dysfunction with alternating constipation and diarrhoea are frequent, as is impotence. Orthostatic hypotension which occurs in the Indiana/Swiss kindred is more often related to the restrictive cardiomyopathy that all members of this kindred develop and which is the usual cause of death. Both syndromes usually occur at about the age of 40 and progress over a 15 to 20 year period. Restrictive cardiomyopathy occurs in the Maryland/German syndrome, but not with the frequency of the Indiana/Swiss, where all persons have the cardiomyopathy. Another distinguishing feature between the two syndromes is eye involvement. The Indiana/Swiss family has essentially 100% incidence of vitreous opacities whereas this is not a reported feature of the Maryland/German disease.

The Indiana/Swiss FAP-II is associated with a transthyretin variant having a serine for isoleucine substitution at position 84. This transthyretin variant has not been found in any other kindred so far. The Maryland/German FAP-II is associated with a histidine substitution at position 58 of the transthyretin molecule.<sup>7</sup> This has been found in other families with no definite connection to the original German kindred. The reason for the early development of carpal tunnel syndrome with these two mutations is not obvious. While the carpal tunnel syndrome does occur in other forms of FAP, the early appearance of the syndrome in the Indiana and Maryland families is a distinguishing feature which is helpful in diagnosis.

### Familial amyloidotic polyneuropathy without significant neuropathy

There are a number of inherited amyloidoses associated with variants of transthyretin which do not show clinically significant degrees of peripheral neuropathy. The alanine 60 transthyretin amyloidosis usually presents as restrictive cardiomyopathy. Peripheral neuropathy is usually present, but not of a clinically significant degree. The carpal tunnel syndrome may occur later in the course of the disease. Autonomic involvement is a greater feature and may result in constipation, diarrhoea, gastric distension, impotence, and bladder retention. The onset of this syndrome is usually after the age of 50 and many patients live to 70 or 80 years before dying of restrictive cardiomyopathy. Gene carriers have been known to reach the age of 90 without significant disease.

The methionine 111 transthyretin variant causes the cardiac amyloidosis originally described by Frederiksen *et al*<sup>8</sup> in 1962. At that time no neuropathy was reported and subsequent re-evaluation of patients in this kindred has not found evidence of peripheral

Table 2 Transthyretin amyloidoses.

Amino acid substitution	Position	Clinical name	Clinical feature	Kindreds
Methionine	30	FAP-I	LLN, bowel, AN, eye	Portugal/Japan/ USA/Sweden
Isoleucine	33	Jewish	LLN, eye	Israel
Histidine	58	FAP-II/Maryland	CTS, heart	USA/Maryland
Alanine	60	Appalachian	Heart, CTS	USA/West Virginia
Tyrosine	77	Illinois/German	Kidney, bowel, LLN	USA/Illinois
Serine	84	FAP-II/Indiana	CTS, heart, eye	USA/Indiana
Asparagine	90	Italian	LLN, eye	USA
Methionine	111	Danish	Heart	Denmark
Cysteine	114	Japanese	LLN, eye	Japan
Isoleucine	122	Senile cardiac	Heart	USA/Scandinavian

LLN=lower limb neuropathy. AN=autonomic neuropathy. CTS=carpal tunnel syndrome.

neuropathy. The isoleucine 122 transthyretin variant is also associated with restrictive cardiomyopathy without significant degree of peripheral neuropathy. This type of amyloidosis presents in older persons and has been called senile cardiac amyloidosis or senile systemic amyloidosis.

#### Other FAP syndromes

FAP type IV (Finnish) was originally described by Meretoja.<sup>9</sup> This syndrome is associated with lattice corneal dystrophy, which has little or no morbidity, and cranial neuropathy. Patients may develop systemic amyloid deposits. Recently these deposits have been found to contain a portion of plasma gelsolin.<sup>10</sup> No specific mutation has been reported for this autosomal dominant condition.

#### Amyloid proteins

Hereditary amyloidosis is most frequently associated with variants of plasma transthyretin, the product of a single copy gene on chromosome 18 (18q11.2-q12.1) (table 2). The gene has four exons which code for the 127 amino acid residue mature protein and an 18 residue signal peptide. The first exon codes for the signal peptide and the first three amino acids of the mature protein. No mutations in this exon have been reported. Exon 2 codes for amino acids 4 to 47 and contains two defined point mutations associated with amyloidosis (methionine 30 and isoleucine 33). Exon 3 contains five point mutations associated with hereditary amyloidosis (histidine 58, alanine 60, tyrosine 77, serine 84, asparagine 90). Exon 4 contains an additional three point mutations reported to be associated with hereditary amyloidosis (methionine 111, cysteine 114, and isoleucine 122). The molecular mass of the transthyretin monomer is 14 500, but in plasma transthyretin is a homotetramer (55 kd) having four units which are non-covalently bound. The monomer shows extensive  $\beta$  structure with eight  $\beta$  pleated sheets arranged in two parallel planes. Two

monomers associate to give a dimer having eight  $\beta$  strands in each of two planes. Two dimers non-covalently bond to give the circulating tetramer. This extensive  $\beta$  structure is probably why prealbumin has such a tendency to form the  $\beta$  amyloid fibrils.

Transthyretin has two known functions. It binds thyroxine in a central channel of the tetramer and is responsible for about 20% of plasma thyroxine binding in humans. Transthyretin also associates with retinol binding protein and presumably transports retinol without loss of the small RBP (21 000 daltons) molecule through the kidney. Variants of prealbumin which have not been found to be associated with hereditary amyloidosis include serine at position 6, threonine at position 109, and methionine at position 119.

Apolipoprotein A1 is part of the HDL complex and is not projected to have extensive  $\beta$  structure. However, the first 55 residues of the 83 residue amino terminal fragment that is found in the Iowa type of hereditary amyloidosis is predicted to have mostly  $\beta$  pleated sheet structure. The gene for apolipoprotein A1 is on chromosome 11 and is linked to apolipoprotein C. Pathogenic mechanisms in this type of amyloidosis may be similar to reactive amyloidosis where serum amyloid A (SAA) is partially degraded to a 76 amino acid moiety, which becomes the building block of amyloid fibrils. SAA is also a part of HDL and indeed may displace apo A1 from the HDL particle. SAA does not cause amyloid deposits in peripheral nerve and there have been no point mutations in SAA, which have been reported to give reactive amyloidosis a hereditary nature.

The gene for gelsolin exists as a single copy on chromosome 9. It codes for a circulating protein which has a mass of 93 000 daltons.<sup>11</sup> Only a 9000 molecular weight fragment which must be from the middle of the molecule is deposited in the amyloid deposits of the Finnish type (FAP-IV). Gelsolin is an actin binding protein which may be involved in dissolution of actin. Two separate proteins, one intracellular and one extracellular with an additional

25 amino acid residues on the amino terminus, are the products of the same gene with different transcription start sites.

Proteins which are associated with localised forms of inherited amyloidosis include cystatin C, which is a protease inhibitor, and also the  $\beta$  protein of Alzheimer's disease, which may also be a protease inhibitor.  $\beta$  protein is coded on chromosome 21 and only the carboxy terminal 42 amino acid residues are incorporated into amyloid fibrils.

### Detection of gene carriers

The hereditary amyloidoses are an excellent example of molecular genetics in medicine. The use of molecular biology to identify genetic mutations which directly relate to clinical syndromes has made a basis for in depth studies on pathogenesis. In addition, the use of molecular biology techniques to identify gene carriers of the many different variant alleles has vastly expanded the scope of the clinical approach to these diseases.

The inherited amyloidoses are all delayed onset and autosomal dominant. The ability to detect gene carriers has not only been of value in genetic counselling and diagnosis, it has also allowed the recognition of inherited diseases which have less than complete penetrance or develop at a very advanced age. It has allowed analysis of differences in clinical syndromes in different ethnic groups where the identical mutation is found.

Since the complete genomic structure of the transthyretin gene is known, it has been relatively easy to develop methods to detect the various variant alleles. Most of the mutations in transthyretin that are associated with amyloidosis have resulted in changes in the restriction enzyme pattern of the transthyretin gene (table 3). This originally allowed the development of tests for these genes using standard Southern analysis with radiolabelled probes. More recently, the development of enzymatic amplification of genomic

segments using the polymerase chain reaction has allowed development of more rapid testing.<sup>12</sup> In this method, specific oligonucleotide primers are used to amplify each of the relatively short exons of the transthyretin gene. Restriction enzymes can then be used to detect the mutant allele associated with amyloidosis. Since we now have 10 different mutations associated with transthyretin amyloidosis, the clinician must have some preliminary information to ask for the appropriate test. First, if the patient with neuropathy belongs to a kindred in which the specific mutation has been previously identified, the appropriate test can be requested. If the patient does not have such a history, then the clinician must use knowledge of the hereditary amyloidoses to proceed with the diagnosis. Since amyloidosis is usually diagnosed by biopsy, appropriate staining with anti-transthyretin antibody can usually identify the transthyretin nature of the amyloidosis and exclude non-hereditary forms and hereditary amyloidoses resulting from other proteins such as apolipoprotein A1 or gelsolin. Unfortunately, immunohistochemistry is not completely specific in all cases. If a patient is suspected of having a transthyretin type of familial amyloidotic polyneuropathy, it is important to know the ethnic origin of the patient and the pattern of neuropathic involvement (type 1 versus type 2 neuropathy). For example, if a patient is Portuguese and has a typical type 1 neuropathy, then the first test to be done is for the methionine 30 gene. This would involve amplification of exon 2 and restriction analysis of the amplified product with the restriction enzyme *NsiI*. If a patient presents with carpal tunnel syndrome, the first test might be for the serine 84 transthyretin allele or the histidine 58 allele. Both of these mutations are in exon 3 of transthyretin. If these tests are negative, the next most appropriate mutation can be pursued. Once the appropriate mutation is found, the patient's family can easily be screened for that particular mutation. While most of the transthyretin variants can be detected by restriction enzyme analysis on PCR products, some of the disease alleles do not give changes in restriction enzyme pattern. For this reason, allele specific analysis has been developed in which amplification of genomic DNA only occurs if the mutation is present. In this test, which is used for the histidine 58 mutation, an oligonucleotide primer is made such that the mutation is at the 3' end of the oligonucleotide. Only in the presence of the point mutation will the primer anneal appropriately and give amplification. This test may be necessary for the cysteine 114 mutant which also does not change the restriction pattern.

Similar testing has been developed to detect the arginine 26 mutant of apolipoprotein A1 in the Iowa type of hereditary amyloidosis. In this test a specific oligonucleotide with the 3' mismatch gives amplification only in the presence of the variant allele. People

Table 3 Direct DNA tests.

Variant	Mutation	Restriction enzyme
<b>Transthyretin</b>		
Met 30	G→A	<i>NsiI</i>
Ile 33	T→A	<i>BclI</i>
His 58	T→A	None*
Ala 60	A→G	<i>PvuII</i>
Tyr 77	C→A	<i>SspI</i>
Ser 84	T→G	<i>AluI</i>
Asn 90	C→A	<i>SphI</i>
Met 111	C→A	<i>DdeI</i>
Cys 114	A→G	None*
Ile 122	G→A	<i>MaeIII</i>
<b>Apo AI</b>		
Arg 26	G→C	None*

\*Use allele specific PCR.

with two normal apo A1 alleles do not show any amplification and therefore are not gene carriers.<sup>13</sup>

### Genetic counselling

The inherited amyloidoses are autosomal dominant diseases as would be expected with a structural gene defect. The majority of persons with transthyretin amyloidoses are heterozygous, having one normal allele and one variant allele of transthyretin. A few patients who are homozygous for the methionine 30 transthyretin allele have been described but with no more severe disease than those who are heterozygotes. Since this is a single copy gene and one mutant allele predicts the disease, each offspring of an affected person has a 50% chance of receiving the allele and therefore developing the disease. Since hereditary amyloidosis is a delayed onset disease, most subjects have already had their children before development of clinical symptoms. Development of the direct DNA tests has now allowed detection of gene carriers before having children and therefore presumably might give more effective genetic counselling. So far this has not shown a definite effect on marriage patterns or family planning. Even prenatal testing, which is now available and which has been done for two of the different mutations, has not been used as a method to prevent transmission of the mutant alleles. It would appear that subjects with the transthyretin amyloidosis are not as concerned with transmission of this delayed onset disease as one might project. On the other hand, the ability to test persons at risk for a mutant gene and determine that they are free of the disease allele can be of considerable psychological benefit. One benefit from recognition of the inherited nature of familial amyloidotic polyneuropathy and the ability to test subjects for the disease allele is in the realm of diagnostic medicine. If a person is shown to have a gene for amyloidosis, that person may be protected from misdiagnosis and therefore not be treated for immunoglobulin or reactive amyloidosis when that is not appropriate. Also, patients with transthyretin restrictive cardiomyopathy are frequently misdiagnosed and treated as for other forms of heart disease.

### Therapy and future prospects

At the present time there is no specific therapy for any form of hereditary amyloidosis. Since the diseases are the result of point mutations which cause amino acid substitutions in structural proteins, some mechanism of altering gene expression would be necessary to prevent the disease at the genetic level. As we understand more about the biochemistry of proteins such as transthyretin, other measures may be used to alter the biochemistry and therefore the formation of fibrils which cause the disease. Of particular impor-

tance may be the understanding of why some subjects with a particular mutation develop the clinical syndrome much later than others with the exact same mutation. Studies on the serine 84 transthyretin has indicated that amyloid fibril deposition does not occur at a young age and progress to a clinical threshold amount. It would appear that fibril synthesis and deposition is indeed a delayed phenomenon involving other biochemical mechanisms and not gene expression.

Although there are no specific therapies for inherited amyloidoses, modern medicine has much to offer to the person afflicted with these diseases. Neuropathic symptoms may be alleviated in large part by medicines such as amitriptyline. Physical therapy and adaptive devices may prolong a person's functional life and feeling of well being. A few patients with end stage renal disease have received transplants or renal dialysis or both. Cardiac disease may be treated with artificial pacemakers for conduction defects and medicines which alleviate symptoms of restrictive cardiomyopathy. Surgical removal of vitreous deposits has restored sight to many subjects with amyloid eye involvement. Hopefully, more specific therapy for these syndromes will be developed as more insight into pathogenesis is obtained.

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