HEREDITARY VITREOPATHY

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SUMMARY

Heterogeneity has long been recognised within the spectrum of inherited vitreo-retinal disease but the extent of the variation has been less easy to quantify. This has been compounded by the small size and numbers of pedigrees available for study, and the phenotypic variation both within and between pedigrees. *Formation abnormalities in the vitreous architecture* have, in the past, been eclipsed by classifications based on general skeletal and morphological differences. Stickler syndrome is the commonest disorder within the spectrum of hereditary vitreous abnormalities and many of the recent published advances relate to this. Stickler syndrome has been subclassified on the basis of vitreo-retinal phenotype: type 1 families with a characteristic congenital vitreous anomaly show linkage without recombination to markers at the COL2A1 locus; type 2 families with different congenital vitreo-retinal phenotypes are not linked to COL2A1. A recent report identifies the COL11A2 mutation in a Dutch pedigree with systemic features of Stickler syndrome but without ocular involvement. Others have implicated COL11A1 in a type 2 Stickler syndrome pedigree *with* ocular abnormalities. Both COL11A1 and COL11A2 are expressed in cartilage, but on the basis of studies of bovine vitreous it is likely that only the α1(XI) chain encoded by COL11A1 is present in vitreous. This would be consistent with the hypothesis that mutations in the genes encoding collagen XI can give rise to manifestations of Stickler syndrome, but of these, only mutations in COL11A1 will give the full syndrome including the vitreo-retinal features.

Recent advances in molecular genetic analysis have contributed notably to the understanding of inherited defects of collagen synthesis.[1–12] Since fibrillar collagens form the main structural component to vitreous, application of these techniques has gone some way to help resolve the genetic heterogeneity of inherited vitreous disorders. Nevertheless, clinical diagnosis is not the exact science that our laboratory colleagues would wish it to be and the clinician continues to play a difficult and vital diagnostic role prior to laboratory investigation.[5]

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THE SPECTRUM OF INHERITED VITREOUS ABNORMALITY

Wagner Syndrome

In 1938, Wagner described a new ocular disease in a three-generation pedigree from the Kanton of Zurich with 13 affected individuals.[13] It featured autosomal dominant inheritance, low myopia (−3.00 dioptres (D) or less), fluid vitreous, cortical cataract and inconstant and variably affected dark adaptation. No affected individual suffered a retinal detachment.

In a follow-up study of Wagner's original pedigree,[14] 10 further affected individuals were identified. The cardinal features noted were the complete absence of the normal vitreal scaffolding and preretinal, equatorial and avascular greyish-white membranes. Clear lenses in childhood developed anterior and posterior cortical opacities in puberty and cataracta complicata during the fourth decade. Dark adaptation was found to be practically normal. Retinal detachment did not occur.

More recently Wagner's original pedigree has been linked to genetic markers on chromosome 5q13–14, which is strong evidence against it being allelic with Stickler syndrome[15] (see below).

Marshall Syndrome

Marshall described a single pedigree with 7 affected individuals which he tentatively classified as 'ectodermal dysplasia with ocular abnormalities and hearing defect.'[16] The pedigree showed dominant inheritance, normal stature, hair and nails but sweating diminished to 75% of normal. All were myopic (range −3.25 to −20 D) with fluid vitreous and congenital cataracts which underwent spontaneous and sudden maturation. Two patients had lens subluxation and one patient had retinal detachment, at the age of 43 years, following severe

trauma. Two of the 7 had micrognathia; the rest have quite prominent chins but the most striking facial feature was absence of the nasal bones producing a short nose with a very flat nasal bridge, anteverted nares and a long philtrum.

Erosive Vitreoretinopathy

This recently described autosomal dominant disorder is characterised by an erosion or translucence of the retinal pigment epithelium (RPE) exposing underlying choroidal vessels. Seventy-three per cent of the original pedigree suffered rhegmatogenous retinal detachment and 50% of these were bilateral. More severely affected patients are distinguished from those with Stickler syndrome by attenuation of retinal vessels and a denuded or scalloped atrophy of the RPE with late pigmentation in a bone spicule fashion. The final fundal appearance may mimic choroideraemia. Also in contrast to Stickler syndrome there are no known associated systemic abnormalities.[17] Further evidence to distinguish erosive vitreoretinopathy from Stickler syndrome is provided by a recent molecular genetic study linking it to chromosome 5q13–14.[15]

Stickler Syndrome

In 1965 Stickler *et al.*[18,19] published their description of hereditary progressive arthro-ophthalmopathy. Information was drawn from a five-generation pedigree with 11 affected members. The features were autosomal dominant inheritance, congenital progressive high myopia and total, and usually bilateral, rhegmatogenous retinal detachment occurring in the first decade of life. This was without trauma and due to a 'very large retinal disinsertion' which would now be classed as a true giant retinal tear.[20] Additional systemic features were a degenerative arthropathy characterised by pain with overuse, joint hypermobility and destruction of the articular cartilage surface. Joint spaces were unusually wide and showed nonconformity with each other. Broadening of metatarsal and metacarpal heads was noted which was not thought to be due to joint disease but moreover to be a cause of the premature articular surface degeneration.

Clinical manifestations were very variable even within Stickler's original family – although one patient had extreme myopia and joint hypermobility, there remained 6 myopic individuals without any evidence of joint disease. A follow-up paper[19] documented degenerative joint disease of the thoracic and lumbar spine and also sensorineural deafness in the proband and mother. Although not commented upon, Stickler *et al.* included a profile photograph showing a rather short nose with flattened nasal bridge and anteverted nares together with micrognathia.

There remained considerable controversy between those who believed that some of these syndromes were one and the same and those who did not[21] (Tables I, II). Baraitser[22] described a single family previously diagnosed as Marshall syndrome by Keith *et al.*[23] showing cleft palate, retinal detachment and joint swelling suggestive of Stickler syndrome. Three single case reports of 'Marshall syndrome' all showing features of Stickler and Weissenbacher–Zweymuller syndromes were documented by Winter *et al.*[24] However, one of these patients had a completely normal ocular examination and another had 'extensive vitreous detachments'.

Ayme and Preus[25] attempted to answer the question of whether splitting of the Marshall and Stickler syndromes was justified at a phenotypic level by examining the published reports available on 18 patients with clinical descriptions, photographs and radiographs. Using cluster analysis of 53 signs they concluded that there was clear evidence to support two distinct phenotypes.

Weissenbacher and Zweymuller Syndrome

Weissenbacher and Zweymuller[26] described a male neonate with the Pierre Robin sequence and chondrodysplasia. Subsequent growth and intelligence were normal.[27] Kelly *et al.*[28] also reported such a neonate with first-degree relatives with Stickler syndrome, and others[29,30] provide further evidence of similarity between the two syndromes. From the published evidence available there seems no good reason to suggest that Weissenbacher–Zweymuller syndrome is anything other than neonatal expression of Stickler syndrome. Schreiner *et al.*[31] go further still, recommending in every case of Pierre

Table I. The Wagner/Stickler controversy

Author	Year	Study type	No. of pedigrees	No. affected	Syndrome heterogeneity
Maumenee[87]	1979	Clinical	Variable	39	Yes
Nielson[45]	1981	Clinical	1	2	No
Liberfarb *et al.*[39,40]	1981, 1982	Clinical	22	70	No
Godel and Lazar[47]	1982	Clinical	1	2	No
Weingeist *et al.*[48]	1982	Clinical	12	47	Yes
Billington *et al.*[38]	1985	Clinical	23	23	No
Spallone[46]	1987	Clinical	12	39	No
Francomano *et al.*[88]	1988	Genetic	7	?	Yes[a]
Fryer *et al.*[93]	1990	Genetic	1	9	Yes

[a]Includes Wagner's original pedigree.

Table II. The Marshall/Stickler controversy

Author	Year	Study type	No. of pedigrees	No. affected	Syndrome heterogeneity
Baraitser[22]	1982	Clinical	1	3	No
Winter *et al.*[24]	1983	Clinical	3	3	No
Ayme and Preus[25]	1984	Literature review	Variable	18	Yes
Stratton *et al.*[102]	1991	Clinical	1	2	No

Robin syndrome, roentgenograms of the patient and close relatives to identify those patients with Stickler syndrome.

Kniest Syndrome

Kniest syndrome[32] is likely to be confused with Stickler syndrome only in the neonatal period.[33] Classically, Kniest dysplasia is an autosomal dominant disorder characterised by kyphoscoliosis, severe short trunked dwarfism, cleft palate, flat face, hearing defects (sensorineural or conductive) and joint contractures.[34] Deformity increases with age and stature is markedly reduced.[33] This contrasts with the normal growth and development in Weissenbacher–Zweymuller syndrome.[27] The differential diagnosis at birth of short-trunked dwarfism is between spondyloepiphyseal dysplasia congenita, metatropic dwarfism and Kniest's dysplasia.[34]

The myopia is congenital, of high degree and non-progressive, but with myopic disc changes. The vitreous shows a 'translucent retrolental mass with a crinkled membrane attached only to peripheral retina'[34] and is associated with lattice degeneration and 'white without pressure' in the peripheral retina.

Nance–Sweeney Syndrome

The oro-facial characteristics of Nance–Sweeney syndrome have led some workers to consider this disorder[35] in the differential diagnosis of Marshall/Stickler syndrome.[29] An autosomal recessive inheritance pattern and absence of myopia and vitreous abnormality are sufficient for exclusion.

Cervenka Syndrome

The combination of dominantly inherited myopia, retinal detachment and submucous cleft palate was described by Cohen *et al.*[36] and called Cervenka syndrome as Cervenka had previously described a family with similar features. Hall[30] reports a three-generation pedigree with Cervenka syndrome indicating that the neonatal and adult features are indistinguishable from Weissenbacher–Zweymuller or Stickler syndrome and that all three represent the same dominant disorder of connective tissue.

OPHTHALMIC FEATURES OF STICKLER SYNDROME

Refractive Error

Myopia is common in Stickler syndrome, of varying degrees and often severe with an incidence of 75–85%.[37–40] Although progressive myopia has been noted in Stickler's original pedigree, in type 1 Stickler syndrome (see below) it is usually of early onset, high degree, non-progressive and not associated with pathological disc changes.[41,42] Congenital axial myopia of high degree has been reported in Stickler syndrome patients examined within the first 2 months of life.[43] Myopia is not a prerequisite for diagnosis, with 20% of type 1 Stickler syndrome patients being emmetropic or hyperopic.[42] Nevertheless, many of these patients still show increased axial lengths on ultrasound, so that the term congenital megalophthalmus syndrome has been introduced.[44]

Anterior Chamber Drainage Angle Anomalies

The true incidence of developmental drainage under anomalies in Stickler syndrome is difficult to quantify. Nielson[45] described drainage angle abnormalities in two brothers with Stickler syndrome consisting of prominent iris processes and hypoplastic iris root with anterior stromal defects. Spallone[46] identified a similar finding in his series, also showing a high incidence of ectopia lentis. Other workers did not identify any developmental drainage angle abnormalities,[47–49] and in some series no raised incidence of glaucoma of any type was found.[37]

Cataract

Cataract is a common finding in Stickler syndrome, the quoted incidence varying from 30% to 80% according to the age range of the patients studied. In one series only 12% of patients over 50 years of age had clear lenses but most series for all ages seem to be in fairly close agreement with an incidence of approximately 45–50%.[38–40,46,48–52]

Although Marshall described ectopia lentis in two patients in his original paper this has not been a feature of any subsequent accounts other than that of Spallone,[46] who reported this finding in 12.8% of patients.

The most comprehensive study on cataract in Stickler syndrome was that by Seery *et al.*[50] Attention was drawn to the highly characteristic 'wedge' or 'fleck' cataracts of these patients accounting for 43% of all cataract types. The strong association between the 'bird', 'wedge' or 'semilunar' cataract and Stickler syndrome has been noted by others.[44,48]

Vitreous

Abnormalities of vitreous structure have long been regarded as the ophthalmic hallmark of Stickler

syndrome. Optical emptiness, liquefaction, vitreous bands and syneresis are common descriptions but contribute little to the understanding of the pathogenesis and even imply a degenerative and progressive disorder. Scott[41,44] was the first to report the congenital vitreous anomalies pathognomonic for subgroups of these patients.

A large number of these pedigrees have now been studied. The criteria for diagnosis have been established[53] and the pedigrees sub-classified on the basis of vitreo-retinal phenotype. Type 1 families with a characteristic congenital vitreous anomaly show linkage without recombination to markers at the COL2A1 locus,[53] type 2 families with different congenital vitreo-retinal phenotypes are not linked to COL2A1.[53,54]

The exact biochemical and pathological nature of the type 1 congenital vitreous anomaly remains unknown. A glial cell origin has been suggested on the basis of cilia, microvilli and cytoplasmic filaments.[55] 'In frame' deletions of entire exons[56] do not alter the reading frame of mRNA or the ability of shortened procollagen chains to participate in trimer assembly. It is not known what elements regulate maturation of normal proteins, but there is abundant evidence that abnormal proteins are retained in the rough endoplasmic reticulum (RER) if they are not folded into a native or near-native conformation within the RER.[57,58] The protein is not transported out of the RER and remains as membrane-limited inclusion bodies. Formation of correctly folded quaternary structure within the RER constitutes a key event that regulates transport of the protein to the Golgi apparatus. Certain structural or conformational features of a protein may be compatible with transport to the Golgi apparatus from the RER, but not for subsequent transport to the cell surface.[58]

By random assortment, three-quarters of procollagen trimers will consist of heterotrimers (normal and abnormal chains) and will be unstable and not secreted. The remaining quarter will be made up homotrimers (normal or abnormal chains, one-eighth each) which might be expected to have normal stability and secretion (Figs. 1, 2). This intracellular

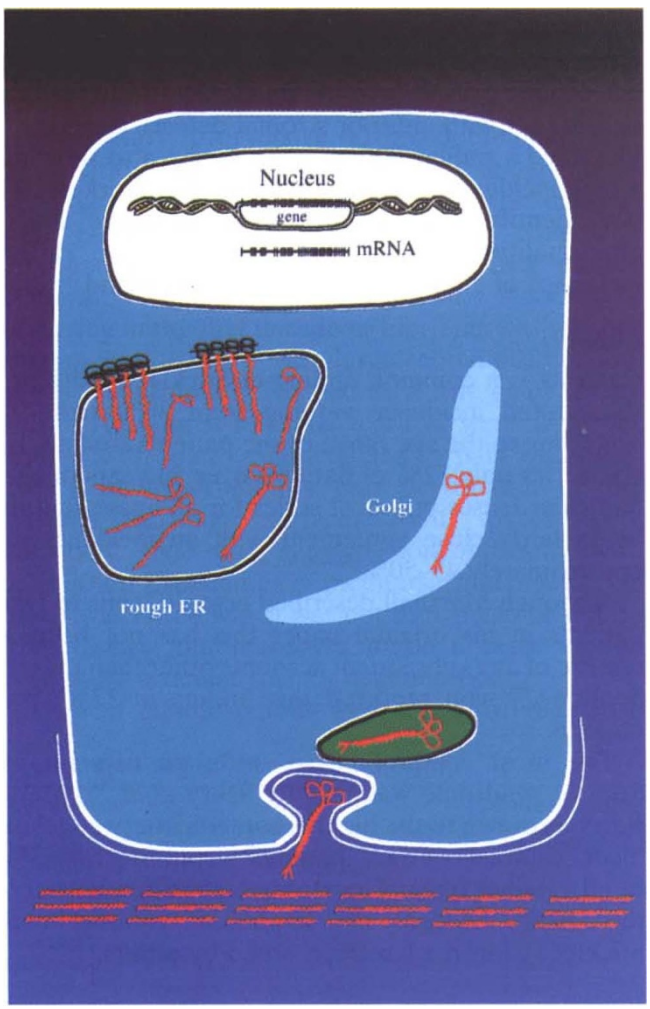

Fig. 1. *Normal production of type II vitreous collagen.*

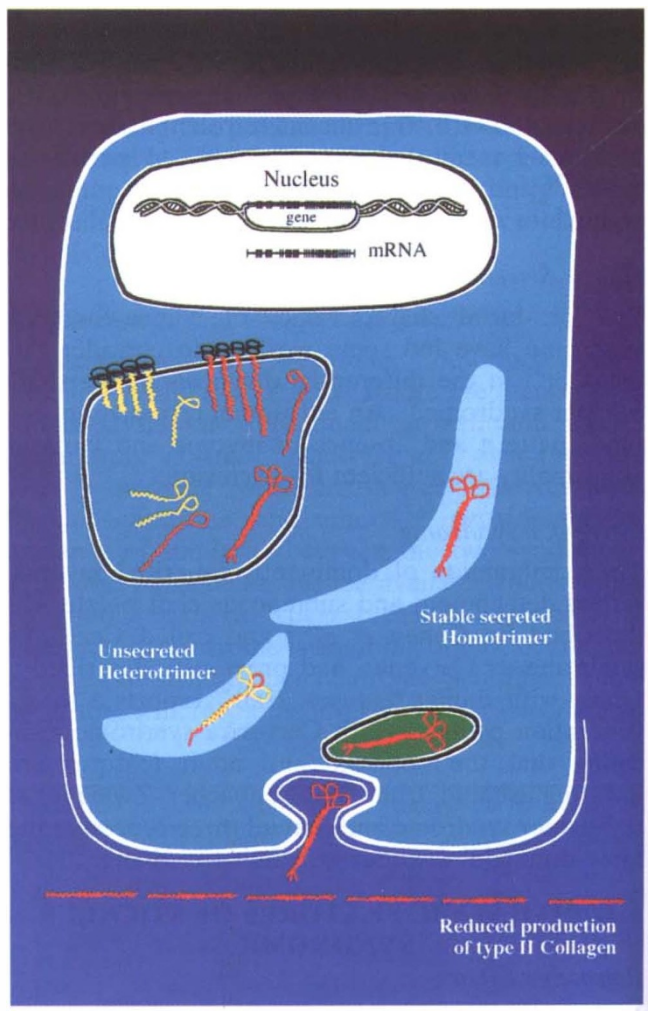

Fig. 2. *Type 1 Stickler syndrome: proposed reduction of type II vitreous collagen.*

'constipation' with unsecreted abnormal type II collagen chains has been demonstrated using α1(II) antibodies in electron microscopic studies of cartilage in SEDC with a G–T transversion causing an exon 20 skip within COL2A1.[59] It is likely that these abnormal proteins are subsequently removed by non-lysosomal pathways.[60,61]

Other workers[62] have shown by *in situ* hybridisation techniques that the mRNA 'signal' in the developing avian eye for type II and IX collagen is strongest in the future ciliary and pars plana region, suggesting that this is the main area of collagen production during embryogenesis.

Combining these two concepts of reduced secretion in this region would be consistent with the clinical appearance – an apparently vestigial reduced vitreous gel occupying the immediate retrolental space, posterior to which there is no discernible collagen gel structure at all. It is also possible that this disorder gives us an important insight into the embryology of normal vitreous development.

In contrast, type 2 Stickler patients do not show the retrolental vitreous anomaly. The type 2 vitreous gel architecture is *also* congenitally abnormal but with apparently very limited and random fibrils coursing through the entire posterior segment space. This may be associated with areas of localised, or even complete, posterior hyaloid membrane separation.

Retina

Rhegmatogenous retinal detachment is the most serious ocular complication of Stickler syndrome. There is a propensity for giant retinal tear formation in childhood[38,41] but a wide variety of retinal breaks have been noted. Younger patients tend to have very little lattice degeneration, and pigmentation, when present, is minimal.[41] The incidence of retinal detachment varies between series (reflecting specialty referral patterns) and ranges from 10% to 48%.[38,50,51,63] The reason why patients with Stickler syndrome are so susceptible to retinal detachment and particularly giant retinal tear is unknown. There is no association between retinal detachment and the presence of wedge or fleck cataract.[50] Weingeist *et al.*[48] alluded to possible structural anomaly both within the vitreous and between the neurosensory retina and RPE predisposing these patients to retinal detachment even in the absence of clinically identifiable 'retinal degeneration'.

Abnormalities in the electroretinogram have been related to the severity of myopia.[50] Those with severe myopia can show a marked decrease in amplitude of the scotopic b-wave, although these findings are not uniformly substantiated with modern standardised techniques.

Young *et al.*[64] reported vascular abnormalities in a pedigree associated with thrombotic glaucoma. Spallone[46] subsequently reported similar vascular abnormalities in the temporal retinal periphery causing leakage and exudate. In conjunction with the ectopia lentis unique to his series amongst the many reported, it is possible that his series represented a separate subgroup.

NON-OCULAR FEATURES OF STICKLER SYNDROME

Rheumatology and Generalised Skeletal Complex

Many musculoskeletal abnormalities have been described in Stickler syndrome. Slender extremities, hyperextensibility of peripheral joints and normal height characterise the body habitus.[65] Fusiform swellings of the proximal interphalangeal joints and hyperextensibility of the knees and elbows are also usually present and may be assessed objectively using the Beighton scoring system.[66] The characteristic joint hyperflexibility of youth gives way to a degenerative arthritis affecting the major weight-bearing joints in middle life.[65,67] The articular manifestations can be extremely variable both within and between families. Weingeist *et al.*[48] found that very few patients had joint laxity greater than would be expected in the general population, in contrast to almost universal radiological abnormalities. The radiographic changes were variable and mild: 'radiologists . . . frequently fail to report them'.[48]

Cardiology

The increased prevalence of mitral valve prolapse in several connective tissue dysplasias such as Marfan's syndrome, Ehlers–Danlos syndrome and pseudoxanthoma elasticum prompted Liberfarb and Goldblatt[68] to evaluate mitral valve function in 57 Stickler syndrome patients. The diagnostic criteria are not clearly specified and mitral valve prolapse was found in 45.6%. As a result of this study, they and others[33] have recommended screening all patients for valvular disease and advise antibiotic prophylaxis prior to surgery. A more recent study did not identify significant valvular disease in any of over 100 affected type 1 or type 2 Stickler syndrome patients and as a result routine echocardiography and antibiotic prophylaxis has not been adopted.[42]

Otology

In Marshall's original report[16] progressive nerve hearing loss was a prominent feature and hearing problems are frequently reported in patients with Stickler syndrome.[19,22–25,46,49,69]

There are two main causes for this. The first is that the association with cleft and high arch palate leads to a elevated incidence of glue ear and serous otitis media causing a conductive hearing deficit which may be treatable. In some patients a mild conductive

element persists because of ossicle defects.[33] The second is due to an associated sensorineural defect.

The pathogenesis of the sensorineural defect in Stickler syndrome patients remains to be confirmed. Experimental evidence would suggest cartilage maldevelopment of the inner ear.[70,71] Whether this mirrors the facial, mandibular and external auditory developmental delay evident in these patients is unknown and the frequency of true progression is difficult to ascertain. A cross-sectional study[72] did not support a correlation between hearing loss and orofacial abnormality.

The prevalence of hearing dysfunction in Stickler syndrome varies enormously between different series from 6% to 87%.[40,48,72] Whatever the true incidence, there seems little doubt that the combined auditory and visual deficit in some of these patients can provide a formidable developmental challenge.[73]

Cleft Palate

The association of retinal detachment and cleft palate was noted prior to the description of hereditary arthro-ophthalmopathy.[74] Others have confirmed the strong association of midline clefting in up to 80% of Stickler syndrome patients.[46,48,75,76] Shreiner *et al.*[31] go further, advocating radiological examination for all Pierre-Robin patients to exclude Stickler syndrome. Whether this is a dependable means of screening for Stickler syndrome remains open to serious doubt. Others[48] have advised against routine radiological screening, arguing that only a low percentage of Pierre-Robin cases are due to Stickler syndrome.[77]

Physiognomy

Differentiation based on facial morphology has been extremely difficult to quantify. Marshall syndrome has been said to exhibit a rounded face with a flat nasal bridge and a normal chin whilst Stickler syndrome shows a long face, normal or prominent nasal bridge and retrognathia.[25] In other series, a long philtrum and flattened nasal bridge were found in three-quarters of Stickler syndrome patients.[40] Facial roentgencephalometry has been employed to examine facial development, showing highly characteristic features of Stickler syndrome[78] allowing correct identification in over 80% of cases. Others[48] have failed to demonstrate abnormal bony facial development using lateral cephalometric radiographs even though clinically the faces appeared unusually flat in profile. The improved facial development from infancy to 3 years has been dramatically illustrated[33] and it is possible that facial development (in contrast to vitreous development) is merely delayed rather than arrested.

COLLAGEN AND COLLAGEN GENETICS

Collagens are defined as proteins that: (a) contain several repeats of the amino acid sequence Gly–X–Y in which the X position is frequently proline and the Y position is frequently 4-hydroxyproline and (b) have the potential for three chains with such repeat sequences to fold into a characteristic triple helix.[3] Collagen is the major macromolecular protein of most connective tissues.[1–3] The various collagen types form a family whose members share the common feature of three polypeptide chains which are folded into a rod-like triple helical molecule about 300 nm long and only 1.5 nm in diameter. Each of the constituent chains of the triple helix is called an α chain and is coiled in a left-handed helix with three amino acids per turn. These constituent amino acids are regularly arranged in the order Gly–X–Y such that glycine, which is the smallest of all amino acids, occupies the restricted space in which the three α helical chains come together. This is crucial for the stability of the macromolecule. The stability of the triple helical conformation is also dependent on the cyclical amino acids proline and lysine which limit rotation of the polypeptide 'backbone'. Collagen molecules lacking hydroxyproline are able to fold into triple helical structures at low temperatures but the helix is unstable at body temperature.[6]

During biosynthesis, mature mRNA is transported to the cytoplasm where translation occurs on the ribosomes of the RER. Chain initiation and elongation proceeds from the carboxy-terminal (C-terminal) to the amino-terminal direction.[6] During and shortly after elongation nearly all prolyl residues in the 'Y' position are enzymatically hydroxylated by prolyl 4-hydroxylase. Several 'Y' position lysine residues are also hydroxylated by lysyl hydroxylase to form 5-hydroxylysine. Only chains that are in coil formation are substrates for this modification, which lags behind chain synthesis by about 200–300 residues. The C-terminal propeptide of each chain folds on itself and is stabilised by interchain disulphide bonds. Individual chains associate via their C-terminal propeptides and the trimers are stabilised via interchain disulphide bonds. Once three chains have associated at their C-terminal ends the trimer propagates to the N-terminus facilitated by prolyl *cis*-isomerase. Once assembled the molecule is transferred to the extracellular space via the Golgi body. Once outside the cell, proteases cleave the N- and C-terminal extensions. The mature collagen molecules assemble into a fibrillar array (Fig. 1).

So far 19 collagen types have been identified, and designated by roman numerals I–XIX.[1,8] These collagen types are formed by trimer combinations of three polypeptide chains designated by arabic numerals. These chains may be the same or different,

so that the collagen molecule may depend on the products of one, two or three genes. There are over 30 different types of polypeptide chains. Human genes are written in upper case letters and non-human genes in lower-case letters.[8] For example:

Human type I collagen is a heterotrimer of two α1 chains of type I collagen and one α2 chain of type I collagen, i.e. $[\alpha1(I)]_2 + \alpha2(I)$.

Human type II collagen is a homotrimer of three identical chains of α1(II) collagen, i.e. $[\alpha1(II)]_3$.

A subclass of the collagen family comprises types I, II, III, V, XI which form banded fibrils and have therefore been called the 'fibrillar' collagens to distinguish them from other collagens unable to aggregate into these highly ordered fibrils.[79] The major fibrillar procollagens, that is, types I–III, are characterised by an uninterrupted triple helical domain flanked by C- and N-terminal non-collagenous domains. The triple helical region is connected to the non-collagenous N-terminal domain by a short region called the N-telopeptide.[8] The N-telopeptide provides the substrate for an N-propeptidase, resulting in cleavage in the extracellular matrix (Fig. 1).

Type II collagen is found chiefly in cartilage, vitreous and nucleus pulposus.[80] It is secreted as individual procollagen molecules into the extracellular matrix where the N- and C-propeptide terminals are cleaved. This allows the trimer molecules to assemble and stabilise by covalent crosslinks and prevents intracellular deposition of collagen.[1,2] The formation of the intermediary procollagen possibly also increases the efficiency of the monomer folding.[1,2]

The gene encoding type II collagen has been cloned[4,81,82] and localised by a variety of methods[83] to 12q13.14 and has been called COL2A1.[84] It has 54 exons[85] which are numbered from the 5′ to 3′[86] and exon numbers, if not size, are highly conserved both within the triple helical domain and also in the N–Y and C-propeptide regions.[86]

MOLECULAR GENETIC ANALYSIS IN STICKLER SYNDROME

The association of the grouped vitreous and articular abnormalities in Stickler syndrome at the suggestion of Maumenee,[87] led Francomano *et al.*[88] to examine and subsequently establish linkage between COL2A1 and Stickler syndrome. Other workers had already shown that excessive breakdown of normal type II collagen was unlikely to be a factor.[48] Using Southern blot analysis of a *Hind*III restriction fragment length polymorphism (RFLP), linkage was established in two Stickler syndrome pedigrees at lod scores of 3.29 and 0.3 giving a Z_{max} of 3.59 at zero recombination. However, no clinical data on the patients were included.

The work of Francomano *et al.* did not necessarily mean that type II collagen was faulty in Stickler syndrome, but that the gene encoding it, or one nearby, was a likely candidate in their two families. As a landmark, it generated great interest in the genetic association of COL2A1 and Stickler syndrome. Other workers followed with variable results. Schwartz *et al.*,[89] again using Southern RFLP analysis, excluded COL2A1 in a Wagner syndrome pedigree and also excluded COL2A1 in two of four Stickler syndrome pedigrees. Further evidence[90] to support the separate entities of Wagner and Stickler syndromes was soon to follow. Linkage analysis carried out on the original Swiss pedigree described by Wagner demonstrated recombinant events between the mutation and COL2A1 markers thereby excluding type II collagen mutations as the cause of this disorder. More recently Wagner's original pedigree has been linked to 5q13.14.[15]

Vintiner *et al.*[91] in a study of six Stickler syndrome pedigrees likewise showed crossovers between COL2A1 and the disease locus in two pedigrees. There were three possible explanations for these results:

1. Stickler syndrome was only loosely linked to COL2A1, the real gene at fault being nearby.
2. There had been intragenic crossovers between their markers and the site of mutation in both their unlinked pedigrees.
3. In spite of careful clinical examination which could not identify any clinical differences between linked and unlinked pedigrees, the syndrome was truly genetically heterogeneous with two or more separate loci responsible.

As COL2A1 encompasses only 30 kilobases, the likelihood of intragenic crossovers being so frequent is extremely low and makes the second explanation very unlikely. As COL2A1 would appear to be implicated in at least some Stickler syndrome families, Vintiner *et al.* concluded that the most likely explanation was that the syndrome was genetically heterogeneous.

The findings of other workers have reflected similar results, with COL2A1 being implicated in approximately two-thirds of cases and excluded by recombination between this locus and the disease locus in the remainder.[92,93]

Mutation Analysis

Following these initial linkage reports, and the rapid advance in DNA sequencing techniques for mutation screening, several workers were able to confirm COL2A1 mutations in some Stickler syndrome pedigrees.[85,94–96]

Ritvaniemi and co-workers[97] comment on the interesting and unusual nature of the mutations

described in Stickler syndrome. They reported a premature stop codon in exon 44, and note that this is the fourth such premature termination mutation described in Stickler syndrome whereas only one such similar termination mutation has been found in over 120 type I and type III collagen mutations. The possible association between this type of mutation and the Stickler syndrome phenotype thus emerged.

Pursuing the theme of Stickler syndrome showing an unusual bias for premature stop mutations, Kokko *et al.*[96] reported a patient with Wagner syndrome due to a substitution of the bulky amino acid aspartate for glycine in exon 10 of COL2A1 and postulated a possible link between the type of mutation manifesting either the Stickler or Wagner phenotypes. However, although the molecular genetic data presented are clearly defined, the clinical diagnoses and phenotype segregation on which their hypothesis rests remain highly questionable. Frequent retinal detachment and to a lesser extent cataract are ascribed to Wagner syndrome whereas, in fact, in Wagners original paper[13] no patient suffered a retinal detachment, 'cataracta complicata' was almost universal and myopia was in all cases less than 3 dioptres. From the data given in the paper by Kokko *et al.* there is no reason to believe that the patients suffered from anything other than Stickler syndrome.

Brunner *et al.*[10,98] have recently reported linkage to COL11A2 in a Dutch pedigree with systemic features of Stickler syndrome but without ocular involvement. Others have implicated COL11A1 in a type 2 Stickler syndrome pedigree *with* ocular abnormalities[99] by investigating linkage to other candidate genes in a large type 2 family with vitreo-retinal, articular, oro-facial and audiometric features of Stickler syndrome. A maximum lod score of 2.7 at zero recombination was obtained. Linkage to COL2A1, COL5A2, COL9A1, CRTL1 and COL11A2 was excluded. This mutation has now been identified as a glycine substitution.[100] Both COL11A1 and COL11A2 are expressed in cartilage, but on the basis of studies of bovine vitreous[101] it is likely that only the α1(XI) chain encoded by COL11A1 is present in vitreous. This would be consistent with the hypothesis that mutations in the genes encoding collagen XI can give rise to certain manifestations of Stickler syndrome, but of these, only mutations in COL11A1 will give the full syndrome including the vitreo-retinal features.

Although there is an apparent clinical correlation between not only the position, but also the type, of amino acid substitution in osteogenesis imperfecta and type I collagen mutations[6] the link in Stickler syndrome remains less well defined. The association with premature termination codons seems established[85,94] but the wide phenotypic variation *within* pedigrees (all presumably carrying the same mutation) and in particular the widely varying articular manifestations, have yet to be explained. The relationship (if any) between termination mutation site and vitreo-retinal phenotype is presently under investigation.

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Key words: Collagen, Marshall syndrome, Stickler syndrome, Vitreous, Vitreous anomaly, Wagner syndrome

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