The pathophysiology of keratoconus remains a mystery, but increased understanding may be on the horizon thanks to efforts of dedicated researchers and analytic advances in genomic medicine, said François Malecaze MD, at the 2nd EuCornea Congress.

“New molecular techniques are allowing new strategies for studying corneal dystrophies, and hopefully they will bring us closer to unraveling the cause of keratoconus,” said Dr Malecaze, professor of ophthalmology, University Hospital of Purpan, Toulouse, France.

Providing an update on keratoconus pathophysiology, Dr Malecaze noted that the development of keratoconus is thought to require the combination of genetic predisposition and environmental factors. However, there are different theories over whether the primary defect in keratoconus is biomechanical or biological.

According to the biomechanical theory, the characteristic corneal deformation of keratoconus is the result of abnormal distribution and orientation of collagen fibrils with loss of cohesion between collagen fibrils and non-collagenous matrix that allows interlamellar and interfibrillar slippage. Evidence to support this concept derives from studies by Meek and colleagues who used X-ray diffraction techniques to investigate the ultrastructure of the cornea. In addition, using second-harmonic imaging microscopy, Morishige et al. showed structural abnormalities in the organisation of the anterior corneal collagen lamella in eyes with keratoconus that are consistent with characteristic changes in collagen organisation and biomechanical properties. They also reported that relative to normal controls, keratoconic eyes had fewer fibres inserting into Bowman’s membrane, shortening of the lamellae that were present, and decreased interweaving of the lamina in the anterior part of the cornea.

Studies investigating possible biological defects in eyes with keratoconus show no significant differences in the composition or amount of stromal collagen in eyes compared with normal controls, and findings from studies investigating the concept that keratoconus develops as a result of increased matrix metalloproteinase activity leading to excessive collagen degradation are contradictory.

“Although it has been shown that the balance of enzymes in keratoconic corneas favours protein degradation, with an increase in matrix metalloproteinase-1 and decrease in tissue inhibitor of metalloprotease-1 (TIMP-1), the enzyme alterations did not co-localise with the lesional area of the cornea,” Dr Malecaze said.

It has also been proposed that the biological defect of keratoconus involves accumulation of abnormal proteoglycans and chondroitin sulfates, and various investigators have reported altered expression or structure of proteoglycans in eyes with keratoconus. However, these changes are thought to be secondary to the disease and not etiologic.

Genetics: Researchers investigating genetic associations for keratoconus have identified candidate regions in some chromosomes, although to date, individual genes have not been identified. However, rapid progress is expected in this area as researchers apply new methods of genetic analysis, Dr Malecaze said.

In a recently published paper, Dr Malecaze and colleagues reported on their findings from transcriptome and network biology analyses conducted to differentiate patterns of gene expression between normal corneas and those with keratoconus.

“This research represents the first genome-wide transcriptome analysis of keratoconic corneas...”