Short Communication
Volume 3:1, 2021

Journal of Surgical Pathology and Diagnosis

ISSN: 2684-4575 **Open Access**

A Short Communication on Structural Polymorphisms Observed in Exfoliation Syndrome Fibrils

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Abstract

Exfoliation syndrome is generally considered an age-related ocular disease that presents with a progressive accumulation of fibrillar aggregates in the human eye. A range of risk factors have been identified that are commonly associated with XFS, including a variety of cellular pathways. However, the exact mechanism of this disease is unknown. In contrast to existing literature, it was recently shown that a variety of structural features exist within these fibrillar aggregates associated with exfoliation syndrome. This hithertofore unknown diversity in fibrillar structures suggests that multiple pathways could exist that contribute to the progression of XFS. Herein, we address these recent findings on the diversity of structural polymorphism observed in fibrils isolated from the lens capsule of various XFS patients and situate this in the context of existing literature on fibrillar structure of these materials. These findings may help to reveal more about the biological functions leading to protein misfolding and aggregation into exfoliation materials.

Keywords

Exfoliation syndrome • Polymorphism • Fibrillar

Description

Exfoliation Syndrome (XFS) is an age-related systemic fibrillopathy with significant manifestations in the human eye where insoluble fibrillar aggregates (XFS materials) accumulate. These aggregates are mostly found on various structures of the anterior chamber such as the lens capsule and trabecular meshwork. XFS interferes with various ocular functions and is known to be associated with cataract formation and Exfoliation Glaucoma (XFG). Various risk factors associated with this ocular disease have been identified. A brief look into the literature shows that a vast majority of research has been focused on genetic risk factors, with LOXL1 likely to be the most studied gene. Since the discovery that LOXL1 variants are strongly associated with XFS and XFG, many studies have been conducted to replicate coding variants or to identify other genetic factors in diverse populations. Moreover, epigenetic factors and cellular pathways have also been implicated in the development of XFS [1]. However, the precise mechanism of this multifaceted disorder remains ill-defined.

Early electron microscopy studies revealed that XFS materials consisted largely of cross-banded fibrillar aggregates, which raised the possibility that XFS fibrils might have structural similarities with amyloid fibrils [2,3]. Upon further examination, using thioflavin dyes, XFS materials in human eye tissue sections showed an intense yellow fluorescence commonly associated with amyloid plaques [3-5]. Similarly, congo red staining of these tissues provided results suggestive of amyloid structures. Although congo red dichroism of XFS material has been observed for this system, it has not always generated consistent results [6,7] and has generally been observed to be variable through many studies of other systems [8, 9]. Furthermore, despite immunofluorescence studies showing selective binding of an anti-amyloid antiserum to XFS materials, because of the lack of high-resolution data, the amyloidogenic propensity of XFS-related proteins has not been widely studied or proven.

The importance of structural polymorphisms is that variations in the structure of fibrils are commonly thought to be a result of variations in biological factors underlying the development of disease [10]. Despite the importance of conformational diversity in understanding the pathomechanism of fibril-related diseases, research in this area has been largely overlooked for XFS. A number of decades after the discovery of XFS, several electron microscopy-based studies were conducted to analyse the structure of XFS fibrils, to investigate their origin, and to identify their distribution in various ocular tissues [11-14]. Later, a review classified XFS fibrils into two general types: type-A fibrils with diameter of 18-25 nm and length of 1 µm and type-B fibrils having diameter of 30-45 nm and length of ~0.4 µm [15]. However, to our knowledge, no study has specifically investigated or reported patient to patient structural variations or structural polymorphisms in general as a key mechanistic factor in XFS fibrils. This structural feature was recently investigated by our group [15].

Human lens capsules were collected from five XFS patients that underwent cataract surgery. Despite the small sample size, a broad range of diversity was observed in XFS fibrils, where certain types of fibrils having dominant morphological features were observed in different patients. Mature XFS fibrils exhibited structural variations in their overall morphology, cross-banding pattern, and helical twist. In terms of the cross-banding pattern, our analysis showed that some XFS fibrils did not exhibit any banding pattern in their ultrastructure or protofilaments, whereas other XFS fibrils showed a very organized banding pattern. Moreover, the observed periodic cross-banding was found to be present at the protofilament level as well, where clear repeating distances of ~7-8 nm was identified. This is in contrast to the two types of XFS fibrils that have been reported to date; one type with a periodic banding pattern of ~50 nm (more frequent) or ~25 nm (less frequent) and another type with less distinct periodic banding patterns, which are composed of microfibrils with diameters ranging from 3-7 nm or 8-10 nm having banding patterns every 10-12 nm.

Helical twist is a key characteristic of amyloid polymorphism, and this was identified, for the first time to our knowledge, as an indicator of polymorphism in XFS fibrils. Some samples showed a clear helical twist

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Received December 30, 2020; **Accepted** January 13, 2020; **Published** January 20, 2021

in fibrils; these helical pitches were not regular for all observed XFS fibrils. In addition to fibril polymorphism, a remarkable variation was identified at the level of protofilament structures, where a wide range of diameters was observed. This variation was also extended into the number of protofilament types in different samples, as some showed only one and others contained three different types of protofilaments with differing dimeters. It has been previously reported that mature XFS fibrils formed *via* lateral aggregation of protofilaments (with diameters ranging from ~5 to ~10 nm), however we found thicker protofilaments (e.g., ~20 or ~48 nm).

This view highlights the possibility of other mechanisms playing a role in forming mature fibrils. The importance of this study lies in the fact that the fibrillar aggregates associated with XFS were studied from a morphological point of view that was not conducted before and a broad range of structural polymorphism was identified even in such a small sample size. The observed morphological variations in XFS fibrils suggest potential diversity in phenotypes or clinical subtypes of XFS. This structural variation might arise from variations in the composition of fibrils which could be linked to different fibrillation precursors or fibrillation mechanisms in different patients. However, further structural analysis focusing on the core structure of XFS fibrils would be required to address this hypothesis. There is a need, therefore, for further biophysical and high-resolution observation of XFS fibrils, which could lead to valuable information about the mechanism of XFS development.

Conclusion

The patient-to-patient fibril polymorphism identified in XFS, illustrates the importance of further research needed in this area, and also demonstrates a need for deeper biophysical insight into the core structure of XFS fibrils. This approach could shed light on the biological and/or ocular environmental factors playing a role in the formation of fibrillar aggregates contributing to the development of XFS/XFG. It is also possible, as speculated in Alzheimer's disease-associated amyloid fibrils, that there may be a correlation between variations in fibril structure and variations in the severity or progression rate of the disease; structural studies would be essential to evaluate this possibility in case of XFS and XFG.

Acknowledgements

Other researchers involved in this study included Dr. Holger Wille, Sara Amidian, Vineet Rathod from the Department of Biochemistry and Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, AB, Canada, and Dr. Andrew Crichton from the Department of Ophthalmology, University of Calgary, Calgary, Canada.

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How to cite this article: Sharaf MG, Damji KF and Unsworth LD. "A Short Communication on Structural Polymorphisms Observed in Exfoliation Syndrome Fibrils." *J Surg Path Diag* 3 (2021).