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Review

Is pseudoexfoliation glaucoma a neurodegenerative disorder?

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Pseudoexfoliation (PEX) is a systemic age-related progressive disorder with ocular manifestations. The earlier stage of the disease, pseudoexfoliation syndrome (PEXS) involves deposition of white fibrillar aggregates on anterior and posterior eye tissues. It is also the cause of most common form of secondary glaucoma known as pseudoexfoliation glaucoma (PEXG). Studies in the past decade highlight the role of many genetic and environmental factors as the underlying cause of PEX pathogenesis. Latest research findings by various researchers and us present the view of PEX as a type of neurodegenerative disorder. Epidemiological studies have shown association of PEX with different forms of neurodegenerative diseases like Alzheimer's, age-related macular degeneration and open angle glaucoma. Also, sharing of common genetic risk factors, abnormal protein aggregation and most importantly, progressive degeneration of neurons with age are some of the identifiable features seen in both PEX and other neurodegenerative diseases. In this review, we have compared the pathological symptoms and factors involved in the disease manifestation of PEXG with various forms of neurodegenerative disorders and categorized PEXG as a progressive neurodegenerative disorder.

Keywords. Alzheimer's disease; extracellular matrix; glaucoma; neurodegenerative disorders; optic nerve head cells; pseudoexfoliation

1. Introduction

Pseudoexfoliation (PEX; OMIM: 177650) is an age-related systemic disorder with ocular manifestations characterized by accumulation of fibrillar protein aggregates called PEX fibrils on the tissue surfaces of anterior eye segment. It has also been seen on the posterior segment of eye tissues such as lamina cribrosa, peripapillary sclera and vitreous fluid (Ritch and Schlotzer-Schrehardt 2001). Clinically, PEX is diagnosed by using a slit-lamp to check the presence of PEX fibrils in the iris-pupillary margin and on the anterior surface of lens capsule. Figure 1 represents a classical form of PEX affected eye with PEX fibrillar deposition along the periphery of lens capsule. The early stage of the disease is known as pseudoexfoliation syndrome (PEXS) with no damage to optic nerve head (ONH) cells. The later severe form is called as pseudoexfoliation glaucoma (PEXG) that involves degeneration of cells in the ONH region and is a significant factor leading to open angle glaucoma (OAG) worldwide (Ritch 1994). Previous studies also have found the presence of PEX aggregates in non-ocular tissues (Amari *et al*. 1994). Demographic studies suggest PEX prevalence can vary from 0% in Eskimos to 38% in Navajo Indians (Shazly *et al*. 2011).

Progression of PEX leads to other ocular complications like zonular weakness, cataract formation, iris depigmentation, xerophthalmia, retinal-vein occlusion, lens subluxation and lens dislocation (Karagiannis *et al*. 2015). Earlier studies have shown that individuals with PEX have higher incidences of various neurodegenerative disorders (ND) (Reniewska *et al*. 2004). In this review, we have discussed the neurodegenerative aspect of PEX and compared its similarity and dissimilarity with other forms of neurodegenerative diseases.

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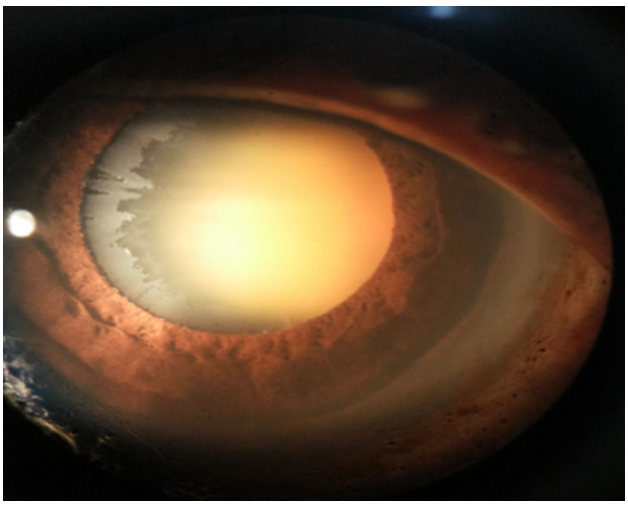

Figure 1. Representative PEX affected eye. A PEX affected eye is shown with deposition of PEX fibrils along the periphery of lens capsule. (Picture Courtesy: Dr. Pranjya P. Mohanty and Dr. Rohit Mendke).

2. Pseudoexfoliation and other neurodegenerative disorders

Earlier studies have reported the interrelation between PEX and the most common form of dementia, Alzheimer's disease (AD; OMIM: 104300). Accumulation of abnormal protein aggregates made up of amyloid-β-peptide and phosphorylated tau protein in the brain tissues results in the degeneration of brain neurons which are required for daily activity and leads to onset of AD. Reniewska *et al*. have shown evidence of patients with AD have more common incidence of PEX in Polish population and have suggested eye examination can be used for early diagnosis of AD (Reniewska *et al*. 2004). Further, two independent studies by Cumurcu *et al*. and Linner *et al*. consistently found a significant association between AD related dementia and PEX (Cumurcu *et al*. 2013; Linner *et al*. 2001). However, a 2-year based epidemiological follow-up study carried out in Swedish cohort didn't find a correlation between PEX and AD (Ekstrom and Kilander 2014).

In addition to AD, previous studies have also shown PEX as a major independent risk factor in the development of open angle glaucoma (OAG) (Schlotzer-Schrehardt and Naumann 2006). OAG is defined as a multifactorial optic neuropathy with a loss of optic nerve fibres and has shown to be a type of sensory neurodegeneration (O'Hare *et al*. 2012). Age-related macular degeneration (ARMD) is another common form of neurodegenerative disease with retinal degeneration and excess deposition of drusen (Kaarniranta *et al*. 2011). Independent studies have shown a significant epidemiological association between ARMD and PEX in population cohorts from Greece (Kozobolis *et al*. 1999), Iceland (Allingham *et al*. 2001) and India (Thomas *et al*. 2005).

3. Pathological alterations involved in PEX is analogous to neurodegenerative disorders

3.1 *Type of tissues and/or cells involved in PEX versus other neurodegenerative disorders*

In PEXG individuals, optic nerve degeneration is the consequence of damage to ganglion cells and inner plexiform layers in the posterior segment of the eye. Death of these cells gradually leads to loss of vision and ultimately to blindness. The severity of ONH damage corresponds to the amount of PEX material deposited on the surface of PEX affected posterior eye tissues. Studies on tissue structure from PEX affected eyes suggest cell loss leading to thinner cornea and decreased endothelial cell densities in comparison to control unaffected eye tissues (Tomaszewski *et al*. 2014). Further, cells in the anterior lens capsule from PEX show more affinity to trypan blue suggesting increased number of dead cells than in control subjects (Hosseini *et al*. 2011). PEXG affected individuals also show more advanced visual field loss, greater mean intraocular pressure (IOP) and poorer response to treatment (Ritch and Schlotzer-Schrehardt 2001). Studies have shown a significantly higher fluctuation in IOP in PEX affected eyes compared to control unaffected eyes (Tojo *et al*. 2016). Previous reports have also shown the optic nerve in AD affected individuals is highly susceptible to elevated IOP with a rapid progression in glaucomatous optic neuropathy compared to non-AD glaucoma affected individuals (Bayer and Ferrari 2002).

Similar to focal deposition of PEX aggregates in eye tissues, abnormal protein deposition in neurodegenerative disorders occurs in their relevant tissue of origin. In Alzheimer's Aβ-deposits accumulate throughout cortex including hippocampal regions and basal neocortex in the beginning stage while tau-deposits spread through connected neurons with accumulation in medial entorhinal cortex, lateral entorhinal cortex, and parasubiculum in an Alzheimer's affected brain (Liu *et al*. 2012). Likewise, Lewy-bodies in Parkinson's affected brain are found to be deposited in multiple-brain regions like substantia nigra, cerebral cortex, thalamus and amygdala (Braak *et al*. 2003). In ARMD,

the macula is the most affected part of the eye with excessive deposition of drusen (Ambati and Fowler 2012). Additionally, altered Bruch's membrane, retinal pigmented epithelium and degenerated photoreceptor cells are also affected with prominent deposition of drusen towards the end stage of the ARMD in these tissues (Ding *et al*. 2009).

Besides ocular tissues, PEX aggregates are also found to be deposited in the non-ocular tissues. Prominently PEX like aggregates are reported in the basement membrane and extracellular matrix of skin tissues (Streeten *et al*. 1990), in the wall of blood vessels (Mitchell *et al*. 1997) as well as in the connective tissues of visceral organs such as lung and heart (Streeten *et al*. 1992). Hence, PEX is labelled as a systemic fibrillopathy disorder with primary ocular manifestations (UM Schlotzer-Schrehardt *et al*. 1992). Furthermore, PEX affected subjects not only presents extraocular deposition of fibrillar aggregates, but also they have higher risk of developing non-ocular disorders such as sensorineural hearing loss (Cahill *et al*. 2002), coronary artery disease (Citirik *et al*. 2007), cerebrovascular (Yuksel *et al*. 2006) as well as vascular disorders including acute myocardial infarction and stroke (Mitchell *et al*. 1997).

3.2 *Progressive degeneration of optic nerve in PEX subjects: a characteristic feature of neurodegeneration*

PEXG individuals have shown an increased number of dense patterns of closely arranged myelinated fibres with lost staining for glial fibrillary acidic protein (GFAP) within the nerve fibre bundles of the retrolaminar optic nerve compared to non-glaucomatous control eyes. GFAP is a general marker for astrocytes and loss of GFAP staining indicates death of astroglial cells in such densified regions. Decreased GFAP was also found in chronic swelling and vacuolation of white matter astroglia in AD (May 2015). PEXG is also related to decrease in blood flow velocity and higher resistance of the middle cerebral arteries (Akarsu and Unal 2005). Also, in the posterior segment of PEXG affected eyes both circumpapillary and macular retinal nerve fibre layer thickness was found to be decreased (Honjo *et al*. 2015). The mean value of choroidal thickness in such regions is further lowered in more severe stage of PEXG than in PEXS (Dursun *et al*. 2016). Lamina cribrosa that forms an integral structural element of optic nerve head is also found to be thinned in PEX and a marked decrease in the stiffness of ONH cells is reported (Braunsmann *et al*. 2012).

Similar to PEX, Alzheimer's patients also show progressive degeneration of neurofibrils, limbic system (Arnold *et al*. 1991), neocortical regions (Terry *et al*. 1981) and synapses (Serrano-Pozo *et al*. 2011) in brain leading to neuronal loss, thereby, impacting regular daily activities. Differential expression of GFAP is also seen in Alzheimer's affected astrocytes like that of PEX (Kamphuis *et al*. 2014). On the other hand, Lewy-bodies in Parkinson's which are initially induced in somata of single nerve cells later spread through the nervous system into the neocortex leading to degeneration of cells like dopaminergic neurons, glutamatergic, noradrenergic and adrenergic nerve cells collectively affecting motor function of the nervous system (Braak *et al*. 2003). ARMD affected patients show concurrent alterations in the affected tissues in disease pathogenesis similar to PEX patients. Pathological alterations such as age-related degeneration of retinal photoreceptors and retinal pigment epithelium, hyper-glial reactivity and altered choroidal capillaries are some of the features seen in ARMD affected tissues (Ding *et al*. 2009).

4. Protein aggregates, a hallmark feature of common neurodegenerative proteinopathies

PEX is diagnosed by characteristic deposition of fibrillar materials composed of proteins on the pupillary margin of lens capsule surface through slit-lamp microscopy. Pathological similarities and dissimilarities between PEX aggregates and various ND are reviewed as follows:

4.1 *Formation of protein aggregates in PEX as compared with other neurodegenerative disorders*

PEX protein aggregates were shown to be deposited in nearly all tissues of anterior eye segment such as lens capsule, iris pupillary border, zonules, ciliary body, corneal endothelial surface, irido corneal angle, trabecular meshwork and also in the juxtacanalicular tissue area adjacent to the inner and outer wall of Schlemm's canal (Schlotzer-Schrehardt and Naumann 1995). Likewise, these aggregates were also found on the tissue surface of posterior eye segment including lamina cribrosa, peripapillary sclera and vitreous fluid (Pena *et al*. 1998). Additionally, electron microscopic

as well as immunohistochemical studies have shown similar deposits in non-ocular tissues such as lid skin (Amari *et al*. 1994), endothelial vessel wall, connective tissue of visceral organs (Andrikopoulos *et al*. 2014), fibrovascular septa and stroma of organs like lung, heart, liver and gall bladder (UM Schlotzer-Schrehardt *et al*. 1992). Presence of PEX fibril like materials on the extra-ocular tissues provide further evidence towards impairment of the blood-aqueous barrier in PEX subjects. Deposition of fibrillar aggregates in the vessel walls and increased oxidative stress might be attributed to PEX related vascular complications (Andrikopoulos *et al*. 2014). However, the site of synthesis for PEX fibril formation is still unknown. Accumulation of these PEX fibrils leads to formation of complex protein aggregates that gradually deposit on the surface of ocular tissues. Vazquez and Lee proposed a protein-sink model to explain such aberrant deposition of PEX material in the anterior eye tissues (Vazquez and Lee 2014). According to this model, in the preliminary stage, a deformed protein complex in the aqueous humour gradually binds to other proteins and forms a large complex protein aggregate. This large aggregate ultimately settles down from the aqueous humour and deposits on the surface of eye tissues.

Similar to PEX, most of the other neurodegenerative disorders also involve deposition of abnormal protein aggregates. In Alzheimer's, accumulation of extracellular amyloid plaques and inter-neuronal Tau-fibrillary tangles occurs in brain tissues including cerebral cortex, cerebellum, hippocampus and basal ganglia (Ghiso *et al*. 2010). Such deposits have also been found in peripheral tissues other than brain, like intramyocardial tissues (Troncone *et al*. 2016), skeletal muscle (Roher *et al*. 2009) and other non-neural tissues (Scudiero *et al*. 1986) analogous to that of PEX aggregates. However, unlike PEX, extensive studies in AD pathogenesis have shown that amyloid plaque formation initiates due to aberrant extracellular deposition of mutant form of amyloid-β peptides and subsequent formation of abnormal Tau-protein aggregates which leads to neurotoxicity and death of nearby neurons (Irvine *et al*. 2008). ARMD which leads to irreversible blindness is a type of neurodegenerative retinal disease diagnosed by deposition of protein aggregates called as drusen in the fundus of the eye including retinal pigment epithelium on Bruch's membrane. Similar to PEX, protein deposits in ARMD are shown to have extracellular matrix proteins including basement membrane proteins, collagen, fibronectins, complement factors and lipids (Lin *et al*. 2018). High oxidative stress, increased local inflammation and auto-immune activation leading to protein aggregation in the retinal pigment epithelium can cause ARMD with retinal degeneration (Kivinen 2018).

4.2 *PEX material composition versus protein aggregates found in ND disorders*

Previous studies have shown that PEX aggregates are made up of extracellular protein deposits arranged in a fibrillar form (Li *et al*. 1988; Ovodenko *et al*. 2007; Ritch and Schlotzer-Schrehardt 2001; U Schlotzer-Schrehardt *et al*. 1992). As seen through transmission electron microscopy (TEM), these fibrils fall into two categories depending on their diameter: type-A fibrils with a diameter of 18–25 nm and type-B fibrils with a diameter of 30–45 nm with a characteristic banding periodicity of 50 nm. The mature PEX fibrils are made up of 8–10 nm diameter microfibrils and are deposited side by side to form large PEX aggregates (Ritch *et al*. 2003). Previous studies have also reported the presence of a core consisting of glycoproteins covered by heavily glycosylated glycoconjugates such as hyaluronan, heparan sulphate proteoglycan, chondroitin sulphate, dermatan and keratin sulphate proteoglycan on the surface of lens capsule, zonules, ciliary body and iris, and has an electron-dense amorphous appearance under electron microscopy (Amari *et al*. 1994; Ritch and Schlotzer-Schrehardt 2001). PEX fibrils in both intra-ocular and extra-ocular tissues are found to contain the same sugar residues of glycoconjugates which implicates PEX is a systemic disorder (Amari *et al*. 1994). AD related proteins such as amyloid beta-peptide, serine proteinase inhibitor and alpha-1-antichymotrypsin were found to be accumulated in PEX deposits in both PEXS and PEXG affected individuals (Janciauskiene and Krakau 2001).

Broadly, these proteins can be grouped into two categories depending on their localization and function: extracellular matrix (ECM) proteins and blood derived proteins. Proteins in the basement membrane and those that form the extracellular scaffold are predominantly present in the PEX aggregates. Evidently, ECM related proteins like fibrillin-1, fibulin-2, tropoelastin, elastin, desmocolin-2, emilin, heparan sulphate, syndecan-3, microfibril associated glycoprotein (MAGP-1), Lysyl oxidase like-1 (LoxL1), vitronectin, fibronectin, laminin, nidogen, matrix metalloproteinases (MMPs), tissue inhibitor of matrix metalloproteinases (TIMPs) and the extracellular chaperone, Clusterin (CLU) are predominantly found in the PEX deposits (Li *et al*. 1988; Ovodenko *et al*. 2007; U Schlotzer-Schrehardt *et al*.

1992). Presence of such proteins in the PEX aggregates suggests that an elastotic process might be involved which leads to improper maintenance of ECM proteins underlying the pathogenesis of PEX. PEX aggregates are also known to contain blood derived proteins such as LTBP1 and -2 (latent transforming growth factor ß binding proteins), Haemoglobin A2, Complement factors (C1q, C3c and C4c) and serum amyloid protein (Li *et al*. 1988; Ovodenko *et al*. 2007; U Schlotzer-Schrehardt *et al*. 1992). Finding of such proteins in the deposits indicates a breakdown in the blood-aqueous barrier which allows leakage of these proteins into the aqueous humor (AH) and their subsequent deposition on the surface of eye tissues.

Similar to PEX, in other neurodegenerative diseases, aggregates consist of misfolded protein fibres within a beta-sheet conformation which progressively deposit in ageing tissues. Amyloids in Alzheimer's, drusen in ARMD, Lewy-bodies in Parkinson's disease share similar properties like that of PEX material in pseudoexfoliation (Davis *et al*. 2018). Subsequent deposition of these aggregates disrupts basal cellular activity in the vicinity leading to increased neurotoxicity, thereby cell death or neurodegeneration. Amyloid plaques made up of amyloid fibrils accumulate in between the brain neurons of Alzheimer's patients. In addition to amyloid plaques, neurofibrillary tangles are also insoluble protein fibres found to be deposited in the brain tissues. While amyloid plaques are made up of abnormal beta-amyloid proteins, neurofibrillary tangles are made up of microtubular tau proteins (Hardy and Selkoe 2002). Mass-spectrometric as well as microscopic analysis of drusen deposited in the retinal pigmented epithelium of ARMD affected patients showed the presence of lipids such as phosphatidylcholine and various oxidized extracellular and membranous proteins such as vitronectin, immunoglobulins, serum albumin, complement factors, clusterin, ATP synthase subunit-beta and retinol dehydrogenase 5 (Wang *et al*. 2010). Parkinson's affected individuals also show an anomalous deposition of protein clumps called Lewy-bodies and are mostly made up of alpha-synuclein and few other proteins involved in ubiquitin-proteasome system such as ubiquitin, cytoskeletal proteins, cell-cycle proteins and various structural proteins (Beyer *et al*. 2009). Concurrently, these proteins have also been shown to be accountable for the incidence of PEX as reported in the past studies by others and our group. Notably, accumulation as well as anomalous expression of proteins like clusterin, complement factors, amyloid peptides and proteins involved in ubiquitin-proteasome system are prominent in PEX affected eye tissues (Hayat *et al*. 2019; Padhy *et al*. 2014).

5. Common factors responsible for both PEX and other ND disorders

5.1 *Epigenetic factors*

5.1.1 *Ageing:* PEX is an age-related disorder, the incidence of which increases with age in the population. Prevalence of PEX varies widely among various populations. PEXS affected individuals at a later stage develop PEXG with deteriorated ONH cells resulting in decreased vision (Jeng *et al*. 2007). Henry *et al*. showed that PEX patients have a ten-fold higher chance of having ocular hypertension and glaucoma within ten years than the normal population (Henry *et al*. 1987). Segregation of study subjects into different age groups showed an increased incidence rate in relatively aged individuals. Around 33% of recruited study subjects were found to be affected by PEX in the age groups of 80–89 years. Similarly, in an Icelandic population, PEX incidence rate is found to be 17.7% in individuals in the age group of 70–79 years which increased to 40.6% in the study subjects aged more than 80 years (Arnarsson 2009). Accordingly, with individuals aged above 50 the chance of getting affected by PEX becomes two-fold with each decade (Arnarsson 2009). Similar to PEX, in other neurodegenerative disorders like Alzheimer's (Guerreiro and Bras 2015), Parkinson's (Hindle 2010) and amyotrophic lateral sclerosis (ALS) (Ingre *et al*. 2015) older individuals show an increased rate of neurodegeneration as well as a higher incidence rate compared to young adults. Age factor plays a significant role in the progression of Alzheimer's through a gradual decrease in neurogenesis and increase in impaired cognitive function in the central nervous system (Villeda *et al*. 2011). Likewise, patients with Parkinson's disease have shown degenerated dopamine neurons, accumulation of α-synuclein as well as higher microglial reactivity with advanced age (Collier *et al*. 2011). As a consequence of ageing factor, PD affects 1% of the population over the age of 60 years while 5% of the population were found to be affected over the age of 85 years (Reeve *et al*. 2014). Similarly, as shown by Nangia *et al*. occurrence of ARMD increases from 1.3% per individual in 30–40 years old group to 8.3% in 71–80 years old group individuals with higher rate of maculopathy leading to blindness in aged individuals (Nangia *et al*. 2011).

5.1.2 *Environmental factors:* Studies in the past suggest that environmental factors are associated with the aetiogenesis of PEX. Epidemiologic studies indicate a profound role of geographic location and work occupation of an individual in developing pseudoexfoliation. A report suggests that study subjects residing in the higher latitude are at higher risk for PEX (Stein *et al*. 2011). This could be due to different amount of UV exposure at various geographic locations. It is well known that absorption of high energetic UV radiation by proteins can alter their native structure and abnormal protein may thus precipitate in the form of protein aggregates as in the case of PEX. Higher the UV exposure, greater is the risk of developing PEX (Damji *et al*. 1998). Studies on participants aged 60 years or more from two United States-based cohorts also suggest that individuals who spend more time outdoors have higher chance of developing PEX probably due to increased exposure to UV radiation (Kang *et al*. 2014). In addition, evidence from a population based epidemiologic study carried out in a south Indian population also suggests that people whose occupation involves outdoor activities have higher risk of PEX (Thomas *et al*. 2005). As observed with PEX, epidemiological studies conducted in ARMD suggest a correlation between long-term ultra-violet radiation exposure and increased risk of ARMD (Plestina-Borjan and Klinger-Lasic 2007). Consistent light exposure induces severe oxidative damage that leads to photochemical damage at both cellular and molecular levels in the retinal pigment epithelium (Chalam *et al*. 2011). Similarly, UV radiations are shown to be a contributing factor towards progressive neurodegeneration in patients with xeroderma pigmentosum (XP) (Andrews *et al*. 1978). Although there is no evidence of a direct relation between UV exposure and aetiology of Alzheimer's, studies have shown that targeted DNA damage caused by UV as well as ionising radiations can heighten the progression of neurodegeneration in Alzheimer's (Kempf *et al*. 2016). Further, studies have shown that ultraviolet B radiation (UV-B) is associated with lower PD risk possibly by increasing the vitamin D levels (Kravietz *et al*. 2017).

5.2 *Genetic factors*

5.2.1 *Clusterin:* Clusterin (*CLU*; Gene ID: 1191, 8p21.1) is an extracellular secreted glycoprotein with multifunctional role in the cell. It plays a crucial role in lipid transport, cell-matrix interaction and in preventing deposition of aggregates in the outer space of the cell. Cell under stress also produces a rare shorter isoform of clusterin that tends to localize inside the nucleus and mediates apoptosis (Caccamo *et al*. 2004). Variants in *CLU* have been associated with PEX as risk factors in German (Krumbiegel *et al*. 2009), Australian (Burdon *et al*. 2008) and Indian (Padhy *et al*. 2014) populations, independently. Earlier reports reveal CLU accumulation progresses with the advancement of the disease from PEXS and PEXG (Padhy *et al*. 2014; Zenkel *et al*. 2006). Further, our previous study has revealed that subjects with risk allele at a *CLU* intronic variant, rs2279590 show an increased *CLU* expression in lens capsule tissues (Padhy *et al*. 2014).

Clusterin variants have also been picked up as risk factors for many other neurodegenerative and ageing disorders like Alzheimer's (Lambert *et al*. 2009), Parkinson's (Gao *et al*. 2011; van Dijk *et al*. 2013), Huntington's (Singhrao *et al*. 1999) and diabetes (Daimon *et al*. 2011) in both genetic and/or proteomic studies. Studies have shown that despite a cytoprotective role of CLU in the clearance of fibrillar aggregates in normal cells, overaccumulation of CLU tends to be cytotoxic governed by CLU to substrate ratio in diseased states (Yerbury *et al*. 2007). Knockout of CLU in an Alzheimer's mice model has decreased fibrillar plaque and neuritic dystrophy (DeMattos *et al*. 2002). Further, AD individuals have shown a faster decline of brain function with over accumulated CLU than unaffected subjects (Giri *et al*. 2016). Also, CLU has been shown in modulating the formation of Lewy bodies during the progression of Parkinson's (Sasaki *et al*. 2002). In ARMD affected eyes, retinal pigment epithelium cells were shown to be secreting more CLU than healthy controls and CLU deposits were found in both aqueous humor and drusen aggregates (Baek *et al*. 2018).

5.2.2 *PTK2B and EPHX2:* Protein tyrosine kinase 2 beta (*PTK2B*; Gene ID: 2185, 8p21.2) gene is located adjacent to *CLU* gene and codes for a protein that colocalizes with tau protein and is suggested as a biomarker in AD pathology through modulating tau toxicity (Dourlen *et al*. 2017). PTK2B is a kinase and phosphorylates Glycogen synthase kinase 3 which in turn induces fibrillation of Tau. Genetic association studies have shown that polymorphisms in the *PTK2B-CLU* locus are associated with AD (Lambert *et al*. 2009; Lambert *et al*. 2013). Increased PTK2B activity as well as its deposition is seen in AD affected brain tissues (Dourlen *et al*. 2017). Recently, studies from our group have shown that the risk allele for PEX at rs2279590 located within the *CLU* loci regulates

PTK2B expression suggesting it may play a role in PEX pathogenesis as well (Padhy *et al*. 2017). In addition to PTK2B, our study has also shown that the PEX associated *CLU* intronic SNP, rs2279590 regulates the expression of Epoxide hydrolase-2 (*EPHX2*; Gene ID: 2053 ,8p21.2-p21.1) gene located at 3' of *CLU* (Padhy *et al*. 2017). EPHX2 metabolises epoxyeicosatrienoic acid which is proven to be neuroprotective, hence increased expression of EPHX2 induces neurotoxicity (Chapuis *et al*. 2017). Also, genetic variants within *EPHX2* gene as well as dysregulated EPHX2 expression are shown to be associated with AD as risk factors (Chapuis *et al*. 2017; Nelson *et al*. 2014). Both PTK2B and EPHX2 may play a crucial role in PEX pathogenesis which is being studied further (Padhy *et al*. 2017).

5.2.3 *Heat shock factors:* Heat shock factor 1 (*HSF1*; Gene ID: 3297, 8q24.3) a member of heat shock family of transcription factors is shown to be a prominent factor involved in neurodegenerative diseases and thereby, considered as a therapeutic target (Neef *et al*. 2011). Under stress, HSF1 localizes to nucleus and regulates expression of genes including heat shock proteins (HSPs) involved in various pathways critical for cell survival. Previously, our studies have shown that HSF1 is found to be upregulated in PEXS lens capsule suggesting its pro-active role in preventing abnormal protein aggregation which in the later PEXG stages loses its potentiality to evade proteotoxic stress (Padhy *et al*. 2017). HSF1 expression is shown to be dysregulated in diseases like Huntington's and polyglutamine-induced neurodegenerative disease (Gomez-Pastor *et al*. 2017; Kondo *et al*. 2013). HSF1 activation in diseased mice model disrupts aggregate formation suggesting a key role of HSF1 in preventing formation of abnormal protein aggregates (Fujimoto *et al*. 2005). Higher autoreactivity of HSPs is seen in the sera of ARMD patients than in control subjects suggesting its role in ARMD pathogenesis (Iannaccone *et al*. 2015). HSFs as well as HSPs are prominently associated with Parkinson's disease at transcriptomic and genetic level (Wu *et al*. 2004). Likewise, subjects affected by AD have shown a decreased level of HSF1 expression compared to that of normal individuals (Goetzl *et al*. 2015). Further, there is a downregulation of HSF1 in the affected brain tissues of mice model for Alzheimer's disease while its upregulation diminishes deposition of β-amyloid proteins and improves cognition (Jiang *et al*. 2013). This indicates a fine balance of HSF1 is necessary in neuronal cells, deviation from which may lead to abnormal protein aggregation in neurodegenerative proteinopathies including PEX.

5.2.4 *Calcium voltage-gated channel subunit-α1A:* Calcium voltage-gated channel subunit alpha1 A (*CACNA1A*; Gene ID: 773, 19p13.13) is a prominent member in the family of calcium channels (CACN) and immunostaining of CACNA1A revealed its presence in both anterior and posterior eye tissues (Aung *et al*. 2015). Aung *et al*. in 2015 discovered a genetic association between an intronic variant, rs4926244 in *CACNA1A* and PEX (Aung *et al*. 2015). It is involved in a variety of calcium dependent processes including neurotransmitter release and gene expression (Kaja *et al*. 2010). Previously, mutations in *CACNA1A* have been associated with autism and eye related disorders (Li *et al*. 2015; Tantsis *et al*. 2016). Electron microscopic studies have shown higher accumulation of calcium in PEX fibrils in the affected tissues which implies a crucial role of calcium in the formation of PEX aggregates (Schlotzer-Schrehardt *et al*. 2001). Calcium is also known to play a role in stabilizing fibrillin-1 to form stable aggregates (Reinhardt *et al*. 1997). Collectively, this insinuates a role of CACNA1A in forming PEX fibrils by altering calcium concentration in the extracellular space (Aung *et al*. 2015). Both at genomic and transcriptomic level, CACNA1A has been associated with various neurodegenerative diseases like Huntington, spinocerebellar ataxia type 6 (SCA6) and episodic ataxia type 2 (EA2) (Denier *et al*. 2001; Friend *et al*. 1999; Mariani *et al*. 2016; Pradotto *et al*. 2016).

5.2.5 *Contactin-associated protein-like 2:* Contactin-associated protein-like 2 (*CNTNAP2*; Gene ID: 26047, 7q35-q36.1) is a membrane protein in the neurons and is a member of neurexin family. It helps in neuron-glial cell interactions and is involved in potassium channel trafficking (Horresh *et al*. 2008). Previously, it has been associated with neuropsychiatric disorders like schizophrenia, epilepsy and autism (Friedman *et al*. 2008). Krumbiegel *et al*. showed a genetic association between *CNTNAP2* and PEX in a German cohort wherein two SNPs, rs2107856 and rs2141388 within the 11th intron of *CNTNAP2* gene were found to be risk factors for PEX pathogenesis through a GWAS approach (Krumbiegel *et al*. 2011). Although, mRNA expression of *CNTNAP2* was not found to be different between control and PEX affected tissues, immunohistochemistry showed a decreased expression of CNTNAP2 in the cell membranes of anterior eye tissues. However, both of these SNPs were not found to

be associated with PEX in a replicate study from an Italian cohort. Later, an independent case-control study conducted in the Polish population also did not find a genetic association with PEX for the two reported SNPs (Malukiewicz *et al*. 2011). Although the exact role of CNTNAP2 in the pathogenesis of PEX is not clear; it is suggested that it may be involved in membrane stabilization and an imbalance in maintaining the ion channel function may lead to cell deformities. Past studies have shown a prominent role of CNTNAP2 in neurodevelopmental disorders such as Alzheimer's, schizophrenia, Parkinson's, autism spectrum disorder and dyslexia (Flaherty *et al*. 2017; Poot 2015; Rodenas-Cuadrado *et al*. 2014). Van Abel *et al*. have shown a downregulation of CNTNAP2 expression in the hippocampus of Alzheimer's affected individuals by a forkhead box transcription factor, STOX1A (van Abel *et al*. 2012). Transcriptomic analysis as well as functional analysis shows a role of CNTNAP2 in altering neuronal gene expression, synaptic abnormalities and aggregate formation in Parkinson's (Flaherty *et al*. 2017; Infante *et al*. 2015; Varea *et al*. 2015) and have shown schizophrenic patients carrying pathogenic variations in CNTNAP2 demonstrating speech and cognitive deterioration (Friedman *et al*. 2008). Similarly, autism affected individuals with mutations in *CNTNAP2* gene suffer from mental retardation, intellectual disability and speech delay (Rodenas-Cuadrado *et al*. 2014).

5.2.6 *Apolipoprotein E:* Apolipoprotein E (APOE) directs lipid transfer between different tissue and/or cell types including neurons. APOE is found to be aggregated along with PEX deposits on the surface of PEX affected lens capsule as shown by MALDI-MS imaging analysis (Ronci *et al*. 2013; Sharma *et al*. 2009). Yilmaz *et al*. also showed a varied risk for developing PEXS in individuals with different genotype background of APOE alleles (Yilmaz *et al*. 2005). However, there are also reports which could not establish association between APOE isoforms and the risk for developing PEX which implicates further studies needs to be carried out in relation to PEX (Chiras *et al*. 2013; Krumbiegel *et al*. 2010). APOPE has also been associated with various NDs (Huang and Mahley 2014). While majority of circulating APOE is produced in liver (Linton *et al*. 1991), in the central nervous system it is extensively produced in cells such as glial cells and choroid plexus cells (Huang and Mahley 2014). APOE plays a key role in the onset of AD by being associated with neuritic amyloid plaques, can form stable precipitates with Aß peptides as well as enhances Aß aggregation (Huang and Mahley 2014). Studies have shown that severity of AD pathogenesis substantially depends on the type of APOE isoforms (ε4, ε3 and ε2). According to Farrer *et al*. individuals with two copies of ε4 have higher risk of developing AD than with ε3 (Farrer *et al*. 1997). In addition to AD, APOE ε4 is also shown to be associated as a risk factor for dementia in Parkinson's as well as Lewy bodies (Fyfe 2020).

5.2.7 *Matrix metalloproteinases and tissue inhibitor of matrix metalloproteinases:* Matrix metalloproteinases (MMPs) are a group of enzymes which are involved in degrading extracellular matrix proteins while tissue inhibitors of metalloproteinases (TIMP1–4) include four protease inhibitors that inhibit the activity of MMPs in the ECM. Together the ratio of MMPs and TIMPs controls the rate of protein degradation and turnover of ECM proteins in the extracellular space (Jiang *et al*. 2002). Impairment in the MMPs/TIMPs ratio has been studied in the development of various forms of cancer and arthritis (Jiang *et al*. 2002; Mohammed *et al*. 2003). Past studies also implicate a possible role of MMPs and TIMPs in the progression of PEX. Fountoulakis *et al*. found a significant upregulation of TIMP4 in the AH of PEXG affected individuals than in control. An increase in TIMP4 activity in the AH may lead to a downregulated activity of MMPs and a subsequent disruption of ECM homeostasis in the PEXG individuals (Fountoulakis *et al*. 2013). Selecuk *et al*. however, showed that there is no difference in the protein level of both MMP2 and TIMP2 in both AH and serum samples of PEX individuals in comparison to control (Kara *et al*. 2014). Studies also suggest an imbalance in the protein level of other family members of MMPs and TIMPs such as TIMP1 and TIMP2 in the PEX affected anterior eye tissues (Zenkel *et al*. 2005). Altogether, dysregulation of MMPs and TIMPs may aid in decreased proteolytic activity and eventually lead to accumulation of aberrant proteins in the extracellular space. Past studies have shown a noted involvement of various MMPs and TIMPs in the pathology of Alzheimer's which have been suggested as diagnostic biomarkers in the disease progression (XX Wang *et al*. 2014). Anomalous expression and altered activity of both MMPs and TIMPs leads to a neurotoxic effect in AD affected brain tissues (XX Wang *et al*. Wang). Similarly, MMPs also have shown to play a role in the development of choroidal neovascularization in ARMD (Steen *et al*. 1998). Also, hyperactivity and imbalance between MMPs/TIMPs

complexes deteriorates ECM structural components as well as degradation of Bruch's membrane, in the RPE and endothelial cells in ARMD affected eyes (Hussain *et al*. 2017). Similar to PEX, MMP2 level is significantly decreased with an elevated expression of TIMP2 in the substantia nigra of Parkinson's affected brains (Lorenzl *et al*. 2002). Also, genetic association studies have shown a role of MMP9 and TIMP1 polymorphisms in Parkinson's pathogenesis (Chen *et al*. 2016). Differential expression of matrix metalloproteinases is seen to be involved in another degenerative disorder, amyotrophic lateral sclerosis (ALS) which is characterized by degeneration of motor neurons in the brain and spinal cord (Brkic *et al*. 2015).

5.2.8 *Cytokines:* Cytokines are involved in mediating inflammation and immunity. Certain proinflammatory cytokines such as interleukin-6 (IL-6) and interleukin-8 (IL-8) are found to be elevated in the AH and in affected tissues of subjects diagnosed with PEXS but not in PEXG cases (Yildirim *et al*. 2013; Zenkel *et al*. 2010). While another study also found elevated level of IL-8 in PEXG in comparison to control (Khalef *et al*. 2017). Both IL-6 and IL-8 were also found to be upregulated in ciliary processes in response to hypoxia or oxidative stress *in vitro*. IL-6 in turn induces the expression of transforming growth factors and elastic fibre proteins in the extracellular matrix. This implicates a role of stress induced cytokines in the onset of excessive production of ECM proteins which is a characteristic feature of PEX (Zenkel *et al*. 2010). Similar to PEX, AD affected brain tissues show differential expression of inflammatory cytokines including IL-6, thereby leading to amyloid deposition (Su *et al*. 2016). Also, at genetic level polymorphisms in genes involved in producing inflammatory cytokines such as IL-6, IL-1 and TNFα have been associated with AD (Su *et al*. 2016). Likewise, levels of different cytokines like IL-2, IL-4, IL-6 and TNFα were found to be increased in the cerebrospinal fluid as well as in the brain tissues of Parkinson's affected individuals (Nagatsu *et al*. 2000). Abnormal expression of these cytokines is suggested to be involved in the apoptosis and degeneration of the nigrostriatal dopamine neurons (Nagatsu *et al*. 2000). Likewise, cytokines are also shown to be involved in diseases such as schizophrenia (Koola 2016) and multiple sclerosis (Wang *et al*. 2018). Upregulated levels of IL-6 and IL-8 is shown in the cortex and cerebellum including plasma of patients affected with Huntington's disease (Silvestroni *et al*. 2009).

6. Cellular pathways involved in the pathogenesis of pseudoexfoliation glaucoma and other neurodegenerative diseases:

6.1 *TGF-β and ECM metabolism*

Transforming growth factor beta 1 (*TGF-β1*; Gene ID: 7040, 19q13.2) belongs to transforming growth factor beta superfamily and is a secreted protein with multifunctional role including cellular proliferation, differentiation and apoptosis. Elevated levels of tissue growth factors (TGF-βs) were reported in the AH of PEX patients in comparison with control (Browne *et al*. 2011; Khalef *et al*. 2017; Wallace *et al*. 2013). It is well known that an increase in tissue growth factor increases the rate of ECM formation while treatment with anti-connective tissue growth factor reduces ECM production in trabecular meshwork and lamina cribrosa cells (Wallace *et al*. 2013). Increase in TGF-βs also induces expression of fibrillin-1, an ECM scaffold protein through JNK (c-Jun N-terminal kinase) and MAPK (Mitogen activated protein-kinase) pathways (Browne *et al*. 2011). TGF-β1 also has a role in stabilizing PEX fibrillar aggregates (Zenkel *et al*. 2010). Thus, increase in TGF-β1 may enhance local synthesis and activation of extracellular proteins in the ECM. Recently, our group has reported a new candidate gene Fibulin-5, an extracellular scaffold protein as a risk factor in PEX pathogenesis. Decreased expression of Fibulin-5 was found in PEX affected tissues (Padhy *et al*. 2019). Studies have also shown an increase in the level of latent TGF-β1 binding proteins (LTBP1; Gene ID: 4052, 2p22.3 and LTBP2; Gene ID: 4053, 14q24.3) in the AH of PEX patients. LTBPs are a group of secreted glycoproteins and are important regulators of TGF-β1 metabolism (Schlotzer-Schrehardt *et al*. 2001). Elevated expression of LTBPs thus, may lead to enhanced metabolism of ECM formation. Likewise, LTBP2 genetic variations are shown to be contributing to the pathogenesis of PEX (Jelodari-Mamaghani *et al*. 2013). Earlier reports have shown a decreased plasma levels of TGF-β1 while it is found to be increased in cerebrospinal fluid including deposition with amyloid aggregates (von Bernhardi *et al*. 2015). Upregulated TGF-β1 increases the production of amyloid precursor protein in brain astrocytes that includes stabilization of APP mRNA which is a pathogenic factor in AD progression (Burton *et al*. 2002). Thus, TGF-β1 signalling pathway is suggested to be a pharmacological target to treat AD (Caraci *et al*. 2011). TGF-βs is involved in choroidal neovascularization and thus in ARMD progression (Wang *et al*. 2019). Additionally, studies have

shown that TGF-βs expression is upregulated in the RPE cells of maculae in early ARMD affected eyes (Kliffen *et al*. 1997). In contrast to this, studies have also shown that TGF-βs concentrations were significantly lower in the AH of neovascular ARMD patients compared to controls (Tosi *et al*. 2018). TGF-βs has a protective role in dopaminergic neurons which delays the progression of Parkinson's (Krieglstein and Unsicker 1994). Also damage to the mouse nigrostriatal system leads to elevated TGF-β2 mRNA levels in the striatum which implies a positive role of TGF-βs in dopaminergic neurons (Schober *et al*. 2007). Furthermore, increased immunoreactivity to TGF-βs is shown not only in Parkinson's but also in other degenerative diseases including ALS and Lewy body dementia (Lippa *et al*. 1995).

6.2 *Homocysteine metabolism*

Level of homocysteine (Hcy), synthesized during the metabolism of methionine is a crucial hallmark for oxidative stress in the cells. Genes involved in homocysteine metabolism have been studied in the past with relation to PEX, both at genomic and proteomic level. Both PEXS and PEXG patients were found to have elevated levels of homocysteine and vitamin B12 in blood plasma and in the AH (Turkcu *et al*. 2013). It is well known that homocysteine can induce vascular injury thereby, altering extracellular matrix proteins and high concentration of homocysteine thus, may trigger abnormal matrix accumulation in the anterior eye surface. Impairment of blood-aqueous barrier may also lead to increase in Hcy level in the anterior segment of the eye (Bleich *et al*. 2004). Elevated homocysteine is also known to be a risk factor for various vascular diseases and is involved in ischemic changes and oxidative stress. Abnormal level of vitamin B12 and folic acid which are required as cofactors in the homocysteine metabolism can elevate Hcy plasma levels (Turkcu *et al*. 2013). Expression of homocysteine metabolism gene, TNFα was also found to be upregulated in PEXG in comparison to control (Khalef *et al*. 2017). A genetic polymorphism tested in TNFα, rs1800629 was found to be strongly associated with PEXG in a Pakistani cohort (Khan *et al*. 2009). Further, an increased level of TNFα was found in the serum of PEX affected individuals (Sorkhabi *et al*. 2013). Higher homocysteine level is also a metabolic risk factor for many neurodegenerative diseases. Studies have shown an increased plasma homocysteine level as well as low serum folate concentration are strong risk factor for Alzheimer's pathogenesis (Arlt *et al*. 2012; Ravaglia *et al*. 2005). Elevated homocysteine as well as parameters involved in homocysteine metabolism leads to increased cognitive impairment by neurodegeneration and accumulation of phosphorylated tau in AD (Arlt *et al*. 2012). Saadat *et al*. have shown that with increased serum homocysteine level there is an increased chance of having Parkinson's (Saadat *et al*. 2018). Studies have shown that homocysteine induces direct toxicity in variety of neuronal populations including cortical neurons, dorsal root ganglion neurons and hippocampal neurons thereby increases the severity of disease progression (Ansari *et al*. 2014). Similarly, plasma homocysteine also has been shown to be a risk factor as well as modulator in the pathogenesis of other neurologic diseases such as Huntington and epilepsy (Andrich *et al*. 2004; Diaz-Arrastia 2000).

6.3 *Oxidative stress*

Aberrant deposition of protein aggregates is also a consequence of increased reactive oxygen species (ROS) and a decrease in antioxidant defence capacity leading to oxidative stress in the tissues of PEX affected eye tissues. This is evident from the elevated protein oxidation in the AH and serum from PEX patients. The amount of carbonyl groups on proteins which is a marker for oxidative stress and protein oxidation was found to be increased in PEX in comparison with control and thus oxidative stress may play a role in the pathology of PEX (Yagci *et al*. 2008). Further, oxidative selenium involved in diminishing oxidative stress was shown to be decreased in AH, conjunctiva and serum of PEX individuals thereby, supporting a decreased antioxidative capacity in the disease progression (Yilmaz *et al*. 2011). Also, components of antioxidative defence system like superoxide dismutase 2 (SOD2), aldehyde dehydrogenase I (ALDHL1) and microsomal glutathione-s-transferase I (mGST1) are also upregulated in affected eye tissues of cases than those of control subjects and indicate an increased oxidative stress in PEX diseased tissues (Lesiewska-Junk *et al*. 2013; Strzalka-Mrozik *et al*. 2013). However, genetic variants in the SOD enzyme, rs10432782 and rs2070424 were not found to be associated with PEXS (Lesiewska *et al*. 2015). Khaled *et al*. have shown that total antioxidant status (TAS) which is a measure of antioxidative defence capacity in the cell of diseased tissues was found to be decreased in the plasma of PEXG individuals; however, this study didn't include the status of TAS in PEXS affected

Table 1. List of genes reported to be involved in PEX pathogenesis and their functions in comparison to other neurodegenerative diseases

Genes	Known Function	Role in PEX pathogenesis	Role in various forms of neurodegenerative disorders
Clusterin (*CLU*; Gene ID: 1191)	CLU codes for a heterodimeric glycoprotein involved in clearance of cellular debris and apoptosis.	Variants in clusterin gene were found to be associated with PEX (Krumbiegel *et al*. 2009; Padhy *et al*. 2014). Expression studies also suggest an impaired regulation of clusterin expression and its deposition in diseased tissues (Padhy *et al*. 2014; Zenkel *et al*. 2006).	CLU has been associated with neurodegenerative diseases like Alzheimer's (Lambert *et al*. 2009; Lambert *et al*. 2013) and Parkinson's (Gao *et al*. 2011; van Dijk *et al*. 2013) at both genetic and functional studies.
Heat shock factor 1 (HSF1; Gene ID: 3297)	HSFs are a group of transcription factors involved in regulating the expression of heat shock proteins.	HSF1 is found to be upregulated in PEX affected anterior eye tissues (Padhy *et al*. 2017).	Dysregulation of HSF1 expression also has been seen in disorders such as Huntington's (Gomez-Pastor *et al*. 2017) and polyglutamine-induced neurodegenerative disease (Kondo *et al*. 2013).
Calcium voltage-gated channel subunit alpha1 A (CACNA1A; Gene ID: 773)	CACNA1A codes for the alpha-1 subunit of the calcium channel CaV2.1.	Previously, impaired regulation of CACNA1A and association of its common genetic variants with PEX was shown (Aung *et al*. 2015).	CACNA1A has been associated with various neurodegenerative diseases like Huntington, spinocerebellar ataxia type 6 (SCA6) and episodic ataxia type 2 (EA2) (Denier *et al*. 2001; Friend *et al*. 1999; Mariani *et al*. 2016; Pradotto *et al*. 2016).
Contactin-associated protein-like 2 (CNTNAP2; Gene ID: 26047)	CNTNAP2 codes for a neuronal transmembrane protein member of the neurexin superfamily.	Variants in the CNTNAP2 gene have been associated with PEX as risk factor. Dysregulated expression of CNTNAP2 was shown in PEX affected tissues (Krumbiegel *et al*. 2011).	CNTNAP2 has been shown to play a crucial role in neurodevelopmental diseases such as schizophrenia, Parkinson's, autism spectrum disorder and dyslexia (Flaherty *et al*. 2017; Poot 2015; Rodenas-Cuadrado *et al*. 2014).
Matrix Metalloproteinases (MMPs) and Tissue inhibitor of matrix metalloproteinases (TIMPs)	MMPs are a group of enzymes responsible for degradation of extracellular matrix proteins while TIMPs are MMP inhibitors.	Deregulated expression of MMPs and TIMPs was shown in the anterior eye tissues and aqueous humor of PEX individuals (Fountoulakis *et al*. 2013; Kara *et al*. 2014; Zenkel *et al*. 2005).	Abnormal expression of MMPs and TIMPs has been reported in Alzheimer's (Duits *et al*. 2015), Parkinson's (Chen *et al*. 2016) and amyotrophic lateral sclerosis (Brkic *et al*. 2015).

Table 1 (continued)

Genes	Known Function	Role in PEX pathogenesis	Role in various forms of neurodegenerative disorders
Cytokines	Cytokines are a group of small proteins involved in signalling cells and act as a part of host defence system.	Proinflammatory cytokines like interleukin-6 and interleukin-8 were shown to be upregulated in aqueous humor of PEX affected cases (Yildirim *et al*. 2013; Zenkel *et al*. 2010). Elevated levels of tissue growth factor were reported in the aqueous humor of PEX individuals (Browne *et al*. 2011; Khalef *et al*. 2017).	Similar to that of MMPs and TIMPs, cytokines was shown to involved in the progression of neurodegeneration in Alzheimer's (Domingues *et al*. 2017; Su *et al*. 2016), Schizophrenia (Koola 2016) and multiple sclerosis (Wang *et al*. 2018).
Homocysteine (Hyc)	Hyc, a non-proteinogenic amino acid and a by-product of cysteine methylation.	Homocysteine, Vitamin B12 (Turkcu *et al*. 2013) and Tumor necrosis factor-α (TNFα) (Khalef *et al*. 2017) was found to be elevated in PEX affected individuals.	Homocysteine imbalance has been reported in Alzheimer's (Arlt *et al*. 2012; Ravaglia *et al*. 2005; Seshadri *et al*. 2002), Huntington's (Andrich *et al*. 2004) and epilepsy (Diaz-Arrastia 2000).
Superoxide dismutase 2 (*SOD2*; Gene ID: 6648), Aldehyde dehydrogenase 1 family member A1 (*ALDH1A1*; Gene ID: 216) and microsomal Glutathione S-transferase 1 (*MGST1*; Gene ID: 4257)	SOD, ALDH and GST are a class of cellular enzymes involved in detoxifying reactive oxygen species.	Protein oxidation (Yagci *et al*. 2008), antioxidative defence system including superoxide dismutase, aldehyde dehydrogenase and glutathione-s-transferase (Lesiewska-Junk *et al*. 2013; Strzalka-Mrozik *et al*. 2013) are found to be elevated in PEX patients. However, oxidative selenium (Yilmaz *et al*. 2011) and total antioxidant status (Abu-Amero *et al*. 2011) were found to be decreased in PEX cases.	Anomalous activity of SOD, ALDH and GST is also shown in neurodegenerative diseases like Alzheimer's (Marcus *et al*. 1998; Omar *et al*. 1999; Wojsiat *et al*. 2018) and Parkinson's (Abraham *et al*. 2005).

individuals (Abu-Amero *et al*. 2008). Additionally, systemic antioxidant capacity measured by ferric-reducing activity was found to be lower in the peripheral blood of PEX patients in a Japanese population (Tanito *et al*. 2012). Levels of antioxidant enzymes like Paraoxonase (PON) and Arylesterase (ARE) were found to be significantly downregulated in AH and serum in PEXG individuals from Turkish population than in control (Dursun *et al*. 2015). Proteomic study of serum collected from PEXG individuals reported differentially expressed proteins that are part of a network related to regulating immune and inflammatory-related processes (Gonzalez-Iglesias *et al*. 2014). A list of proteins that are shown to be involved in the pathogenesis of PEX and other forms of neurodegenerative diseases are presented in table 1. Dysregulation in the level of ascorbic acid, nitric oxide (NO) and TNFα, an inflammatory cytokine in the AH was also found in both PEXS and PEXG individuals implicating a local oxidative stress led inflammation (Sarenac Vulovic *et al*. 2016). Further, deletion genotypes in the isoforms of the gene, glutathione s-transferase (GST; GSTθ1 and GSTμ1) were significantly associated with PEX in Arab population (Abu-Amero *et al*. 2008). Increased levels of GSH (Glutathione, an antioxidant measure), malondialdehyde (MDA, lipid peroxidation product), mitogen activated protein kinase (MAPKp38), heat shock proteins (HSP40, HSP60, and HSPA5) and superoxide dismutase 2 (SOD2) were also seen in PEX (Hayat *et al*. 2019; Zenkel *et al*. 2005). In the past, our

group has also shown increased expression of genes involved in unfolded protein response such as Synoviolin1 (*SYVN1*), Caspase 12 (*CASP12*) and Calnexin (*CANX*) in PEX affected lens capsules while expression of proteasome subunits like 26 S proteasome non-ATPase regulatory subunit 1 (*PSMD1*) and Proteasome subunit alpha type-5 (*PMSA5*) genes were found to be decreased (Hayat *et al*. 2019). Other cytoprotective genes like microsomal glutathione transferase 1 (mGST1) and glutathione transferase θ1 (GSTT1), ubiquitin conjugating enzymes (UBE2A and UBE2B), DNA repair protein mutL homolog 1 (MLH1) and stress inducible transcription factor (GADD153) were found to be decreased in PEX (Zenkel *et al*. 2005). Further, a very recent study from our group suggests hypermethylation in the cytosolic chaperone, HSP70 leads to its decreased expression which ultimately aids in PEX progression (Hayat *et al*. 2020). Increased expression of DNA methyltransferase 3A following hypermethylation of CpG islands located in the exon of HSP70 leads to decreased HSP70 expression and diminishes its cytoprotective effect in the lens capsule of PEXS subjects and suggests HSP70 as a risk factor in PEX pathogenesis.

With a dramatic rise in ROS species with ageing there is an increase in irreversible processes such as lipid peroxidation, protein and DNA oxidation in brain neurons and suggested to be the primary cause in degenerative processes like Alzheimer's (Markesbery 1999). Studies have shown that amyloid peptides exert their toxicity on nearby neurons through production of ROS species (Huang *et al*. 2016). Decreased SOD, glutathione peroxidase and catalase activity in AD frontal and AD temporal cortex has been seen in AD affected brains compared to that of normal controls (Wojsiat *et al*. 2018). The level of these antioxidant enzymes including glucose-6-phosphate dehydrogenase (G6PD) are found to be lowered in the erythrocytes of Parkinson's (Abraham *et al*. 2005). Similarly, there is decreased activity of antioxidant enzymes in the retinal pigmented epithelial cells of ARMD affected eyes with subsequent increase in ROS species leading to retinal degeneration (Jarrett and Boulton 2012).

7. Genetic factors unique to NDs and/or glaucoma

7.1 *Autoinflammatory factors*

Recent studies synonymously associated genes responsible for activation and/or enhancing inflammation with neurodegenerative diseases. For instance, RAGE (Receptor for Advanced Glycation End products) which is responsible for inducing receptor-dependent autoinflammatory reactions has been shown to regulate aggregation of Aß (Fang *et al*. 2018). Polymorphisms in phospholipase C gamma 2 (PLCγ2) which are risk factors in AD pathogenesis (Sims *et al*. 2017) is also has been linked to autoinflammatory diseases (Ombrello *et al*. 2012; Zhou *et al*. 2012). Likewise, variants in triggering receptor expressed on myeloid cells 2 (TREM2) has been associated with NDs such as AD (Jonsson *et al*. 2013), ALS (Cady *et al*. 2014) and frontotemporal dementia (Lattante *et al*. 2013). TREM2 expresses as a microglial receptor and plays both as an anti-inflammatory protein as well as to amplify inflammation depending on the cell types and cellular pathways. In cells, decreased expression of TREM2 leads to upregulation of various proinflammatory cytokines (Yin *et al*. 2016) while knockdown of TREM2 in AD mouse models shows decreased inflammatory mediators (Jay *et al*. 2017). Similarly, gut microbiota has been shown to regulate neuroinflammatory responses in the progression of Parkinson's disease (Sampson *et al*. 2016) as well as in Alzheimer's progression (Itzhaki *et al*. 2016). Altogether, these studies corroborate the fact that genetic factors responsible for autoinflammation augments in the progression of neurodegenerative diseases. Concurrently, so far association of these genes involved in autoinflammation are not studied in the context of pseudoexfoliation pathogenesis. Yet, wide association of autoinflammatory factors with NDs strongly warrants future studies in relation to pseudoexfoliation cases.

7.2 *CAG repeats*

Trinucleotide long repeats such as CAG repeats accounts for several neurodegenerative diseases (Usdin and Grabczyk 2000; Wanker 2000). Long stretch of CAG repeats in the *HTT* gene codes for a long polyglutamine stretches within huntingtin protein corresponding to the severity of the disease (Zheng *et al*. 2010). In patients with spinocerebellar ataxia not only CAG repeats but CTG repeats are reported with an elongated polyglutamine domains in the proteins (Honti and Vecsei 2005; Usdin and Grabczyk 2000). Wang *et al*. has shown that CAG repeats in the gene, Ataxin-2 is a genetic risk factor for developing amyotrophic lateral sclerosis (X Wang *et al*. 2014). Similarly, study subjects with CAG expansions in the spinocerebellar ataxia type 7 gene are shown to have

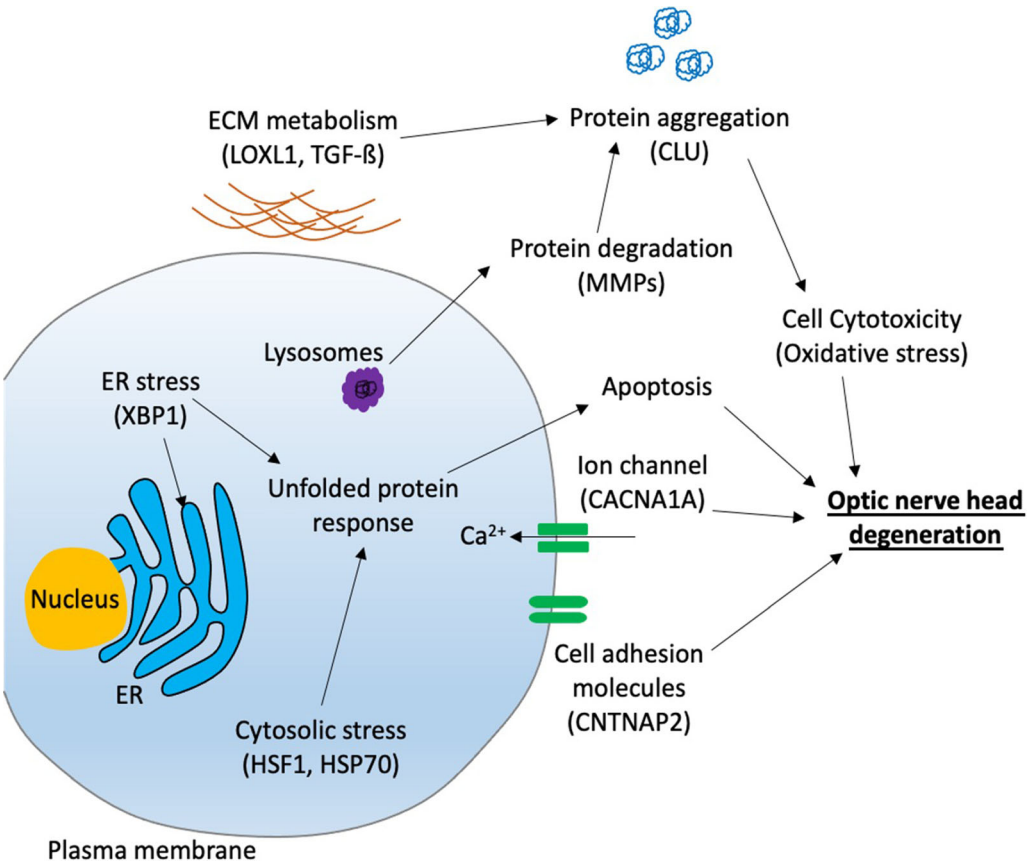

Figure 2. A schematic representation depicting the role of various genetic factors contributing towards the aetiogenesis of pseudoexfoliation in ocular tissues. Key genetic factors associated with pathogenesis of PEX till date are presented. Aberrant expression of genes like LoxL1 and TGFβ leading to abnormal ECM metabolism in PEX aggregate formation in tissues such as trabecular meshwork and lamina cribrosa are one of the primary causes (Browne *et al*. 2011; Pasutto *et al*. 2017; Wallace *et al*. 2013). Subsequently, decrease in the clearance of cellular debris as well as increased toxicity by accumulation of extracellular deposits by proteins like Clusterin (Padhy *et al*. 2014; Zenkel *et al*. 2006) and MMPs (Kara *et al*. 2014; Zenkel *et al*. 2005) in lens capsule and aqueous humor enhances PEX aggregate formation. Further, deregulated calcium channelling by CACNA1A presumably in ciliary body and iris (Aung *et al*. 2015; Schlotzer-Schrehardt *et al*. 2001), disrupted cell-cell interactions by CNTNAP2 in tissues like ciliary epithelium and trabecular meshwork (Krumbiegel *et al*. 2011) and diminished activity of proteins involved in unfolded protein response (Hayat *et al*. 2019) in lens capsule tissues may ultimately leads to apoptosis and cell death.

macular degeneration (Abe *et al*. 2000). Despite wide range of phenotypes in these disorders this hint towards a common genetic cause behind polyglutamine expansion and in the progression of these neurodegenerative diseases. To date, CAG repeats as a causative risk factor in the pathogenesis of pseudoexfoliation is not reported and may be researched as a potential target in the future studies.

7.3 *Glutamate metabolism*

Glutamate plays a vital role as a neurotransmitter in the central nervous system. Deposition of glutamate has been associated with various neurodegenerative diseases such as Alzheimer's (Simpson *et al*. 2010), Huntington's (Faideau *et al*. 2010) and amyotropic lateral sclerosis (Rothstein 2009). Accumulation of extracellular glutamate mediates neurotoxicity and/or excitotoxicity which is prevented by glutamate transporters like high-affinity excitatory amino acid transporter 2 (EAAT2) (Kim *et al*. 2011; Rothstein *et al*. 1996). For instance, decrease in the expression of EAAT2 leads to deposition of glutamate which then results in neuronal death and has been reported in several NDs (Li *et al*. 1997; Tanaka *et al*. 1997; Trotti *et al*. 2001). Similarly, depletion of glutamate transporters like glial glutamate transporter (GLT-1) and excitatory amino acid transporter 1 (EAAT1) leads to accumulation of glutamate thereby neurodegeneration

in the progression of epilepsy (Rothstein *et al*. 1996). In contrast, riluzole, an anti-glutamatergic drug which inhibits the release of glutamate is used to treat ALS (Blasco *et al*. 2014).

In reference to the optic system, glutamate plays a crucial role in transporting visual information from the optic to the brain (Brandstatter *et al*. 1998). Studies have shown that in subjects with glaucoma there is an increase in extracellular glutamate levels in the vitreous humour which in turn is responsible for the death of retinal ganglion cells (Vorwerk *et al*. 1996). Additionally, MK-801 a non-competitive antagonist for glutamate receptor shows neuroprotective properties against retinal ganglion cells (RGC) death with increased IOP in mice (Chaudhary *et al*. 1998; Schori *et al*. 2001). Although, the role of glutamate in the progression of PEX is not investigated so far, precipitation of glutamate in the posterior as well as anterior chamber of eye may lead to cytotoxicity and increased IOP which in turn amplifies apoptosis in ONH cells and RGCs.

7.4 *Optineurin*

Optineurin (Optn) plays a prominent role in autophagy as an autophagy receptor in addition to other cellular functions (Weil *et al*. 2018). In addition to ALS (Fifita *et al*. 2017; Liu *et al*. 2018) and Huntington's (Schwab *et al*. 2012), Optn also has been associated with primary open angle glaucoma (POAG) (Rezaie *et al*. 2002). At both genomic (Fifita *et al*. 2017) and proteomic level (Sundaramoorthy *et al*. 2015), Optn has been linked to ALS which progresses through spinal motor neuron degeneration. Schwab *et al*. have shown colocalization of Optn along with inclusion bodies in the affected cortex tissues of Huntington's patients (Schwab *et al*. 2012). Likewise, mutations in Optn are also linked with frontotemporal dementia (FTD) that manifests through deterioration of frontal-temporal lobes (Pottier *et al*. 2015). Various studies have also shown genetic associations of mutations in Optn with POAG (Fan *et al*. 2005; Park *et al*. 2007). Further, these reports suggests that mutations in POAG associated genes such as myocilin (Fan *et al*. 2005) and APOE (Park *et al*. 2007) may acts cooperatively at molecular level in the background of POAG pathogenesis. Association of Optn with NDs as well as its role in autophagy justifies it as a strong candidate gene which needs to be studied in association with PEX.

8. Summary

Gradual loss of optic nerve in pseudoexfoliation glaucoma strongly categorizes it as a neurodegenerative disorder of visual system. Similarities between PEXG and other neurodegenerative diseases not only confines to the type of cells affected in the disease pathology but also due to identical genetic risk factors involved in the aetiology of the disease as depicted in the figure 2. Considering PEXG as an optic neurodegenerative disorder opens a fresh approach to understand the mechanism of PEX pathogenesis. This strongly emphasizes for future studies to be done to explore the role of previously reported neurodegenerative disease associated genetic candidates with that of pseudoexfoliation.

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