Cataract is the opacification of the lens that causes loss of vision. Age-related cataract (ARC) is one of the most common form of cataracts, characterized by a progressive increase in fluorescence, yellowing/tanning and precipitation of lens proteins (crystallins), primarily in the inner core of the lens. It occurs mainly in the elderly persons after about 45-50 years of age. The incidence of ARC is expected to rise with increasing average age of populations in many countries and the only treatment available is surgical extraction of opacified lens. It is desirable to develop non-surgical treatment or measures to delay/prevent the onset and progress of cataracts. To achieve this, clear understanding of the structure, development and function of the normal lens, and mechanisms that lead to ARC formation is required.

**2.1 STRUCTURE OF THE HUMAN EYE**

The architecture of human eye is complex and it performs the function of visual perception very precisely and in an amazing manner. Figure-2.1 depicts the structure of the human eye. The outermost part of the eye comprises sclera and cornea. Sclera is a white strong fibrous protective coat covering 85% of the posterior surface of the eye and the cornea is a transparent viscoelastic tissue covering the anterior portion of the eye that focuses incoming light onto the lens. Beneath this is the choroid, containing the iris and the ciliary body, which together are known as the uvea. The iris is a ring of muscle fibres located behind the cornea and in front of the lens. It contains melanocytes that have the pigment melanin which prevents scattering of light. There is an opening in the iris called pupil, which contracts and expands in response to the brightness of the surrounding light. The lens is a transparent tissue located behind the iris and the pupil. It is positioned between the aqueous and vitreous humor by the zonular fibres that are attached to the ciliary body. The contraction and expansion of these zonular fibres alter the curvature of the lens thus facilitating adjustable focus, a process known as lens accommodation (Harding, 1991). The iris and the lens bathe in the aqueous humor, a transparent watery fluid that contains various enzymatic and non-enzymatic antioxidants. Watery fluid present in the aqueous humor maintains intraocular pressure. Behind the lens is the vitreous humor that provides growth factors and support to the eye. It also serves as a shock absorber against mechanical damage. The light focused by the lens passes through the vitreous humor and reaches the
retina, the centre of the visual process. The retina is composed of photoreceptor cells, rods and cones which convert light rays into electrical signals and are transmitted to the brain through the optic nerve. Rods and cones provide the ability to see in dim light and to see in colour, respectively. Rod cells present at the peripheral region of retina are mainly responsible for night vision and seeing movements and objects present on the sides (i.e., peripheral vision). Most of the cone cells are located in macula, present in the center of retina, is responsible for central vision, seeing colour, and distinguishing fine details. The optic nerve, located behind the retina, transmits signals from the photoreceptor cell to the brain. Each eye transmits signals of a slightly different image, and the images are inverted. Once they reach the brain, they are corrected and combined into one image. This complex process of analyzing data transmitted through the optic nerve is called “Visual Processing”.

(https://www.capioeye.co.uk/eyeinfo/anatomy/index.html)

**Figure-2.1:** The cross-section of the human eye
2.2 THE HUMAN LENS

The lens is an essential part of the eye that maintains normal vision. It typically contributes one third of the eye’s total dioptric power (the degree to which a lens converges or diverges light), and by changing its shape, it is able to fulfill the requirements of the accommodative processes. The normal human lens is a transparent, pale yellow, biconvex body contained within an elastic collagenous capsule (Figure 2.2). The capsule allows the diffusion of small molecules such as oxygen, glucose, amino acids, fatty acids and other nutrients into the lens tissue and few molecules like lactose and carbon dioxide out of the lens tissue. The elastic nature of lens capsule is important for controlling the lens shape during focusing the image. Optic lens is an avascular organ that obtains all nutrients from the aqueous and vitreous humors where it bathes (Berman, 1991).

![Figure 2.2: The cross-section of the human lens](Modified figure adapted from Wormstone et al, 2006 and Harding, 1991)

All cells within the lens are derived from epithelial cells, which are located at anterior pole. In the normal lens, growth begins at the equatorial germinative zone, where epithelial cells differentiate into fibre cells. Fibre cells elongate from the anterior region of the lens, curving around towards the posterior end, where they meet to form lens sutures. New fibre cells are laid down as concentric layers on the previously formed embryonic fibres located at the centre i.e. lens nucleus. Fibre cells experience loss of the nuclei and other intracellular organelles, thus becoming metabolically quiescent (Tardieu and Delaye, 1988). Due to the lack of nuclei, DNA and RNA, there is little or no turnover of lens
proteins as the cell ages (Bloemendal, 1977). Therefore, cells contained within the lens nucleus are amongst the oldest cells in the body and have some of the oldest proteins. The lens is thus an exceptional system for the study of age-related processes.

2.2.1 Development and Growth of Human Lens

Formation of the lens (Figure-2.3) is the result of a series of inductive process. The human lens is anatomically first visible at 3 to 4 weeks of gestation. The ectoderm surface over the eye field thickens and forms the lens placode, and then invaginates into an optic cup, forming the lens pit. At the end of fifth week the lens pit closes and the resulting lens vesicle pinches off from the surface ectoderm leading to the formation of anterior segment of the eye.

(Adapted from http://www.nature.com/nrg/journal/v4/n11/fig_tab/nrg1202_F2.html)

Figure-2.3: Schematic diagram of various stages in growth and development of the lens

The inner lining of the vesicle consist of a layer of epithelial cells covered by a basal lamina which eventually thickens to become the lens capsule. The lens vesicle is nearly spherical with a central cavity. During the seventh week of development the cavity is filled by the posterior cells which elongate anteriorly to fill the lumen. The tiny developing lens is surrounded by a basement membrane that becomes the lens capsule and is filled with nearly structureless primary lens fibres. These cells expel their nuclei, mitochondria, Golgi bodies and endoplasmic reticulum in due course and the structure becomes a spherical, optically clear embryonic nucleus which is 0.35mm in diameter and stays unchanged throughout life. From this time a life long process of formation of secondary fibre cells around the embryonic lens nucleus is initiated. This region of secondary fibre formation surrounding the lens nucleus is referred to as the cortex. The mid line that passes through
the secondary lens fibres from the opposite ends of the equator joins to form the lens sutures - anterior and posterior lens sutures.

The human lens grows continuously throughout the lifespan of an individual, with the maximum rate being observed in the fetus. Humans are born with ~1.6 million fibre cells. This reaches 3 million at age 20 years and almost 3.5 million fibre cells at age 80 years (Horwitz, 2003). The mass of the lens starts at ~65 mg at birth and increases to ~125mg by the end of the first year to ~260mg by 90 years of age (Saude, 1993).

The anatomical and physiological features of the lens are designed to keep light-scattering to a minimum, and maintain lens transparency in the visible region of the spectrum (400 to 800nm). These include a high concentration (up to 500mg/ml) of proteins known as crystallins and enucleated fibre cells grouped in hexagonal arrays with minimal extracellular spaces (Delaye and Tardieu, 1988). Tight control of electrolyte balance in the lens is necessary to maintain a constant hydration level. Disorganization of the fibre membranes and the lens proteins is believed to be a factor in visual impairment.

2.3 COMPOSITION OF LENS

The lens is comprised of ~60% water and 35% proteins (crystallins) by mass. The remainder includes varying quantities of amino acids and trace minerals (e.g. sodium, potassium, copper, iron, zinc, selenium, chromium and cobalt) and many low molecular mass compounds including antioxidants (e.g. glutathione (GSH), ascorbic acid, uric acid) and UV filter compounds.

2.3.1 Lens Proteins

The crystallins of the human lens constitute more than 90% of the lens proteins. The other proteins present in the lens include those associated with membranes and the cytoskeleton, and enzymes involved in lens metabolism. The majority of protein synthesis occurs in the lens cortex from amino acids that have been transported into the lens from the aqueous humor.

Crystallins are structural proteins that maintain refractive properties and stability of the lens. Bovine and human lens proteins contain three distinct groups of crystallins,
designated α, β and γ, based on decreasing molecular mass. α-Crystallin is by far the largest of the crystallin proteins and is not sequence-related to the β- and γ-crystallins. There are two α-crystallin proteins, αA and αB, found in a three to one molar ratio in human lenses. Each α-crystallin subunit is ~20kDa, however, they exist as a heterogenous multimeric assembly with a molecular mass distribution ranging from 500 to 1000kDa. The amino acid sequence homology between αA (acidic) and αB- (basic) crystallins is approximately 60%. αA and αB-crystallins are continuously synthesised and are found in the lens epithelial cells. While αA-crystallin is found mainly in the lens, with trace amounts in other tissues, αB-crystallin is considered to be a ubiquitous protein with measurable levels found in the brain, muscles and heart. In addition to their structural role, α-crystallins function as molecular chaperones in the lens, regulating protein folding and preventing non-specific protein aggregation in the intact lens (Horwitz, 1992). The β- and γ-crystallins are structural and fibre cell specific proteins. β-Crystallins exist as multiple forms of aggregated proteins from dimers to octamers, with molecular masses from 5 to 200kDa. β-Crystallins comprise seven proteins, βA1-A4 (acidic) and βB1-B3 (basic). The γ-crystallins exist as monomers (~20kDa) and are structurally and sequence wise related to the β-crystallins. Hence, they are often categorised together as the β, γ-crystallin superfamily. In human lenses, the γ-crystallins are comprised of seven proteins, γA-γF and γS, with γC, γD and γS being the dominant polypeptides.

2.3.2 Antioxidants in Lens

There are several different mechanisms that protect the lens from the effects of oxidation. These include both enzymatic (superoxide dismutase, catalase, glutathione redox cycle enzymes and Indole amine 2, 3–dioxygenase) and non-enzymatic factors (GSH, ascorbic acid, α-tocopherol, β-carotene, uric acid). The activities of the various protective systems are generally higher in the cortex than in the nucleus, with the epithelial layers being particularly active. Antioxidants present in the lens play a major role in the protection of cells from harmful reactive oxygen species including peroxides, reduction of disulfides, removal of xenobiotic electrophiles and inhibition of oxidation of endogenous chemicals such as ascorbate, catechols and aminophenols. This protection, however, is not absolute and low levels of damage may accumulate throughout life.
2.3.3 UV filters in Lens
The damaging wavelength of UV radiation that reaches the lens is in the range of 300-400nm. The majority of this UV radiation (~90-95%) is effectively absorbed by low molecular mass lenticular UV absorbers, known as UV filters which are biosynthesised in the lens in the anterior cortical epithelial cells. They have a maximum absorption at 360-370nm and, protect the lens from UV induced photodamage (Vanheyningen, 1973).

Quantitatively, 3-hydroxykynurenine-\(\cdot\)D-glucoside (3OHKG) is the most prevalent one (~50-400 nmol/g) among the UV filters, followed by the glutathione adduct of 3OHKG (GSH-3OHKG; ~0-600nmol/g), 4-(2-amino-3-hydroxyphenyl)-4-oxobutanoic acid-\(\cdot\)D-glucoside (AHBG; ~5-80nmol/g), kynurenine (Kyn; ~5-30nmol/g), 3-hydroxykynurenine (3OHKyn; ~2-15nmol/g) and 4-(2-amino-3-hydroxyphenyl)-4-oxobutanoic acid-\(\cdot\)D-diglucoside (AHBDG; ~0.2-9.8nmol/g; Bova et al, 2001). With ageing the levels of free UV filters get decreased and are involved in covalent modification of lenticular proteins.

2.4 LENS OPACIFICATION OR CATARACT
With ageing, a broad spectrum of molecular, biochemical and structural changes occur in lens, which leads to opacification and loss of transparency resulting in cataract formation. Cataract becomes clinically significant when the lens opacification interferes with visual function. Progression of cataract decreases the lens transparency leading to increased light scattering, diminished focus of light on to the retina and vision impairment. Mechanism of cataract formation involves the disrupted structure of the lens fibre cells, accumulation of protein aggregates, or cytoplasmic dysfunction in the lens cell.

2.5 TYPES OF CATARACTS BY ORIGIN
Cataracts can be generally developed as primary or secondary cataracts based on their origin. Along with these two types there are other types of cataracts like traumatic cataract and radiation cataract. These cataracts may be caused by variations in genome, ageing degeneration, birth defects, diabetes, nutritional deficiency, radiation, and trauma.
2.5.1 Primary Cataract
Primary cataract evolves by itself rather than as the unintended consequence of a surgical procedure, as a medication side effect, or as a result of some other associated condition. Primary cataracts may develop at any age, at the time of birth (congenital) or with ageing (age-related). Children born with congenital cataract without any history of metabolic disorders or exposure to pathogens, radiation etc. while in mother’s womb come under primary cataracts. Most of the age-related cataracts without any associated conditions are considered as primary cataracts. They generally develop after the fourth decade of life as a multi-factorial condition. Both environmental and genetic factors are associated with development of ARCs.

2.5.2 Secondary Cataracts
Cataracts can sometimes develop after undergoing eye surgery, such as surgery for glaucoma, retina etc. Patients with diabetes, retinitis pigmentosa, hypoparathyroidism, atopic dermatitis, and uveitis may develop cataracts earlier than normal. Patients who are treated with steroids for an extended period of time lead to the development of secondary cataracts.

Other rare types of cataracts which include traumatic and radiation cataract result due to trauma or injury to the eye and long term exposure to radiation, respectively. Traumatic cataracts may develop immediately or years after an event that damages the eye. It often occurs after blunt trauma to the eye or from exposure to certain chemicals.

2.6 CLASSIFICATION OF AGE-RELATED CATARACTS (ARCs)
Different classification systems are available for ARCs. Basic classification is based on the anatomy and location of opacities and the other classifications are based on further grading of each type of cataract using standard photographs.

2.6.1 Based on the Anatomic Location of Opacity
Age-related cataracts are divided into 3 types based on the anatomy and location of opacities in the lens (Figure-2.4) as Nuclear, Cortical and Posterior subcapsular types.
Patients commonly develop opacity in more than one area of their lens which can cause overlap in the classification of cataracts. They are classified under Mixed Type.

A) Slit lamp photographs of different types of cataracts

B) Illustration of types of age-related cataract

Figure-2.4: A) Slit lamp photographs and B) Illustration of the types of age-related cataracts 1) Nuclear cataract (NC) 2) Cortical cataract (CC) 3) Posterior subcapsular cataract 1] NC, a cross-sectional view of the lens showing the location of a nuclear opacity in the central fibre cells and the Pattern of fibre cells shown in left panel. A view of the lens through the maximum dilated pupil shown in right-hand panel. The cataract is in the center of the visual axis. 2] CC, opacity in a cluster of cortical fibre cells shown in left and a view from the pupil is shown in the right panel. The opacity is not significant until it reaches the visual axis. 3] PSC, cluster of cells accumulated at the posterior pole of the lens. The opacity that lies in the visual axis causes maximal degradation of visual acuity.

a) Nuclear Cataract (NC)
It is the most frequently occurring cataract observed in general population. It is seen as yellowing and hardening of the central portion of the crystallin lens progressing slowly over years. As the core of the lens hardens, it often causes the lens to increase the refractive power and nearsightedness.
b) Cortical cataracts (CC)

It occurs when the portion of lens fibres surrounding the nucleus become opacified and gradually gets extended from the periphery to the center. The impact on vision is related to how close the opacities are to the center of the visual axis and their impact can vary greatly. Progression is variable over years. The most common symptom of cortical cataracts is glare, especially from headlights during night driving.

c) Posterior subcapsular cataracts (PSC)

Opacities located in the most posterior cortical layer, directly under the lens capsule progresses more quickly. This type of cataract tends to occur in younger patients than cortical or nuclear cataracts. Progression is variable but tends to occur more rapidly than the nuclear cataract. Symptoms include glare, difficulty seeing in bright light, and near vision is often more affected than the distance vision.

2.6.2 Cataract Grading Systems

Most systems for the classification of cataracts are designed based on slit-lamp assessment where grading is done by comparison with standard diagrams, with the alternatives of microscopic or photographic grading. The nature and complexity of the scaling varies markedly between the systems used. Objective classification schemes use photographic standards to subdivide each major type into grades. These grades are based on density and colour in the case of the nucleus or according to the anatomical area of the cataract in the case of the cortical and posterior subcapsular areas. The grades of opacification are determined following any of the methods given below

1. Oxford Cataract Classification System
2. Lens Opacities Classification System III (LOCS III)
3. Optical Biometry Based Cataract Grading System (OBBCGS)

1. The Oxford Clinical Cataract Classification and Grading System

Sparrow et al, (1986) developed the Oxford Clinical Cataract Classification and Grading System. This technique, which has found wide acceptance and has been used in many clinical trials, is a slit-lamp-based system in which cataracts are classified based on morphological features.
2. **Lens Opacities Classification System III (LOCS III)**

The LOCS III is a highly practiced classification system developed by Chylack et al, 1993. It uses a set of colour photographs as standards for comparison to further divide each type of cataract. Research has demonstrated that the LOCS III system is highly reproducible. The gradings are

- Nuclear opalescence (NO1-NO6)
- Nuclear colour (NC1-NC6)
- Cortical cataract (C1-5)
- Posterior subcapsular cataract (P1-5)

3. **Optical Biometry Based Cataract Grading System (OBBCGS)**: By the procedures planned for phacoemulsification, LOCS III can be converted into newer cataract grading systems. Pardianto (2009) introduced Optical Biometry Based Cataract Grading System (OBBCGS) that is helpful in cataract grading due to phacoemulsification planning.

<table>
<thead>
<tr>
<th>LOCS III</th>
<th>OBBCGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC0, C0 and P0</td>
<td>No or absence of cataract</td>
</tr>
<tr>
<td>NC1-3, C1-3, P1-4</td>
<td>Optical Biometry Examined Cataract (OBEC)</td>
</tr>
<tr>
<td>NC4-5, C4-5, P4-5</td>
<td>Optical Biometry Unexamined Cataract (OBUC)</td>
</tr>
</tbody>
</table>

2.7 **SYMPTOMS AND DIAGNOSIS OF CATARACT**

Age-related cataracts develop slowly, without pain and cause few symptoms until they noticeably block light and affect vision. Symptoms and diagnosis of cataract include

- **Decreased visual acuity**, one of the first signs of cataract development. Visual acuity testing is conducted to detect changes in visual function, using the Snellen Visual Acuity Chart but it is not always the best measure to indicate for cataract surgery.
Reduced contrast sensitivity and glare that cause difficulty in seeing objects due to poor vision in bright sunlight or strong lights at night, such as on coming headlights. All cataracts lower contrast sensitivity, but it is most severe in posterior subcapsular cataract.

Myopic shift which is associated with nuclear cataract. The opacities develop in the nuclear region of the lens and changes the way light bends (or refracts). This produces greater nearsightedness referred as a myopic shift.

Double vision and colour shift also form the signs of cataract. Monocular diplopia (double vision in one eye) occurs with lens opacities, particularly cortical spoke cataracts. Colour shift is produced by a lens that is more absorbent at the blue end of the spectrum, causing colour perception to fade. Colour shift is common with nuclear cataracts.

2.8 CAUSAL MECHANISM OF DIFFERENT TYPES OF ARCS
Age-related cataracts generally develop as three main types, which include nuclear, cortical and posterior subcapsular cataract. Development of each type of age-related cataract has its own specific mechanism which include oxidative damage, covalent binding of UV filters to lens proteins, protein aggregation, breakdown of the glutathione, damage to fibre cell membranes, protein breakdown, high calcium, abnormal lens epithelial cell migration, or aberrant changes in lens fibre cells.

2.8.1. Nuclear Cataract
Nuclear cataracts are formed due to increased oxidative damage of lens proteins and lipids resulting in protein-protein interactions that in turn leads to aggregation of proteins ending in light scattering. There is a strong connection between aging and high levels of oxidized glutathione in the lens nucleus indicating an imbalance between protein and lipid oxidation, and glutathione-dependent reduction. Nuclear cataract formation may result due to separation of lens cell cytoplasm (a jelly-like substance) into protein-rich and protein-poor liquid phases accounting for the opacity.
2.8.2 Cortical Cataract
Cortical opacities start in small portion of the lens periphery and it may spread around the circumference of the lens. Damage of the fibre cell plasma membrane, loss of molecules like glutathione, increased proteolysis, and lack of calcium homeostasis are few interrelated mechanisms as any one of them leads to another during the initiation of cortical opacities. Damage to systems responsible for calcium homeostasis spreads opacification in the peripheral region of lens and later on towards the nucleus. Increased calcium levels have been recorded in damaged cells of lens with cortical cataracts. Elevated calcium leads to breakdown of protein, aggregation of proteins, and light scattering.

2.8.3 Posterior Subcapsular Cataract
Environmental stresses such as ultraviolet light, diabetes, and drug ingestion are factors causing posterior subcapsular opacities. In this type of cataract, opacities develop at the back of the lens, beneath the lens capsule associated with abnormal migration of lens epithelial cells or aberrant changes in lens fibre cells. Opacities lying within the line of sight, in these cataracts can be particularly debilitating.

2.9 RISK FACTORS ASSOCIATED WITH LENS OPACIFICATION
Several National and International studies have emphasized the role of different risk factors in the development of cataract. Cataract is acquired with age as a multi-factorial condition involving complex interactions between environmental and genetic risk factors.

2.9.1 Epidemiological Factors
Epidemiological studies helped to figure out that there are multiple risk factors that cause ARCs like ageing, gender, body mass index, size of the lens, exposure to sunlight or radiation, nutrition, habits like smoking and alcohol consumption, systemic conditions like hypertension and diabetes mellitus. Intake of few drugs like corticosteroids, phenothiazines, miotic cholinergic compounds, cancer chemotherapy agents, various photosensitizing drugs, diuretics are associated with cataract development.
Age is considered as important risk factor for age-related cataract with greater chance of developing the condition as the person ages. With ageing, numerous post translational modification of proteins present in the lens leads to cataract development.

Women are at higher risk of developing most types of cataracts as compared to men (Delcourt et al, 2000), though few studies suggests that estrogen may protect female gender against cataract formation (Klein et al, 1994). Long term use of anti-estrogen drug tamoxifen (used to block estrogen receptors) increases the risk of cataract.

Longitudinal studies showed that presence of larger lens increases risk for developing nuclear opacities over a 5-year follow up period but in the case of cortical cataract it is linked with having a smaller lens (Taylor et al, 1988; Klein et al, 1998; Klein et al 2000 and Praveen et al, 2009).

BMI is frequently identified as one of the risk factor for cataract development. BMI affected by the glucose levels are associated with higher risk for cataract. Few studies showed that higher BMI increases the levels of uric acid leading to gout which in turn is associated with lens opacification. It is an important determinant of hypertension which has a controversial relationship with cataract. Few evidences support that there is a possible protective effect of restriction of energy intake on the risk of cataract by protection against oxidative stress to the lens. In developing countries few studies showed the association between low BMI and cataract.

Geographical areas like tropical countries with more hours of sunshine have a greater prevalence of cataract, showing an association between ultraviolet B irradiation and cataract formation. Exposure to X-rays or gamma radiation also acts as a risk factor for cortical and posterior subcapsular cataracts in humans.
**Nutrition**
A diet lacking adequate intake of antioxidants, particularly vitamins A, C, and E, fails to protect the lens from cataract formation.

**Smoking and Alcohol addiction**
Smoking is one of the most important risk factor for developing cataract. Nicotine, free radicals, and carbon monoxide present in smoke increases oxidative stress leading to pathogenesis of ARC. Many epidemiologic studies suggest that smoking was associated with an increased risk for nuclear cataract. Alcohol consumption also acts as one of the risk factors for opacification, which depends on quantity of intake.

**Associated conditions**
Several ocular and other diseases are found to be associated with age-related cataract, which include glaucoma, myopia, coronary disease, hypertension and diabetes. In few cases hypertension and diabetes collectively leads to the development lens opacities.

**Drugs**
Use of cataractogenic potential drugs like phenothiazines, miotic cholinergic compounds, cancer chemotherapy agents, various photosensitizing drugs, diuretics, major tranquilizers, gout medications, cholesterol-lowering medications, and many others leads to lens opacification which is similar in appearance to age-related cataracts. Intake of corticosteroids is strongly associated with the development of posterior subcapsular cataracts, but less strong for others.

### 2.9.2 Genetics Factors
Genetic studies conducted from past few decades have emphasized the involvement of genes in the development of ARCs. In Framingham eye study, (1994) strong association was found between sib ship for nuclear and posterior subcapsular cataract. In Beaver Dam eye study the result on segregation analysis suggested that a single major gene may account for 58% of the variable risk of development for cortical cataract and another single major gene may account for 35% of nuclear cataract (Heiba et al, 1993 & 1995). As per Cat-Map database about 200 genes and loci have been implicated in the development of Mendelian and age-related forms of cataract (Shiels et al, 2010). Hereditary (Mendelian)
forms of cataracts are most frequently inherited as autosomal dominant, but also can be inherited as an autosomal recessive or in X-linked fashion. Of the Mendelian forms, congenital cataracts can be inherited as highly penetrant Mendelian traits, with autosomal dominant inheritance than as recessives. Around 39 genetic loci have been mapped for isolated congenital cataracts. Most of the mutations associated with congenital cataract are confined to crystallins, followed by connexins, heat shock transcription factor-4 (HSF4), aquaporin-0 (AQP0, MIP), and beaded filament structural protein-2 (BFSP2).

Cat-Map database showed the involvement of around 20 genetic loci in the development of age-related cataracts. Of which, variations in at least eight genes linked with inherited cataract have been associated with age-related cataract. These include EPHA2 (1p), GJA8 (1q), GALT (9p), SLC16A12 (10q), HSF4 (16q), GALK1 (17q), FTL (19q), and CRYAA (21q). Variations in at least eleven other genes not directly associated with inherited cataract have been tentatively implicated in age-related cataract. These include genes that function in antioxidant metabolism (GSTM1, 1p; GSTT1, 22q), xenobiotic detoxification (NAT2, 8p), DNA repair (ERCC2, 19q), folate metabolism (MTHFR, 1p), lactose metabolism (LCT, 2q), RNA demethylation (FTO, 16q), lipid/cholesterol transport (APOE4, 19q), kinesin/microtubule motor transport (KLC1, 14q), Tryptophan metabolism (IDO1) and one of unknown identity (ARCC1, 6cen). In addition to these, variants of several other genes involved in diverse biological functions mediating estrogen metabolism, systemic inflammation, folate metabolism, and kinesin motor transport are indicated as contributing factors in the development of cataracts.

Family-based linkage studies and case control association studies do help to identify, test, and validate candidate genes for age-related cataract. In addition, the advent of whole genome sequencing techniques capable of deciphering genetic variation in large numbers of individuals will provide powerful insights regarding the molecular genetic basis of age-related cataract. Ultimately, a molecular genetic understanding of age-related cataract may aid the design of targeted drugs to help treat and manage cataract, thereby reducing the need for surgery.

So far the only treatment available for cataract is the surgical removal of opacified lens, which is a cost burden to the community as well as to the governments. Research carried
out by several investigators will throw light on better understanding of etiology, development and progression of cataract. These studies may help in developing the drugs to prevent and delay the onset or cataract progression. Finally it lowers the burden to the individual family and the government by avoiding the cost of surgery.