Genetics of congenital cataract, its diagnosis and therapeutics

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Abstract
Congenital cataract is defined as an opacification of the eye lens appearing at birth or shortly thereafter. Congenital cataract is one of the highest significant causes of blindness or optical impairment in the childhood. Cataract, the cloudiness of the lens is the most frequent reason of blindness worldwide, demonstrating nearly half of all causes of loss of sight worldwide. A significant amount of isolated congenital cataract has monogenic roots. It is genetically heterogeneous, and all the modes of Mendelian inheritance have been described. Numerous genes linked with inherited and paediatric cataracts have been recognised. Inherited congenital cataract has been linked with mutations in particular genes, comprising of crystallins, membrane transport channel proteins, gap junction proteins, the development transcriptional factors and the cytoskeleton. Discovering the mutations and the genes responsible for cataractogenesis are important in achieving a response to the molecular deficiencies and pathophysiological features of inherited congenital cataracts.

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1. Introduction

The human eye is an organ of vision. It plays a major role in life, giving us the sense of sight, and allows to understand about the world around us. Visualization and interpretation of colours, shapes and dimensions of numerous objects are made possible by eye. Inherited eye diseases comprise 1/3 of all reported human genetic disorders [1]. Congenital cataract is the type of cataract, which occurs at the early stages of life [2]. It is described as an opacity of the crystallin lens causing an impaired vision [3], and the abnormality of the lens can impede with the normal development of the eyes [4]. The prevalence varies with socioeconomic rank affecting 1–6 cases out of 10,000 live births in the developed countries and about 5–15 out of 10,000 cases in the developing countries of the world. Autosomal dominant, autosomal recessive and X-linked genetic type of congenital cataracts, which may be sequestered (nonsyndromic) or associated with systemic disorder or syndromes [5]. The phenotypic arrangement is founded over the site & the type of the lens imperviousness that containing posterior polar, anterior polar, lamellar, and nuclear, coralliform, and cataract, pulverulent, cortical, polymorphic and total cataract [6]. Phenotypically same cataracts might be caused by mutation at different genomic loci and possibly control, unlike inheritance pattern, whereas physically variable cataracts might be seen in a particularly large population [7]. About 50% of cases have a genetic root with other causes counting intrauterine infection, malnourishment and metabolic diseases [3]. Mutation in more than 30 genes is identified to cause non-syndromic forms of innate cataracts [8]. The discovery of the mutations affecting congenital cataract should result in a better way of the procedure concerned in cataractogenesis and give further insights into the normal lens development and structure [9]. Hereditary research has recognised mutations in various genes associated with cataracts like crystallin that are severe enough to cause accumulation of protein in the fibre cells increase larger refractive indices, responsible for about 38% of the wet mass of the lens. A large quantity of protein in the fibre cells work together by Crystallin, which is responsible for about 38% of the wet mass of the lens. A large quantity of protein in the fibre cells increase larger refractive indices, which give concrete phenotype to the lens, known as transparency.

2. Embryology

The lens development is happening through the collections of controlled processes. Embryology and morphogenesis of the eye lens in the animal as well as in human beings provided an insight into the sophisticated and innate disorder that may concern in the characteristic eye phenotypes present in congenital cataract. The optical vesicle that causes the lens is covered by ectodermal cells. The lens placode interferes on the optical vesicle initiate from the forebrain, about the 25 days of pregnancy, it is a shortening of the ectoderm, which is the only layer of cuboidal cells that invaginate into the neural ectoderm of the optic vesicle as the lens depths become clear from the ectoderm by the 33rd day. The anterior epithelial cells at that time they move to the equatorial region and produce the lens bow. The cells in the bow area generate secondary lens fibres in the third gestational month, which spread until they cover the primary lens fibres.

Lens sutures are formed in the second month at the anterior extremities [11]. The secondary lens fibres are retained in a determinedly controlled way, such that a distraction grating is, establish with a destructive disorder to decrease the scattering of light. After the birth, the secondary lens fibres are constantly forming and these post-natal fibres make the lens cortex. The mature lens is avascular, aneural and alveolate. The lens includes a great number of proteins, so-called crystallin. About 90% of the soluble protein in the eye lens is work together by Crystallin, which is responsible for about 38% of the wet mass of the lens. A large quantity of protein in the fibre cells increase larger refractive indices, which give concrete phenotype to the lens, known as transparency. The lens centre is often dehydrated and compressed, for this reason, it inhabits greater protein concentration (Fig. 1).

Fig. 1. Typical eye development (http://faculty.washington.edu/tomreh/eyedev.html).
3. Genetic factors of congenital cataract

The genesis of congenital cataract is still not discovered well and very little is identified because of lack of modern techniques, long-term accurate data required and the lack of intense investigative techniques. Various sets of symptoms and infections prior birth suggestion to the malformations in the eye and helps in congenital cataracts development. Although various causes have been bringing into being, the particular aetiology is often difficult to determine, mostly in the patient’s suffering from unilateral hereditary cataracts, clinically and genetically heterogeneous situation [12]. In addition, different mutations in the identical gene are able to cause similar cataract forms, in spite of the fact that the similar mutation in a distinct gene might clue to dissimilar phenotypes are indicated by variable morphologies of cataracts in few families. Isolated congenital cataracts are likely to be expressively autosomal dominant with penetrant Mendelian charismas are more common than autosomal recessive cataract. Many of these are related with additional abnormalities, mainly as a portion of developing syndromes. The key cytoplasmic proteins of human lens are encoded by mutations in different genes and are linked with cataracts of different morphologies, containing genes encoding crystallin (CRYA, CRYB, and CRYG), lens specific connexin (Cx43, Cx46, and Cx50), major intrinsic protein (MIP) or Aquaporin, paired-like homeodomain transcription factor 3 (PITX3), avian musculoaponeurotic fibrosarcoma (MAF), cytoskeletal structural proteins and heat shock transcription factor 4 (HSF4) [13]. An important concern is an αβ-crystallin gene, CRYAB, which is extensively appeared in different tissues mainly in the muscle. Mutations in CRYAB can cause a range of defects ranging from isolated cataracts to minor cataracts linked with myopathy. Another example is the ferritin gene that gives rise to the hyperferritinemia-cataract syndrome [13].

4. Congenital cataracts with inherited ailment set of symptoms

The genes up to date recognized to cause autosomal recessive congenital cataract is crystallin, the heat shock transcription factor, the lens intrinsic membrane protein, the connexin and the cytoskeletal protein.

4.1. Crystallin

The crystallin lens of the eye has been a model system for the intricacies of tissue induction and morphogenesis as well as cell specification and differentiation. Crystallin is main essential constituents of the vertebrate eye lens and exhibit more than 90% of the water-soluble total lens proteins; they play important roles in maintaining the clearness and diversion function of the lens [14]. Crystallin has been categorised into α, β, γ crystallin [15]. They are soluble protein and own an important role in developing the transparency of the lens.

4.2. Alpha (α)-crystallin

α-Crystallin (αA-crystallin and αB-crystallin) belong to the chaperone-like small heat shock protein family (σHSPs). They block the formation of stress protein aggregates to avoid toxic effects [16]. Alpha-crystallin produces 40% of the human lens crystallin [15]. The αA-crystallin in the lens is enormous, complex and comprises of two subunits: the αA polypeptide and αB polypeptide. These subunits possess mechanical roles within the lens but also the member of minor heat shock protein family representing a crucial molecular chaperone action [17].

4.3. CRYAA and CRYAB: genes for α-crystallins

There are two α-crystallin genes, CRYAA and CRYAB, coding α- and α-Crystallin in humans (and superficially most terrestrial vertebrates) [18]. They are situated on the chromosomes (21 and 11), but they are closely combined in a sequence, gene structure and are clearly the consequence of initial gene replication. Both of the genes are 3 to 4 Kb long with three exons. They possess open reading frames (ORFs) of 173 (α) and 175 codons (α). Genetically the gene for αA-crystallin controlled three exons, and this is replicated in the great number of species from fish to birds. However, during the evolution of the mammalian lineage, there was a novelty with the assemblage of an alternatively spliced exon, giving rise to a greater protein product (αAIns) [19]. The ‘insert exon’ is involved in many species, mostly in the rodents. In primates, this alternative splice form was recovered, but the remaining of the insert exon continue in human CRYAA as a pseudoexon. Whereas the sequence is no longer spliced into developed mRNA, it is largely sustaining; raising the curious possibility that mutation could re-establish splicing and possibly lead to a novel cataractogenic deficiency.

5. Beta (β)-crystallin

β-Crystallin is the most prominent protein of the lens, where their firmness and association into innovative track developments are intense for the lens clarity and refraction. The dimerization is an initial step in the determination of β-crystallin complexes. β-Crystallin connection into dimmers is significantly preferred, but rapidly revocable under physical circumstances. β-Crystallin dimmers can interchange monomers, maybe through a brief and extremely not preferred monomer intermediate circumstance.

5.1. Mapping of crystallin, BETA-B3; CRYBB3 ON CHR22q11.23

BB3 is the 11th most important soluble proteins in the young human lens. The BB3 is present on mouse chromosome number 5 [20]. Mutation in the CRYBB3 genes identified in two Pakistani families with autosomal recessive congenital nuclear cataract and G-C exchange at nucleotide 493 in exon 6 of the CRYBB3 gene [21].

5.2. Lens intrinsic membrane protein 2 (LIM2)

Mammalian lens integrity cell membrane surroundings five main proteins [22]. One of the most essential membrane proteins of a lens integrity cell is the MP19. It works in certain ways as a combining component possibly gets connected with the lens cell messages and has been demonstrating to be linked with cataractogenesis.

5.3. Mapping of LIM 2 ON CHR 19q 13.33

The gene for the MP19 was linked to human chromosome number 19. Mapping the L1M2 gene to mouse chromosome number 7 in an area of reserved synteny with human chromosome number 19 [22]. Another research identified an innate Iraqi Jewish family of autosomal recessive manner with a late pulverulent cortical cataract at 19q. Sequencing of L1M2 gene discovered a homozygous T-to-G change, and this declared to be the first report of cataract development in humans associated with a mutation in L1M2.

5.4. Glucosaminyl (N-acetyl) transferase 2 gene (GCNT2)

In the human erythrocytes in the embryonic growth, the foetal (i) antigen is changed by the adult (I) antigen as the significance of
the expression of the (beta-1), 6-N-acetylgalactosaminyltransferase, 1-branching (GCNT2) enzyme, which translates the linear Poly-N-acetyllactosaminoglycans into branched Poly-N-acetyllactosaminoglycans. Commonly the fully-grown erythrocytes entirely express the I antigen, however, in a small number of peoples, the erythrocytes are ironic in the I antigen except I, and this is known as the mature I-phenotype and it is suggested to be influenced by the absence of 1-branching transferase activities.

5.5. Mapping of GCNT2 on Chr 6p24.2

Genetic study of the mature I phenotype in Taiwanese peoples who also suffered from congenital cataracts [23]. Mutation detection has indicated an association among molecular discrepancies in the gene (IGNT) of the mature I-phenotype. Conserved the locus for the autosomal recessive congenital cataract in the 4 Arabic families to the region of 6p24 containing I blood type locus [24]. A novel nonsense mutation, G-A exchange was identified in the GCNT2 gene.

5.6. Heat shock transcription factor HSF4

HSF4 is a mammalian factor that changes the makeup of DNA-binding homotrimer and regulates the minor and the major heat shock proteins. Heat-shock transcription factors (HSFs) activate heat-shock response genes in the phases of temperature or other pressures [25].

5.7. Mapping of HSF4 ON CHR 16q22.1

By using fluorescence, in situ hybridization processing map the HSF4 gene to chromosome 16q2. Mapping of the locus causing autosomal recessive congenital total cataract while in the large number peoples in the Tunisian family at chromosome number1 [26]. Sequencing discovered a homozygous A-G mutation in the 5’ splice site [27]. Mutation analysis of HSF4 display homozygous mutations in the two consanguineous Pakistani families [28].

6. Connexin

A peculiar behaviour of the human lens is the distinguished organization of the low-resistance gap junctions between lens fibre cells. Connexin are gap junction protein that is necessary for a cell to cell transmission in a number of tissues. Three different connexins (CX) genes (CX43, the CX46, and the CX50) are discovered in the lens [29].

7. Mapping of CX50 (GJA8) CHR lq21.1

The GJA8 locus was characterised on mouse chromosome number 3. Mutations in GJA8 have been identified in the family with autosomal dominant cataract [30]. First time measured the connection of GJA8 in autosomal recessive cataract in the family of southern Indian populations [31]. The mutation analysis indicates a solitary base internal increasing of the frameshift at the codon 203 of the connexins 50 and shown to co-separate with the disorder in the family. The CX50 (GJA8) gene mutation can also result in dominant cataract. A novel G > C exchange at nucleotide position c.235 give rise to the exchange of very much conserved valine by leucine at the codon 79 (V79L) with cataract like “full moon” with the Y Sutural opaqueness in an Indian family population (Fig. 2).

8. Eph2

The EPHA2 (ephrin receptor A2) gene encodes a transmembrane tyrosine kinase receptor (epithelial cell) which comprises an extra-cellular ligand-binding domain and is expressed in the human lens [32]. Inhibition of EPHA2 induces apoptosis and repeals tumorigenic development of tumour cells [33]. Actually, the downstream signalling of stimulated EPHA2 encourages the ant oxidative capability of lens epithelial cells to eliminate the overproduction of ROS [34]. It is possible that the loss of EPHA2 role could affect the structural stability of the cell, cell-to-cell crosstalk, protein folding and transcriptional activation [35]. Thus, the cytoprotective and ant apoptotic functions of EPHA2 in the lens specify the promising role of EPHA2 in evading lens opacity.

9. The use of the mouse models for studying cataract

Mouse models have made significant contributions to the area of cataract study. Primarily, they have confirmed the significance of numerous genes and proteins in the maintenance of lens transparency [36]. Furthermore, the widespread synteny between the mouse and human genomes has aided the identification of novel candidate genes for human cataract development. Also, it is now clear that the lens acts a crucial role in regulating normal eye growth and the identification of certain mutations has facilitated this procedure to be dissected. The mouse mutants are shown here which are known human corollary (Table 1) [37].

10. Clinical diagnosis and treatment

Congenital cataract is the cause of visual failure, which can destroy the developing optical organization of a child; consequently, initial diagnosis and management are essential. It is put forward that all newborn be screened through red reflex investigation at the time of birth and suspected infant be referred to ophthalmic centres. Early surgery can be done at the age of 6 weeks, newborn health is important for the accomplishment of the best optical concerns predominantly in the case of unilateral cataract [38]. In bilateral cases, surgery is more essential before the appearance of strabismus or nystagmus. The bilateral case should apply at the age of 10 weeks with no more than a one-week gap between the associated eyes. Cataract surgery is not an ending point but is essentially the starting point of treatment for a child. All newborns offspring should have observed and passed through screening eye test, called red reflexes. The Red reflex check-up at birth is the easy way to screen for congenital cataract [39]. The red reflex
is the significant section of the examination that gives an assessment of size and position within the visual axis, even if the child is obstructive. The red reflex test is most effective if it is applying in a dark room and contain the shining of the straight ophthalmoscope into both of the eyes at the same time from a distance of 1 to 2 feet. Nurses, paediatricians, ophtalmologists and family doctors can perform the test for routine. The most essential part of the operation is the complete ophthalmologic exam; it includes slit lamp check-up of both eyes, checking intraocular pressure, and an ultrasound of the posterior pole if undistinguishable. Not every congenital cataract needs operation. Phenylephrine or tropicamide with pharmacologic pupillary dilation can be useful. Atropine with dilation can be evaded, as it is amblyogenic. Casual obstruction may be crucial in unilateral cases, which are at risk for amblyopia. These measures can be late the persistence for operation until a point when the growth of eyes has strengthened and the IOL can be injected with less refractive uncertainty [40]. These patients should be treated in an observant way. Typical to advance cataract affects vision, or a cataract which affect one eye, should require surgical measures like cataract removal operation. Usually, the young child needs early surgery for removing the cataract because it will give rise to amblyopia. For ideal optical development in the innate and young child, an optically important unilateral congenital cataract would be identified and cured prior than the age of 6 weeks, while optically significant bilateral congenital cataracts would be operating before the age of 10 weeks [41]. Usually, ophthalmologists choose operation is ideal when the patient’s age is less than two months, so it can stop irreversible amblyopia and sensory nystagmus in bilateral congenital cataracts. The delay in surgery give rise to glaucoma [42], most of the physicians delay the cataract surgery which leads to glaucoma since glaucoma happens in 10% of surgeries of congenital cataract [20].

The cataract intraocular lens technique should be done only in recognised centres. If the physicians notice the cataract, then they recommend clinical involvement. For optical development, the time of surgery is critical [43]. Abnormalities such as ocular hypoplasia and early or late clinical difficulties for example inflammation and glaucoma have an adverse effect on vision in children experiencing congenital cataract surgery. Late surgery is supposed to be one of the particular of reduced best-corrected visual acuity (BCVA), and only 53% of cases with a history of late congenital cataract surgery achieved BCVA of 0.60 Log MAR or better [44]. There are two types of operations that can be performed to treat congenital cataract.

### 11. Extra-capsular cataract extraction (ECCE)

In this technique, the removal of the lens of the eye takes place, while the flexible capsule, which covers the eye lens, is left half sustained to the insertion of an intraocular lens (IOL) [45]. This procedure is changed from an older procedure known as intracapsular cataract extraction (ICCE) in which the lens was entirely removed from its capsule while leaving the eye aphakic. The patient’s vision was put right by contact lenses or by extremely thick eyeglasses after intracapsular cataract extraction [46]. ECCE has two types, manual expression, the removal of lens occurs by an incision that made in the sclera or in the cornea, and phacoemulsification, in which the lens is broken into segments inside the capsule by ultrasound and removed by aspiration [47]. Therefore, the clear vision will be brought back by removing of the affected lens and replacing that lens with an IOL. The anterior capsule of a child is much flexible as compared to an adult lens. This makes continuous curvilinear capsulorhexis (CCC) stronger. Many more choices are there to open the anterior capsule in cataracts. The best anterior capsulotomy procedure has outcomes in the low occurrence of radial tears and is easily achieved. While in dense cataract cases, the anterior capsule can be stained by the use of the dye that can make this step much easier and safer. A manual continuous curvilinear capsulorhexis (CCC), which is the distinctive method in the eyes of adults, can be tough in the cases of paediatric capsule because of the plasticity of the paediatric capsule. However, when it can be finalised and controlled, makes an edge, which has a low manifestation of radial tears [48]. The rhexis would be retained small (4–5 mm) as the lens matter can easily be articulated with a Simcoe cannulae. A primary capsulotomy is done by some doctor at the end of the ECCE. However, this needs re-evaluation, particularly in children.

### 12. Intraocular lenses (IOLs)

The most common impairments related specifically with IOL implantation in children are secondary opacification of the visual axis due to cortex reprofiliation and irregular deviations in refractive error as the kid matures [49]. In newborn children, it is important to put right Aphakia after an operation [50]. Another option is to insert an IOL after the removal of the cataract. The lens of the child’s eye is more spherical as compare to the lens of the adults [51]. That has a power of around 30D, which repay for the petite axial length of the child’s eye. This decreases to roughly 20–22D at the age of five years. It means that an IOL will lead to significant myopia to a child at the older age, as it gives normal vision to newborns. It is further constituted by changes in the strength of the cornea and axial enlargement of the ball. These discrepancies are much fast within the first few years of life and make it almost uncertain to estimate the right strength of lens for any inborn. The IOL implantation is easy for grown-up children but in the children, it is still very conflictive, predominantly under the age of two years. The IOL implantation in children is supposed to be harmless and acceptable at the age of one year [52].

### 13. Conclusion

Inherited cataracts typically are symmetric in affected individuals. The maximum awareness of congenital cataract is attained
from linkage study and by the analysis of candidate-mutated genes. The candidate genes cannot have linked with some mapped cataract mutants and the same situation also happens in the mouse model. Studies and research related to gene function are essential to clear the condition within the genes implicated in ocular lens cataractogenesis. However, the medical use of some agents like antioxidant, vitamin increment, carotenoids, nutrition and gene therapy will prevent opacification. Next-generation sequencing (NGS) technologies have revolutionised the approach to the study and diagnosis of human disease. Targeted-NGS approaches for the diagnosis of paediatric cataract have proven highly successful and are providing a strong model for the advantageous use of detailed phenotypic data and genomic information to dissect the molecular mechanisms and pathways underpinning ocular development and disease.

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