·Review·

Advancement of congenital cataract in the responsible gene

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Abstract

• Congenital cataract is the leading cause for children's blindness in most countries. Approximately one third of all the causes of Congenital cataract are familial and autosomal dominant blindness infants. The etiology of congen ital cataract is heterogenous. With the development of molecular biology techniques, researches on the mechanism of congenital cataract have made great progress. This review focused on the molecular mechanism of congenital cataract.

• KEYWORDS: congenital cataract; responsible gene

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INTRODUCTION

Congenital cataract (ADCC) is appear to be the most common type. Autosomal regreesive and X-linked forms are also seen but are peculiar [1]. Currently, there are about 39 genetic loci to which isolated or primary cataracts have been mapped [33],although the number is constantly increasing and depends to some extent on definition. At least 14 genes and more than 20 distinct loci have been identfied for various primary forms of ADCC. The identification of responsible genes causing autosomal dominant congenital cataract will improve our understanding for cataractmechanisms underlying cataractogenesis.

PATHOGENESIS OF CONGENITAL CATARACT

Cataracts can be defined by the age at onset: a congenital or infantile cataract presents within the first year of life; a juvenile cataract presents within the first decade of life; a presenile cataract presents before the age of about 45 years, and senile or age-related cataract after that. Between 8.3 and 25 percent of congenital cataracts are believed to be inherited [2].The lens alone may be involved, accounting for approximately 70% of congenital cataracts [1]. Cataracts may also be part of multisystem genetic disorders such as chromosome abnormalities.

There are several classification systems which have been developed based on the anatomic location, size, density and progression of the opacity. Cataracts can be isolated or can occur in association with a large number of metabolic diseases and genetic syndromes [18]. The consequent decrease in lens intercellular communication and changes associated with intracellular retention of the mutant connexin may contribute to cataract formation[3].

CONGENITAL CATARACT IN THE RESPONSIBLE GENE

There are lots of factors involved in the etiology and development of cataract. accumulating evidence indicates that genetic background plays an important role in the whole process. Some researches on hereditary congenital cataracts led to the identification of several classes of candidate genes that encode proteins such as the crystalline proteins (CRYAA, CRYAB, CRYBA1/A3,CRYBB1, CRYBB2, CRYBB3, CRYGC, CRYGD and CRYGS) [25,26], the gap junction protein [24], major intrinsic protein (MIP/MIP26), lens integral membrane protein 2 (LIM2/MP19), the beaded filamentprotein (BFSP2) [27], paired-like homeodomain transcription factor 3 (PITX3) [8], heat shock protein (HSF4) and galactokinase [6,21]. There is detail in Table 1[34].

Some researches in recent 5 years A Arora *et al* [3] said that the pulverulent cataracts present in members of this family are associated with a novel GJA8 mutation, Cx50D47N, that acts as a loss-of-function mutation. HSF4 have been associated with both autosomal dominant and recessive cataracts. The lop11 mouse is an excellent resource in transparency of the lens [6]. A gene causing the novel congenital cataract phenotype is located on the long arm of the X chromosome[7].A novel nonsense mutation in CRYGC was detected in a Chinese family with consistent autosomal dominant congenital nuclear cataract, providing clear

Table 1 Identified human congenitial cataract mutation

Locus	Gene	Protein	Mutation	Reference
1q21-q25	G JA 8	Connexin 50	m issen se	14
2q33-q35	CRYGD	γ -D crystalline	m issen se	15
2q33-q35	CRYGC	γ -C crystalline	m issen se	16
3q21.2-q22.3	BFSP2	BFSP2	m issen se	17
3q21-q22	BFSP2	BFSP2	deletion	18
10q24-25	P ITX 3	P itx 3	m issen se	19
12q13	M IP	M IP/AQP0	m issen se	20
13q11-q13	CX 46	Connexin 46	m issen se	21
16q21	H SF4	H SF4	m issen se	22
17q11.1-q12	CRYBA 1	β -A 1crystalline	splice site	11
21q22.3	CRYAA	α -crystalline	m issen se	23
21q11.2	CRYBB2	β -B2crystalline	chain termination	24
21q11.2	CRYBB2	β -B2crystalline	m issen se	25

evidence of a relationship between the genotype and the corresponding cataract phenotype [8]. a novel GJA8 mutation and has a different Clinical phenotype from previously described GJA8 mutants[14]. The novel R11H mutation[9] was responsible for the autosomal dominant nuclear congenital cataract in this pedigree.The R12C mutation in CRYAA was responsible for a variable type of inherited cataract associated with microcornea in this Chinese family [10]. The Gly154Glu mutation involves a non-conservative change that presumably results in loss of function of the MP19 protein. This study shows the involvement of LIM2 in human congenital cataract [11].A putative CAT region that peaked at 96.07 Mb with genome-wide significant test statistics and extended over 1.3 Mb on CFA1 in the EMD. A significant marker-trait association based on haplotypes corroborated this CAT region [12]. Unidentified gene associated with Posterior polar cataract maps to the long arm of chromo-some14q22-23[13]. There is a new gene for infantile cataract on chromosome 20p12.2-p11.23. New genes for infantile cataract could be found through further study of candidate genes at the 20q locus, which may provide insights into the pathogenic mechanisms of cataracts [15]. This is the first report of a recessive mutation in CRYAB causing cataract [16]and of alocus for isolated inherited cataract on the X chromosome [18]. This is the first report Simple microphthalmia was dominantly inherited in this Chinese pedigree with typical phenotypes, which resulted in severe visual deterioration by middle age. A novel locus is predicted to be responsible for the microphthalmia in this family, which may prove a high genetic heterogeneity in microphthalmia [19]. 38% of paediatric cataract mutations in the literature,only two causative mutations were detected in 38 pedigrees,suggesting that crystall in mutations area relatively rare cause of the cataract phenotype in this population [17]. L7Q is a novel mutation in connexin 50 (Gja8), causing semi-dominant pulverulent cataracts [20]. A novel nonsense mutation in CRYGC associated with autosomal dominant cataracts and microcornea in a Chinese family. spectrum of CRYGC mutations associated with congenital cataract and confirms the role of γ-crystallin in the pathogenesis of congenital nuclear cataracts [22]. A novel nonsense mutation (Y56X) in CRYGD and a previously reported missense mutation (R12C) in CRYAA associated with nuclear cataract in Brazilian families. Both tyrosine in amino acid 56 in CRYGD and arginine in amino acid 12 in CRYAA have been highly conserved throughout evolution in different species. A new polymorphism (S119S) in CRYGC was also observed in one family [23]. Epha2 [4] in two independent strains of mice developed progressive cortical cataract. This is the first reported case of a congenital coralliform cataract phenotype associated with the mutation of Gly61Cys (P.G61C) in the CRYGD gene[5].

Researches in China Cataract accounts for about 41.06% of blindness and is the leading cause of visual impairment in China[24]. Furthermore, the incidence of cataract continues to rise. In one paper, the authors report a novel S276F (827C>T) mutation in the connexin 50 gene in a Chinese five-generation family with the pulverulent nuclear cataract. This is a missense mutation that has not been reported previously with an inherited cataract. In the proband's mother, there are opacities in the fetal nucleus and embryonal nucleus. The structure of the opacities is puffy, and the fibers are tangled. Sequencing of the exonic region of GJA8 in eight participants (three affected and five unaffected) showed a heterozygous mutation 827C>T in all the affected members [27]. The congenital cataract conditions

in three families are inherited as an autosomal dominant (ADCC) trait.Derecet DNA sequence analysis revealed that a C-to-A transition at nucleotide 70 of the CRYGD gene, resulting in an Pro58-to-Thr substitution,segregated with the phenotype of aculeiform cataract in CA-001 families[28].

Researches in the world [1] Three Moroccan Jewish families with autosomal dominant posterior polar cataract were recruited at Sapir Medical Center [29],Kfar Saba,and the Kaplan Medical Center, Rehovot, Israel. In the study, an autosomal dominant posterior polar cataract been seeing in three Moroccan Jewish families is assigned to anovel locus residing in an 11.3cM (11.2Mb)interval on chromosome 14q22-23.Sequencing of five genes within our linkage area on 14q22-23,also the OTX2 and ARHJ genes and three members of the SIX gene family,shows no disease associated mutations. AdCTPP is an example of a true dominant disease in which a single copy of the mutated allele results in the same degree of involvement as in the homozygous state of the mutated gene [29].A three-generation Libyan Jewish family (56091) manifesting vertical transmission of congenitalcataract (ADCC; OMIM 604219) and a history of multiple spontaneous abortions and perinatal child deaths. Karyotype results from one miscarried 11-week-old fetus (5609133) and two malformed newborns (5609127 and 5609131) with multiple congenital anomalies showed the same unbalanced translocation 46,XY, -5,+der(5)t(3:5) (p22: p15.1) [30].Patients with a positive family history of childhood cataract were recruited from the Pediatric Ophthalmology Clinic, Aravind Eye Hospital (AEH), Madurai, India. The family members were interviewed to obtain a detailed medical, ophthalmic, and family history and were included in the study based on their availability and willingness. Patients with a history suggestive of intrauterineinfection such as rubella, complicated cataract, and traumatic cataract were excluded from the study.

The first nonsense mutation (p.R405X) in exon 11 of HSF4 in a large consanguineous Pakistani family with autosomal recessive cataract[31]. A missense mutation in CRYBB2 in a family of Basotho with autosomal dominant congenital cataract (ADCC). In summary, this new missense allele is the probable causative molecular lesion for the observed phenotype in this family[32].

PROSPECT

Congenital Cataract is complicated in terms of clinical manifestations and the genetic characteristics. Gene mutation makes the protein changed as a result of a certain type of cataract. Through the research on the pathogenesis of Congenital Cataract, gene therapy becomes possible to achieve the fundamental cure in purpose.It needs in-depth and extensive research because of genetic heterogeneity,with more finding on genetic factors. Human being will know more disease-causing genes and their relationship.

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