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Mutation profiles of congenital cataract genes in 21 northern Chinese families

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Purpose: To identify disease-causing gene mutations in 21 northern Chinese families with congenital cataracts.
Methods: Medical record collection and ophthalmologic examinations were conducted for 21 families with congenital cataracts. A volume of 5 ml of peripheral blood was drawn from each participant for genomic DNA isolation. Thirty-four known candidate genes for congenital cataracts were analyzed in the probands of 21 families with targeted next-generation sequencing (NGS). Bioinformatics analysis of the sequence variants was performed through computational predictive programs. Sanger sequencing was used to perform the cosegregation analysis. Genotyping and haplotype analyses were performed in two patients with a p.V44M mutation in the *GJA8* gene.
Results: Twelve disease-causing mutations were detected in 13 of the 21 patients, and the mutation detection rate was 61.9%. The 12 gene mutations included one nonsense, one splice site, seven missense, and three insert and deletion (INDELs) mutations. Four mutations were novel. Of the 13 patients with pathogenic gene mutations, five (38.5%) were affected by mutations in lens crystallin genes, three (23%) were affected by mutations in connexin genes, three (23%) were affected by mutations in transcription factor genes, one (7.7%) was affected by a mutation in a transmembrane transporter gene, and one (7.7%) was affected by a mutation in a chromatin-modifying protein gene. Two families carried the p.V44M mutation in the *GJA8* gene. Haplotype analysis revealed a chromosome region of 475 kb containing the mutation in the *GJA8* gene was harbored by two families.
Conclusions: Compared with traditional Sanger sequencing, targeted NGS for genetic testing of congenital cataracts markedly increases the mutation detection rate and is cost-effective. The p.V44M mutation in the *GJA8* gene was the most common mutation and was due to a founder effect within the Chinese cohort studied. The results of this study expand the gene mutation spectrum of congenital cataracts.

Congenital cataracts are the most common treatable cause of pediatric visual disability and are characterized by lens opacity at birth. Congenital cataracts have a neonatal incidence of approximately 1–6 per 10,000 individuals and are the most common cause of childhood blindness [1]. Approximately one third of congenital cataracts are inherited, most commonly by non-syndromic, autosomal dominant inheritance. To date, 34 genes have been identified and linked to congenital cataracts (Cat-Map). Nearly 50% of non-syndromic congenital cataracts are caused by mutations in lens crystallin genes, approximately 15% are caused by mutations in connexin genes, and approximately 10% are caused by mutations in transcription factors [2]. Congenital cataracts are a group of genetic heterogeneous conditions. In most cases, there is no clear correlation between clinical phenotype and genotype, suggesting the involvement of additional genetic or environmental factors. Previous studies regarding gene mutations in congenital cataracts have used Sanger sequencing in known disease-causing genes. However, this approach is becoming increasingly infeasible as the list of candidate genes to be tested grows. To address this problem, targeted enrichment strategies combined with next-generation sequencing technologies for genetic screening in congenital cataracts can increase the mutation detection rate to 50–70% [3,4]. In this study, to explore a time-saving, cost-effective testing method and report the mutation profiles of known genes for congenital cataracts in a Chinese cohort, we performed targeted sequencing of 34 known congenital cataracts genes in 21 families.

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METHODS

Sample collection and genomic DNA preparation: A total of 41 patients (22 males, 19 females; age: 4-46 years) from 21 Chinese families with congenital cataracts were recruited from the eye clinic of Beijing Tongren Hospital. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The study also adhered to the ARVO statement on human subjects. All experimental procedures described in this study were approved by the Ethics Committees of the Beijing Tongren Hospital. To perform the genomic mutation analysis, written informed consent was obtained from all participants. Probands of 21 enrolled families with congenital cataracts underwent detailed medical history collection and ophthalmologic examinations, including best-corrected visual acuity, slit-lamp examination, anterior segment photography, and fundus examinations with dilated pupils. Blood samples were collected from the probands of 21 families and available relatives. Genomic DNA was extracted using a whole blood DNA extraction kit (Vigorous Biotechnology, Beijing, China). Venous blood samples were collected from the probands of 21 families and available relatives. Genomic DNA was extracted using a whole blood DNA extraction kit (Vigorous Biotechnology, Beijing, China), according to the manufacturer's instructions.

Target gene capturing and sequencing: This study used the GenCap exome capture kit (MyGenostics GenCap Enrichment technologies, Beijing, China) to enrich the exons, splicing sites, and untranslated region (UTRs) of 34 known candidate genes of congenital cataracts (Appendix 1). In summary, 1–3 µg of genomic DNA was randomly fragmented into an average size of 180 bp with a Bioruptor sonicator (Diagenode, Denville, NJ), ligated with Illumina adaptor (San Diego, CA) oligonucleotides. Paired-end sequencing libraries were then prepared using a DNA sample prep reagent set 1 (NEBNext). Library preparation included end repair, adaptor ligation, and PCR enrichment, which was performed as recommended by Illumina protocols. The enrichment libraries were sequenced using an Illumina HiSeq X Ten sequencer for paired reads of 150 bp.

Bioinformatics analysis: Contaminants and adaptor sequences were removed from the raw sequencing data. Raw data were then filtered via GATK VariantFiltration. The filter standards were as follows: a) variants with mapping qualities <30, b) total mapping quality zero reads <4, c) approximate read depth <5, d) quality value <50.0, and e) Phred scale p value using Fisher's exact test to detect strand bias >10.0. The filtered data were mapped to the UCSC Human Reference Genome (hg19) using Burrows-Wheeler Aligner (BWA). Single nucleotide variations (SNVs) and INDELs were identified through GATK and annotated by ANNOVAR. Variants with a read greater than 10, a mutation ratio greater than 30%, and an allele frequency of less than 0.01 in the healthy human databases were included. The public human genome databases included the 1000 Human Genome Project, the Exome Variant Server, and Exome Aggregation Consortium (ExAC). The biologic relevance of amino acid substitutions within proteins was predicted using PolyPhen-2 and Mutation Taster. The effects of the splice site mutation were predicted using NetGene2.

Mutation validation: Sequence variants were validated via PCR-Sanger sequencing. PCR primers were designed using the online program Primer 3.0. In brief, after an initial denaturation at 95°C for 5 minutes, PCR mixes underwent 35 cycles of 95 °C for 30 s, 56 °C for 30 s, and 72 °C for 30 s followed by 72 °C for 7 min. PCR products were sequenced using an ABI 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA). Cosegregation analysis was performed in ten families. Potential gene mutations were screened via PCR-Sanger sequencing in 100 healthy controls.

Haplotype analysis: Three microsatellite markers and five single nucleotide polymorphisms surrounding the *GJA8* gene (Gene ID 2703, OMIM 600897) were amplified. Detailed primer information is shown in Table 1. PCR products were sequenced using an ABI 3130 Genetic Analyzer (Applied Biosystems).

RESULTS

Clinical examinations and family analysis: Of the 21 probands, 19 had a family history of autosomal dominant congenital cataracts (Figure 1), and two were sporadic cases. Among the 21 probands with congenital cataracts, three also had binocular alternating esotropia, exotropia of the left eye, and binocular nystagmus, respectively. Based on the location of the lens opacity (Figure 2), three cases were classified as nuclear cataracts, three as zonular cataracts, three as posterior subcapsular, two as mixed, one as cortical, one as anterior polar, and eight as unclear due to cataract extraction.

Mutation screening results: Approximately 42.9 kb of the exons and adjacent intronic regions of 34 genes were captured and sequenced in 21 probands. The mean coverage for an individual with 150 bp paired reads was 99.69%, the median depth was 420X, and the accuracy of a variant call was more than 99%.

Through targeted NGS, 12 potentially pathogenic gene mutations were identified in 13 of 21 patients with congenital cataracts (Table 2). The mutation detection rate was 61.9% (13/21). In 13 patients with pathogenic gene mutations, five

Table 1. Primer information used in haplotype analysis.

Name	Sequence (5′-3′)	Product size
STR1F	FAM-TGCTCACATTTTATGCCTTCTTT	230
STR1R	AAGAGGGGAATGAGGTAGGAT	
STR2F	FAM-TAAATTCAGAGGGCGCAGTG	208
STR2R	TGGGACTACAGGTGTGCAC	
STR3F	FAM-AACTTTACCCGCCTCTCCTC	184
STR3R	GAGTCGGAGGTTGCAATGAG	
rs9437983F/rs1495960F/rs7541950F	TGGCCATTGAACACTTTGGA	539
rs9437983R/rs1495960R/rs7541950F	TGAGATCACACCACTGCACT	
rs1532399F	TCCTAGAGTTGCCTGGAGTG	237
rs1532399R	CAACAGATGATGCCAGACCC	
rs111711592F	GGGTTGCCTCATAGCCTTTT	295
rs111711592R	GGTTGGATTTCTGGCTTCCC	

(38.5%) were affected by mutations in lens crystallin genes, three (23%) were affected by mutations in connexin genes, three (23%) were affected by mutations in transcription factor genes, one (7.7%) was affected by a mutation in a transmembrane transporter gene, and one (7.7%) was affected by a mutation in a chromatin-modifying protein gene. We detected four novel mutations: *CHMP4B* (Gene ID 128866, OMIM 610897) p.H57R, *FOXE3* (Gene ID 2301, OMIM

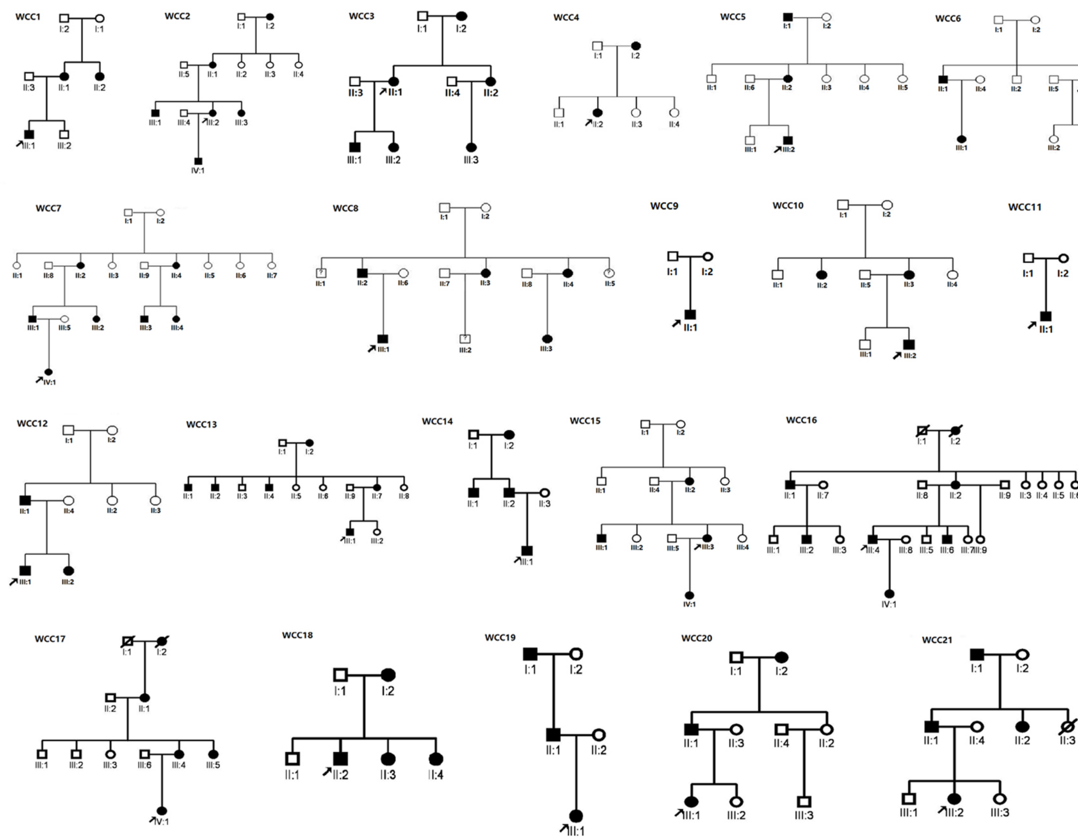

Figure 1. Pedigree of 21 families with congenital cataracts in this study.

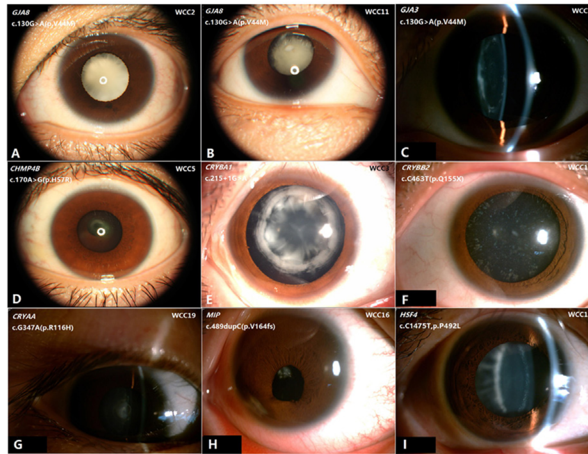

Figure 2. Lens opacity of nine patients with congenital cataracts. **A** and **B**: The proband of WCC2 and WCC11, respectively, nuclear cataracts. **C**: The proband of WCC7, zonular cataract. **D**: The proband of WCC5, posterior subcapsular cataract. **E**: The proband of WCC3, mixed cataract. **F**: The proband of WCC17, cortical punctate cataract. **G**: The proband of WCC19, posterior subcapsular cataract. **H**: The proband of WCC16, posterior capsule opacity. **I**: The proband of WCC18, zonular cataract.

601094) p.60_61del, *MIP* (Gene ID 4284, OMIM 154050) p.V164fs, and *HSF4* (Gene ID 3299, OMIM 602438) p.P492L. The mutation in *GJA8* p.V44M was detected in two patients affected by nuclear cataracts. All mutations were absent in 100 healthy controls. We did not identify disease-causing mutations within the target genes in eight of the 21 probands (Table 3). Haplotype analysis revealed that a common haplotype, spanning 475 kb on chromosome 1, was harbored by two patients with the p.V44M mutation (Appendix 2).

DISCUSSION

This study conducted targeted NGS of 34 candidate genes causing congenital cataracts and Sanger sequencing in 21 families with congenital cataracts. Pathogenic gene mutations were found in 13 families, and the detection rate was 61.9%. Gene mutations in crystallins, connexins, and transcription factor proteins accounted for 38.46%, 23.08%, and 23.08% of all patients carrying mutations, respectively. Sun et al. [3] performed targeted NGS on the same 34 known pathogenic genes in 18 southern Chinese families with congenital cataracts, and the mutation detection rate was 50%. Mutations in the *NHS* gene were most common in that study, accounting for 44.4% of all patients carrying mutations. Patients with mutations in the *NHS* gene also showed microcornea or high myopia. However, we did not find mutations in the *NHS* gene in the cohort patients. None of the cohort patients exhibited microcornea or high myopia. All the patients in this study cohort came from northern China; thus, the genetic background of these patients may be different from that of the patients examined by Sun et al., who were from southern China. Ma et al. [4] used NGS of 32 known genes to analyze mutations in 46 non-syndromic congenital cataract patients, and the detection rate was 70%. Mutations in crystallin and connexin genes accounted for 39% and 21% of all patients carrying mutations, respectively. The mutation spectrum in those results was similar to that of the present study. In that study, 80.4% of the participants were Caucasian, 15.2% were Middle Eastern, and 4.3% were Asian. Therefore, the common causative genes of congenital cataracts in the Chinese population were similar to those in the Caucasian population.

The current study identified four novel gene mutations, among which the mutations in *CHMP4B* and *FOXE3* were not common in congenital cataracts. To date, only two mutations in the *CHMP4B* gene have been reported to cause congenital cataracts: the p.D129V mutation in an American Caucasian family and the p.E161K mutation in a Japanese family [5]. The patient carrying the p.D129V mutation exhibited posterior subcapsular opacity, similar to the phenotype of the patient who carried the p.H57R mutation in the *CHMP4B* gene in the present study. The p.H57R mutation and the other two reported mutations were all located in the SNF7 domain of the *CHMP4B* gene. This domain is involved in endosome- and lysosome-associated protein sorting and trafficking [6]. It has been suggested that gain-of-function defects in an endosome-sorting complex (ESCRT-III) subunit trigger loss of lens transparency [5]. Another novel mutation detected in the present study was the *FOXE3* c.179_181del, p.60_61del mutation, located in the forkhead domain of the *FOXE3* gene. Apart from causing congenital cataracts, mutations in the *FOXE3* gene may also lead to anterior segment dysgenesis, including posterior embryotoxon, microphthalmia, and Peter's anomaly [7-9]. However, in the present study, anterior segment dysgenesis was not observed in patient

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Table 2. Clinical manifestation of 13 patients with gene mutations in this study.

ID	Gender	Family history	Age of arrival (years)	BCVA (OD/OS)	Type of lens ppacity	Other ocular defects	Gene mutation	Poly-Phen2	Muta-tion taster	NetGene2	ExAC	Cosegre-gation	100 controls	Refer-ence
WCC2	Female	Yes	26	0.1/LP	nuclear	-	*GJA8* c.130G>A, p.V44M	PD	DC	/	-	Y	ND	[5]
WCC11	Male	No	0.5	unable to cooperate	nuclear	-	*GJA8* c.130G>A, p.V44M	PD	DC	/	-	Y	ND	[5]
WCC7	Female	Yes	9	0.7/0.5	zonular	-	*GJA3* c.130G>A, p.V44M	PD	DC	/	-	Y	ND	[15]
WCC5	Male	Yes	25	NA	posterior subcap-sular	-	*CHMP4B* c.170A>G, p.H57R	PD	DC	/	-	NA	ND	this study
WCC9	Male	No	22	0.5/0.6	NA	-	*FOXE3* c.179_181del, p.60_61del	/	DC	/	-	NA	ND	this study
WCC3	Female	Yes	39	NA	mixed (cortical nuclear)	-	*CRYBA1* c.215+1G>A	/	/	Donor site abolished	-	Y	ND	[16]
WCC17	Female	Yes	25	NA	cortical punctate	-	*CRYBB2* c.C463T, p.Q155X	/	/	/	-	Y	ND	[17]
WCC10	Male	Yes	3	unable to cooperate	NA	exotro pia	*CRYAA* c.34C>T, p.R12C	PD	DC	/	-	Y	ND	[18]
WCC12	Male	Yes	2	unable to cooperate	NA	-	*CRYAA* c.61C>T, p.R21W	PD	DC	/	-	Y	ND	[19]
WCC19	Female	Yes	3	unable to cooperate	posterior subcap-sular	nystag mus	*CRYAA* c.G347A, p.R116H	PD	DC	/	-	Y	ND	[20]
WCC13	Male	Yes	14	0.9/1.5	NA	-	*PITX3* c.656_657insGCC CTGCAGGGC CTGGG, p.G219fs	/	/	/	-	Y	ND	[21]
WCC16	Male	Yes	28	NA	nuclear	-	*MIP* c.489dupC, p.V164fs	/	/	/	-	Y	ND	this study
WCC18	Male	Yes	38	0.6/0.6	zonular	-	*HSF4* c.C1475T, p.P492L	PD	Polymor-phism	/	8.63E -05	NA	ND	this study

Abbreviation: NA, not available; D, damaging; PD, probably damaging; DC, disease causing; ND, not detected.

Table 3. Clinical manifestation of 8 patients without gene mutations.

ID	Gender	Family History	Age of arrival (years)	BCVA (OD/OS)	Type of Lens Opacity	Other ocular defects
WCC1	Male	Yes	38	NA	NA	-
WCC4	Female	Yes	25	NA	anterior subcapsular	-
WCC6	Female	Yes	41	HM/0.05	Nuclear	esotropia
WCC8	Male	Yes	26	0.4/0.6	Nuclear	-
WCC14	Male	Yes	23	0.5/0.3	Zonular	-
WCC15	Female	Yes	44	0.15/0.1	NA	-
WCC20	Female	Yes	15	0.4/0.3	NA	-
WCC21	Female	Yes	24	0.1/0.4	mixed (cortical+nuclear)	-

WCC9, who carried the *FOXE3* p.60_61del mutation. Most mutations examined in previous studies were missense and small insertions. Therefore, we speculate that the *FOXE3* p.60_61del mutation had little effect on the function of the protein, other than missense or frameshift mutations. Dominique et al. found a mutation in the *FOXE3* gene in 4% of all French patients with congenital cataracts [10]. In the present study, the frequency of mutations in the *FOXE3* gene was approximately 5%. Due to restricted expression of *Foxe3* in the lens epithelia of developing and adult mice, researchers found that chamber angle defects associated with mutations in mouse *Foxe3* might result from changes in *Pitx3*, a gene in the same regulatory pathway as *Foxe3* [7]. In the present study, patient WCC16 carrying the novel c.489dupC, p.V164fs mutation in the *MIP* gene had nuclear cataracts. The mutation was in the transmembrane domain H5 of the *MIP* gene. In Chinese patients with congenital cataracts, a missense mutation in the *MIP* gene leads to progressive cortical punctate cataracts [11,12], a nonsense mutation in the *MIP* gene leads to Y sutural associated with cortical punctate cataracts [13], and a splice mutation in the *MIP* gene results in nuclear cataracts [14], suggesting strong genetic heterogeneity of the *MIP* gene. The fourth novel mutation in the present study was the p.P492L mutation in the *HSF4* gene, which caused a zonular cataract in patient WCC18. This mutation was located in the COOH-terminal intracellular domain of the protein. The phenotype of the cohort patients was similar to that of patients reported by Bu et al. [15], showing a perinuclear shape with a transparent embryonic nucleus.

The results of this study suggest that there is a relationship between some pathogenic genes of congenital cataracts and the specific type of lens opacity. The mutation in *GJA8* p.V44M was detected in two families (9.5%, 2/21). Patients in these two families had uniform lens nuclear opacity. This mutation was first reported in Chinese families with congenital cataract by Sun et al. [3], but they failed to obtain information about lens opacity. Individual alleles of eight polymorphism markers composing the haplotype were highly conserved in two patients, demonstrating a founder effect of the p.V44M mutation. Patients in two families may be descended from a common ancestor. In eight (38.1%) of the 21 families without gene mutations, the causative mutations were speculated to lie in the non-coding regions or in other genes that have not been identified yet.

In general, using targeted NGS for mutation screening of congenital cataracts could increase the mutation detection rate. The four novel gene mutations identified in this study expand the mutation spectrum of congenital cataracts. The results suggest that crystallin genes are still the major pathogenic genes for congenital cataracts in the Chinese population.

APPENDIX 1. LIST OF 34 CANDIDATE GENES OF CONGENITAL CATARACTS SEQUENCED IN THIS STUDY.

To access the data, click or select the words “Appendix 1”

APPENDIX 2. HAPLOTYPE OF TWO PATIENTS WITH THE C.130G>A MUTATION OF GJA8.

To access the data, click or select the words “Appendix 2”

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