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.
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
(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

| Name                                      | Sequence (5′-3′)                | Product size |
|-------------------------------------------|---------------------------------|--------------|
| STR1F                                     | FAM-TGCTCACATTTATGCCTTCTTT      | 230          |
| STR1R                                     | AAGAGGGGATGAGGTAGGAT            |              |
| STR2F                                     | FAM-TAAATTCAAGGGGCCAGTG         | 208          |
| STR2R                                     | TGGGACTACAGGTGTGCAC             |              |
| STR3F                                     | FAM-AACTTTACCCGCTCTCTCTC       | 184          |
| STR3R                                     | GAGTCGGAGGTTGCAATGAG            |              |
| rs9437983F/rs1495960F/rs7541950F          | TGGCCATTGAACACTTTGGA            | 539          |
| rs9437983R/rs1495960R/rs7541950F          | TGAGATACACACTGCACT              |              |
| rs1532399F                                | TCCTAGAGTTGCGCTGGAGTG          | 237          |
| rs1532399R                                | CAACAGATGATTGAGCAGACC          |              |
| rs11711592F                               | GGTTGCTCTACAGCTTTTT            | 295          |
| rs11711592R                               | GGTTGATTTCTGGCTTTCC            |              |

Table 1. Primer information used in haplotype analysis.

Figure 1. Pedigree of 21 families with congenital cataracts in this study.
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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.D129N mutation in an American Caucasian family and the p.E161K mutation in a Japanese family [5]. The patient carrying the p.D129N 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-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...
| ID   | Gender | Family history | Age of arrival (years) | BCVA (OD/OS) | Type of lens opacit y | Other ocular defects | Gene mutation          | Poly-Phen2 | Mutation taster | NetGene2 | ExAC | Cosegregation | 100 controls | Reference |
|------|--------|----------------|------------------------|--------------|----------------------|----------------------|----------------------|------------|----------------|----------|------|--------------|-------------|-----------|
| WCC2 | Female | Yes            | 26                     | 0.1/LP       | nuclear              | -                    | GJA8 c.130G>A, p.V444M | PD         | DC             | /        | -    | Y            | ND          | [5]       |
| WCC11| Male   | No             | 0.5                    | unable to cooperate | nuclear          | -                    | GJA8 c.130G>A, p.V444M | PD         | DC             | /        | -    | Y            | ND          | [5]       |
| WCC7 | Female | Yes            | 9                      | 0.7/0.5      | zonular posterior subcapsular | -                    | CHMP4B c.170A>G, p.H57R | PD         | DC             | /        | -    | Y            | ND          | [15]      |
| WCC5 | Male   | Yes            | 25                     | NA           | NA                   | -                    | FOXE3 c.179_181del, p.60_61del | /          | DC             | /        | -    | NA           | ND          | this study |
| WCC9 | Male   | No             | 22                     | 0.5/0.6      | NA                   | -                    | Donor site abolished | /          | DC             | /        | -    | NA           | ND          | this study |
| WCC3 | Female | Yes            | 39                     | NA           | mixed (cortical nuclear) cortical punctate | -                    | CRYBA1 c.215+1G>A | /          | /              |          | Donor site abolished | Y    | ND          | [16]       |
| WCC17| Female | Yes            | 25                     | NA           | NA                   | -                    | CRYBB2 c.C463T, p.Q155X | /          | /              | /        | -    | Y            | ND          | [17]       |
| WCC10| Male   | Yes            | 3                      | unable to cooperate | NA               | exotropia            | 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 subcapsular | nystagmus             | CRYAA c.G347A, p.R116H | PD         | DC             | /        | -    | Y            | ND          | [20]       |
| WCC13| Male   | Yes            | 14                     | 0.9/1.5      | NA                   | -                    | PITX3 c.656_657insGCC | /          | /              |          | -    | 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         | Polymorphism | 8.63E-05 | NA   | ND           | this study  | this study |

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

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