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· Review Article ·

# Classification of congenital cataracts and prospects for treatment and diagnosis

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## HIGHLIGHTS

· This paper summarized the existing research on the classification of congenital cataracts and considered the potential directions for future studies in this field.
· A literature review on classification systems for congenital cataracts.
· The classification of congenital cataracts based on multidimensional phenotypes holds promise for aiding treatment decisions, discovering new candidate genes, and identifying systemic disorders.

**Abstract:** The congenital cataract is one of the leading causes of treatable childhood blindness. Existing classification systems for congenital cataracts are primarily utilized for the diagnosis of the disease. However, these systems provide limited information necessary for the evaluation, formulation, and optimization of treatment plans. Furthermore, research on the classification of congenital cataracts still requires exploration to provide additional evidence supporting molecular diagnosis and syndromic disease diagnosis. This paper reviews relevant studies on the classification of congenital cataracts and discusses the prospects for future research in this area.

**Keywords:** congenital cataracts; classification; treatment; diagnosis; research frontiers

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Full Text

Congenital cataracts are characterized by lens opacities that are present at birth or the first 12 months of life,[1-3] and they are among the most common causes of treatable blindness in children. Globally, congenital cataracts affect 1 to 10 per 10,000 children.[4] In addition to causing vision impairments, congenital cataracts also led to psychological and financial problems for the children and their families.[5-6] Early diagnosis and timely intervention of congenital cataracts can help achieve better visual outcomes, improve the children's eye-related quality of life, and reduce the burden of the disease.

Congenital cataracts exhibit considerable variability in presentation. They may be unilateral or bilateral and differ widely in size, morphology, and degree of opacification—from small white dots on the anterior capsule to complete lens opacification. This variability significantly impacts vision, treatment approaches, and prognosis. Therefore, a robust classification system is essential for guiding clinical decision-making and improving outcomes.

Historically, efforts to classify congenital cataracts have been complex. In 1961, Frederick C. Cordes et al.[7] published Cataract Types, a complex manual for classifying congenital cataracts that proved difficult for clinical use. In 1979, Maumenee IH et al.[8] proposed that classification systems for congenital cataracts should consider morphology, location, age of onset, genetic and environmental factors, ocular, and systemic abnormalities. However, subsequent classification systems mainly focused on a single factor, such as lens phenotype or hereditary cataract gene. In addition to displaying a variety of lens opacities and ocular comorbidities, congenital cataract patients can also present with systemic symptoms. Furthermore, the disease has over 100 pathogenic genes,extending beyond the hereditary cataract genes.[9]

Given these complexities, no single classification system has successfully addressed all relevant aspects of congenital cataracts. This underscores the need for future research to develop more integrated and clinically applicable systems. This article will focus on the current classification systems of congenital cataracts and the prospects for future research in this area.

## CURRENT CLASSIFICATION SYSTEMS OF CONGENITAL CATARACTS

### Phenotype-based classification systems

Classifying congenital cataracts using clinical phenotypes, especially based on the location and morphology of lens opacities, helps clinicians determine the severity of visual deprivation.According to the location and morphological characteristics of the lens opacities or their combination,[10-14] congenital cataracts can be classified as total, lamellar, pulverulent, anterior polar, posterior polar, sutural, coraliform, nuclear, anterior subcapsular, posterior subcapsular, lenticonus, etc.While using the location and morphology of lens opacities to classify helps understand the opacity density and size, the inconsistent terminology and unclear evaluation criteria of the current classification systems are not conducive to quantitative assessments and standardized application in clinical practice. Based on anatomic location in slit-lamp examinations and Scheimpflug imaging, Lin et al.[15] proposed a simplified four-category classification for congenital cataracts: anterior, interior, posterior, and total cataracts.The classification system showed an association between lens opacities and coexisting anterior segment abnormalities, suggesting that incorporating lens opacities and coexisting anterior segment abnormalities could improve the current classification systems.

The British Congenital Cataracts Interest Group proposed a 3-category classification considering coexisting phenotypes besides lens opacities.[16] According to this classification system, congenital cataracts are classified as follows: cataracts that are isolated; cataracts that have a particular ipsilateral ocular abnormality associated with them but are not related to a systemic disease; and cataracts that have a specific systemic disease linked with them, regardless of coexisting ocular diseases.[16] This classification system focuses on the coexisting systemic and ocular abnormalities of congenital cataract patients, which helps reduce the risk of a delayed, missed, or wrong diagnosis.If congenital cataracts coexist with systemic symptoms, it suggests a possible genetic syndromic cause and supports further genetic testing.However, because this classification system cannot distinguish the constituent of coexisting ocular abnormalities, it is impossible to reveal the ocular

changes of congenital cataract patients through this method, nor can it inform the potential visual prognosis.

### Gene-based classification systems

The etiology of congenital cataracts remains unknown in approximately 50%–63% of cases.[9, 17] In certain cases of congenital cataracts, the variants causing the condition can be identified. Gene-based classification can narrow the screening scope of genes, thereby assisting genetic testing to clarify the molecular diagnosis of patients with congenital cataracts. Messina-Baas et al.[18] previously summarized the genes associated with congenital cataracts and proposed a four-category classification system for congenital cataracts based on genes: genes associated with syndromic cataracts, genes associated with syndromic cataracts but only reported with congenital cataracts, genes presenting cataracts exclusively, and genes associated with cataracts and coexisting ocular abnormalities.

The list of congenital cataract control genes is incomplete. New congenital cataract loci are being mapped, and the corresponding genes are being identified.[19] About 71 loci and 56 causative genes have been identified in highly penetrant Mendelian congenital cataracts.[20] Based on linkage analysis studies in families,[21-23] genetically modified animal models,[24-25] genome-wide association studies,[26] and transcriptome analysis studies,[27] congenital cataracts have been found to be associated with over 100 genes so far.[9] Further identification of novel pathogenic genes and exploration of the genotype-phenotype relationshipswould help improve the gene-based classification systems of congenital cataracts.

However, the current gene-based classification systems of congenital cataracts provide limited guidance for clinical practice. Despite advancements in genetic testing methods and genomic tools, molecular diagnosis of congenital cataracts remains challenging when there is no indication of any inheritance pattern.[28] Furthermore, it is also difficult to determine whether a newly discovered variant of a novel gene is the cause of the disease.[29] Additionally, making treatment decisions through gene-based classification is highly challenging, given the complex genotype-phenotype associations.[30]

The current classification methods, their underlying principles, and their respective advantages and disadvantages are summarized in Table 1.

## PROSPECTS OF THE CLASSIFICATION OF CONGENITAL CATARACTS BASED ON MULTIDIMENSIONAL PHENOTYPES

### Contributing to treatment decision-making

The multidimensional phenotypes of congenital cataracts entail identifying varied phenotypic

**Table 1 Summary of the basis of current classification methods, together with their advantages and disadvantages**

| Grouping basis | Advantages | Disadvantages |
|---|---|---|
| Morphology and localization of lens opacities | It encompasses common lens opacities in clinical practice and helps to understand the degree and extent of lens opacities. | It lacks unified standards, hindering clinical quantitative evaluation and standardized application. |
| Anatomical distribution of lens opacities | It offers a streamlined yet comprehensive clinical taxonomy for congenital cataracts, ensuring practical utility and ease of implementation in clinical settings. | It does not provide a clear indication of the child's visual prognosis. |
| Other ocular and systemic abnormalities | It helps alert clinicians to comorbidities. | It does not specify the nature of the ocular abnormality or the child's visual prognosis. |
| Genes implicated in inherited congenital cataracts | It facilitates the identification of potential genes of hereditary congenital cataracts. | Determining the relationship between candidate genes and phenotypes in congenital cataract patients remains challenging. It does not apply to all congenital cataract patients. |
| Multidimensional phenotypes | It provides preliminary information about the visual prognosis of congenital cataract patients. | The current classification criteria are preliminary and further consideration of the role of additional phenotypes in visual prognosis is needed. |

characteristics in this condition and are associated with visual prognosis. Demographic and clinical characteristics,as well as eye growth parameters, such as laterality and axial length, have been associated with visual prognosis in congenital cataract patients.[31-32] In addition to lens opacities, congenital cataract patients can coexist with other ocular abnormalities, such as microcornea, iris/choroid/optic nerve coloboma, etc.[17, 33] However, with the one-dimensional phenotypes used in current classification systems, which focus primarily on lens opacities, the visual prognosis of congenital cataracts is poorly understood. If there are any retinal or other ocular abnormalities, it becomes challenging for the affected eye to achieve a good visual prognosis, even with standard cataracts and amblyopia treatment.[34] Therefore, additional evidence to support clinical decision-making is needed, which might be obtained by analyzing multidimensional phenotypes and developing corresponding classification systems.Tan et al.[35] developed a novel classification for congenital cataracts based on multidimensional phenotypes. They identified two clusters of eyes with congenital cataracts that exhibited different phenotypes and visual prognoses, leading to a clinically significant classification that aids in identifying patients with distinct prognoses and facilitates the provision of individualized treatment regimens.

### Identifying novel candidate genes

It was discovered that 56.3%–88.9% of isolated or syndromic congenital cataracts harbored likely pathogenic variants.[9, 36] The genetic mechanism underlying congenital cataracts and its coexistence with other phenotypes are complex,[37] and the association between novel pathogenic genes and specific phenotypes remains unclear.[38] Despite decades of relevant research, identifying novel pathogenic genes continues to be challenging. However, if congenital cataract patients can be classified based on their multidimensional phenotypes and subsequently sequenced, it may lead to the discovery of novel pathogenic genes.This could facilitate reinterpreting the variants of uncertain significance and aid in genetic counseling.[28]

### Identifying systemic disorders

The systemic phenotypes of some syndromic congenital cataracts may be overlooked in clinical practice, resulting in underdiagnosis of the corresponding syndrome.[38] A large congenital cataract cohort that identifies the current phenotypic spectrum could benefit syndromic diagnosis while supporting the identification of syndromic cataractcategories through phenomics. Artificial intelligence can assist in identifying phenotypes in clinical practice, making the diagnosis more efficient, but a prerequisite is that the phenotypes have been described previously.[39] Based on a standardized description of phenotypes in congenital cataract patients, the use of artificial intelligence might help discover the latent phenotypes within syndromes, thereby enabling the identification of syndromes and the provision of appropriate therapy.

## SUMMARY

We reviewed relevant studies on the classification of congenital cataracts and discussed research prospects in this area. The classification systems for congenital cataracts were based on different methods, including the morphology and localization of lens opacities, cataract anatomical distribution,cataract-associated ocular and systemic abnormalities, the implicated genes in inherited congenital cataracts, and multidimensional phenotypes in congenital cataracts. The classification of congenital cataracts and their implications warrant further exploration.

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(II) Administrative support: Zhenzhen Liu, Hui Chen
(III) Provision of study materials or patients: Yuan Tan
(IV) Collection and assembly of data: Yuan Tan, Yunqian Li
(V) Data analysis and interpretation: All authors
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

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## Conflict of Interests

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## Patient consent for publication

None

## Ethical Statement

None

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