STARZYK, Agnieszka and CHARZEWSKI, Piotr. The Genetic Basis of Congenital Cataracts: Advances in Diagnostics and Therapeutics. Quality in Sport. 2025;38:58250. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.38.58250
https://apcz.umk.pl/QS/article/view/58250

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 26.01.2025. Revised: 02.02.2025. Accepted: 07.02.2025 Published: 07.02.2025.

The Genetic Basis of Congenital Cataracts: Advances in Diagnostics and Therapeutics

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ABSTRACT

Introduction: Congenital cataracts are a significant cause of childhood blindness, resulting from a combination of genetic mutations, syndromic associations, and environmental factors. Autosomal dominant inheritance is prevalent, with mutations in genes such as **CRYAA** and **GJA8** often implicated. Early surgical intervention and advancements in genetic diagnostics have enhanced outcomes, while emerging therapies provide hope for personalized treatments.

Materials and Methods: This study reviewed peer-reviewed literature on congenital cataracts from 2000 to 2023, focusing on genetic etiology, surgical interventions, and emerging therapies. Key sources included PubMed and Scopus. Data was synthesized across three categories: genetics, management, and innovative treatments.

Results: Genetic mutations in structural proteins like crystallins and connexins account for over half of congenital cataracts. Early surgery is critical, with intraocular lens (IOL) implantation improving outcomes in children over two years old. Emerging approaches such as gene therapy and pharmacological interventions, including small-molecule chaperones, show potential in addressing underlying genetic causes.

Conclusions: Though rare, congenital cataracts significantly impact vision when untreated. While surgical techniques and postoperative care have improved, complications remain common. Advances in genetic testing and emerging therapies, including gene editing, are reshaping the field, promising better outcomes and personalized treatments. Continued research is essential to refine these innovations and improve accessibility.

Keywords: congenital cataracts, vision health, genetic mutations, gene therapy, visual rehabilitation, pediatric cataract surgery

INTRODUCTION

Congenital cataracts are a significant global cause of visual impairment and blindness in children, accounting for approximately 10% of blindness in this age group. These lens opacities, present at birth or developing shortly thereafter, disrupt the normal development of the visual

system, leading to lifelong visual deficits if left untreated. While the incidence varies globally, it is estimated at 2.5 to 3.5 per 10,000 live births in developed nations and higher in resource-limited settings [1, 3]. The etiology of congenital cataracts is highly diverse, encompassing genetic mutations, chromosomal abnormalities, metabolic disorders, and environmental factors such as infections or trauma during pregnancy. In many cases, the condition is idiopathic, with no identifiable cause [6].

Genetic factors are a predominant cause, with autosomal dominant inheritance being the most common pattern observed. Mutations in genes such as **CRYAA**, **CRYBB2**, and **GJA8**, which are essential for maintaining lens transparency and homeostasis, are frequently implicated [9, 10]. Syndromic forms of congenital cataracts often coexist with systemic abnormalities, as seen in conditions like Lowe syndrome, Alport syndrome, and Smith-Lemli-Opitz syndrome. These syndromes highlight the multisystemic nature of the condition and the necessity for multidisciplinary care [5-23].

Management strategies for congenital cataracts have undergone significant evolution, with advances in surgical techniques, optical rehabilitation, and amblyopia therapy improving outcomes. However, optimal results depend on early detection and timely intervention, as prolonged visual deprivation during critical periods of visual development can lead to irreversible amblyopia [3, 8]. Furthermore, recent advancements in genetic diagnostics and emerging therapeutic approaches, such as gene therapy, present new avenues for personalized treatment and prevention. This article aims to comprehensively review the genetic underpinnings of congenital cataracts, the current state of management, and emerging therapeutic innovations.

MATERIALS AND METHODS

This study integrates findings from a systematic review of peer-reviewed literature, focusing on the genetic basis and management of congenital cataracts. The search was conducted in databases such as PubMed, Scopus, and Google Scholar, using keywords including “congenital cataracts,” “genetic mutations,” “intraocular lens implantation,” and “pediatric ophthalmology.” Articles published between 2000 and 2023 were prioritized, with a focus on studies addressing genetic etiology, surgical advancements, and therapeutic innovations [5].

The inclusion criteria encompassed:

- Clinical studies and case series examining the genetic mutations associated with congenital cataracts [8].
- Research articles on the outcomes of surgical interventions, including intraocular lens (IOL) implantation and postoperative management [20].
- Reviews and preclinical studies exploring emerging therapies, such as gene therapy and molecular interventions [7].

The data extraction process categorized findings into three primary areas: etiology, surgical management, and emerging therapeutic approaches. Knowledge from genetics, ophthalmology, and pediatrics was synthesized using a multidisciplinary lens. Studies with incomplete methodologies or unclear conclusions were excluded to ensure data quality. Relevant case studies and systematic reviews were analyzed to provide a comprehensive understanding of the condition [9].

RESULTS

Etiology and Genetic Insights

Congenital cataracts represent a diverse and complex group of conditions where genetic factors play a predominant role. Studies have established that over 50% of cases are linked to mutations in genes responsible for encoding structural or functional proteins of the lens. Among these, mutations in **CRYAA** and **CRYBB2**, which encode crystallin proteins, are particularly common [9-12]. Crystallins are essential for maintaining lens transparency and refractive function; their disruption leads to protein aggregation, light scattering, and opacity in the lens. Mutations in **GJA8**, encoding connexin 50, are another critical factor. Connexin 50 is integral to the formation of gap junctions, enabling intercellular communication and metabolic homeostasis within the lens. Loss of its function disrupts ionic balance and contributes to cataract formation. Similarly, mutations in **HSPB4**, a gene encoding alpha-crystallin B-chain protein with chaperone activity, highlight the role of stress response proteins in preventing abnormal protein aggregation in the lens [8-24].

In addition to single-gene mutations, chromosomal abnormalities significantly contribute to congenital cataracts. Conditions such as trisomy 13, 18, and 21 are well-documented examples where lens opacity is part of a broader syndromic phenotype. Syndromic associations, including Lowe syndrome, characterized by renal dysfunction and developmental delays, and Alport

syndrome, involving renal and auditory deficits, further demonstrate the multisystemic involvement often observed in congenital cataract cases. These syndromes necessitate a multidisciplinary approach to diagnosis and management.

Despite advances in genetic diagnostics, nearly 50% of bilateral cataracts and most unilateral cases remain idiopathic. This underscores the need for enhanced genetic testing modalities, such as whole-exome sequencing and gene panels, to uncover novel mutations and expand our understanding of the genetic landscape. The integration of advanced diagnostic tools into routine practice not only facilitates precise identification of the underlying etiology but also informs prognostic discussions and family counseling, emphasizing the critical role of genetics in this condition [23, 24].

Surgical Management and Optical Rehabilitation

Surgical intervention remains the cornerstone of managing visually significant congenital cataracts. Early removal of opacities is crucial to prevent irreversible visual deprivation during critical developmental windows. Evidence suggests that surgery performed within six weeks of birth for unilateral cataracts and ten weeks for bilateral cases yields the best visual outcomes. Beyond these timeframes, prolonged visual deprivation risks inducing dense amblyopia, which can severely limit the effectiveness of later rehabilitative efforts [19-22].

Advances in surgical techniques have enhanced both safety and precision. Procedures such as small-incision lensectomy, posterior capsulotomy, and anterior vitrectomy are now standard practices, particularly for dense cataracts. The decision to implant an intraocular lens (IOL) remains nuanced, especially in infants. While primary IOL implantation has proven beneficial for children over two years old, it remains controversial in younger infants due to potential complications, including posterior capsule opacification (PCO) and secondary glaucoma. Studies have demonstrated that while IOL implantation reduces the reliance on aphakic contact lenses or spectacles, it is associated with a higher incidence of postoperative complications and additional surgical interventions [21].

Even with optimal surgical techniques, postoperative complications are not uncommon. Glaucoma is a significant concern, particularly in children operated on before 12 months of age. Other issues, such as nystagmus, strabismus, and posterior capsule opacification, necessitate long-term monitoring and multidisciplinary care. Postoperative visual rehabilitation is equally

critical. Amblyopia therapy, involving occlusion or penalization of the better-seeing eye, is often required to maximize visual outcomes. Evidence indicates that with timely surgery and adherence to postoperative therapy, over 60% of children achieve functional vision, defined as visual acuity better than 6/60 in the affected eye. This underscores the importance of combining surgical precision with rigorous rehabilitative strategies to ensure the best outcomes [3-19].

Emerging Therapeutics

The rapid advancements in genetic and molecular medicine have opened new horizons in the management of congenital cataracts. Genetic testing, including whole-exome sequencing and targeted gene panels, has revolutionized our understanding of the condition, enabling the precise identification of causative mutations. This knowledge facilitates targeted therapies and personalized management plans, tailored to the underlying genetic defect. Moreover, genetic counseling for affected families provides critical insights into recurrence risks and informs reproductive decisions [3-19].

Gene therapy represents a promising frontier in addressing congenital cataracts at their root cause. Preclinical studies have demonstrated the feasibility of using CRISPR-Cas9 technology to correct pathogenic mutations in lens structural proteins. For instance, experiments in animal models have shown restoration of lens transparency and prevention of cataract progression by editing defective genes. While these approaches are still in experimental stages, they highlight the potential for a paradigm shift from symptomatic treatment to curative interventions [1, 6, 9].

Pharmacological therapies are also under active investigation. Small-molecule chaperones that stabilize misfolded lens proteins and antioxidant compounds targeting oxidative stress are showing efficacy in delaying cataractogenesis in preclinical models. Oxidative stress plays a pivotal role in lens opacification, particularly in syndromic and metabolic contexts. Drugs that modulate oxidative damage and protein homeostasis could complement or, in some cases, replace surgical interventions. These innovations, combined with advancements in drug delivery systems, such as intravitreal injections or nanoparticle-based carriers, offer new avenues for managing congenital cataracts [1-7].

Collectively, these emerging therapeutic strategies highlight the transition toward a more personalized and precise approach to treating congenital cataracts. By addressing the underlying

genetic and molecular defects, these innovations hold the promise of not only improving visual outcomes but also reducing the global burden of this condition [6-9].

CONCLUSIONS

Congenital cataracts, with an estimated incidence of 2.5 to 3.5 per 10,000 live births, are a significant cause of lifelong visual impairment if not promptly treated. These lens opacities disrupt the critical process of visual development, often leading to irreversible deprivation amblyopia without timely intervention. Genetic factors are implicated in over 50% of cases, with mutations in genes like **CRYAA** and **GJA8** disrupting lens structure and function. Advanced diagnostic tools, such as whole-exome sequencing, play a vital role in identifying these mutations, enabling precise diagnoses, personalized interventions, and genetic counseling for affected families [7-10].

Surgical management remains the cornerstone of treatment, with early cataract removal essential for preventing long-term visual impairment. Advances in techniques, such as small-incision lensectomy and intraocular lens (IOL) implantation, have significantly improved outcomes. However, challenges like posterior capsule opacification (PCO), secondary glaucoma, and nystagmus persist, necessitating long-term follow-up and amblyopia therapy. Despite these hurdles, early and effective surgical intervention ensures many children achieve functional vision and improved quality of life [20-22].

Emerging therapies offer new possibilities for addressing congenital cataracts at their root cause. Gene-editing technologies, including CRISPR-Cas9, have demonstrated potential in correcting genetic mutations linked to cataract formation, while pharmacological approaches, such as small-molecule chaperones and antioxidants, aim to stabilize lens proteins and reduce oxidative stress [6, 7].

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All authors have read and agreed with the published version of the manuscript.

Founding Statement: The study did not receive funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Conflict of Interest Statement: The authors declare no conflicts of interest.
Acknowledgments: Not applicable.

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