Eva Elksne

ORCID 0000-0002-0511-3552

Visual Function Assessment and Genetic Analysis in Primary Congenital Glaucoma Patients

Summary of the Doctoral Thesis for obtaining the scientific degree "Doctor of Science (*PhD*)"

Sector Group – Medical and Health Sciences

Sector – Clinical Medicine

Sub-Sector – Ophthalmology

Riga, 2026

The Doctoral Thesis was developed at the Eye Disease Clinic of the Children's Clinical University Hospital, the Latvian Biomedical Research and Study Centre, and the Molecular Genetics Research Laboratory of Rīga Stradiņš University, Latvia

Supervisors of the Doctoral Thesis:

Dr. med. **Sandra Valeiņa**,
Children's Clinical University Hospital, Latvia

Dr. med. Associate Professor **Artūrs Ozoliņš**,
Rīga Stradiņš University, Paula Stradiņš Clinical university hospital, Latvia

Scientific Advisors:

Dr. med. **Linda Gailīte**,
Rīga Stradiņš University, Latvia

Dr. biol. **Inna Iņaškina**,
Latvian Biomedical Research and Study Centre,
Riga East Clinical university hospital, Latvia

Dr. med., Assistant Professor **Ēriks Elksnis**,
Rīga Stradiņš University, Latvian American Eye centre, Latvia

Official Reviewers:

Dr. med., Assistant Professor **Juris Vanags**,
Rīga Stradiņš University, Latvia

Dr. med., Professor **Reda Žemaitiene**,
Lithuanian University of Health Sciences

Dr. med., Associate Professor **Valeria Coviltir,**
Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Chair of the Doctoral Committee:

Dr. habil. med., Professor **Jānis Gardovskis**,
Rīga Stradiņš University, Latvia

Members of the Doctoral Committee:

Dr. biol., Tenured Professor, **Dace Pjanova**,
Rīga Stradiņš University, Latvia

Ph. D., Assistant Professor **Artūrs Zemītis**,
Rīga Stradiņš University, Latvia

Dr. med., Professor **Guna Laganovska**,
Rīga Stradiņš University, Latvia

Dr. med., Associate Professor **Juris Vanags**,
Rīga Stradiņš University, Latvia

Defence of the Doctoral Thesis will take place at the public session of the Doctoral Committee of Clinical Medicine on 1 of October 2026 at 13.00 in the Hippocrates Lecture Theatre, 16 Dzirciema Street, Rīgas Stradiņš University.

The Doctoral Thesis is available in RSU Library and on RSU website:
https://www.rsu.lv/en/dissertations

This research was performed within the framework of the project "Rīga Stradiņš University internal and Rīga Stradiņš University with Latvian Academy of Sport Education external consolidation" (No 5.2.1.1.i.0/2/24/I/CFLA/005), funded by the European Union's Recovery and Resilience Mechanism and the Republic of Latvia

Table of Contents

Abbreviations used in the Thesis

AH	Aqueous humour
BKUS	Children's Clinical University hospital
CMEC	Central Medical Ethics committee
CYP1B1	Cytochrome P450 family 1 subfamily B member 1, protein
DNA	Deoxyribonucleic acid
FOXC1	*Forkhead box C1*, protein
FOXC2	*Forkhead box C2*, protein
IOP	Intraocular pressure
LTBP2	Latent transforming growth factor beta-binding protein 2
MMC	Mitomycin C
MYOC	Myocilin
OCT	Optical coherence tomography
PCG	Primary congenital glaucoma
PITX2	Paired-like homeodomain transcription factor 2
TEK	Tyrosine kinase, endothelial
WGS	Whole genome sequencing

Introduction

Primary congenital glaucoma (PCG) is a rare, potentially blinding disease that affects children worldwide (Aponte et al., 2010; Papadopoulos et al., 2007). The underlying pathogenesis is characterised by isolated dysgenesis of the anterior chamber angle, resulting in abnormalities of the trabecular meshwork and, less frequently, Schlemm's canal. Dysgenesis of the aqueous humour (AH) outflow pathway promotes the development of elevated intraocular pressure (IOP), which, if left untreated, leads to progressive optic nerve damage and irreversible blindness (Spaeth, 2021). Epidemiological data indicate that PCG is the most common cause of childhood glaucoma worldwide, with an average incidence ranging from 1:10,000 to 1:20,000 live births in Western populations (Sarfarazi & Stoilov, 2000).

Clinically, PCG most commonly manifests during the first year of life (Fung et al., 2013). Elevated IOP results in characteristic ocular changes, including Haab's striae (ruptures in Descemet's membrane), corneal clouding, enlargement of the globe (buphthalmos), and loss of the neuroretinal rim of the optic nerve head. Patients typically present with the classical triad of symptoms: epiphora (excessive tearing), photophobia (marked light sensitivity), and blepharospasm (involuntary eyelid muscle contractions) (Badawi et al., 2019).

The primary goal of treatment is to reduce IOP and prevent further damage to retinal ganglion cells. Management of PCG is predominantly surgical. Goniotomy and trabeculotomy are considered the gold-standard procedures for this condition, whereas more complex cases may require trabeculectomy with or without mitomycin C (MMC), implantation of glaucoma drainage devices, or cyclophotocoagulation (Badawi et al., 2019).

PCG is a genetically heterogeneous disorder, and pathogenic variants in several genes have been associated with its development. The most frequently implicated gene is *CYP1B1* (Cytochrome P450, family 1, subfamily B, polypeptide 1). The enzyme encoded by this gene is involved in the development and function of the trabecular meshwork and regulates the ocular response to elevated IOP (Bejjani et al., 2002; Zhao et al., 2013, 2015). In addition, PCG has been associated with variants in *LTBP2* (Latent Transforming Growth Factor Beta-Binding Protein 2), *MYOC* (myocilin), *TEK* (Tyrosine Kinase, Endothelial), *FOXC1* (Forkhead Box C1), *FOXC2* (Forkhead Box C2), and *PITX2* (Paired-Like Homeodomain Transcription Factor 2*)*, highlighting the importance of molecular genetic testing in the diagnosis of this disease (Leysen et al., 2022).

Early diagnosis and effective treatment are essential to preserve visual potential and ensure an adequate quality of life for children affected by PCG throughout their lifetime (Gothwal et al., 2020).

Aim of the Thesis

To evaluate the long-term treatment outcomes of patients with a clinically confirmed diagnosis of PCG and to identify genetic variants associated with the development of the disease.

Objectives of the Thesis

To achieve the aim of the Doctoral Thesis, the following objectives were established:

1 To determine the incidence of PCG by identifying patients diagnosed with PCG at the Eye Disease Clinic of the Children's Clinical University Hospital (BKUS).
2 To record the age of the patients and document the objective clinical findings at the time of diagnosis.
3 To evaluate the surgical treatment modalities and associated complications. To analyse IOP values during the postoperative period and at the final follow-up visit.
4 To assess visual function and structural changes of the optic nerve by performing visual field testing using standard automated perimetry and objective evaluation of the optic nerve with optical coherence tomography (OCT).
5 To identify and analyse factors potentially associated with blindness or with better long-term visual outcomes.
6 To perform exome sequencing or whole-genome sequencing (WGS) in patients and compile information on the results of genetic testing. To identify the most common genetic variants, evaluate their impact on disease course, and analyse genotype–phenotype correlations.

Hypothesis of the Thesis

1 Trabeculectomy provides a significant reduction in IOP during the postoperative period and results in favourable long-term visual outcomes in patients with infantile PCG.
2 Pathogenic variants in genes associated with anterior segment dysgenesis play a significant role in the development of PCG in the Latvian population.

Novelty of the Thesis

This Doctoral Thesis represents the first study of PCG in Latvia, incorporating retrospective data analysis, prospective patient follow-up, and genetic investigations.

PCG has a significant impact on visual function and overall child development. The rarity of the disease often delays early diagnosis. However, timely diagnosis and effective

treatment are the only means of ensuring an adequate quality of life and successful social integration for affected children (Dahlmann-Noor et al., 2017; Spaeth, 2021).

Data regarding the clinical course of PCG in different European populations and the results of genetic testing remain very limited because of the rarity of the disease, thereby hindering research in this field. To date, the epidemiology, long-term clinical outcomes, and genetic causes of PCG have not been investigated in Latvia or the Baltic States. Furthermore, such studies remain scarce even at the European level.

PCG has been extensively studied in regions with a high disease incidence, including Saudi Arabia, India, and the Slovak Roma population. However, comparatively little is known about populations in which PCG development is not associated with consanguinity or familial inheritance. By highlighting differences in clinical presentation, long-term outcomes, and the importance of evaluating genetic factors, this study contributes to a better understanding of disease pathogenesis and may facilitate the identification of novel therapeutic approaches.

This study provides unique insights into the clinical characteristics and genetic background of PCG in the Latvian population, thereby making a significant contribution to the global understanding of the disease. Genetic analyses performed in probands support an opportunity to identify population-specific genes and evaluate the potential role of additional genes in disease development. Furthermore, the obtained data allow comparison of genetic findings with those reported in other European populations and contribute substantially to the investigation of the genetic basis of PCG.

Pathogenic variants associated with disease development can be identified in only a proportion of patients within European populations (Giuffre', 2011; Leysen et al., 2022; López-Garrido et al., 2013). This observation indicates that the complete genetic architecture of PCG has not yet been fully elucidated and that additional, as yet undescribed, candidate genes may be involved in the pathogenesis of the disease.

Practical significance of the Thesis

The results obtained during the development of this Doctoral Thesis will make a significant contribution to the counselling and management of newly diagnosed patients with PCG.

As part of the study, a standardised examination protocol for newly diagnosed patients will be developed, based on the inclusion of clinically relevant diagnostic investigations, and a structured patient history questionnaire will be created. Furthermore, clinical management algorithms for the treatment and follow-up of newly diagnosed patients will be established at the Eye Disease Clinic of the CCUH. These algorithms will incorporate age-specific reference

curves to facilitate the interpretation and comparison of objective clinical findings during longitudinal follow-up.

The identification of genetic variants will provide an opportunity to determine specific molecular causes of disease development, identify previously undescribed genomic alterations, and compare findings with data reported from other countries. In addition, these results will support genetic counselling by enabling more accurate assessment of inheritance risks for future generations.

Ethical considerations

The study was conducted in accordance with internationally recognised bioethical standards, including the World Medical Association's Declaration of Taipei and Declaration of Helsinki, while ensuring full compliance with the applicable laws and regulations of the Republic of Latvia.

The study received approval from the Ethics Committee of Rīga Stradiņš University (Approval No. 9, 25 May 2017, and Approval No. 2-PĒK-4/46/2022).

Genetic analyses were performed following approval from the Central Medical Ethics Committee of Latvia (CMEC) (Approval Nos. 01-29.1.2/6407 and 01-29.1.2/4613) and the Genome Research Council (Approval Nos. A-8/19-04-26 and A-19/24-12-11).

Author's Contribution

In collaboration with the supervisors, the study methodology was developed in accordance with fundamental ethical principles, and the study aims, objectives, relevance, and novelty were refined. The author coordinated the implementation of the study with the participating healthcare institution and prepared the necessary applications for submission to the ethics committees.

The author retrospectively collected and reviewed all data from patients' medical records and informed patients and their legal guardians about the opportunity to participate in the subsequent stages of the study. During the prospective phase, the author personally performed all diagnostic examinations during outpatient visits to assess treatment efficacy and determine the stage of glaucoma. The research grant awarded to the author was utilised to conduct genetic analyses in patients with PCG.

The author compiled the study database, performed the statistical analyses, and prepared all resulting publications. As part of the Doctoral Thesis, a standardised examination protocol for newly diagnosed patients was developed based on clinically relevant diagnostic investigations, and a structured patient history questionnaire was created. Clinical management algorithms for the treatment and follow-up of newly diagnosed patients were established for

use at the Eye Disease Clinic, incorporating age-specific reference curves for the comparison and interpretation of objective clinical findings during longitudinal follow-up.

In addition, a PCG Registry was established at the clinic, and participation was initiated in the international paediatric glaucoma registry, the Robison Harley Childhood Glaucoma Research Network International Paediatric Glaucoma Registry.

Conclusions

1 The incidence of PCG in the study cohort between 2003 and 2021 was comparable to that reported in other Western populations, with the unilateral form of the disease being predominant.

2 In the majority of patients, the diagnosis of PCG was established before one year of age. The most common clinical finding was enlargement of the anterior segment of the eye, which developed as a consequence of elevated IOP.

3 Trabeculectomy resulted in a substantial reduction in IOP with a low rate of complications. Furthermore, the use of MMC was associated with a significantly higher long-term success rate. A substantial reduction in IOP without the need for additional medical therapy was maintained in the majority of patients at the final follow-up visit.

4 At the final follow-up visit, more than half of all eyes affected by PCG achieved good visual acuity (*visus* ≥ 0.5), corresponding to the proportion of eyes demonstrating only mild visual field defects. In contrast, severe visual loss was observed in approximately one-tenth of eyes. Amblyopia was diagnosed in more than half of the eyes included in the study, highlighting that successful management requires not only surgical treatment but also identification and correction of amblyogenic factors.

5 Analysis of preoperative factors did not reveal any statistically significant predictors of favourable or unfavourable long-term visual outcomes. However, larger horizontal corneal diameter and older age at diagnosis were associated with a greater likelihood of significant visual loss. In addition, patients presenting with Haab's striae had a lower probability of achieving a favourable visual outcome.

6 DNA from PCG probands and their first-degree relatives was analysed, providing unique insights into the potential molecular genetic determinants of the disease and, for the first time, characterising the genetic findings associated with PCG in Latvia. Next-generation sequencing did not identify pathogenic variants in the most commonly reported PCG-associated genes in any of the probands. These findings suggest the possible involvement of other candidate genes specific to our region, as well as a potential polygenic contribution to disease risk. These factors warrant further investigation in future PCG research.

7 The hypothesis of the study was partially confirmed. Trabeculectomy was shown to provide a significant reduction in intraocular pressure during the postoperative period and favourable long-term visual outcomes. However, no pathogenic genetic variants associated with the development of PCG were identified.

Proposals

1 Further research should be continued by expanding the study cohort with additional patients diagnosed with PCG. Longitudinal evaluation of clinical findings is recommended to provide a more accurate characterisation of disease progression and clinical outcomes within our population.

2 Early clinical manifestations, including photophobia, blepharospasm, epiphora, and enlargement of the anterior segment of the eye, should be considered potential indicators of congenital glaucoma. In such cases, comprehensive ophthalmological evaluation at BKUS is warranted to establish the diagnosis promptly, initiate appropriate treatment, and include patients in the unified clinical registry.

3 Long-term follow-up after trabeculectomy is essential, with particular emphasis on the assessment of visual function, taking into account potential surgical complications and sequelae that may resemble those observed in adult populations. Systematic evaluation of the long-term impact of trabeculectomy on visual outcomes in patients with PCG is recommended.

4 Further genetic investigations should be pursued through detailed analysis of the already acquired exome sequencing and WGS data, with the aim of identifying previously undescribed genes that may be associated with disease development. Future collaboration with other clinics and research centres specializing in the genetic basis of PCG is encouraged to facilitate the identification and analysis of genotype–phenotype correlations.

5 WGS and mitochondrial DNA analysis in all patients included in the study may provide deeper insights into the genetic causes of PCG. Such an approach would enable the investigation not only of coding regions but also of regulatory and non-coding genomic regions, while additionally assessing the potential role of mitochondrial genes in disease pathogenesis.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. **Elksne, E**., Lace, B., Stavusis, J., Tvoronovica, A., Zayakin, P., Elksnis, E., Ozolins, A., Micule, I., Valeina, S., Inashkina, I. 2025. Genetic Analysis of *CYP1B1* and Other Anterior Segment Dysgenesis-Associated Genes in Latvian Cohort of Primary Congenital Glaucoma. *Biomedicines*, *13*(5), 1222. https://doi.org/10.3390/biomedicines13051222
2. **Elksne**, **E**., Baumane, K., Ozolins, A., Valeina, S. 2021. The Epidemiological and Clinical Findings from the Latvian Registry of Primary Congenital Glaucoma and Evaluation of Prognostic Factors. *Medicina (Kaunas)*. 7;57(1), 44. doi: 10.3390/medicina57010044.
3. **Elksne, E**., Mercieca, K., Prokosch-Willing, V. 2022. Canaloplasty with mitomycin C after previous combined cataract surgery and Schlemm's canal microstent implantation. *European Journal of Ophthalmology*. 32(1), 712–716. doi: 10.1177/11206721211000275.
4. **Elksne, E**., Stingl, J., V., Schuster, A., K., Wagner, F., M., Hoffmann, E., M. 2022. Do biometric parameters improve the quality of optic nerve head measurements with spectral domain optical coherence tomography? *BMC Ophthalmology*. 5;22(1), 56. doi: 10.1186/s12886-022-02281-6.
5. **Elksne, E**., Steiner, V., Hohensinn, M., Reitsamer, H.A., Lenzhofer, M. 2023. Radius-Maumenee syndrome: A case series with a long-term follow-up. Clinical Case Reports. 19;11(2):e6918. doi: 10.1002/ccr3.6918. PMID: 36814708; PMCID: PMC9939581.

Reports at international congresses and conferences:

1. **Elksne, E**., Lace, B., Stavusis, J., Tvoronovica, A., Zayakin, P., Elksnis, E., Ozolins, A., Micule, I., Valeina, S., Gailite, L., Inashkina, I. 2025. Genetic Screening for Primary Congenital Glaucoma in Latvia: A Cohort-Based Study. Forum Ophthalmologicum Balticum 2025. Riga, Latvia
2. **Elksne, E**., Lace, B., Stavusis, J., Tvoronovica, A., Zayakin, P., Elksnis, E., Ozolins, A., Micule, I., Valeina, S., Gailite, L., Inashkina, I. 2025. Genetic Testing Insights From the Primary Congenital Glaucoma Registry in Latvia. World Glaucoma Congress 2025. Honolulu, United States of America
3. **Elksne, E**., Ozolins, A., Valeina, S. 2022. Lessons Learned about Primary Congenital Glaucoma in the Latvian Population. *World Ophthalmology Congress 2022*. Online
4. **Elksne, E**., Ozolins, A., Valeina, S. 2022. Long-term Follow-up for Patients with Primary Congenital Glaucoma in Latvia. *European Glaucoma Society Congress.* Athens, Greece.
5. **Elksne, E**., Stingl, J., V., Schuster, A., K., Wagner, F., M., Hoffmann, E., M. 2020. Clinical Quality Assessment of Optic Nerve Head Measurements with Spectral Domain Optical Coherence Tomography – Preliminary Results. *Deutsche Ophthalmologische Gesellschaft (DOG) Congress.* Online.
6. **Drucka, E**. (maiden name), Borroni, D., Valeina, S., Viksnins, M., Sperga, V., Treija, A., Baumane, K., Laganovska, G. 2017. Assessment of Primary Congenital Glaucoma in Latvia. *7th World Glaucoma Congress*. Helsinki, Finland.
7. **Drucka, E**. (maiden name), Valeina, S., Viksnins, M., Sperga, V., Treija, A., Baumane, K., Laganovska, G. 2017. Long-term Outcomes of Trabeculectomy Undertaken within the First 2 Years of Life for Primary Congenital Glaucoma. *European Society of Ophthalmology Congress*. Barcelona, Spain.

Theses at international congresses and conferences:

1. **Elksne, E**., Ozolins, A., Valeina, S. 2023. Functional and Structural Outcomes of Primary Congenital Glaucoma in the Tertiary Medical Centre**.** European Society of Ophthalmology Congress. Prague, Czech Republic.
2. **Elksne, E**., Ozolins, A., Valeina, S. 2023. Morpho-functional Characteristics of Primary Congenital Glaucoma in Latvia. Medicina (Kaunas). 59, Suppl.2, p. 579. RSU Research week 2023: Knowledge for Use in Practice, Riga, Latvia. https://science.rsu.lv/ws/portalfiles/portal/62290221/SHORT_TERM_RESULTS_AFTER_REVISION.pdf
3. **Elksne, E**., Elksnis, E. 2020. Changes of Intraocular pressure after Cataract Surgery in Glaucomatous and non-glaucomatous Eyes. *European Society of Cataract and Refractive Surgeons (ESCRS) 25th Winter Meeting*. Marrakech, Morocco.
4. **Drucka, E**. (maiden name), Baumane, K., Viksnins, M., Sperga, V., Treija, A., Valeina, S. 2019. Outcomes of Trabeculectomy Undertaken within the First Year of Life for Reduction of Intraocular Pressure in Primary Congenital Glaucoma. *European Paediatric Ophthalmological Society Congress.* Riga, Latvia.
5. **Drucka, E**. (maiden name), Valeina, S. 2019. Paediatric Embryonal Rhabdomyosarcoma: A Case Report. *Riga Stradins University International Research Conference*. Riga, Latvia
6. **Drucka, E**. (maiden name), Schuster, A., K., Pfeiffer, N., Hoffmann, E., M. 2019. Efficacy of Cataract Surgery Combined with Concurrent Trabecular Micro-bypass Stent Implantation for Patients with Open-angle Glaucoma. *European Society of Cataract and Refractive Surgeons (ESCRS) 23rd Winter Meeting*. Athens, Greece.

References

1. Aponte, E. P., Diehl, N., & Mohney, B. G. (2010). Incidence and clinical characteristics of childhood glaucoma: a population-based study. *Archives of Ophthalmology (Chicago, Ill. : 1960)*, *128*(4), 478–482. https://doi.org/10.1001/archophthalmol.2010.41
2. Badawi, A. H., Al-Muhaylib, A. A., Al Owaifeer, A. M., Al-Essa, R. S., & Al-Shahwan, S. A. (2019). Primary congenital glaucoma: An updated review. *Saudi Journal of Ophthalmology : Official Journal of the Saudi Ophthalmological Society*, *33*(4), 382–388. https://doi.org/10.1016/j.sjopt.2019.10.002
3. patterns of cytochrome P4501B1 (Cyp1b1) in FVB/N mouse eyes. *Experimental Eye Research*, *75*(3), 249–257. https://doi.org/10.1016/S0014-4835(02)92025-7
4. Khaw, P. T., & Papadopoulos, M. (2017). Quality of Life and Functional Vision in Children with Glaucoma. *Ophthalmology*, *124*(7), 1048–1055. https://doi.org/10.1016/j.ophtha.2017.02.024
5. Epidemiology and characteristics of childhood glaucoma: results from the Dallas Glaucoma Registry. *Clinical Ophthalmology (Auckland, N.Z.)*, *7*, 1739–1746. https://doi.org/10.2147/OPTH.S45480
6. Functioning and Quality of Life in Primary Congenital Glaucoma and Secondary Childhood Glaucoma. *American Journal of Ophthalmology*, *209*, 62–70. https://doi.org/10.1016/j.ajo. 2019. 09.002
7. primary congenital glaucoma: Implications in disease management and counseling. *European Journal of Medical Genetics*, *65*(1). https://doi.org/10.1016/J.EJMG.2021.104378
8. Martínez-De-La-Casa, J. M., García-Antón, M., & Escribano, J. (2013). Null CYP1B1 genotypes in primary congenital and nondominant juvenile glaucoma. *Ophthalmology*, *120*(4), 716–723. https://doi.org/10.1016/j.ophtha.2012.09.016
9. Childhood Glaucoma (BIG) Eye Study. *Investigative Ophthalmology & Visual Science*, *48*(9), 4100–4106. https://doi.org/10.1167/iovs.06-1350
10. *Eye (London, England)*, *14 (Pt 3B)* (3), 422–428. https://doi.org/10.1038/EYE.2000.126
11. Glaucoma, 5th Edition. *The British Journal of Ophthalmology*, *105*(Suppl 1), 1–169. https://doi.org/ 10.1136/BJOPHTHALMOL-2021-EGSGUIDELINES
12. Conway, S. J., Jefcoate, C. R., & Sheibani, N. (2013). Cyp1b1 mediates periostin regulation of trabecular meshwork development by suppression of oxidative stress. *Molecular and Cellular Biology*, *33*(21), 4225–4240. https://doi.org/10.1128/MCB.00856-13

Acknowledgments

I would like to express my sincere gratitude to everyone who contributed to the completion of this research project through their time, patience, and professionalism, all of which played a significant role in the development of my Doctoral Thesis and my growth as an early-career researcher.

I would especially like to thank the patients and their family members for their participation in the study, which made it possible to investigate the impact of PCG on visual function and to analyse the genetic causes of the disease in our region.

I am deeply grateful to *Dr. med*. Sandra Valeiņa, Head of the Eye Disease Clinic at the Children's Clinical University Hospital, for the trust she placed in me by allowing me to participate in the management of highly complex patients, their long-term follow-up, and comprehensive ophthalmological assessment. I particularly appreciate her invaluable support throughout the research process and her constant encouragement to pursue the goals of this project. I am thankful for the opportunities she provided for my professional development, for her confidence in my abilities, and for recognising and fostering my potential. This supportive and inspiring environment motivated me to strive for excellence both clinically and academically within the field of ophthalmology.

I am sincerely grateful to *Dr. med*. Associate Professor Dr. Artūrs Ozoliņš for his extensive scientific expertise and academic insight, which proved invaluable throughout the preparation of this Doctoral Thesis. His knowledge, precision, and ability to view the research within a broader scientific context significantly contributed to the conceptual development and overall quality of the work. I especially appreciate his support in my scientific growth, as well as his careful, responsible, and professional supervision and review of the Thesis. His recommendations and constructive criticism helped refine both the structure of the study and its methodological approach.

I would like to thank my scientific advisors, *Dr. biol.* Inna Iņaškina and *Dr. med.* Linda Gailīte, for their professional support in the analysis and interpretation of genetic data, which greatly contributed to the accurate understanding of the study findings. I am grateful for their careful and constructive review of the work and for their assistance in clarifying complex genetic findings, thereby ensuring the high scientific quality of the Thesis. I would also like to express my sincere gratitude to *Dr. med*. Baiba Lāce for supporting the idea of conducting genetic analyses and for helping to translate this concept into practice. I am particularly thankful for her assistance in genome data analysis, which made a substantial contribution to both the implementation and the scientific quality of the study.

My deepest and most heartfelt gratitude goes to *Dr. med.* Assistant Professor Ēriks Elksnis for his substantial contribution to the clinical component of this study. Beyond serving as an outstanding professional role model, he has been a source of unwavering support and a trusted advisor. His presence, encouragement, and guidance provided me with confidence and strength to continue this work, even during its most challenging stages.

My sincere thanks go to biostatistician Māra Grēve of the Statistics Laboratory for her support in evaluating the statistical analyses performed in this study and for her valuable recommendations for their improvement. I greatly appreciate her professional approach and contribution to the enhancement of the data analysis.

I would also like to thank all my colleagues at the Eye Disease Clinic of BKUS for their collaboration and support throughout this work.

Finally, I would like to express my sincere gratitude to my parents for instilling in me, from an early age, a deep appreciation of the value and importance of knowledge. Thank you for your continuous support, encouragement, and belief in me throughout my professional journey and personal development.