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Hereditary Angioedema: Clinical and Genetic Research

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

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Abbreviations used in the Thesis

ACMG	American College of Medical Genetics
AAE-C1INH	Acquired angioedema due to C1-inhibitor deficiency
AAS	Angioedema Activity Score
AE	Angioedema
AE-MC	Mast cell-mediated angioedema
AE-QoL	The Angioedema Quality of Life Questionnaire
AE-UNK	Angioedema of unknown aetiology
AECT	Angioedema Control Test
ACEI	Angiotensin-converting enzyme inhibitors
ANGPT1	Angiopoietin 1
Asn	Asparagine
AUC	Area under the curve
C1-INH	C1 inhibitor
C1q	Complement component 1q
C4	Complement component 4
C5	Isovalerylcarnitine
CNV	Copy number variation
CPN1	Carboxypeptidase N1
DAB2IP	Disabled homolog 2-interacting protein
EAACI	European Academy of Allergy and Clinical Immunology
F12	Coagulation factor XII
g/L	Grams per litre
Gly	Glycine
HAE	Hereditary angioedema
HAE I	Hereditary angioedema Type I
HAE II	Hereditary angioedema Type II
HIV	Human immunodeficiency virus
HS3ST6	Heparan sulphate-glucosamine 3-sulfotransferase 6
IQR	Interquartile range
KNG1	Kininogen-1
BMI	Body mass index
LC–MS	Liquid chromatography–mass spectrometry
MS	Mass spectrometry
MYOF	Myoferlin
MLPA	Multiplex ligation-dependent probe amplification
n	Number
nC1-INH HAE	Hereditary angioedema with normal C1 inhibitor

OH-Pro	Hydroxyproline
PLG	Plasminogen
RSU	Rīga Stradiņš University
SNV	Single nucleotide variant
FFP	Fresh frozen plasma
WAO	World Allergy Organization
GS	Genome sequencing

Introduction

Hereditary angioedema (HAE) is a rare, life-threatening, autosomal dominant inherited disorder that clinically manifests with skin, gastrointestinal, and airway oedema (Uminski et al., 2025). Its prevalence averages approximately 1 case per 50 000 population, with regional variation ranging from 1 per 10 000 to 1 per 100 000 inhabitants (Maurer et al., 2022; Uminski et al., 2025). In Latvia, HAE diagnosis has been biochemically and genetically confirmed in 12 patients; however, considering the challenges in disease recognition and precise diagnostic determination, the total number of affected patients is potentially higher.

Although HAE was first described in 1888, the pathogenesis of this disease remains incompletely understood. Similarly, the reasons for the heterogeneity in clinical manifestations, prognosis, and therapeutic efficacy among HAE patients remain unclear (H. Longhurst & Cicardi, 2012). The primary role in HAE development is attributed to the level and activity of C1 esterase inhibitor (C1-INH). HAE is classified into three types: type I – HAE with decreased C1-INH level and functional activity; type II – HAE with normal or elevated C1-INH level, but decreased function; and nC1-INH HAE with normal C1-INH level and normal function (Zafra, 2022).

C1-INH-associated HAE (types I and II) is caused by pathogenic variants in the *SERPING1* gene, which encodes C1 esterase inhibitor. As a result of pathogenic variants, quantitative and/or qualitative C1 inhibitor deficiency develops, leading to increased bradykinin synthesis, which results in the development of massive localised oedema (Sinnathamby et al., 2023). Despite pathogenic *SERPING1* variants being the only known cause of types I and II HAE, approximately 15 % of symptomatic HAE patients with decreased C1-INH level and/or activity remain undiagnosed at the molecular level, as pathogenic variants cannot be identified even after rigorous genetic investigation, including sequencing of both the coding and non-coding regions of the entire *SERPING1* gene and copy number variation analysis (Jacobs & Neeno, 2021). Given the specific C1-INH-associated phenotype, we propose that intragenomic and extragenomic non-coding point and structural variants within the *SERPING1* gene, which cannot be detected by standard diagnostic methods (Sanger sequencing, MLPA), are responsible for types I and II HAE in patients with negative genetic findings.

In contrast, C1-INH-independent HAE – nC1-INH HAE, has a more complex aetiology and pathogenesis related to gain-of-function pathogenic variants in genes involved in the contact/bradykinin system (*F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, *HS3ST6*) (Obtulowicz et al., 2021). Currently, nC1-INH HAE diagnosis can be confirmed only through genetic analysis. Unfortunately, no biomarkers are currently available in clinical practice that would aid in identifying nC1-INH HAE. This not only complicates HAE diagnosis, particularly

nC1-INH HAE type, but also compromises its differentiation from other forms of angioedema (Muna et al., 2024).

Furthermore, the current diagnostic parameters for types I and II HAE – namely, C1 esterase inhibitor level and activity determination – require strict adherence to precise specimen collection, storage, transport, and analysis protocols. Inaccuracies result in false-positive or false-negative results, thus impeding timely diagnostic confirmation. Moreover, to confirm the diagnosis, analysis must be performed at least twice. Determination of these parameters is preferably performed on fresh blood samples or on frozen and transported specimens according to specific instructions designated for immunological parameter analysis (Magerl et al., 2025; Muna et al., 2024; Radojicic & Anderson, 2024). In Latvia, C1 esterase inhibitor determination on fresh blood samples is available only at the Joint Laboratory of Pauls Stradiņš Clinical University Hospital, thus complicating accurate analysis for patients from regional areas.

It is essential to identify novel biomarkers that are readily accessible in routine clinical practice, independent of laboratory location, thereby improving HAE diagnosis.

HAE patients require clarification of the genetic aetiology of their disease, as this is of paramount importance not only for understanding disease causation, pathogenesis, and discovering novel effective therapies, but also for patient clinical management – including diagnostic confirmation, prognostic determination, family planning, prevention of disease exacerbations, and the selection and optimisation of personalised therapy (Bocquet et al., 2025; Lyons et al., 2023). Currently available medications for HAE treatment are expensive and modulate distinct pathogenic pathways (Dias de Castro et al., 2024; Ren et al., 2023). Therefore, identification of biomarkers capable of elucidating determinants of disease severity gradation and differential therapeutic efficacy is essential. This would enable more precise determination of disease prognosis and more accurate selection of the required medication for disease treatment.

Aim of the Thesis

To determine the genetic aetiology of hereditary angioedema and to investigate potential biomarkers for disease diagnosis.

Objectives of the Thesis

The following specific objectives have been established to achieve the aim of this Doctoral Thesis:

1. To identify all patients with clinically and biochemically confirmed HAE in Latvia and determine the prevalence of hereditary angioedema in the Latvian population;

2. To analyse the clinical data of Latvian HAE patients;
3. To perform genetic analysis of hereditary angioedema using Sanger sequencing of the *SERPING1* gene in patients with HAE types I/II and analysis of *F12*, *PLG*, and *ANGPT1* gene regions in patients with suspected nC1-INH HAE;
4. To conduct advanced genetic analysis using genome sequencing in HAE types I/II patients in whom pathogenic variants were not identified by standard genetic testing, with the aim of detecting rare non-coding and structural variants; and to perform gene panel analysis using exome sequencing in patients with suspected n-C1-INH HAE;
5. To determine a metabolite profiling in blood samples from study and control group participants to identify potentially novel laboratory biomarkers for the diagnosis of hereditary angioedema.

Hypotheses of the Thesis

1. In HAE patients in whom standard genetic testing does not identify a causative pathogenic variant, the disease aetiology is attributed to non-coding and structural variants that can be detected by genome sequencing.
2. The serum metabolite profile in HAE patients differs from that of healthy individuals and patients with other types of angioedema, and these metabolic alterations can be applied as potential diagnostic biomarkers for HAE.

Novelty of the Thesis

For the first time, a comprehensive serum metabolite profiling study has been performed on HAE patients and control group participants to identify potential biomarkers for HAE diagnosis.

This is the first comprehensive study conducted in Latvia to establish the prevalence of HAE, characterise the clinical heterogeneity of disease manifestations, and determine its genetic aetiology, identifying previously undescribed genetic variants in the *SERPING1* gene worldwide.

Standardised, validated questionnaires for assessing health-related quality of life, disease activity, and disease control in HAE patients have been introduced in Latvia for the first time, providing clinical tools applicable in specialist practice not only for HAE evaluation but also for assessment of angioedema of alternative aetiologies.

1 Materials and Methods

1.1 Study participants

To ensure comprehensive data collection and analysis in Latvia and to effectively investigate the clinical manifestations and genetic factors associated with hereditary angioedema (HAE), the study comprised both retrospective and prospective phases. The retrospective phase commenced in June 2020 and included all known Latvian patients with a clinically and biochemically confirmed diagnosis of HAE.

Within the prospective phase, these patients underwent detailed clinical evaluation, and additional data regarding disease manifestations were collected. The study also included their relatives for screening purposes as well as individuals with clinical suspicion of HAE. Patients with other types of angioedema – including idiopathic, bradykinin-mediated, mast cell-mediated, or angioedema of unclear aetiology – as well as healthy individuals were enrolled as control groups.

The diagnosis of HAE was established based on patient and family history, complement component C4 level, C1 esterase inhibitor (C1-INH) concentration, C1-INH functional activity, and genetic testing results, in accordance with the WAO/EAACI 2021 guidelines (Maurer et al., 2022).

In total, the study included 100 individuals: 45 patients with clinical suspicion of HAE, 20 first-degree relatives of HAE patients, 15 previously examined patients with idiopathic (unexplained) angioedema for the metabolomic control group, and 20 healthy individuals for the metabolomic control group. Laboratory testing – including determination of C4 levels, C1-INH concentration, and activity – was performed for all participants in the study groups ($n = 80$). Genetic testing was conducted for 38 patients, metabolomic profiling for 45 individuals, and 12 patients with confirmed HAE were enrolled in the clinical evaluation section of the study.

1.2 Clinical data collection

Clinical data were obtained from medical records and patient interviews, including sex, date of birth, weight, height, family history, and detailed information on the clinical manifestations of the disease, such as the mean annual number of attacks, localisation of oedema, the most common trigger factors, type and effectiveness of treatment, age at onset of disease-specific symptoms, and age at which the diagnosis of HAE was established. Data on chronic comorbidities were also collected.

1.3 Evaluation of treatment effectiveness

Information on HAE management during acute attacks, long-term prophylactic therapy, and the effectiveness of the medications used was obtained from medical records, patient interviews, and patient-completed questionnaires.

1.4 Laboratory sample collection and analysis

Functional activity of C1 inhibitor was determined using a chromogenic substrate assay, and the concentrations of complement component C4 and C1-INH were measured by nephelometry. To exclude acquired angioedema, antibodies against the C1q component were additionally assessed in patients with idiopathic or angioedema of unclear aetiology using an enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions. All analyses were performed at the Joint Laboratory of Pauls Stradiņš Clinical University Hospital.

1.5 Quality of life, disease activity, and control questionnaires

To assess health-related quality of life, disease activity, and control in patients with angioedema, standardised questionnaires validated for this purpose were employed: the Angioedema Quality of Life Questionnaire (AE-QoL), Angioedema Activity Score (AAS), and Angioedema Control Test (AECT).

1.6 Comorbidity assessment in hereditary angioedema patients

A comprehensive comorbidity analysis was performed in symptomatic HAE patients included in the study (n = 10), with primary focus on cardiovascular, psychoemotional, dermatological, respiratory, and systemic pathologies. Data collection was based on retrospective analysis of medical documentation, encompassing disease history records, detailed clinical anamnesis, laboratory and instrumental investigation results, specialist consultation conclusions, and standardised psychoemotional status evaluation using validated diagnostic methods.

1.7 Diagnosis and classification of hereditary angioedema

HAE type I was diagnosed in patients with C4 levels below the reference range (< 0.12 g/L), C1-INH concentration below the reference range (< 0.21 g/L), and C1-INH functional activity below the reference range (< 70 %). HAE type II was diagnosed in patients with C4 levels below the reference range (< 0.12 g/L), C1-INH concentration within or above the reference range (0.21–0.39 g/L or > 0.39 g/L), and C1-INH functional activity below the reference range (< 70 %). nC1-INH HAE was diagnosed in patients with C4 levels within the reference range (0.12–0.36 g/L), C1-INH concentration within the reference range

(0.21–0.39 g/L), C1-INH functional activity within the reference range (70–130 %), and confirmation by genetic testing.

1.8 Control groups

Two control groups were established: healthy individuals and patients with recurrent angioedema of other aetiologies, including idiopathic, bradykinin-mediated, mast cell-mediated, and angioedema of unclear origin. For metabolomic analysis, healthy controls matched for sex and, as closely as possible, age to the study participants were utilised.

1.9 Latvian population

Data on Latvian demographic indicators were obtained from the Central Statistical Bureau of Latvia database (April 2025). Point prevalence was expressed as the number of living patients per 100 000 inhabitants at a specific time point (April 2025) (Central Statistical Bureau of Latvia, 2025).

1.10 Genetic testing

A multi-step molecular diagnostic approach was applied for genetic analysis of HAE patients, in accordance with international guidelines (WAO/EAACI, 2021) (Maurer et al., 2022). The initial diagnostic strategy involved sequencing analysis of known HAE-associated genes, with primary focus on the *SERPING1* gene, which encodes C1 inhibitor and accounts for the majority of HAE types I and II cases. Sanger sequencing was utilised to identify genetic variants, enabling precise detection of point mutations. For one HAE type I patient, MLPA analysis of the *SERPING*1 gene was performed to detect large deletions or duplications.

In patients with angioedema of unclear aetiology and no pathogenic *SERPING1* variants identified, extended genetic analysis was conducted, including examination of the *F12*, *PLG*, and *ANGPT1* gene regions to exclude rarer HAE variants.

In cases where Sanger sequencing failed to identify pathogenic variants in patients suspected of HAE types I/II, GS was performed to investigate potential intragenic and extragenic non-coding point and structural variants in the *SERPING1* gene that could affect C1-INH expression, as well as sequencing of other HAE-associated genes.

For patients suspected of nC1-INH HAE with negative Sanger sequencing results for *F12*, *PLG*, and *ANGPT1* gene regions, diagnoses were reviewed to identify alternative causes of symptoms. Patients responsive to standard-dose antihistamine therapy, dose escalation to fourfold, or omalizumab received a diagnosis of mast cell-mediated angioedema (AE-MC), with no further genetic testing performed. In cases where no alternative cause was identified in patients suspected of nC1-INH HAE, ES was conducted with SNV and CNV analysis in

described nC1-INH HAE (candidate) genes (*F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, and *HS3ST6*). The distribution of genetic testing methods across patient groups is shown in Figure 1.1.

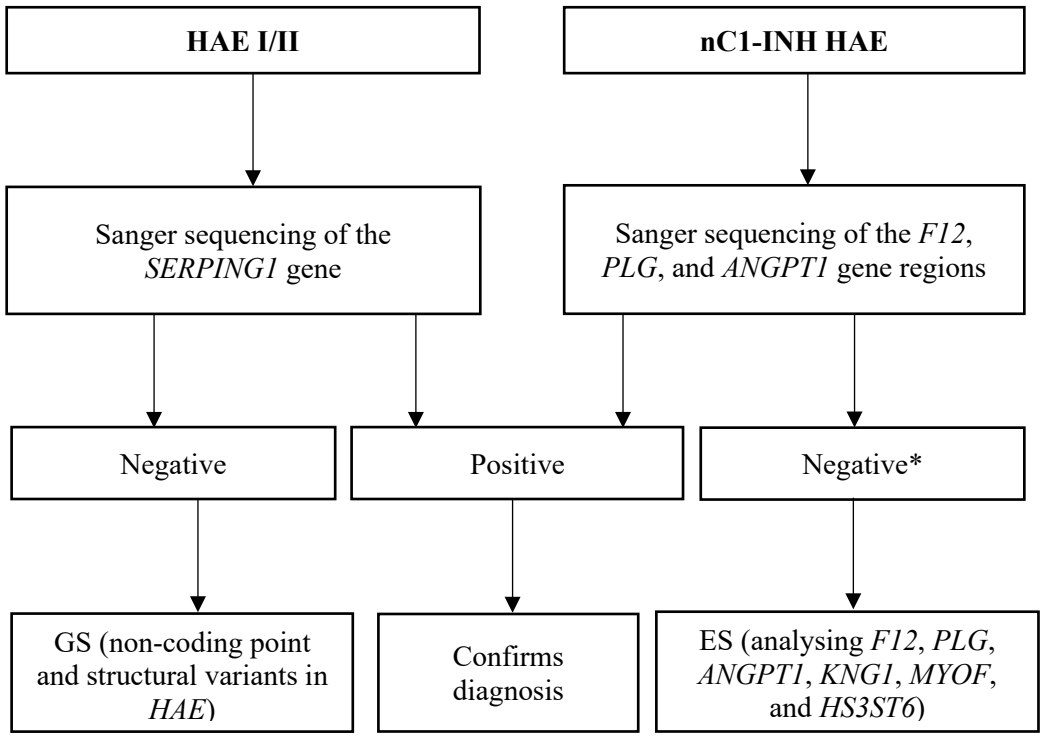

Figure 1.1 **Genetic testing approach and distribution of methods across patient groups**

HAE I/II – hereditary angioedema types 1 and 2; nC1-INH HAE – hereditary angioedema with normal C1 inhibitor; *F12* – coagulation factor XII gene; *PLG* – plasminogen gene; *ANGPT1* – angiopoietin-1 gene; *KNG1* – kininogen-1 gene; *MYOF* – myoferlin gene; *HS3ST6* – heparan sulphate–glucosamine 3-O-sulfotransferase 6 gene; GS – genome sequencing; ES – exome sequencing; *without alternative cause of symptoms

1.11 Metabolomic analysis

In this study, a targeted metabolite panel was quantified in blood samples from the study group (HAE patients) and control group (healthy individuals) to identify potential HAE disease biomarkers. The metabolomic analysis included 10 patients with C1-INH HAE, 15 patients with idiopathic angioedema, and 20 healthy individuals. Specificity of identified biomarkers was validated in the group with angioedema of other aetiologies (idiopathic).

Metabolite determination was performed in blood serum during the asymptomatic period, i. e. at least 8 days after an angioedema episode. Targeted quantitative liquid chromatography – mass spectrometry (LC–MS) was used for metabolomic analysis. Of 52 targeted metabolites analysed, including amino acids, amino acid-related metabolites, and acylcarnitines – 33 were detected and quantified in all study samples. These metabolites were selected as they are routinely measured using mass spectrometry in clinical laboratories for newborn screening.

1.12 Statistical analysis

Data processing and organisation were performed using Microsoft Office Excel, while statistical analyses were conducted with IBM SPSS Statistics version 23, MetaboAnalyst 5.0, and GraphPad Prism 9.0. Given the rare disease nature and small sample size, non-parametric statistical methods were primarily employed. Percentage data presentation enabled comparative analysis with studies from other countries, ensuring international comparability of results.

For LC–MS metabolomic analysis, principal component analysis (PCA) was applied to assess overall metabolite profile differences between study groups. Group comparisons utilised T-tests and comparative change analysis. Additionally, receiver operating characteristic (ROC) curve analysis was performed to evaluate potential diagnostic value. Statistical significance was set at $p < 0.05$ for all tests.

2 Results

The study results are divided into three main sections: clinical data, genetic findings, and metabolite biomarkers.

2.1 Prevalence of hereditary angioedema in Latvia

During the study, HAE diagnosis was biochemically and genetically confirmed in 12 patients in Latvia (8 females, 4 males). According to the Official Statistics Portal, Latvia's population in April 2025 was 1 862 700 inhabitants (Central Statistical Bureau of Latvia, 2025). The prevalence of HAE in Latvia is 0.64 per 100 000 inhabitants.

2.2 Types of hereditary angioedema

Of the 12 HAE patients, 10 were confirmed with HAE type I, 1 patient with HAE type II, and 1 patient with nC1-INH HAE.

2.3 Demographic and clinical data of hereditary angioedema patients

Demographic and clinical data are presented in Table 2.1.

Table 2.1

Demographic and clinical data of hereditary angioedema patients

Demographic and clinical data (n = 12)	Finding
Median age, years (IQR)	40 (IQR)
Sex	
Females	8
Males	4
HAE type	
HAE I	10
HAE II	1
nC1-INH HAE	1
Median age at first HAE symptoms, years (n = 10)	15
Median age at diagnosis, years (n = 12)	39
Median diagnostic delay (from first symptoms to diagnosis), years (n = 10)	24 (9–37)
Positive family history	8 (from 12)

HAE – hereditary angioedema; IQR – interquartile range

2.4 Clinical presentation and trigger factors of hereditary angioedema

The summary of hereditary angioedema clinical presentation and trigger factors is presented in Table 2.2.

Table 2.2

Characterisation of hereditary angioedema clinical presentation and trigger factors

Clinical manifestations	Finding
Annual attack frequency since HAE diagnosis (n = 10)	29
Annual attack frequency since HAE diagnosis (n = 10) by category	
1–5	2
6–11	3
12–24	0
> 24	5
Attack frequency in the last 12 months (n = 10)	29
HAE severity by attack frequency in the last 12 months (n = 10)	
Asymptomatic	0
Mild	2
Moderate	3
Severe	5
Disease days	50
Hospitalisations	
Total number of hospitalized patients	10
Median number of hospitalisations	2
Oedema localisation	
Lips	9
Tongue	7
Abdominal	7
Airway	7
Urogenital	3
Prodromal symptoms (n = 9)	
Fatigue	8
Paraesthesia/pain	8
Abdominal pain	7
Nausea	3
Erythema marginatum	2
Trigger factors (n = 8)	
Stress	5
Trauma	3
Surgical/dental procedures	2
Infection	1
Menstruation	1

2.5 Treatment and prophylaxis

Medications used for HAE treatment available in Latvia and their effectiveness are presented in Table 2.3.

Table 2.3

Medications used for hereditary angioedema attack treatment and their effectiveness

On-demand treatment	Patients	Effect
Bradykinin B2 receptor-antagonist	10	3
FFP	2	1
Opioids	2	1
NSAIDs	2	1
Glucocorticoids	8	0
Antihistamines	9	0

Treatment effectiveness was assessed on a 4-point scale (no effect = 0, weak effect = 1, moderate effect = 2, high effect = 3). FFP – fresh frozen plasma; NSAIDs – non-steroidal anti-inflammatory drugs.

Latvian-available HAE prophylactic therapy and its effectiveness are presented in Table 2.4.

Table 2.4

Medications used for hereditary angioedema prophylaxis and their effectiveness

HAE prevention	Patients	Effect
FFP	2	1
Antifibrinolytics (tranexamic acid)	3	2
Attenuated androgens (Danazol)	3	2

Prophylactic effect assessed on a 4-point scale (no effect = 0, weak effect = 1, moderate effect = 2, high effect = 3). FFP – fresh frozen plasma; HAE – hereditary angioedema

2.6 Quality of life

Summary of AE-QoL questionnaire results reflecting quality of life data in HAE patients is presented in Table 2.5.

Table 2.5

Angioedema quality of life data

Domen	Result %
Fears/Shame	46.67
Fatigue/Mood	33.5
Food	32.5
Functioning	22.5

2.7 Angioedema control

Disease control was assessed using the validated AECT questionnaire over the preceding four weeks and three months.

Evaluation of the total score for each time period showed that AECT scores in Latvia were similar over both the 4-week and 3-month intervals, with median values of 10.1

(range 4–16) and 10 (range 5–15), respectively. A total score of 10 or higher indicates well-controlled disease.

2.8 Angioedema activity

Angioedema activity in HAE patients was assessed using the validated AAS questionnaire over the preceding 28 days. Six HAE patients experienced disease attacks during the last four weeks. Disease activity according to AAS was low to moderate in these six patients (ranging from 10 to 70 points).

2.9 Comorbidities in hereditary angioedema patients

For an overview of comorbidities in HAE patients, refer to Table 2.6.

Table 2.6

Representation of comorbidities in patients with hereditary angioedema

Comorbidities	Number of patients
Anxiety	
Generalized anxiety	3
Moderate anxiety	2
Mild anxiety	5
Psoriasis	2
Bronchial asthma	2
Systemic diseases	1
Arterial hypertension	1
Carpal tunnel syndrome	1

2.10 Genetic testing

Genetic testing was performed in 38 patients in total. All patients initially underwent Sanger sequencing targeting the *SERPING1* gene and the *F12*, *ANGPT1*, and *PLG* gene regions, where pathogenic variants associated with HAE have been previously described. If no pathogenic variant was identified, next-generation sequencing was performed: three patients – GS and nine – ES.

2.11 Genetic testing in patients with hereditary angioedema types I/II

Standard genetic testing using Sanger sequencing of the *SERPING1* gene was initially performed in 12 patients – eight patients with clinical and laboratory suspicion of HAE type I (reduced C1-INH level and C1-INH activity; patients No 2, 3, 5, 6, 8, 9, 10, and 11) and four patients with clinical and laboratory suspicion of HAE type II (normal or elevated C1-INH level but reduced C1-INH activity; patients No 1, 13, 14, and 15).

Identified pathogenic variants are presented in Table 2.7.

Table 2.7

Identified pathogenic variants in patients with hereditary angioedema types I/II

Patient	HAE type	Identified variants HGVS nomenclature, dbSNP	Number of identified individuals (total number*)	Pathogenicity according to ACMG	Previously reported*	Patient characteristics		
						Age in years	Sex	Number of attacks per year
1	II	NM_000062.2 (*SERPING*1):c.1396C>T p.(Arg466Cys), rs28940870	1	Pathogenic	ClinVar ID:3947 Literature reported (Szabó et al., 2022)	63	Female	2
2	I	NM_000062.2 *(SERPING1):*c.550G>A p.(Gly184Arg), rs281875170	1	Pathogenic	ClinVar ID:79144 Literature reported (Hashimura et al., 2021)	53	Female	48
3	I	NM_000062.2 *(SERPING1):*c.1195C>T p.(Pro399Ser)	1 (2)	Pathogenic	Literature reported (Grombirikova et al., 2023)	55	Female	50
4						28	Male	-
5	I	NM_000062.2 *(SERPING1):*c.1312del, p.(Val438PhefsTer12)	1 (3)	Likely pathogenic	Novel variant	34	Female	8
6						62	Female	10
7						1	Male	-
8	I	NM_000062.2 *(SERPING1):*c.1249+4A>G, p.?	1 (2)	Likely pathogenic	Novel variant	35	Female	60
9						58	Female	48
10	I	[GRCh38] chr11:g.57600729_57603011del	1	Pathogenic	Novel variant	32	Male	2
11	I	NM_000062.2 *(SERPING1):*c.1136T>C, p.(Phe379Ser)	1	Likely pathogenic	Novel variant	40	Male	48

HAE – hereditary angioedema; HGVS – Human Genome Variation Society nomenclature;; ACMG – American College of Medical Genetics and Genomics; * n cases where more than one individual in the family was identified with this variant

Three HAE I/II patients, in whom no pathogenic variants were identified in known genes using Sanger sequencing, underwent GS to detect rare non-coding and structural variants (patients No 10, 13, and 14). For these three patients, GS was performed, initially focusing on coding SNVs (single nucleotide variants) and CNVs (copy number variants) in the *SERPING1* gene, followed by analysis of other structural variants and non-coding SNVs only in known HAE-associated genes. In one HAE type I patient with a *SERPING1* gene exon 7 deletion, the genetic diagnosis was confirmed solely by GS, which failed to detect it using Sanger sequencing due to limitations of the applied algorithm (patient No 10). The exon 7 deletion was later confirmed by MLPA analysis of the *SERPING1* gene.

In two patients (from two families) with HAE I/II, no pathogenic gene variants were detected even after analysis of structural variants and non-coding gene regions (patients No 13 and 14). This prompted ongoing observation of these patients, with dynamic evaluation of both the clinical presentation and laboratory results – specific to HAE and consistent with other angioedema-causing diseases and conditions. After two years, serum protein electrophoresis in one of these patients (patient No 13) revealed paraprotein presence. Changes in blood analyses indicated an alternative symptom aetiology – thus revising the diagnosis to acquired angioedema. The patient also had reduced C1q antibodies, confirming the acquired angioedema diagnosis.

In patient No 14, suspected of HAE II, C1 functional activity normalised on repeat testing (with previously reduced C1-INH activity), necessitating diagnostic revision. The patient currently has a clinically confirmed diagnosis of angioedema of unknown origin.

In patient No 15, suspected of HAE II and without identification of a pathogenic variant by standard genetic testing, extended genetic investigation was not performed. This patient was later diagnosed with HIV (human immunodeficiency virus), currently regarded as one cause of moderately reduced C1-INH activity. As HIV is not included in the angioedema classification and the patient lacks C1-INH deficiency, the diagnosis is defined as angioedema without precisely known aetiology. Additionally, the patient is currently receiving combination antihypertensive therapy, components of which (ACEIs) may serve as a cause or provoking factor for recurrent oedema.

2.11.1 Genetic Testing in Patients with nC1-INH HAE

Genetic testing was performed in 24 patients suspected of having nC1-INH HAE – i. e. patients with recurrent oedema unresponsive to antihistamines and glucocorticoids, abdominal oedema, and/or positive family history. All patients initially underwent Sanger sequencing of *F12*, *ANGPT1*, and *PLG* gene regions where pathogenic variants have been

described (patients No 12, 16–38), and eight patients (patients No 31–38) also underwent ES, focusing on coding SNV and CNV analysis in the described nC1-INH HAE (candidate) genes (*F12*, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, and *HS3ST6*). In patients identified with an alternative cause of symptoms – AE-MC – further genetic testing was not performed (patients No 16–30). In one patient (patient No 12), Sanger sequencing identified a pathogenic variant in the *PLG* gene, confirming the nC1-INH HAE diagnosis. The variant NM_000301.5(*PLG*):c.988A>G p.(Lys330Glu) was identified, which is registered in the ClinVar database (RCV001507288.7) and has been previously described (Bork, Wulff, et al., 2020). This variant was identified in a 40-year-old woman experiencing up to 10 attacks per year. In the remaining patients, no (likely) pathogenic or rare variants of uncertain significance were identified after standard and extended genetic testing in the genes of interest. Following these genetic analyses, all patients underwent comprehensive reassessment of their clinical disease manifestations, resulting in a revision of their diagnoses, with attention also paid to recurrent angioedema in family history. During re-evaluation of angioedema aetiology after negative genetic testing results, patients were diagnosed with acquired angioedema (AAE-C1INH), mast cell-mediated angioedema (AE-MC), drug-induced angioedema (AE-DI), or angioedema of unknown aetiology (AE-UNK). A detailed overview of patient diagnoses following negative genetic testing results is presented in Table 2.8.

Table 2.8

Overview of diagnoses in patients with negative genetic testing results

Patient	Initial diagnosis	Genetic testing			Final diagnosis
		Sanger sequencing	GS	ES	
13	HAE II	negative	negative	–	AAE-C1INH
14	HAE II	negative	negative	–	AE-UNK
15	HAE II	negative	negative	–	AE-ACEI/AE-UNK
16	nC1-INH HAE	negative	–	–	AE-MC
17	nC1-INH HAE	negative	–	–	AE-MC
18	nC1-INH HAE	negative	–	–	AE-MC
19	nC1-INH HAE	negative	–	–	AE-MC
20	nC1-INH HAE	negative	–	–	AE-MC
21	nC1-INH HAE	negative	–	–	AE-MC
22	nC1-INH HAE	negative	–	–	AE-MC
23	nC1-INH HAE	negative	–	–	AE-MC
24	nC1-INH HAE	negative	–	–	AE-MC
25	nC1-INH HAE	negative	–	–	AE-MC
26	nC1-INH HAE	negative	–	–	AE-MC
27	nC1-INH HAE	negative	–	–	AE-MC
28	nC1-INH HAE	negative	–	–	AE-MC

Table 2.8 continued

Patient	Initial diagnosis	Genetic testing			Final diagnosis
		Sanger sequencing	GS	ES	
29	nC1-INH HAE	negative	–	–	AE-MC
30	nC1-INH HAE	negative	–	–	AE-MC
31	nC1-INH HAE	negative	–	negative	AE-UNK
32	nC1-INH HAE	negative	–	negative	AE-UNK
33	nC1-INH HAE	negative	–	negative	AE-UNK
34	nC1-INH HAE	negative	–	negative	AE-UNK
35	nC1-INH HAE	negative	–	negative	AE-UNK
36	nC1-INH HAE	negative	–	negative	AE-UNK
37	nC1-INH HAE	negative	–	negative	AE-UNK
38	nC1-INH HAE	negative	–	negative	AE-UNK

HAE II – hereditary angioedema type 2; nC1-INH HAE – hereditary angioedema with normal C1 inhibitor; AAE-C1INH – acquired angioedema; AE-UNK – angioedema of unknown aetiology; AE-MC – mast cell-mediated angioedema; AE-ACEI – angiotensin-converting enzyme inhibitor-induced angioedema; GS – genome sequencing; ES – exome sequencing.

2.11.2 Genetic testing in relatives of hereditary angioedema patients

Two first-degree relatives of HAE patients were also genetically tested. Genetic analysis revealed a pathogenic variant in the *SERPING1* gene (patients No 4 and 7), molecularly confirming the previously asymptomatic HAE type I diagnosis. One of the relatives (patient No 7) is a child.

2.11.3 Association of pathogenic variants with disease course

As a numerically small group of HAE patients was analysed and described, no differences were observed between clinical symptoms, oedema localisation, disease severity, attack intensity, oedema response to therapy, prodromal symptoms, provoking factors, and the genetic finding.

2.12 Metabolome analysis results

Targeted quantitative metabolite analysis was performed using liquid chromatography – mass spectrometry (LC–MS).

Of the 52 targeted metabolites analysed, 33 metabolites, including amino acids, acylcarnitines, and biogenic amines, were detected and quantified in all samples. No significant differences were found between the study groups (HAE patients, patients with idiopathic angioedema or angioedema of unknown aetiology, and healthy individuals), indicating that the overall metabolite profiles of each group were similar.

Analysis of phenotypic characteristics (sex, age, BMI) of individuals included in the metabolome study and angioedema course features (oedema localisation and attack intensity) revealed no significant correlations between metabolite levels and phenotypic

characteristics or disease course. Data used for phenotypic characteristics analysis are presented in Table 2.9. The correlation map is shown in Figure 2.1.

Table 2.9

Characterisation of individuals included in the metabolome study

Parameter	HAE	Idiopathic AE	Healthy individuals
n	10	15	20
Females	9	14	20
Males	1	1	0
Median age, years (IQR)	55 (35–62)	49 (34–56)	47 (23–67)
Median BMI kg/cm^2 (IQR)	26 (26–32)	26 (24–29)	26 (18–36)
Skin oedema	10	15	0
Abdominal oedema	8	0	0
Airway oedema	8	0	0
Number of oedema episodes per year (IQR)	7 (2–39)	9 (2–13)	0

Data are presented as median and IQR. HAE – hereditary angioedema; AE – angioedema; BMI – body mass index; IQR – interquartile range.

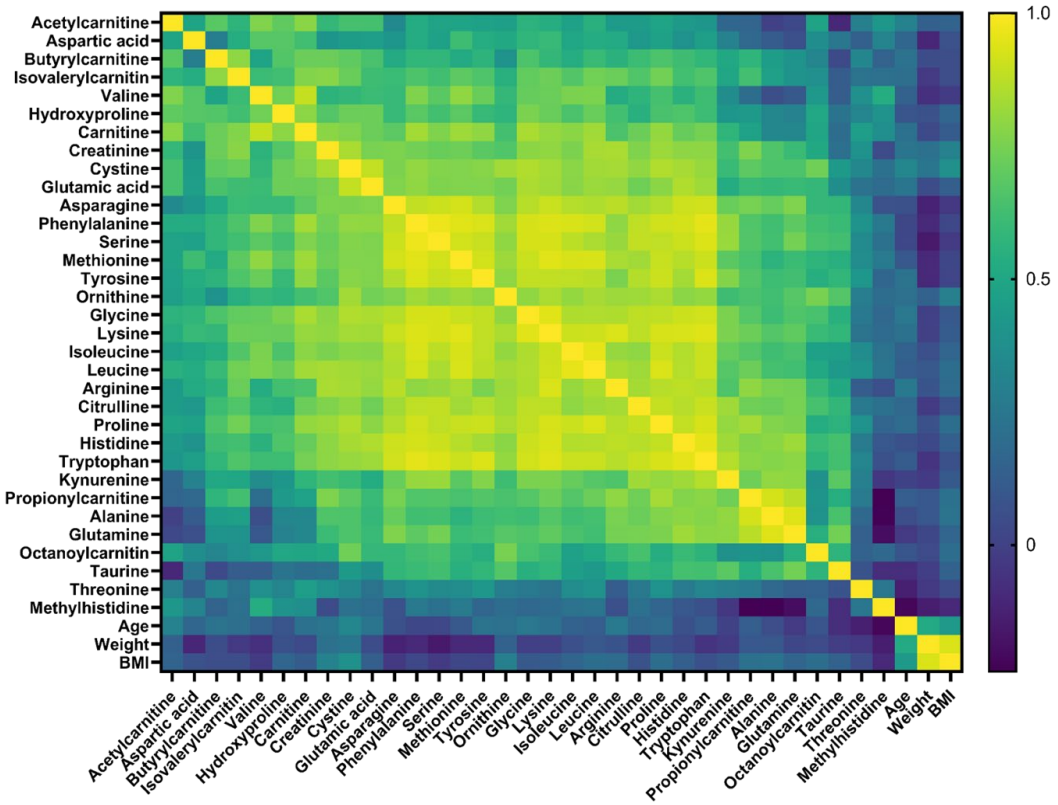

Figure 2.1 **Correlation map of metabolites and phenotypic characteristics**

Mutual correlation of 33 detected metabolites and phenotypic characteristics (age, weight, BMI – body mass index) for all individuals included in the metabolome study, including control group participants. No statistically significant correlations were identified in the analysis.

Statistically significant differences in the concentrations of individual metabolites between the study groups were observed when comparing patients with HAE, patients with idiopathic angioedema, and healthy controls. The most pronounced differences were

identified in the levels of cystine, isovalerylcarnitine, and hydroxyproline. A statistically significant reduction in cystine levels ($p < 0.01$) was detected in the HAE group compared with the control group, indicating the relevance of this metabolite in the pathogenesis of HAE. A statistically significant decrease in isovalerylcarnitine (C5) levels ($p < 0.01$) was likewise observed in the HAE group compared with the healthy control group, supporting the potential role of C5 as a biomarker for HAE.

When analysing plasma samples from HAE patients, a statistically significant increase in hydroxyproline levels ($p < 0.05$) was found compared with the healthy control group. The study also demonstrated a markedly elevated aspartic acid level ($p < 0.01$) in HAE patients compared with idiopathic angioedema patients, suggesting its potential utility as a differential diagnostic biomarker. Differences in metabolite levels between the groups are shown in Figure 2.2.

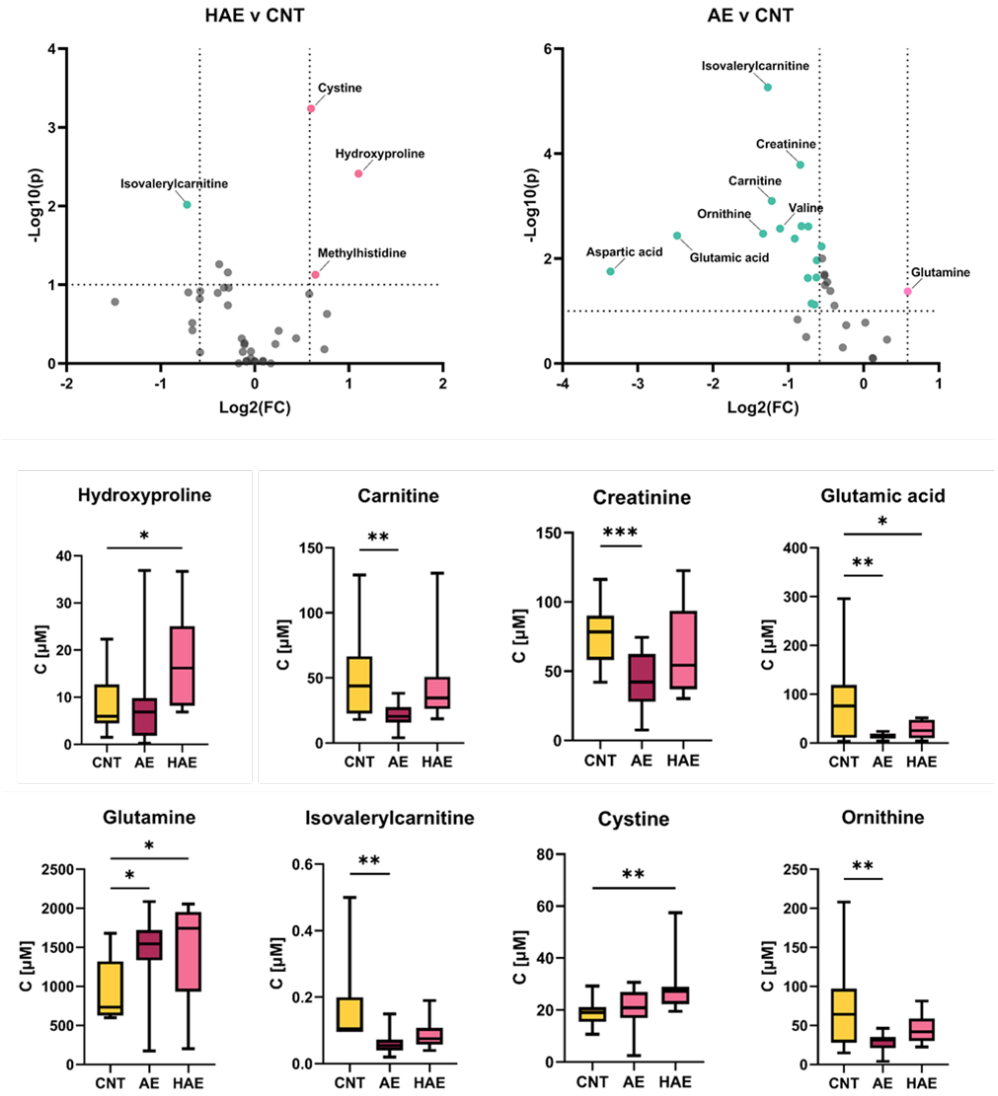

Figure 2.2 **Differences in metabolite levels (hydroxyproline, carnitine, creatinine, glutamic acid, glutamine, isovalerylcarnitine, cystine, ornithine) between study groups**

CNT – control group; AE – idiopathic angioedema; HAE – hereditary angioedema

To objectively evaluate the diagnostic value of individual metabolites, ROC curve analysis was performed. Statistical analysis revealed that the use of metabolite combinations provided substantially higher diagnostic accuracy ($p < 0.01$) compared with individual biomarker determination. Of the 11 metabolites examined, with AUC (area under the curve) values exceeding 0.7, two specific metabolite combinations were particularly noteworthy. The first significant combination, (hydroxyproline × cystine) / (creatinine × isovalerylcarnitine), with a threshold value > 27.13, demonstrated high diagnostic accuracy, with 100 % sensitivity and 90 % specificity. The second significant combination, the glycine/asparagine ratio (Gly/Asn) > 3.763, showed 90 % sensitivity and 85.7 % specificity for differentiating HAE from idiopathic angioedema. Notably, the observed differences in metabolite levels were not associated with patient age. ROC analysis with metabolite combinations is shown in Figure 2.3.

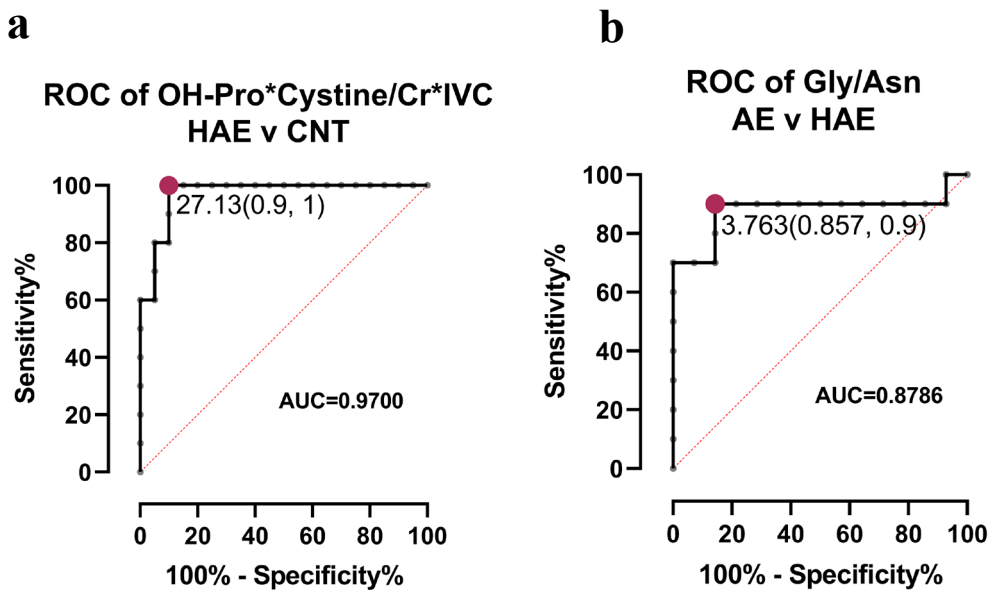

Figure 2.3 **Biomarker ROC analysis for metabolite combinations**

CNT – control group; AE – idiopathic angioedema; HAE – hereditary angioedema; OH-ProCystine/CrIVC – hydroxyproline × cystine/creatinine × isovalerylcarnitine; Gly/Asn – glycine/asparagine; ROC – receiver operating characteristic curve; AUC – area under the curve

3 Discussion

The Thesis is dedicated to investigating the clinical heterogeneity of HAE, elucidating its genetic underpinnings, and identifying potential novel metabolic biomarkers.

3.1 Prevalence and clinical heterogeneity of hereditary angioedema

According to national study data, 12 HAE patients have been diagnosed in Latvia, which, given a population of 1,862,700, constitutes a prevalence of 0.64 cases per 100 000 inhabitants. Compared with the average global prevalence of 1 in 50 000 inhabitants or 2.0 cases per 100 000, approximately 37 patients with an HAE diagnosis would be expected in Latvia. This discrepancy indicates that the actual prevalence in Latvia is lower than stated in the literature or compared with studies from other European countries.

Lower HAE prevalence in Latvia compared with other developed countries is explained by inadequate disease recognition and diagnostic shortcomings.

During the study, it was concluded that among known Latvian HAE patients, eight are women and four are men. It was also concluded that women have more frequent disease attacks and more disease days per year, which coincides with data from other studies (Aygören-Pürsün et al., 2018; Kyrle & Eichinger, 2024; Nordenfelt et al., 2016). Proportional gender differences in HAE patients could be explained by several factors and their combinations; for example, women's hormonal factors, particularly oestrogen levels, can intensify HAE symptoms, triggering more frequent and severe HAE attacks than in men.

Of all patients, HAE type I was diagnosed in ten patients, corresponding to 83.3 % of C1-INH HAE. HAE type II was diagnosed in one patient, corresponding to 16.7 % of C1-INH HAE, which largely aligns with literature data (respectively 85 % vs 15 %) (Aygören-Pürsün et al., 2018; Cicardi et al., 2014; Lumry & Settipane, 2020; Proper et al., 2020).

Although HAE is an autosomal dominant disease, de novo cases are observed in approximately 20–25 % of cases (Batlle-Masó et al., 2025). The study identified patients from eight mutually unrelated families, with a total of one to three individuals per family. For most patients, HAE screening was performed on first-degree relatives, determining C4 levels, C1-INH levels, and activity. Cascade genetic testing was also performed in two relatives. Thanks to screening, HAE was detected in the daughter of an HAE patient, who had no HAE symptoms during his lifetime up to age 28. HAE was also detected in a child at a very early age. HAE screening is extremely important, reducing the risk of emergency, life-threatening attacks. HAE screening is essential not only for symptomatic individuals but also for asymptomatic first-degree relatives of HAE patients, as timely disease detection allows initiation of prophylactic therapy when necessary and ensures the patient has the necessary

information and medications in case of an attack. For investigating HAE relatives, not only biochemical (complement C4, C1-INH level and function determination) but also genetic testing in known HAE genes – cascade genetic testing – is used (Bocquet et al., 2025; Lyons et al., 2023). Genetic testing can not only confirm pathogenic variants in the *SERPING1* gene but also identify pathogenic genetic variants in nC1-INH HAE cases (Bork, Machnig, et al., 2020; Dias de Castro et al., 2024). In such cases, genetic testing is the only means of diagnosis.

Unfortunately, HAE screening activity is low in Latvia for patients with unclear angioedema. To improve screening activity, educational campaigns are recommended, informing healthcare professionals and the public about HAE signs, symptoms, and diagnostic methods. Screening can also be improved by developing and implementing easily understandable standardised uniform screening and diagnostic protocols and algorithms, emphasising the main signs and symptoms that raise suspicion of HAE, and introducing routine screening tests for first-degree relatives of HAE patients, as recommended in guidelines. These measures can help identify HAE early and manage it more effectively in Latvia. Due to low screening activity, it is possible that some HAE patients have not been identified, particularly asymptomatic patients or patients with mild and infrequent disease attacks.

The median age of first HAE symptoms in Latvia is 15 years. For one patient, the first HAE attack occurred at age 43, with 10 attacks per year, including airway oedema and 15 hospitalisations during lifetime. Although HAE is a hereditary disease and its first symptoms most often manifest in childhood or adolescence, there are patients whose first attacks are observed at a later stage of life. Late disease onset by no means indicates that the disease will be mild and attacks infrequent. This emphasises that this diagnosis cannot be ruled out even in patients whose first manifestations occurred well beyond childhood.

The median age of first HAE symptoms (15 years, n = 10) and the median age at HAE diagnosis (39 years, n = 12) were also analysed to determine the time symptomatic HAE patients spent without an accurate diagnosis. The median time to diagnosis in Latvia was 24 years (n = 10). Andrea Zanichelli et al., aggregating HAE data from 11 countries (Austria, Brazil, Czechia, Denmark, France, Germany, Greece, Israel, Italy, Spain, and the United Kingdom), concluded that the median time to HAE diagnosis since first symptoms was 2.6 years (0.13 to 17.3 years) (Zanichelli et al., 2013). In the United States, the time from first symptoms to diagnosis averages 8–10 years (Wilkerson & Moellman, 2022; Zanichelli et al., 2018). The age at which HAE was diagnosed and the time from first symptoms to diagnosis confirmation in Latvia indicate substantially delayed diagnosis. Reasons for delayed HAE diagnosis in Latvia may include the disease's rarity mentioned above, resulting in specialists being insufficiently informed about its symptoms and diagnostic methods. Likewise,

nonspecific HAE symptoms such as oedema, abdominal pain, and breathing difficulties can resemble and mimic other more common diseases, such as allergic reactions, appendicitis, or gastrointestinal tract disorders. The variability of HAE symptoms in attack frequency, severity, and location hinders diagnosis recognition and establishment. The relatively late age at diagnosis and the long-time HAE patients in Latvia spend without an accurate diagnosis significantly affect patient quality of life and overall health status.

Assessing annual attack frequency since first HAE symptoms, thereby determining disease severity, it can be concluded that HAE manifestations among patients in Latvia are highly variable; however, patients with > 24 attacks per year outnumber those with 1–5 attacks per year. In a cohort of 242 HAE patients from France, the United Kingdom, Spain, Canada, Australia, Switzerland, Germany, and Austria, it was concluded that 31.8 % experience > 24 attacks per year (Mendivil et al., 2021). This situation indicates the need for individualised therapy strategies to manage the disease more effectively in diverse patients. For patients with frequent disease attacks, long-term prophylactic therapy would be appropriate. Unfortunately, plasma-derived C1-INH, recommended in guidelines as the first-line long-term prophylaxis agent, is not available in Latvia. In Latvia, only attenuated androgens (danazol) and antifibrinolytic agents (tranexamic acid) are available for long-term prophylaxis, which can be used as alternatives (Maurer et al., 2022).

Assessing the number of attacks per year in the last 12 months, HAE is classified as mild, moderate, and severe. For the majority of Latvian patients, HAE intensity based on attack count is moderate and severe, respectively in three and five of 10 patients. This indicates that HAE represents a significant problem for Latvian patients, reflecting inadequate therapy efficacy and insufficient access to the latest and most effective treatment and prophylaxis methods. A German study concluded that severe HAE was present in approximately 20 % of patients, in Japan 27.1 %, with the remainder of patients experiencing infrequent attacks – accordingly, for most, the disease course is mild or moderately severe (Magerl et al., 2023; Yamamoto et al., 2023).

HAE patients had a median of 50 disease days in the last 12 months, indicating high disease activity and considerable severity. German HAE patients spend approximately 8–28 days per year with disease symptoms (Magerl et al., 2023). The large number of disease days per year in Latvian patients indicates insufficient efficacy of current treatment. This may be related to inadequate prophylactic therapy or ineffective attack abatement.

All 10 symptomatic HAE patients had been hospitalised during their lifetime. Although the median number of hospitalisations is small, the range varies from one to as many as 20 times. Comparatively, in a Brazilian study involving 799 HAE patients, it was found that

50.6 % of patients required at least one HAE-related hospitalisation during lifetime, of which 69 % had 1–2 hospitalisations, 16 % 3–6, and 15 % 7 or more hospitalisations (Ritter et al., 2024). A high number of hospitalisations may indicate frequent and severe disease attacks, inadequate outpatient disease control and prophylaxis, and limited access to effective treatment and prophylaxis agents. Frequent and repeated hospitalisations affect not only the patient and their quality of life but also the healthcare system economics overall, which aligns with conclusions from the study by Antony J. Castaldo et al. (Castaldo et al., 2021). To reduce the number of hospitalisations, it is necessary to improve outpatient disease control and access to effective treatment and prophylaxis options.

Skin, lip, and tongue oedema has affected HAE patients in Latvia most frequently. Most patients have also experienced abdominal and airway oedema. Patients have complained of urogenital oedema least frequently. Analysing oedema localisation, it aligns with data from other studies and the literature (Alonso et al., 2020; Azmy et al., 2020; Nordenfelt et al., 2016).

Prodromal symptoms were observed prior to oedema development in eight patients. Most commonly observed were fatigue, paraesthesia/pain, abdominal pain, and nausea; erythema marginatum less frequently. According to data from studies in other countries, prodromal symptoms have been experienced by 68 % to 82.5 % of HAE patients, and similarly to our study – most commonly experiencing fatigue, physical sensations at the site of swelling, abdominal symptoms, and typical rashes – erythema marginatum (Leibovich-Nassi & Reshef, 2021; Magerl et al., 2014; Nordenfelt et al., 2016; Reshef et al., 2013).

The effect of HAE attack therapy was evaluated to demonstrate the significantly superior efficacy of specific drugs compared with alternative agents. In contrast, prophylaxis efficacy was low, as guideline-recommended specific prophylactic medications are unavailable, requiring reliance on alternative therapeutic agents with limited effect (Maurer et al., 2022). Comparing the obtained data with studies from other countries is challenging, as the spectrum of available medications differs in each country.

Summarising AE-QoL questionnaire results, they reveal that emotional disturbances such as fear of disease attacks, concerns about one's health, and shame about venturing out in public during an attack represent the primary quality-of-life aspect impacted by angioedema in this study. Compared with other domains, fears/shame was the most prominently affected domain, closely followed by fatigue/mood and nutrition. Functioning was relatively least affected. HAE substantially impairs patient quality of life, and studies across various countries provide insight into the most affected domains. For example, in a multinational study involving countries such as Australia, Austria, Canada, France, Germany, Spain, Switzerland, and the United Kingdom, the greatest impact on HAE patients was in the fears/shame and

fatigue/mood domains. Fears/shame showed a mean score of 54.68 %, fatigue/mood 46.24 %, functioning 42.46 %. In contrast, the least affected domain was nutrition, with a score of 36.16 % (Kulthanan et al., 2019; Mendivil et al., 2021; Vanya et al., 2023). These findings align with other international studies, which frequently report high levels of anxiety, fear, and social interaction impairment among HAE patients. Such impacts are often considered more significant than physical well-being limitations, underscoring the disease's considerable emotional and social burden (Kulthanan et al., 2019; Vanya et al., 2023). Similar data from a European study revealed that emotional disturbances were among the most affected (Mendivil et al., 2021; Vanya et al., 2023). This highlights the need for targeted interventions to address these specific impact areas among HAE patients. Inform HAE patients about international support organisations that aid in improving HAE patients' quality of life worldwide by providing necessary support and resources.

Evaluating AECT control test results, overall HAE control in Latvia is good. This is evidenced by the average AECT score. However, evaluating each HAE patient individually, disease control is poor for some of them and seriously impacts these patients' quality of life. Therefore, the utility of the AECT test is more favourably assessed for individual evaluation of disease course and its control over time rather than for representing overall disease control at the national level. Unfortunately, specific average AECT results enabling direct comparison between Latvia and other countries are not widely available in the scientific literature at present. To obtain such a comparison, specific studies with similar criteria and methodology across different countries would be necessary.

Evaluating AAS 28 results, angioedema activity in HAE patients in Latvia has been moderate or low. AAS 28 results across different countries may vary depending on study groups, geographical factors, available treatments, study design, and applied methods. Unfortunately, specific results from this questionnaire that could be compared between different countries are not widely available in the scientific literature.

Validation and inclusion of the AE-QoL, AECT, and AAS questionnaires in the study were initially aimed at objectifying HAE severity, control, and activity to evaluate metabolite differences across patient categories. Due to the small total number of study patients and their uneven distribution across groups, this was not analysed. However, analysis of these questionnaires was included in the HAE clinical research section of the study, with the objective of demonstrating the multifaceted ways in which HAE disease severity can be assessed, which depends not only on attack frequency but also on oedema localisation, duration, and impact on patient quality of life in both physical and emotional aspects. HAE is a variable disease with potentially frequent and severe attacks and remission periods of varying duration. Likewise,

the introduction of these questionnaires as a standardised angioedema monitoring tool in Latvia is regarded as a positive contribution not only to the daily clinical practice of various specialists, including allergologists, immunologists, and dermatologists, but also to research.

The results obtained in the study indicate that symptomatic HAE patients are characterised by a substantial comorbidity burden, reflecting this disease's systemic impact on the body. The comorbidity spectrum selected in the study (cardiovascular, psychoemotional, dermatological, respiratory, and systemic pathologies) is justified by several key aspects that reflect both the pathogenesis of HAE itself and current scientific discoveries regarding HAE-associated comorbidities. The high prevalence of psychoemotional disorders observed in the study – generalised anxiety in three patients, moderate anxiety in two patients, and mild anxiety in five patients – clearly demonstrates that chronic symptoms caused by HAE and unpredictable oedema episodes significantly affect patient mental well-being. These data align with trends identified in international studies, which emphasise the need for regular mental health monitoring. The prevalence of dermatological pathologies, particularly psoriasis in two patients, may point to shared immunopathological mechanisms. Similarly, bronchial asthma cases in two patients warrant consideration of a possible association between HAE and airway hyperreactivity. Metabolic and gastrointestinal disorders identified in one patient, as well as the less frequently observed cardiovascular and neurological pathologies (one patient each), may be linked both to HAE itself and to the pharmacological therapies used for its treatment. These results overall underscore that HAE is not merely recurrent angioedema but a systemic condition requiring comprehensive comorbidity monitoring and an individualised treatment approach. Future studies should preferably include a larger number of patients to more accurately assess the prevalence of specific comorbidities and their association with HAE clinical course and therapy efficacy.

3.2 Research on genetic causes of hereditary angioedema

Although pathogenic variants in *SERPING1* are the only known cause of types I and II HAE development, approximately 15 % of symptomatic HAE patients with reduced C1-INH levels and/or activity fail to yield pathogenic variants even after thorough genetic investigation (including sequencing of the entire coding and non-coding regions of the *SERPING1* gene and copy number variation analysis) (Bork, Machnig, et al., 2020; Lyons et al., 2023; Santacroce et al., 2021). It should be noted that the aforementioned publications did not specify whether clinical diagnoses were re-evaluated in all patients with negative results. Considering the specific C1-INH-associated phenotype, we hypothesised that intragenic and extragenic non-coding point and structural variants in the *SERPING1* gene, undetectable by Sanger

sequencing, are the cause of types I and II HAE in patients with negative genetic findings and can be identified using GS.

Of 38 patients suspected of HAE who underwent genetic testing at various levels, pathogenic variants in HAE genes were identified in 12 patients. In 11 cases, pathogenic variants were detected using Sanger sequencing of known HAE genes. As in other reports, pathogenic variants were predominantly located in exons 7 and 8 (Jiang et al., 2025; Ren et al., 2023). To confirm the proposed hypothesis, GS was performed in three patients suspected of HAE type I/II with negative Sanger sequencing results. One patient had a positive genetic finding with a deletion in exon 7 (patient No 10), which could have been detected using MLPA analysis. No pathogenic variants were identified in the two other patients even with GS, prompting re-evaluation of the clinical diagnosis and confirming they did not have HAE. This finding confirms that for HAE type I/II patients with negative genetic testing results (no genetic variants identified in the *SERPING1* gene using Sanger sequencing and MLPA or next-generation sequencing methods encompassing single-nucleotide variants and large deletions in the *SERPING1* gene), re-evaluation of the clinical assessment and verification of the diagnosis is necessary.

Genetic testing, particularly GS or ES sequencing, enables acquisition of comprehensive data and simultaneous information on both gene point variants and larger deletions or duplications. Cost-effectiveness should be evaluated for HAE types I/II, where genetic variants are exclusively in the *SERPING1* gene. Causes of angioedema are diverse; however, due to the potential for life-threatening airway oedema severity, only HAE and medication-induced angioedema (primarily ACEI) are critical among them (Maurer et al., 2022). Diagnosis of medication-induced angioedema is relatively straightforward, requiring discontinuation or replacement of the potentially causative medication with one from a different class, whereas HAE diagnosis is considerably more complex, especially in nC1-INH HAE cases, where genetic testing is the sole diagnostic tool (Magerl et al., 2025; Muna et al., 2024). A negative genetic finding provides substantial benefit in ruling out HAE; however, it must be borne in mind that HAE, particularly nC1-INH HAE, is one of the diseases with significant discoveries of new candidate genes over the past decade. In place of the previously known *F12* gene, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, and *HS3ST6* are now known and described (Christiansen et al., 2025; Dias de Castro et al., 2024; Zuraw et al., 2025). Recent publications have also described pathogenic variants in *CPN1* and *DAB2IP* genes, which play a role in nC1-INH HAE development associated with urticaria (D'Apolito et al., 2024; Hintze et al., 2022; Parsopoulou et al., 2022). Our study had no patients with HAE and urticaria, thus analysis of *CPN1* and *DAB2IP* genes was not targeted. In nC1-INH HAE cases, next-generation sequencing methods

are more pertinent, as information on new genes continues to be published, and ES/GS allows expansion of the analysed gene panel. In our study, nC1-INH HAE was molecularly confirmed in only one patient, identifying a previously described *PLG* gene variant. This prompts not only review of the disease's clinical and laboratory course but also re-evaluation of genetic testing, with particular attention to newly discovered candidate genes.

Two patients (patients No 13 and 14) suspected of HAE I/II, in whom no pathogenic gene variants were detected even after structural variation (SV) and analysis of non-coding gene regions, were carefully monitored, dynamically assessing both the clinical picture and test results – specific for HAE and consistent with other angioedema-causing diseases and conditions. In one patient (patient No 13), serum protein electrophoresis revealed the presence of paraproteins. Paraproteins had not been detected in previous serum protein electrophoresis tests. Changes in blood tests indicate an alternative aetiology for symptoms – acquired angioedema. C1q antibodies were also determined in the patient, which were reduced, thereby confirming the diagnosis of acquired angioedema (Patel & Pongracic, 2019; Polai et al., 2023). In HAE cases, levels of these antibodies are typically unchanged (Maurer et al., 2022; Patel & Pongracic, 2019). For the other patient (patient No 14) suspected of HAE-II, C1 functional activity normalised upon repeat testing (C1-INH activity had previously been reduced), necessitating diagnosis review. These deviations could be related to laboratory methods, transient fluctuations, or sample storage and transport conditions. Transient, particularly mild fluctuations in C1-INH level or function can also be caused by various inflammatory processes, including chronic infections or chronic or subclinical autoimmune disorders, even if classical markers are negative. Since C1-INH is produced in the liver, mild liver function impairments can cause changes in its level or function without substantial impact on C4 levels. Likewise, C1-INH can be excessively excreted in urine, particularly in nephrotic syndrome. Medication effects, such as oestrogen preparations as oral contraceptives or hormone replacement therapy, can influence C1-INH synthesis; similarly, ACEIs (e. g. enalapril, ramipril, etc.) can cause angioedema even if C1-INH level and function are only mildly reduced (Durmaz & Sevimli, 2025; Maurer et al., 2022; Sinnathamby et al., 2023). The patient's current confirmed diagnosis is angioedema of unknown cause.

For patient No 15 suspected of HAE type II, in whom Sanger sequencing failed to identify pathogenic variants, the newly diagnosed HIV is considered one of the reasons for moderately reduced C1-INH activity. Likewise, ACEIs in the currently used combined antihypertensive therapy may serve as a cause or provoking factor for recurrent oedema.

Of 24 genetically tested patients with clinical suspicion of nC1-INH HAE (including recurrent oedema unresponsive to antihistamines and glucocorticoids, abdominal oedema and/or positive family history), pathogenic variants were detected in one patient (No 12). The pathogenic *PLG* gene variant identified in this patient matches changes described in scientific sources associated with nC1-INH HAE. One of the most common variants, NM_000301.5(*PLG*):c.988A>G (p.Lys330Glu), also identified in our study patient, causes functional changes in plasminogen leading to enhanced bradykinin formation and, consequently, characteristic HAE symptoms. According to available literature, pathogenic *PLG* gene variants are detected in approximately 3–5 % of patients with nC1-INH HAE, indicating their relatively rare occurrence. This discovery is significant for planning the patient's further diagnostic and treatment strategy (Bork et al., 2018; Farkas et al., 2021; Hintze et al., 2022).

For patients in whom no pathogenic variants were identified, diagnoses are reviewed not only by long-term monitoring and symptom correction where possible but also by repeating tests that might indicate an alternative cause of angioedema.

Our study involved a relatively small number of patients, and conclusions are based on this limited sample group. To obtain a broader and more detailed perspective, it is necessary to expand the study and include a larger number of patients to gain deeper insight into the genetic causes of HAE.

3.3 Identification of metabolic biomarkers

Specific metabolites were selected for the study based on their roles in various biochemical processes and potential association with angioedema, including HAE. The metabolites included in the analysis were primarily amino acids, acylcarnitines, and biogenic amines, as these molecules play key roles in metabolism, antioxidant systems, and immune response pathways – critical factors in angioedema pathogenesis (Jans et al., 2022; Mordaunt et al., 2020). Furthermore, the metabolite panel used in the study is a standard tool for newborn screening, ensuring its broad availability and applicability in other laboratories and medical institutions (Jans et al., 2022; Mordaunt et al., 2020; Schönig et al., 2013).

The study identified a statistically significant reduction in cystine levels ($p < 0.01$) in the HAE patient group compared with the control group, suggesting the importance of this metabolite in HAE pathogenesis. The reduced cystine level may be associated with several pathophysiological mechanisms. First, elevated oxidative stress in HAE may lead to increased cysteine consumption for glutathione synthesis. Second, cystine deficiency could be linked to excessive activation of the complement system and bradykinin pathway, characteristic of HAE. Third, alterations in cystine metabolism may arise from endothelial dysfunction manifesting as

dysregulation of disulphide bonds. Future studies should focus on cystine level changes during attacks and its association with C1-inhibitor activity (McBean & Flynn, 2001; Yu & Long, 2016).

The statistically significant reduction in isovalerylcarnitine (C5) levels ($p < 0.01$) in the HAE patient group compared with the healthy control group confirms C5 as a potential HAE biomarker. Our study's results align with those obtained by Xue Wang and co-authors in urine metabolome studies, affirming C5's potential role as an HAE biomarker (Wang & Zhi, 2022). Pathophysiological mechanisms potentially explaining the C5 level reduction in HAE include accelerated leucine metabolism associated with plasmin activation and increased proteolysis due to C1-inhibitor deficiency, as well as mitochondrial dysfunction induced by elevated bradykinin concentrations causing β-oxidation impairment (Smith-Byrne et al., 2022; Wang & Zhi, 2022; J. Wu et al., 2024). In a diagnostic context, the combination of C5 with other metabolites, particularly hydroxyproline and cystine, demonstrated high diagnostic accuracy, suggesting potential use as an HAE diagnostic biomarker. Future studies should explore broader correlations between C5 levels and kallikrein-kinin system activity.

Analysis of blood plasma samples from HAE patients revealed a statistically significant elevation in hydroxyproline levels ($p < 0.05$) compared with the healthy control group. The hydroxyproline level changes observed in our study may be linked to several pathophysiological mechanisms. First, elevated bradykinin concentrations in HAE may stimulate collagen breakdown, releasing hydroxyproline. Second, oxidative stress characteristic of HAE may impair collagen structural integrity, promoting its degradation. In a diagnostic context, hydroxyproline level changes in combination with other metabolites (particularly cystine) demonstrated high diagnostic accuracy. Notably, the OH-Pro/creatinine ratio shows potential as an HAE diagnostic biomarker. These results suggest that collagen metabolism disturbances represent one aspect of HAE pathogenesis, opening new avenues for both disease diagnosis and therapy efficacy assessment (Hu et al., 2022; Langrock & Hoffmann, 2019; Z. Wu et al., 2019).

The study identified a significantly elevated aspartic acid level ($p < 0.01$) in HAE patients compared with idiopathic angioedema patients. Our research suggests that aspartic acid may aid in differentiating HAE from idiopathic angioedema. These differences may be associated with several pathophysiological mechanisms. First, elevated aspartic acid levels may reflect accelerated protein catabolism triggered by activation of proteolytic processes linked to C1-inhibitor deficiency. Second, it may indicate disruptions in nitrogen metabolism associated with increased nitric oxide production in endothelial cells in HAE. In clinical practice, these findings offer several opportunities. First, aspartic acid level changes could serve as a new diagnostic indicator in HAE differential diagnosis. Second, they could be used for monitoring

therapy efficacy and selecting personalised therapy. Future studies could focus on aspartic acid's association with bradykinin pathway activity and its role in regulating endothelial function in HAE (Holeček, 2023a; Yang & Zubarev, 2010).

To evaluate the diagnostic value of individual metabolites, ROC curve analysis was performed, revealing that combined metabolite indices achieve substantially higher diagnostic accuracy compared with single biomarker use. Among 11 analysed metabolites with AUC values above 0.7, two metabolite combinations showed particularly promising results for HAE diagnostics. The first significant combination – (hydroxyproline × cystine)/(creatinine × isovalerylcarnitine) – exhibited outstanding diagnostic accuracy with 100 % sensitivity and 90 % specificity.

The second significant combination – the glycine/asparagine ratio (Gly/Asn) – demonstrated substantial diagnostic value, manifesting as 90 % sensitivity and 85.7 % specificity for distinguishing HAE from idiopathic angioedema.

Use of biomarker combinations provides a more comprehensive view of disease pathogenesis and opens new opportunities in differential diagnosis. These indicators are particularly valuable in severe HAE forms or when clinical manifestations are nonspecific, as well as in situations requiring rapid differential diagnosis among various angioedema types. Future studies could focus on exploring the dynamics of this metabolite profile during attacks, along with its association with C1-inhibitor activity and kallikrein-kinin system activation. Such an approach could create new opportunities for early disease diagnosis and therapy efficacy monitoring (Holeček, 2023a; Hyung et al., 2004; Kikuchi et al., 2008; Yang & Zubarev, 2010).

The obtained results indicate that metabolic alterations in HAE are complex and affect multiple interconnected metabolic pathways. Joint analysis of several metabolites offers considerable diagnostic advantages, enabling not only more accurate disease identification but also more objective assessment of its progression dynamics and prediction of therapy efficacy. This approach is particularly relevant in clinical practice, where standard diagnostic methods are often insufficiently sensitive. Future studies should prioritise validation of the obtained data in larger and more diverse patient populations to ensure result reliability. Equally important would be investigating metabolite level dynamics across different disease stages, particularly during attacks, which could uncover new pathogenetic mechanisms. Another promising avenue is detailed correlation analysis between specific metabolites and C1-inhibitor activity, potentially fostering development of novel therapeutic approaches. This study demonstrates that the metabolomics approach, especially combined analysis of multiple metabolites, creates new opportunities for HAE diagnosis and differential diagnosis. The identified metabolic

differences not only enhance early diagnostic capabilities but also provide a foundation for personalised treatment strategies tailored to each patient's unique metabolic profile. Moreover, the findings substantially enrich our understanding of HAE pathogenesis, opening new research avenues aimed at improving diagnostic precision and therapy efficacy, thereby enhancing patient quality of life.

Conclusions

1. The prevalence of HAE in Latvia is lower than reported in the literature and in comparison, with epidemiological studies from other countries.
2. Clinical manifestations of HAE in Latvia, encompassing angioedema distribution, prodromal symptoms, and triggering factors, aligned with previously described literature findings; conversely, the diagnostic delay – defined by the time elapsed from initial presentation to confirmed diagnosis – was substantially longer in the Latvian cohort compared to international comparative studies.
3. Causal variants in the *SERPING1* gene were detected in patients with HAE types I and II using standard genetic analysis. Among the nC1-INH HAE patient group, molecular diagnosis was confirmed in one individual through identification of a pathogenic variant in the *PLG* gene.
4. Genome and exome sequencing performed as part of advanced genetic analysis did not yield additional pathogenic variants in the HAE patient group. Upon clinical diagnosis review following negative genetic results in HAE type I/II patients, alternative aetiologies accounting for the clinical presentation were identified.
5. Metabolomic analysis revealed characteristic alterations in the metabolite profiles of HAE patients compared with control groups, highlighting the diagnostic utility of metabolomic analysis for identifying this rare disorder:
   a) altered levels of isovalerylcarnitine, hydroxyproline, and cysteine distinguish HAE patients from healthy controls and patients with idiopathic angioedema, indicating their potential utility as diagnostic biomarkers for HAE;
   b) metabolite ratio combinations, particularly the (hydroxyproline × cystine) / (creatinine × isovalerylcarnitine) ratio (OH-Pro × Cystine)/(Cr × IVC), may provide adjunctive diagnostic criteria for enhanced HAE diagnosis.

Proposals

1. To promote the recognition of HAE and facilitate timely diagnostic establishment, comprehensive and recurring educational initiatives targeting both multidisciplinary healthcare professionals and the general public must be implemented, encompassing HAE clinical manifestations, diagnostic approaches, and available therapeutic options.
2. The establishment of screening protocols targeting patients presenting with angioedema of undetermined origin and relatives of HAE-affected individuals would constitute a valuable tool for enhancing HAE diagnostic recognition.
3. Further investigation is warranted to elucidate mechanisms underlying genetically negative HAE cases. Research strategies should include:
   a) expanding patient cohorts through international collaboration with specialised hereditary angioedema centres;
   b) implementing longitudinal clinical reassessment with extended follow-up to monitor diagnostic stability and disease evolution;
   c) investigating epigenetic modifications, microRNA-mediated regulation, and environmental factors contributing to HAE pathogenesis;
   d) the underlying disease aetiology in genetic-negative HAE patients may involve dysregulated gene expression or gene-gene interactions not directly attributable to detected noncoding or structural variants. Consequently, investigation of transcriptional regulatory mechanisms and protein-protein interaction networks would be valuable for elucidating disease pathogenesis.
4. To confirm the specificity and sensitivity of the metabolomic findings and ensure their diagnostic accuracy, validation in an independent prospective cohort is recommended. Furthermore, metabolomic analysis of HAE patients should be compared not only with patients presenting idiopathic angioedema, but also with distinct angioedema phenotypes, particularly those mediated by bradykinin and mast cell-derived mediators. Additionally, metabolite level alterations should be compared between acute disease exacerbations and remission periods to characterise dynamic metabolomic signatures associated with disease activity.
5. To substantiate the clinical significance of these findings, enrolment of larger patient cohorts through multi-centre collaboration with specialised HAE centres is recommended. This expanded multi-centre approach would enable investigation of metabolomic associations with HAE clinical classification, pathogenic variant characteristics, and disease severity status, thereby advancing understanding of disease pathogenesis and supporting implementation of precision medicine strategies in HAE management.

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

Publications:

1. Kanepa, A., Nartisa, I., Rots, D., Gailite, L., Farkas, H., Kurjane, N. 2023. National survey on clinical and genetic characteristics of patients with hereditary angioedema in Latvia. Allergy Asthma Clin Immunol. 19, 28 (2023). DOI:10.1186/s13223-023-00783-6.
2. Rozevska, M., Kanepa, A., Purina, S., Gailite, L., Nartisa, I., Farkas, H., Rots, D., Kurjane, N. 2024. Hereditary or acquired? Comprehensive genetic testing assists in stratifying angioedema patients. Allergy Asthma Clin Immunol. 2024 Mar 30;20(1):28. doi: 10.1186/s13223-024-00889-5.
3. Kanepa, A., Fan, J., Rots, D., Vaska, A., Ansone, L., Briviba, M., Klovins, J., Kurjane, N.*, Klavins, K.*. 2024. Exploring disease-specific metabolite signatures in hereditary angioedema patients. Front Immunol. 2024 Apr 25;15:1324671. doi: 10.3389/fimmu.2024.1324671.
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5. Kurjane, N., Kanepa, A., Purina, S., Lapina, L., Ress, K., Savisaar, M., Gasiuniene, E., Bajoriuniene, I., Linauskiene, K., Chomiciene, A., Gradauskiene, B., Malinauskiene, L. Epidemiological and clinical characteristics of hereditary angioedema in the Baltic states. Front Immunol. 2026 Feb 25;17:1696479. doi: 10.3389/fimmu.2026.1696479. PMID: 41822472.

Reports and theses at international congresses and conferences:

1. Kanepa, A., Purina, S., Rots, D., Nartisa, I., Gailite, L., Kurjane, N. 2021. Abdominal attacks as a first manifestation of hereditary angioedema: case report. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice". 24.–26.03.2021.
2. Kanepa, A., Malinauskiene, L., Sitkauskiene, B., Bajoriuniene, I., Purina, S., Lozovskis, V., Milta, S., Kurjane, N. 2021. Hereditary angioedema in Latvia and Lithuania. 79th Scientific Conference of the University of Latvia. The International Scientific Conference on Medicine. 23.–24.04.2021., Medicina (Kaunas) 2021; 57(Supplement 1):82.
3. Kanepa, A., Gailite, L., Nartisa, I., Isakova, J., Rots, D., Kurjane, N. 2021. Clinical and genetic diversity of hereditary angioedema in Latvia. 12th C1-inhibitor Deficiency & Angioedema Online Workshop. 3.–6.06.2021.
4. Kanepa, A., Malinauskiene, L., Sitkauskiene, B., Bajoriuniene, I., Ress, K., Savisaar, M., Purina, S., Milta, S., Kurjane, N. 2021. Hereditary angioedema in the Baltic states. The European Academy of Allergy and Clinical Immunology (EAACI) hybrid congress. 10.–12.07.2021.
5. Kurjane, N., Kanepa, A., Nartisa, I., Gailite, L. 2022. Hereditary angioedema: complicated diagnosis even in the era of genomic testing. The European Academy of Allergy and Clinical Immunology (EAACI) hybrid congress 2022. 1.–3.07.2022.
6. Kanepa, A., Kurjane, N., Ansone, L., Jingzhi, F., Klovins, J., Klavins, K. 2023. Altered Blood Metabolome in Hereditary Angioedema Patients. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice". 29.–31.03.2023.
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