"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY BUCHAREST

DOCTORAL SCHOOL

MEDICINE

PHD THESIS

ABSTRACT

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PhD student:
POPESCU SILVIA

2024

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MEDICINE

Genodermatoses

Etiopathogenic, clinical, diagnostic and therapeutic considerations, with practical applications in medical case studies

PHD THESIS SUMMARY

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2. Introduction to the topic

The human body contains about 20,000 genes arranged on chromosomes. Morgan et al concluded that each gene is assigned a specific position on the same chromosome and that some genes are always transmitted together [1,2,3]. Although the transmission of genetic information usually occurs extremely accurately, DNA replication in eukaryotic cells presents a spontaneous error rate ranging from 10^{-8} – 10^{-3}/nucleotide/replication, resulting in 1-2 new mutations in each generation that can alter the nucleotide sequence, leading to structural and functional modifications of the expressed proteins [4,5,6].

Mutations occur when the number or order of nucleotide bases is disrupted through 3 major mechanisms: their deletion, the addition of one or more nucleotides (insertion) and the replacement of one or more nucleotides (substitution), resulting in abnormalities of various proportions depending on the number, type and location of the involved nucleotides. In the case of point mutations, three different forms are distinguished: synonymous/silent mutations that do not show phenotypic expression, missense mutations that determine the transcription of different information than that contained in the replaced codon and, respectively, nonsense mutations which involve replacing the nucleotides of a codon with a premature STOP codon [7].

Genodermatoses represent a heterogeneous group of over 1000 cutaneous conditions with genetic determinism. These diseases can affect the skin, its appendages (hair and nails), present a polymorphic clinical evolution characterized by varied clinical manifestations, and are often associated with multiorganic and multisystem involvement (neuropsychiatric, cardiovascular, gastrointestinal, osteoarticular, etc.) [8,9,10, 11], as well as with a complex oncological pathology.

The clinical overlap of certain genodermatoses (Darier's disease, acrokeratosis verruciformis of Hopf, familial benign pemphigus Hailey-Hailey) is likely to stimulate medical interest in further investigating these conditions. Genodermatoses are frequently associated with neuropsychiatric disorders, and the relationship between dermatological and neuropsychiatric disorders - specifically, the possibility that they represent the expression of the same genetic abnormality, is an issue that has often been raised in the specialized literature [12].

Genodermatoses are relatively rare conditions, with an incidence ranging between 1:6000 and 1:500.000 [13], depending on the type of genodermatosis and the studied

population. For example, Darier's disease and type I neurofibromatosis have estimated incidences of 1-4:100.000 inhabitants [14] and 1:2600-3000 inhabitants, respectively [15]. Recent studies indicate a continuous increase in the reported incidence of genodermatoses, possibly due to several factors, including increased awareness of these conditions in the medical community and in the general population, as well as the development of more effective diagnostic methods and increased access to diagnostic technologies.

Although genodermatoses are rare conditions, their impact is not limited to the physical appearance of patients, but also extends to psychosocial aspects and quality of life. Chronic and sometimes disfiguring cutaneous conditions can significantly affect patients' emotional state and social interactions. Moreover, some genodermatoses are associated with severe comorbidities, with an increased risk of malignant degeneration and disabling disabilities, often without concrete therapeutic solutions and requiring a complex multidisciplinary therapeutic regimen. This emphasizes the importance of a comprehensive and interdisciplinary approach in the management of these conditions, which constitute important public health issues in terms of resource consumption.

The varied symptomatology and clinical manifestations of these conditions present significant challenges in their diagnosis and management, requiring collaboration between specialists from different medical fields in order to improve diagnostic accuracy, enhance the quality of medical services provided to patients, and optimize the cost-benefit ratio. Improving medical services involves rigorous clinical and paraclinical assessment, providing clear information to patients and their relatives and implementing modern treatments adapted to the clinical and paraclinical evolution.

Currently, patient education regarding these diseases is insufficient, as is the use of genetic counseling or prenatal diagnosis methods. In this regard, the inaccessibility of expensive diagnostic techniques to the entire population may also be incriminated.

The diagnosis of genodermatoses is based on correlations between the clinical aspect observed in patients and the results of paraclinical investigations, including histopathological examination, immunohistochemical tests and genetic tests, which play an essential role. In recent years, considerable progress in DNA sequencing technologies has led to a better understanding of the molecular mechanisms involved in genodermatoses, thus facilitating the establishment of an accurate diagnosis and providing new perspectives in the medical care of patients, family counseling and prenatal diagnosis.

Genetic counseling, described in 1975 by the Ad-Hoc Subcommittee of the American Society of Human Genetics for Genetic Counseling, plays an essential role in screening and identifying genetic conditions, providing patients and their families with psycho-emotional support and referring them to other specialists and dedicated organizations. Genetic counseling is particularly important for couples with advanced maternal age or a family history of genetic diseases. It is recommended that genetic testing and counseling be performed before conception, and that reproductive decisions be made by patients without external influences [16,17].

Methods of screening and prenatal diagnosis are essential in the early detection of severe conditions, allowing affected couples to make informed decisions, taking into account the implications for quality of life and vital risk, without neglecting the associated complex ethical issues. Additionally, prenatal diagnosis plays a special role in the preparation of the parents and in the choice of therapeutic methods for the safest possible evolution of the pregnancy and childbirth.

Prenatal screening encompasses the totality of non-invasive investigation methods represented by maternal blood tests and fetal ultrasound accessible to all pregnant women, capable of being performed in the first two trimesters of pregnancy (up to the 26th week) and which are capable of early detection of multiple fetal anomalies. Standard methods of maternal serum screening include measuring alpha-fetoprotein, human chorionic gonadotropin, and estradiol, which are useful for detecting Down syndrome, trisomy 18q-, neural tube defects, and X-linked ichthyosis [18].

Prenatal diagnostic techniques include all means of prenatal (both preimplantation and in utero) investigation capable of accurately identifying genetic abnormalities of the conception product. Since many of these techniques are invasive, they are associated with a risk of maternal-fetal complications, including spontaneous abortion. Indications for performing prenatal diagnosis of genodermatoses include patients with a personal history of affected pregnancies, parents with a family or personal history of genetically determined conditions - including healthy carriers, as well as patients in whom abnormalities were detected during prenatal screening [18]. These diagnostic methods are particularly useful and recommended in the case of parents with a family or personal history of harlequin ichthyosis or ectodermal dysplasia [19]. Unfortunately, preimplantation diagnostic techniques are extremely expensive, not currently widely available, and are not infallible.

Current therapeutic options for genodermatoses are limited and include symptomatic treatment, topical treatment, surgical interventions, and oncologic therapies. Hygienic and dietary measures play an important role in disease management and improving the patients' quality of life. Prevention of secondary infections, specific dietary regimens and oral hygiene are essential aspects in the management of these conditions.

The 21st century marked a spectacular progress in the use of biological agents for the treatment of genodermatoses, with multiple studies being carried out and some cases of therapeutic success reported, as follows: treatment with erlotinib (an epidermal growth factor receptor blocker, EGFR) in the case of palmoplantar keratodermas with mutations in the TRPV3 potential vanilloid receptor, treatment of Gorlin syndrome with vismodegib (inhibitor of the smoothened SMO oncogene from the hedgehog pathway), treatment of ichthyosis with omalizumab (an inhibitor of the tumor necrosis factor TNFα), ustekinumab (a human monoclonal antibody that binds to the p40 subunit shared by IL_{12} and IL_{23}), secukinumab (an IL_{17} inhibitor), dupilumab (an α-chain blocker of the IL_4 receptor that produces both IL_4 and IL_{13} inhibition) or tofacitinib (a JAK inhibitor), as well as the treatment of epidermolysis bullosa with topical products based on diacerein (an IL_1 signaling cascade inhibitor) [20,21,22,23,24].

Given the genetic determinism of the described conditions, all genodermatoses represent potential candidates for gene therapy. The main obstacle to this therapeutic approach is related to the possibility of targeted, efficient and safe gene delivery. In most cases, gene therapy research focuses on gene replacement treatment by means of vectors capable of introducing functional copies of the defective gene into the organism, which can be achieved both ex vivo, with the gene payloads being delivered injectably or therapeutically grafted via modified cells harvested from patients, and in vivo by transfusion of the vectors with specific tropism to the targeted organ, as well as by in situ injection or application of topical products [20,21,22,23,24].

3. Working hypothesis and objectives of the work

The main objective of this study is to conduct a comprehensive, exhaustive and interdisciplinary study on genodermatoses, with an emphasis on their etiopathogenic, diagnostic and therapeutic aspects. Methodology that combines epidemiological, clinical and paraclinical research methods was planned in order to achieve this objective. This integrative approach aims to thoroughly examine the clinical spectrum of genodermatoses and identify correlations with the paraclinical expression of genetic abnormalities.

The epidemiological, diagnostic, clinical, paraclinical and therapeutic study conducted over a period of 10 years included patients admitted to the dermatology and surgery departments of reference hospitals in Bucharest, suffering from various genodermatoses, particularly those at the dermatological-neurological interface (such as neurofibromatosis and Darier's disease) and the dermato-surgical interface (such as the association of Fox-Fordyce disease with uterine fibromatosis, linear IgA dermatosis with renal tumors or various skin lesions with colonic polyposis and colorectal cancer).

Genodermatoses present extremely complex and varied clinical forms, with multiple implications in other medical specialties. Therefore, understanding these correlations must be constantly in the focus of any dermatologist, who has the great advantage of accesibility to the skin and its appendages for clinical examination. Taking into account these considerations and the rarity of many forms of genodermatoses, an important objective of this study is also to present relevant clinical cases, aiming to make progress in the recognition of the clinical manifestations of these rare and redoubtable conditions, which could have significant practical applications in the prophylaxis and establishment of effective multidisciplinary methods of diagnosis and treatment.

Last but not least, this work is also conceived from the desire to unite medical specialties in a common effort to clarify some complex aspects raised by genodermatoses, thus aiming at prophylaxis through genetic counseling and the establishment of efficient prenatal diagnosis methods, as well as improving vital prognosis and enhancing the quality of the patients' life through early detection of diseases, prompt initiation of correct treatment, and interdisciplinary collaboration in patient monitoring.

4. Research methodology

In the present study, an open prospective and retrospective, observational clinical-epidemiological study was performed on a number of 257 patients, of which 253 patients were newly diagnosed with various clinical forms of genodermatoses and 4 patients suffered from surgical conditions associated with cutaneous lesions suggestive of genodermatoses. These patients were admitted to the Dermatology departments of the Elias University Emergency Hospital and the Clinical Hospital for Infectious and Tropical Diseases "Doctor Victor Babeș" and, respectively, to the General Surgery department of the CF 2 Clinical Hospital Bucharest between January 2013 and July 2023. The severity of comorbidities in some of the included patients required an immediate surgical approach followed by oncological treatment and predominantly oncological and surgical monitoring; these 4 patients were presented as a special mention, as their cases were truly spectacular, but they were not included in the epidemiological study.

From the examined observation charts, there were extracted informations regarding patient identification, age, gender, place of origin, personal and family history, disease history and clinical evolution, comorbidities, paraclinical examinations, discharge diagnosis, treatment received by patients, hospitalization length, type of heredity of the condition, genetic counseling, and screening methods.

Determination of the hereditary nature of the studied conditions, identification of the hereditary transmission pattern of the studied conditions, and calculation of the transmission risk of the genetic defect to the offspring were performed through family investigation, including the anamnesis and the clinical examination of the probands' (individuals affected by genodermatoses) relatives, among which the aim was to identify clinical manifestations and symptoms similar to or identical with those of the probands (isotypy) in the ascending and descending filiation involving 3-5 generations, or the presence of other dermatological comorbidities among the probands (heterotypy).

For the optical microscopy study of the biopsy specimens taken from the patients included in the present study, the sections were stained with hematoxylin-eosin in all cases, except for one case of porphyria for which PAS staining was used.

This paper presents 11 clinical cases in detail and multiple significant clinical-paraclinical images selected from the included patients.

5. Results and Discussions

Following the study carried out between January 2013 and July 2023 on a cohort of 36.899 patients diagnosed with dermatovenerological and surgical conditions admitted to the Dermatology departments of the Elias University Emergency Hospital and the "Doctor Victor Babeș" Clinical Hospital for Infectious and Tropical Diseases, and respectively, to the General Surgery department of the CF 2 Clinical Hospital in Bucharest, a total of 253 patients (0.68%) were identified as diagnosed with various clinical-etiopathogenic forms of genodermatoses with predominantly mild or moderate clinical manifestations, and a number of 4 patients suffered from surgical conditions associated with cutaneous lesions suggestive of genetically determined diseases (figure 5.1).

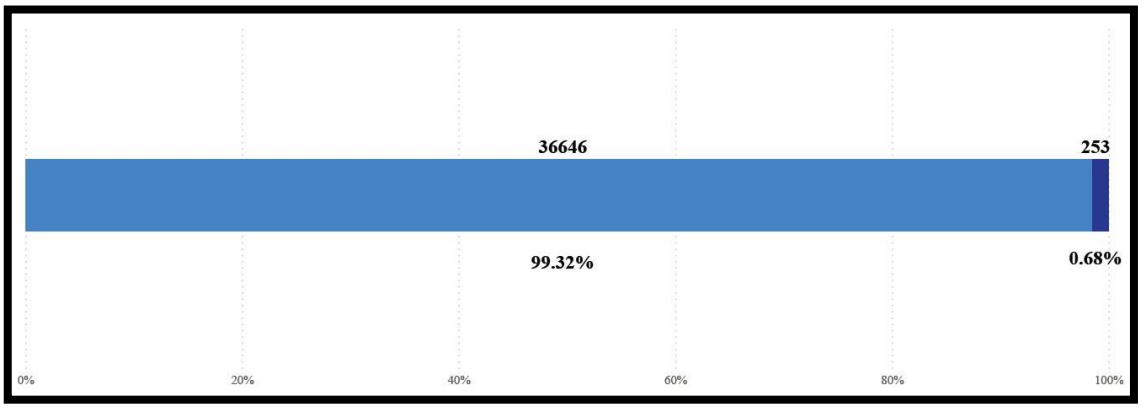

Figure 5.1. Numerical and percentage relationship between the total number of patients diagnosed with dermatological conditions and the total number of patients diagnosed with genodermatoses during January 2013 – July 2023

The present study showed that the most frequent genodermatoses encountered between January 2013 and July 2023 (figure 5.2) in two dermatology departments in Bucharest are represented by neurofibromatoses, followed by palmoplantar keratodermas, ichthyoses, porphyrias, Darier's disease and epidermolysis bullous.

In terms of gender distribution of the patients included in the study (figure 5.3), a predominance of the female sex was observed. In the case of patients diagnosed with ichthyosis vulgaris, the predominance of the female sex does not correspond to the data from the specialized literature, where a relatively equal distribution is described between the sexes, so it can be speculated that in the case of mild forms of ichthyosis vulgaris, it is possible that the addressability of female patients to specialized services might be increased due to aesthetic criteria. Similarly, the predominance of the female sex in the

case of benign familial pemphigus Hailey-Hailey does not correspond to the information in the specialized literature, where an equal distribution between the sexes is described.

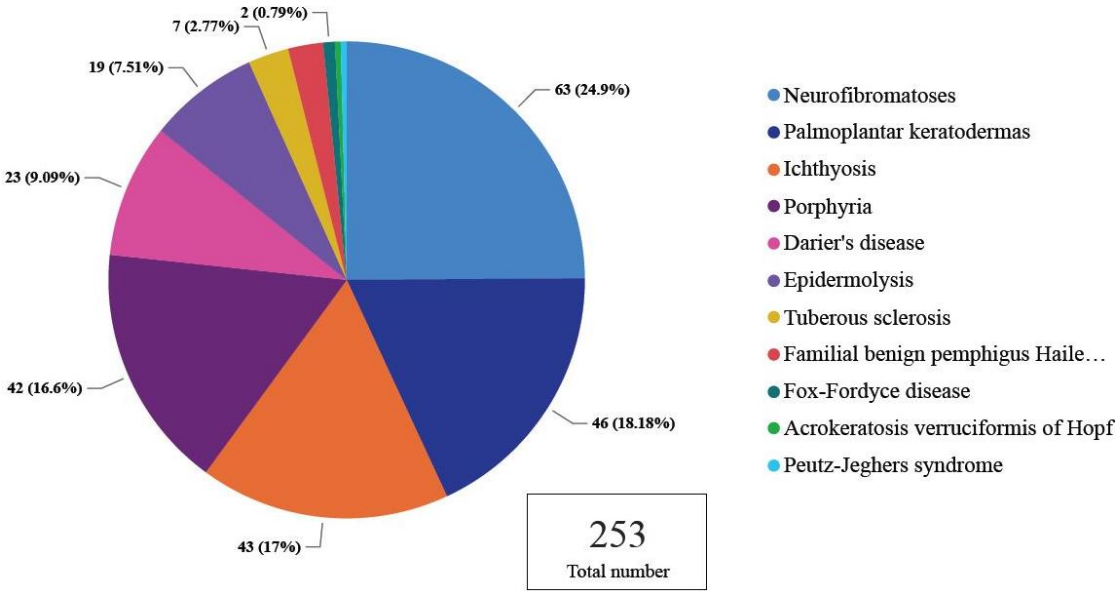

Figure 5.2. Distribution of genodermatoses according to the clinical-etiopathogenic form of the disease

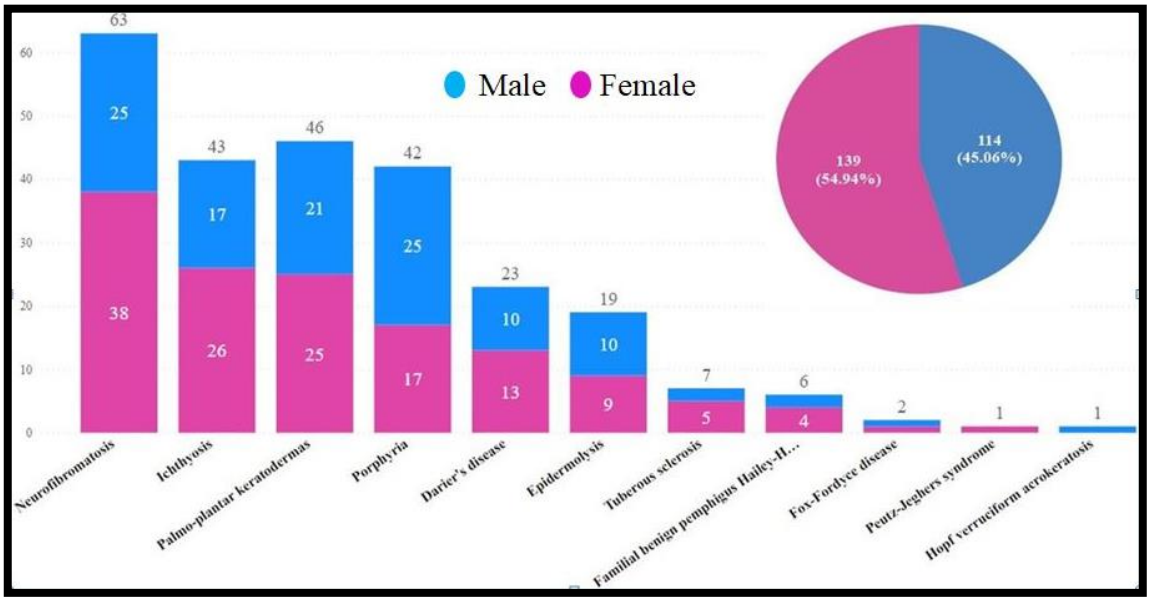

Figure 5.3. Distribution of various clinical-etiopathogenic forms of genodermatoses by patient gender

From the analysis of data regarding the included patients' place of origin (figure 5.4), a predominance of patients from urban areas was observed, a fact that can be attributed to the lack of medical information of the patients and their tendency to avoid or delay seeking specialized medical services until advanced stages of the disease.

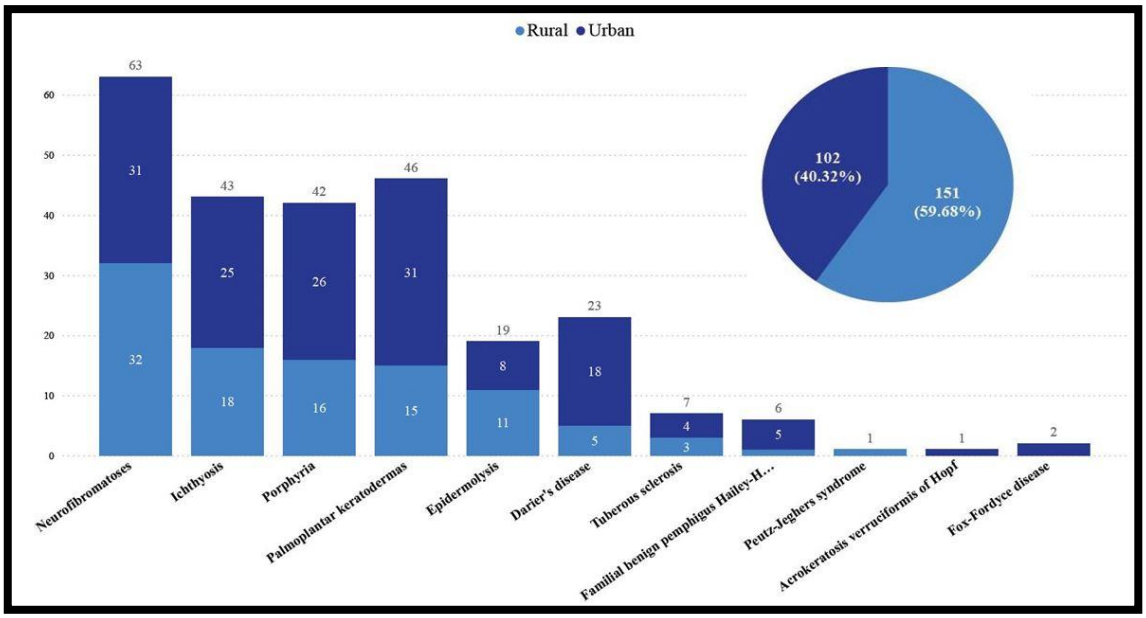

Figure 5.4. Distribution of various etiopathogenic clinical forms of genodermatoses according to the patients' environment of origin

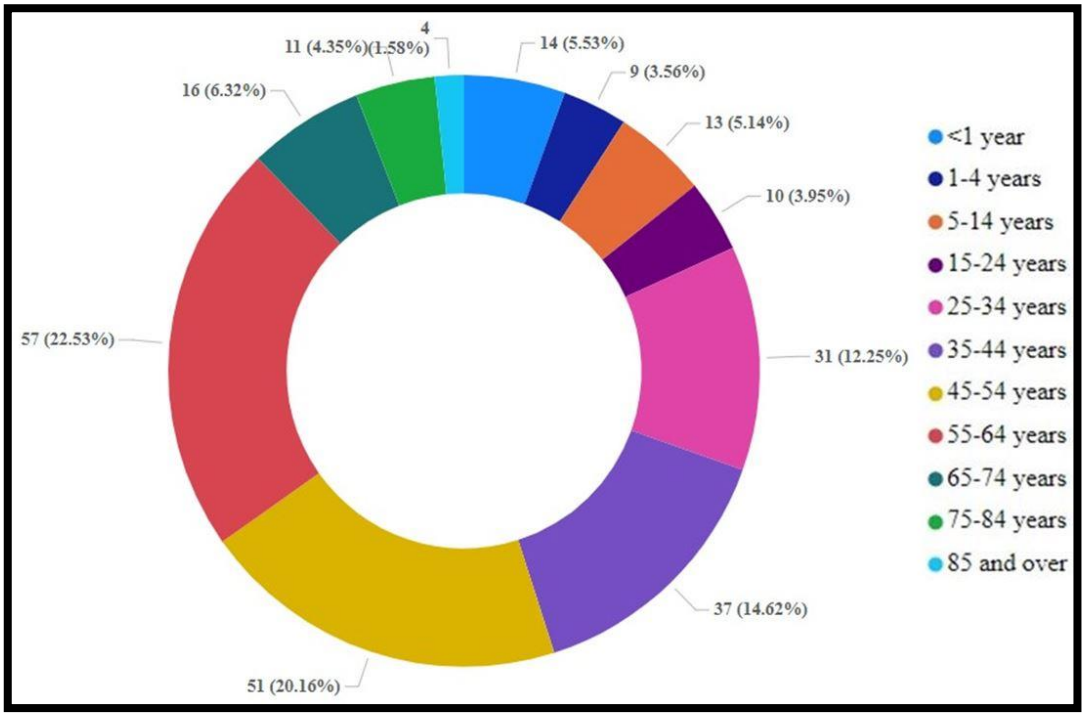

Figure 5.5. Distribution of studied genodermatoses according to the patients' age

Regarding the distribution by age groups (figure 5.5), the age at diagnosis coincided in most cases with the onset age of the condition, especially in the case of genodermatoses with moderate to severe symptoms and clinical manifestations (congenital ichthyoses, severe forms of bullous epidermolyses, neurofibromatoses and tuberous sclerosis). On the other hand, in the case of genodermatoses with mild symptoms and clinical manifestations

(mild forms of ichthyoses and palmoplantar keratodermas, Darier's disease), the condition was often neglected for a long period of time, so the onset age did not correspond to the age of diagnosis. This may be due to a lack of medical awareness among the general population.

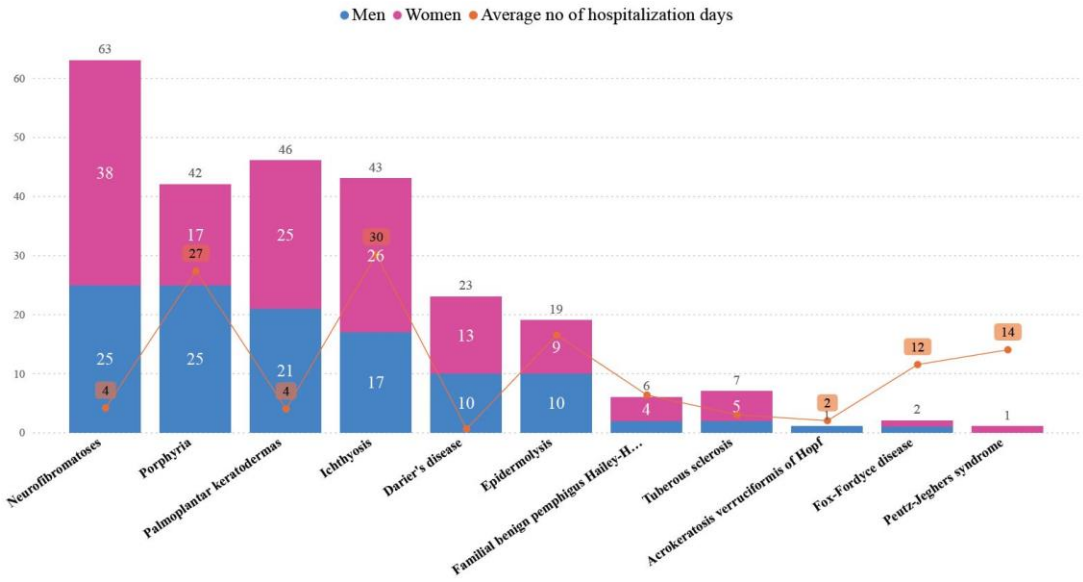

Figure 5.6. Distribution of the various forms of genodermatoses included in the study according to patients' gender and the average number of hospitalization days for the total number of discharged patients

In relation to the number of hospitalization days (figure 5.6), for the 253 patients suffering from genodermatoses included in the study, a total number of 1428 hospitalization days was recorded. Among these, the highest number of hospitalization days was observed among patients diagnosed with ichthyoses, cutaneous porphyrias, neurofibromatoses and palmoplantar keratodermas, which may be due to the severity of the clinical manifestations and the increased number of cases compared to the total number of diagnosed genodermatoses. A lower number of hospitalization days was recorded among patients diagnosed with epidermolysis bullosa, benign familial pemphigus Hailey-Hailey, Fox-Fordyce disease and tuberous sclerosis, which can be explained by the smaller number of patients, as well as by the presence of pediatric patients reffered to specialized services. The lowest number of hospitalization days was recorded among patients diagnosed with Darier's disease and acrokeratosis verruciformis of Hopf, which may be explained by the presence of milder clinical manifestations. In the case of the single patient diagnosed with Peutz-Jeghers syndrome, the increased number of hospitalization days was due to thorough clinical and paraclinical investigations and the need for surgical intervention for diagnostic

and curative purposes due to suspicion of malignancy of colonic polyps detected at colonoscopy.

Starting from the results of the family survey, it was highlighted that some genodermatoses have a higher incidence among certain families included in the study than in others, with conditions with the highest frequency of hereditary transmission being constituted in descending numerical order by ichthyoses, palmoplantar keratodermas, neurofibromatoses and porphyrias. From the standpoint of the statistical relevance of these data, the percentage distribution was considered particularly significant (figure 5.7), noting a higher number of cases with familial aggregation among small patient cohorts, as observed in the case benign familial pemphigus Hailey-Hailey or Darier's disease.

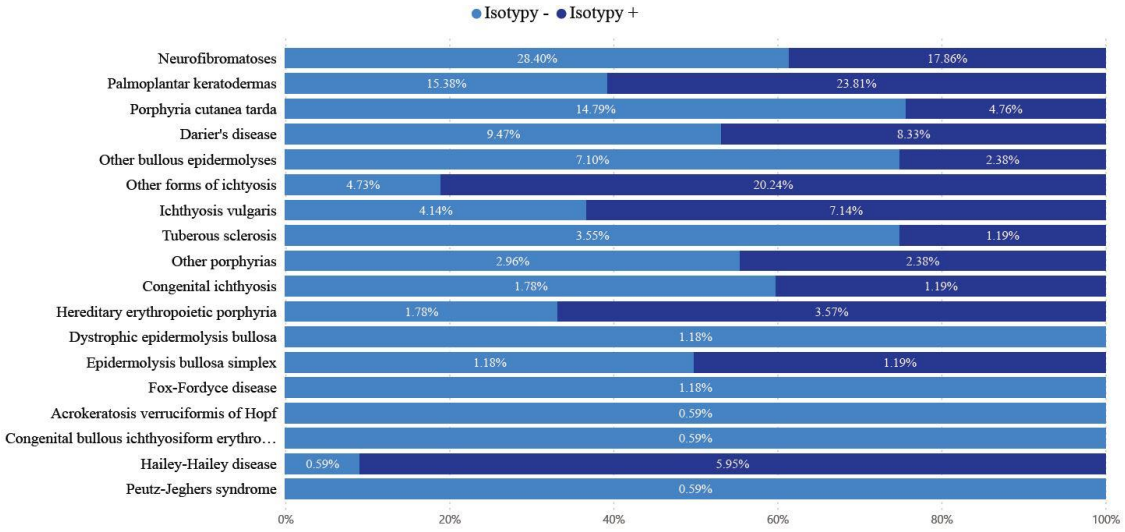

Figure 5.7. Family aggregation incidence among patients included in the study

Regarding the incidence of heterotypy (figure 5.8), a low number of genodermatoses associated with dermatological comorbidities was recorded, and the most frequent cases of heterotypy were noted among patients suffering from ichthyoses, palmoplantar keratodermas and familial benign pemphigus Hailey-Hailey.

These observations correspond to those in specialized literature, with particular linkages rarely reported between various clinical-etiopathogenic forms of genodermatoses and other cutaneous conditions, with a few exceptions, among which ichthyoses and especially ichthyosis vulgaris, which can be associated with various dermatological conditions (especially atopic dermatitis, but also keratosis pilaris).

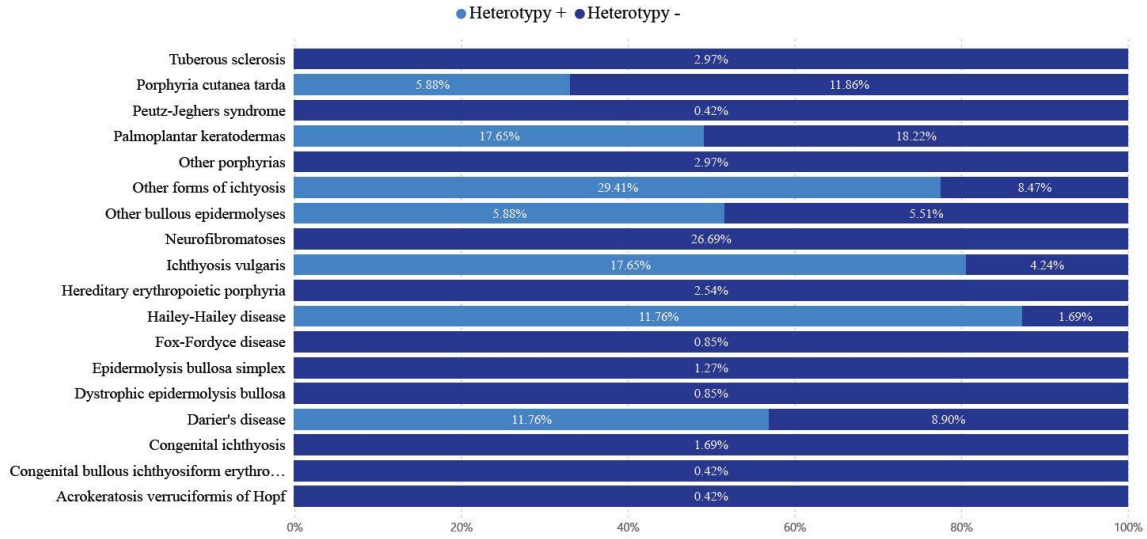

Figure 5.8. Incidence of heterotypy among patients included in the study

Regarding the information related to the pattern of hereditary transmission highlighted among the studied genodermatoses, it corresponds to the data in the specialized literature, where cases with familial aggregation are described, as well as cases where a Mendelian pattern of genetic transmission cannot be identified. In terms of the type of genetic defect transmission, genodermatoses are associated with both autosomal dominant and autosomal recessive transmission. Lastly, the fact that in 169 cases no obvious inheritance pattern was observed can be explained by the occurrence of de novo mutations or the recessive nature with incomplete penetrance of the genetic defect.

Paraclinical investigations, especially histopathological examination, played an essential role in confirming the diagnosis and establishing the prognosis. From the histopathological analysis of biopsy specimens taken from the patients included in the study, common ultrastructural elements were noted for each genodermatosis, which provided anatomopathological diagnostic criteria in accordance with the data found in the specialized literature for the 11 categories of genodermatoses included in the study.

Although the predominant clinical manifestations were of mild or moderate intensity, associated comorbidities sometimes represented aggravating factors leading to complications and the necessity of a multidisciplinary therapeutic approach.

The most frequently recorded comorbidities were cardiovascular diseases, type II diabetes and gastrointestinal diseases. Among the observed dermatological comorbidities, atopic dermatitis has the highest incidence and is often encountered among patients

suffering from ichthyosis vulgaris. Other associated conditions include neuro-psychiatric disorders, gynecological pathology, neoplasms and thyroid conditions.

Out of the 257 patients included in the present study, 10 patients suffered from conditions requiring surgical treatment. Among these, 4 patients presented cutaneous lesions suggestive of an etiopathogenesis with a genetic component, and in 6 cases a diagnosis of a genodermatosis associated with a complex multidisciplinary pathology was established, as follows:

- 1 patient diagnosed with Darier's disease associated with left testicular seminoma, who underwent local corticosteroid therapy and left orchiectomy;

- 1 patient diagnosed with palmoplantar keratosis associated with T3N0M0 G1 gastrointestinal stromal tumor incidentally discovered during the surgical cure of the umbilical hernia, who received local treatment with 30% urea-based products and underwent segmental enterectomy with termino-terminal entero-enteroanastomosis;

- 1 patient diagnosed with palmoplantar keratosis associated with Meckel's diverticulum discovered during exploratory laparotomy for ovarian peritoneal carcinomatosis, who received topical treatment with keratolytics and urea-based products and underwent segmental enterectomy with termino-terminal entero-enteroanastomosis, peritoneal biopsy, resection of nodules invading the transverse colon and ileum, as well as lateral colostomy on the transverse colon;

- 1 patient diagnosed with palmoplantar keratosis associated with Hirschsprung's disease and Dupuytren's contracture, who underwent classic sigmoidectomy with temporary terminal colostomy and subsequent reintegration through termino-terminal colorectal anastomosis with laparoscopically assisted circular stapler, followed by surgical treatment of Dupuytren's contracture;

- 1 patient diagnosed with hypertrophic lichen planus associated with left T2bN0M0 G2 Grawitz tumor who underwent local corticosteroid therapy for the cutaneous lesions and left adrenalnephrectomy with splenectomy;

- 1 patient diagnosed with genital Fox-Fordyce disease associated with uterine polyfibromatosis with endometriosis foci, for whom total hysterectomy with bilateral salpingo-oophorectomy was performed;

- 1 patient diagnosed with occipital angioma associated with multiple vertebral hemangiomas and voluminous sigmoid tubular adenomatous polyp with foci of low-grade dysplasia and moderate intraepithelial dysplasia who underwent laparoscopic sigmoid resection with mechanical termino-terminal colorectal anastomosis;

- 1 patient with Leser-Trélat syndrome, initially suspected of having LEOPARD syndrome, with hypostature, cardiac polyvalvulopathy, multiple hyperpigmented lesions and multiple seborrheic keratoses associated with pT4N1M1 G3 occlusive sigmoid adenocarcinoma (peritoneal, liver, lung metastases), who underwent initial lateral colostomy followed by oncological treatment (adjuvant chemotherapy) and subsequent laparoscopic left hemicolectomy à la Hartmann with terminal colostomy in the left iliac fossa;

- 1 patient diagnosed with linear IgA dermatitis and left adrenal pheochromocytoma T2aN0M0 G2, who received systemic corticotherapy and topical treatment with a neomycin and corticosteroid-based product, as well as left nephrectomy associated with adrenalectomy and splenectomy;

- 1 patient diagnosed with Peutz-Jeghers syndrome who underwent laparoscopic sigmoidectomy with mechanical termino-terminal colorectal anastomosis.

In all 10 cases described above, positive dermatological, surgical and oncological outcomes were recorded, without perioperative incidents or postoperative complications. The 6 patients diagnosed with neoplastic conditions were referred to oncology services.

Regarding the treatment of the individuals included in the study, the patients diagnosed with various mild or moderate clinical forms of ichthyoses received local corticotherapy associated with urea-based or other topical emollients or topical treatment with vitamin A derivatives. Patients diagnosed with mild or moderate forms of palmo-plantar keratodermas received keratolytic treatment with 5-25% salicylic acid in combination with 5-30% urea-based emollients, other topical emollients, as well as systemic treatment with aromatic retinoids. The only patient diagnosed with acrokeratosis verruciformis of Hopf underwent surgical treatment (surgical excision of one of the 2 lesions and superficial electrotherapy of the contralateral lesion). Patients diagnosed with Darier disease received treatment with topical 10-30% urea-based emollients, topical products containing 15% lactic acid and topical aromatic retinoids, and in some cases, systemic treatment with aromatic retinoids or vitamin A was also administered. Among

patients diagnosed with mild, moderate or severe forms of epidermolysis bullosa, 10 pediatric patients under 1 year of age were referred to the pediatric service, 1 patient diagnosed with dystrophic epidermolysis bullosa with multiple spontaneous amputations of phalanges of the hands was referred to the plastic surgery service, and the remaining patients received systemic corticotherapy associated with systemic administration of vitamins (A, B12, C and E) and topical treatment with various dyes and products containing antibiotics and corticosteroids. Patients diagnosed with mild or moderate forms of benign familial pemphigus Hailey-Hailey received systemic anti-inflammatory treatment with paracetamol associated with topical treatment with 0.1% tacrolimus, a product containing betamethasone, clotrimazole and gentamicin, local antimicrobial prophylaxis, application of dyes and local treatment with antibiotic-based products (neomycin, gentamicin or tetracycline), antifungals (clotrimazole) and corticosteroids, and in 1 patient, corticosteroid therapy and systemic antibiotic therapy were also necessary. Patients diagnosed with cutaneous porphyrias received vitamin therapy and systemic treatment with beta-carotene and hepatoprotectors, as well as treatment with iron chelating agents, activated charcoal, erythropoietin and systemic corticotherapy. Three patients diagnosed with tuberous sclerosis aged between 0-18 years were referred to the pediatric service, and the remaining tuberous sclerosis patients received local treatment with retinoic acid. Of the 63 mild, moderate or severe cases of neurofibromatoses, 15 cases aged between 0-14 years were referred to the pediatric service, and the remaining 48 cases were referred to the neurology service for clinical and paraclinical reevaluation and specialized treatment initiation.

6. Conclusions

Following the epidemiological, clinical, paraclinical and therapeutic study conducted on a number of 253 newly diagnosed patients with various clinical forms of genodermatoses and 4 patients suffering from surgical conditions associated with cutaneous lesions suggestive for genetically determined cutaneous pathology that were admitted to the Dermatology-Venereology departments of Elias University Emergency Hospital and "Doctor Victor Babeș" Clinical Hospital for Infectious and Tropical Diseases and, respectively, to the General Surgery department of CF 2 Clinical Hospital Bucharest, during the period January 2013 - July 2023, the following observations emerged:

1. Genodermatoses are rare conditions, with a low reported incidence during the period of this study. Out of the total of 36.899 patients diagnosed with dermatovenerological conditions between January 2013 and July 2023, only 253 patients (0.68%) were diagnosed with various etiopathogenic and clinical forms of genodermatoses (pages 136, 277).

2. Regarding the gender distribution of the studied genodermatoses, a slight predominance of the female sex was observed, which correlates with both autosomal and gonosomal transmission patterns. Thus, out of the 253 patients diagnosed with genodermatoses, 114 patients (45.06%) were male and 139 patients (54.94%) were female. In most etiopathogenic disease categories, a relatively equal gender distribution was noted, with the exception of porphyria cutanea tarda (predominance of the male sex) and, respectively, ichthyosis vulgaris, benign familial pemphigus Hailey-Hailey and neurofibromatoses (predominance of the female sex) (pages 140 -143, 277, 278).

3. Regarding the patients' environment of origin, a predominance of patients from urban areas was observed, which can be attributed to better medical information among the urban population and the possibility of easier access to quality medical services in urban areas. Thus, out of the 253 patients diagnosed with genodermatoses, 151 (59.68%) came from urban areas and 102 (40.32%) came from rural areas (pages 143-146, 278).

4. In terms of etiopathogenic disease forms, a heterogeneous distribution of the genodermatoses included in the study was noted, which were classified into the following categories: congenital keratinization disorders (ichthyoses, palmoplantar keratodermas, Darier’s disease, acrokeratosis verruciformis of Hopf), bullous genodermatoses (bullous epidermolysis, benign familial pemphigus Hailey-Hailey, porphyrias), congenital

neurocutaneous syndromes (neurofibromatoses, tuberous sclerosis), chromosomal abnormalities with potential for malignant degeneration (Peutz-Jeghers syndrome) and conditions with uncertain etiology (Fox-Fordyce disease). Among these, the most common genodermatoses encountered between January 2013 and July 2023 are keratinization disorders (113 cases, 44.66%) (pages 137-140, 277).

5. The 253 cases included in the epidemiological study were divided into 11 clinical-etiopathogenic disease categories. The conditions with the highest incidence between January 2013 and July 2023 are represented by neurofibromatoses (63 patients, 24.90%), palmoplantar keratodermas (46 patients, 18.18%), ichthyoses (43 patients, 16.99%) and cutaneous porphyrias (42 patients, 16.60%). The genodermatoses with the lowest incidence are benign familial pemphigus Hailey-Hailey (6 cases, 2.37%), Fox-Fordyce disease (2 cases, 0.79%), acrokeratosis verruciformis of Hopf (1 case, 0.40%) and Peutz-Jeghers syndrome (1 case, 0.40%) (pages 137-140, 277).

6. Regarding the distribution by age categories, it was found that the maximum incidence of the studied cases was in the 55-64 years group (57 cases, 22.53%), followed by the 45-54 years group (51 cases, 20.15 %), which is discordant with data from the specialized literature and that can be explained by the lack of medical information among patients and the presence of mild or moderate forms of disease that were therapeutically neglected. In the specialized literature, onset at young ages is often described, but in the studied cohort, 14 patients (5.53%) were recorded in the age category < 1 year, 9 patients (3.55%) in the age category 1-4 years and 13 patients (5.13%) in the age category 5-14 years (pages 146-153, 277, 278).

7. Regarding the hospitalization length, the highest number of hospitalization days was recorded among patients diagnosed with keratinization disorders (605 hospitalization days, representing 42.36% of the total of 1428 hospitalization days recorded for the 253 patients diagnosed with genodermatoses). Among all cases of keratinization disorders, the highest number of hospitalization days was recorded among patients diagnosed with ichthyoses (43 patients - 405 days, 28.36%). Other clinical-etiopathogenic categories in which a high number of hospitalization days was recorded are porphyrias (42 patients - 380 days, 26.61%) and neurofibromatoses (63 patients - 261 days, 18.27%), which can be explained both in terms of the therapeutic needs of the patients, but also by the increased number of patients. On the other hand, in relation to the average number of hospitalization days, Peutz-Jeghers syndrome (14 days of hospitalization for 1 single patient) and Fox-

Fordyce disease (23 days of hospitalization for 2 patients) are in first place, which is due to the comorbidities that required surgical treatment (laparoscopic sigmoidectomy with mechanical termino-terminal colorectal anastomosis for colonic polyposis with suspected malignant degeneration and histopathologically confirmed dysplasia and, respectively, total hysterectomy with bilateral adnexectomy for uterine polyfibromatosis with endometriosis foci) (pages 153- 162, 280, 281).

8. Regarding the clinical manifestations, among the 253 patients diagnosed with genodermatoses included in the present study, predominantly mild or moderate forms of disease were identified, with severe cases being extremely rare (pages 182, 184, 185, 287 , 288).

9. The main comorbidities detected among the patients included in the study, for the diagnosis and treatment of which multidisciplinary collaboration was necessary, were represented by cardiovascular diseases (120 cases, 46.69%), type II diabetes (75 cases, 29.18%), gastrointestinal diseases (57 cases, 22.17%), atopy (50 cases, 19.45%), neuro-psychiatric conditions (20 cases, 7.78%), gynecological pathology (15 cases, 5.83%), neoplasms (6 cases, 2.33%) and thyroid diseases (5 cases, 1.94%) (pages 134, 185, 283-285).

10. A well-conducted family survey, with a detailed history of probands, is of particular importance in the diagnosis of genodermatoses, providing the possibility to calculate the risk of transmission to the offspring and to offer genetic counseling, as well as to institute prenatal diagnosis techniques. Thus, out of the 253 patients diagnosed with genodermatoses included in the study, family aggregation was noted in 84 cases (33.20%) and heterotypy in 17 cases (6.72%). Genodermatoses with the highest frequency of isotypy are represented by ichthyoses (24 cases out of 43 patients), palmoplantar keratodermas (20 cases out of 46 patients) and neurofibromatoses (15 cases out of 63 patients). The most frequent cases of heterotypy were observed among patients diagnosed with ichthyoses (8 cases out of 43 patients, representing 18.6%), and the comorbidity with the highest incidence among these patients is atopic dermatitis. Regarding the heredity pattern observed among the patients included in the study, 68 cases (26.88%) showed evident familial aggregation with variable penetrance and expressivity. Among these, in 52 cases (76.47% of the 68 cases and 20.55% of the 253 patients), an autosomal dominant transmission model was noted, with a 50% risk of inheritance, and respectively, in 16 cases (23.53% of the 68 cases and 6.32% of the 253 patients) an autosomal recessive

transmission pattern was found, with a 25% risk of inheritance (pages 163-175, 282-285). Additionally, variability in the degree of kinship and the number of affected family members was observed in various forms of genodermatoses, with an average of 2-3 affected patients in the same generation or in 2 often successive generations (frequently father/mother - son/daughter) in the case of ichthyoses, palmoplantar keratodermas, Darier's disease, epidermolysis bullosa, benign familial pemphigus Hailey-Hailey, cutaneous porphyrias and neurofibromatoses (pages 163-175, 282-285).

11. Paraclinical investigations played a significant role in establishing the clinical-etiopathogenic form of genodermatoses, and the histopathological examination served to highlight criteria for a certainty diagnosis in accordance with data found in the specialized literature (pages 176-181).

12. Genodermatoses are chronic, incurable conditions, sometimes with severe clinical manifestations and the potential for serious complications, so the main objectives of their treatment are to reduce the duration of flare-ups and increase the remission period in cases where achieving clinical remission is possible, as well as to prevent complications, to improve the quality of life and to reduce morbidity and mortality.

In conclusion of this study, genodermatoses are conditions whose management poses a continuous challenge for the medical community, considering the complexity and rarity of these diseases. Improving access to specialized diagnostic and treatment services, promoting research in the field, and providing ongoing education for doctors, medical personnel and patients are essential elements in ensuring optimal care for these patients. The treatment of genodermatoses remains predominantly symptomatic, but recent advances have opened new perspectives, and therapies targeting the correction of genetic abnormalities and cell therapy offer hope for improving the prognosis and quality of life of patients with genodermatoses. In this regard, therapeutic methods intervening in disease pathways are promising for the future, and considerable progress has been reported in understanding the pathophysiological mechanisms of genodermatoses, paving the way for innovative treatments aimed at correcting abnormalities in intercellular signaling pathways, suppressing inflammation by replacing defective proteins or through cell therapy, and genetic engineering techniques attempting genome editing (rearrangement, insertion or deletion of abnormal genes, insertion of a normal gene, manipulation of interfering RNA, and post-transcriptional gene silencing).

This work is important not only from the perspective of advancing scientific knowledge in the field of dermatology, but also from a social and humanitarian point of view. Through the realization of this study, significant contributions are aimed at deepening the understanding and appropriate approach to genodermatoses, with the aim of improving the prophylaxis, diagnosis, management and prognosis of these conditions, potentially opening up new directions for future research and clinical practice in this field.

7. Selective bibliography

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8. List of published papers

Poster

1. **Popescu S.**, Kövér ZJ., Giurcăneanu C., Gorecki G. The Importance of Preimplantation Diagnosis in Genodermatoses (poster). 4th *International Exhibition InventCor* 14-16.09.2023, Deva, Romania. Awarded with the silver medal. (Reference 529, Chapter 6, pages 309-315).

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1. Popescu MA, Diaconu DJ, **Vasile S**, Grigore M, Vasile C. Darier's disease: Etiopathogenic, anatomical-clinical and differential diagnostic considerations. *DermaVenerol,* Bucharest 2014; 59(1):49-64. https://revistasrd.ro/includes/files/articles/art_6_en_219.pdf. Indexed BDI. (Reference 78, Chapter 1, pages 44-46; Chapter 5, pages 205-304).

2. **Popescu S.**, Kövér ZJ., Toma D., Gorecki GP., Carazanu L., Popescu MA., Cristea IT., Giurcăneanu C. Multidisciplinary Approach to Peutz-Jeghers Syndrome – Disscussions on a Clinical Case. *DermatoVenerol (Buc) 2023*; 68(2):7-14. ISSN 1220 – 37334. https://revistasrd.ro/includes/files/articles/1_en_466.pdf. Indexed BDI. (Reference 528, Chapter 5, pages 262-266).

3. **Popescu S.**, Pețа D., Kövér ZJ., Toma D., Cristea IT., Popescu MA., Balan G., Giurcăneanu C. Giant Renal Cell Carcinoma in a Patient with Ipsilateral Lower Limb Hypertrophic Lichen Planus – A Case Report and Literature Review. *Journal of Mind and Medical Sciences*, 2023; 10(2):21. DOI: https://doi.org/10.22543/2392-7674.1425. https://scholar.valpo.edu/jmms/vol10/iss2/21. Indexed ISI IMPACT FACTOR 1.8. (Reference 527, Chapter 5, pages 248-261).

4. **Popescu S.**, Kövér ZJ., Toma D., Gorecki GP. Carazanu L., Popescu MA., Orzan AO., Giurcăneanu C. Uderstanding Genodermatoses – Insights from Epidemiological Analysis on a Selected Case Cohort. *DermatoVenerol (Buc) 2024*; 69(1):7-18. ISSN 1220 – 37334. https://revistasrd.ro/includes/files/articles/1_en_482.pdf. Indexed BDI. (Reference 526, Chapter 5, pages 145-261, 299-304).