IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 4 Ser. 4 (April. 2026), PP 58-64
www.iosrjournals.org

Frequency Of Genodermatosis Among Libyan Patients Tripoli Central Hospital 2013 – 2020

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Abstract:
Background: *Genodermatosis are hereditary skin anomalies which can be grouped into three categories: chromosomal, single gene, and multi factorial. Most genodermatoses show single gene or mendelian inheritance. The most frequent genodermatoses differ from one country to another and are affected by several factors such as endogamy and the place of residence.*
Objectives: *to study the frequency and clinical profile of different genodermatoses among Libyan patients who attended our genodermatoses clinic for diagnosis or management. Our case series study included genodermatosis patients who attended to genodermatosis clinic in Tripoli Central Hospital Between 2013 - 2020. Diagnosis of the diseases was based on full history, clinical impression and skin biopsy. Collected data is presented in tables and suitable figures and analyzed using SPSS program version-20 with appropriates statistical methods.*
Results: *a series of 260 patients was studied, 146 (56.2%) patients were females and 114 (43.8%) patients were male. The most common genodermatoses were; icthyosis, neurofibromatosis and and epidermolysis bullosa, The family history was positive in 52% of patients, Family history was not recorded in patients with incontinentia pigmenti, crest syndrome, cowden syndrome, hopp syndrome and dyschromatosis universalis. Regarding the consanguinity, it was positive in 152 (58.5%) patients of the total number of patients.*
Conclusion: *The most common genodermatoses were; icthyosis (31.9%), From the 83 patients with Icthyiosis, (56.1 %) of patients presented as ichthyosis vulgaris. (56%) of cases with Epidermolysis bullosa had Epidermolysis bullosa simplex. 21% of the cases of keratoderma from ALkhoms city, and 17% from Amazigh ethnicity. 26% of the cases of (XP) belong to the Wershafana tribe. Strategies for the prevention of genodermatosis should include integration of community genetics into the primary healthcare system, education, and strengthening the existing specialized genetic service. This data can be gathered to establish the regional registries for the genodermatosis which can further contribute to the national registries.*
Keywords: *Genodermatosis, Ichthyosis, Xeroderma.*

Date of Submission: 13-04-2026 Date of Acceptance: 23-04-2026

I. Introduction:

Genodermatoses are a group of inherited disorders with a conglomeration of cutaneous and systemic signs and symptoms [1]. They do not always manifest at birth, have a variable degree of inheritance and cause considerable morbidity and psychosocial distress due to lack of concrete treatment [2]. Genetic disorders are often grouped into three categories; chromosomal, single gene and multifactorial [3]. Chromosomal disorders can be either numerical such as trisomy and monosomy or structural resulting from translocations, deletions and duplications [3]. The commonest genodermatoses registered in our patients are:

Ichthyosis: which forms clinically and etiologically a large heterogeneous group of cornification disorders that are characterized by accumulation of hyperkeratotic scales on the skin surface [4]. Ichthyosis vulgaris is the most common type of ichthyosis, with an incidence of 1:250 live births [5] ,the genetic mutation involves decreased production of a protein in the skin called filaggrin [6].

Epidermolysis bullosa (EB): a heterogeneous group of hereditary disorders characterized by extreme fragility of the skin and mucous membranes, which gives rise to the formation of blisters and ulcers following minor trauma [7], the areas of the body most often affected are sites subject to frequent pressure or friction so; conditions are also called mechanobullous disorders [8]. The reported incidence varies from one geographical zone to another, affecting approximately1in17,000 live births with an estimated 500,000 cases worldwide [9,10]. The forms of (EB) are categorized into the following three subtypes: EB simplex, junctional EB, dystrophic EB. Simplex is the most common form (92%) and dystrophic has the second highest incidence (5%) followed by junctional EB (1%) [11].

Neurofibromatosis: Neurofibromatosis represents a form of disseminated phakomatosis[12], the term "phakoma" is used for a lentil shaped object such as a mark on the skin or the retina[13], the disorder is transmitted as an autosomal dominant condition, but 50% of cases arise ass spontaneous mutations. There is no

gender predilection [14]. Neurofibromatosis is a group of heterogeneous diseases. Although several variants of neurofibromatosis have been proposed, only two distinct types have been defined to date. Neurofibromatosis type 1 (NF1) is also termed peripheral NF, and Neurofibromatosis type 2(NF2) as central NF, due to their more peripheral and central involvement, respectively.

Palmoplanter keratoderma: (PPKs) refer to a thickening of the skin of the palms and soles caused by excessive keratin [15]. They are a heterogeneous group of disorders that are classically grouped as either hereditary or acquired [16,17]. In addition, PPKs are classified in terms of epidermal involvement: diffuse, focal and punctuate [17]. The primary distinguishing factors that stratify hereditary and acquired groups of PPKs are age of onset, positive family history, and associated features.

Xeroderma pigmentosum: Which is defined by extreme sensitivity to sun light , resulting in sunburn , pigment changes in the skin ,and a greatly elevated incidence of skin cancers[18], it is an autosomal recessive disease with the potential of causing more than 1000- fold increase in the frequency of all types of major skin cancers in areas exposed to sunlight compared to normal population[19] the basic defect underlying the clinical manifestations is a nucleotide excision repair (NER) defect leading to a defective repair of DNA damaged by ultraviolet radiation[20] .

Pseudoxanthoma elastium (PXE): is an autosomal recessive disease of connective tissue, which is characterized by mutations in the ABCC6 gene complex, located in chromosome 16p13. The precise prevalence is unknown, although it is estimated at 1/50,000 people. Women are more often affected than men, in a ratio of 2:1. The skin lesions start to develop in the first or second decade as a symptomatic small papule (1-5mm), yellowish or skin tone, which blend together into large reticular plaques affecting the lateral and posterior regions of the neck, the flexural areas, and the periumbilical area [21].

Ectodermal dysplasia: a heterogeneous group of disorders characterized by a constellation of finding involving a primary defect of the skin, teeth and appendageal structures including hair, nail, exocrine and sebaceous glands [22]. Freire Maia described 117 possible varieties of ectodermal dysplasia involving all possible mendelian modes of inheritance [23]. In addition, there are defect of central nervous system, the adrenal medulla, the oral nasal and rectal mucosa and their associated glands. The pharyngeal and laryngeal mucosa may be atrophic that it results in dysphonia and hoarseness of voice [24].

Darier disease: an autosomal dominant genodermatosis with complete penetrance and variable expressivity. Men and women are equally affected [25]. It presents commonly with follicular and extra follicular greasy keratotic red to brown papules and plaques; arising primarily in seborrheic areas involving the scalp, face, trunk and lateral aspect of the neck [26]

Prevention and Education : prevention can be done by integration of community genetic services into primary healthcare system , such as the integration of preconception counselling and screening into existing reproductive health workers , education of the public specially communities with high prevalence of genodermatoses with respect to local cultural and religious beliefs, strengthening human resources with more emphasis on practical guidelines for how to approach common genetic and congenital disorders and introducing new technology and strengthening of existing genetic service .

Aim of the study: to study the frequency and clinical profile of different genodermatoses among Libyan patients who attended our genodermatoses clinic for diagnosis or management.

Objectives:

- to find out the frequency of different genodermatoses in our patients.
- to describe the clinical profile of the most common genetic disease in our patients

II. Material And Methods:

Study design: A case series study.

Sample size: This survey came across 260 individuals.

Study place: Genodermatoses clinic in Tripoli central hospital.

Study period: January 2013 to January 2020

Study population: all patients attending the clinic for diagnosis and management.

Study Tools: Through searching in medical data available in the genodermatoses clinic at Tripoli Central Hospital were obtained and put in the form of checklist sheet that included the following information: age, gender, type of disease, nationality, residency, family history and consanguinity.

Data Analysis: SPSS software package (IBM Corp. Version 25) was used for data analysis. Data were displayed in tables and graphs and expressed as frequencies, percentages, means, and standard deviations.

Ethical consideration:

Informed consent was not obtained due to retrospective nature of the study, however, all information was displayed anonymously without any indicative information to guarantee individuals privacy.

III. Results:

260 patients with different Genodermatoses were studied, 146 (56.2%) patients were females and 114 (43.8%) patients were male (figure-1).

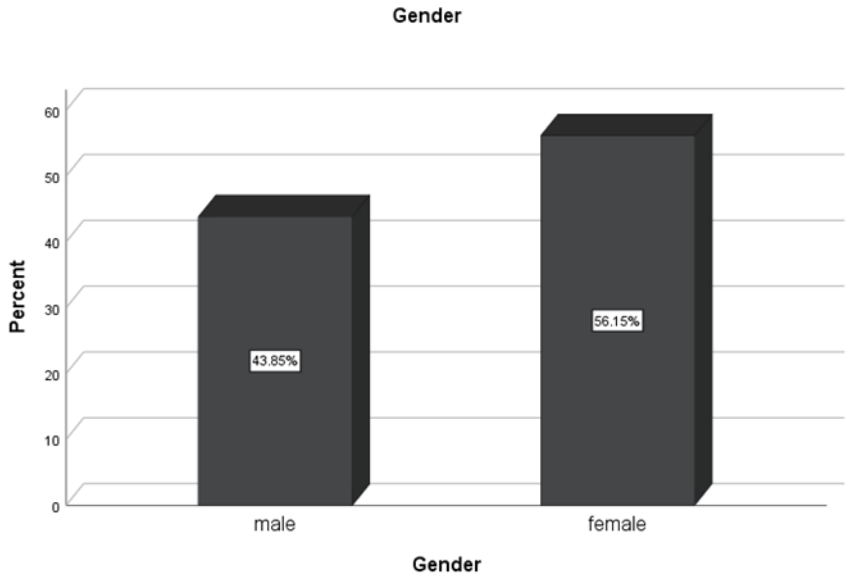

Figure 1. Distribution Of Sample According To Gender

The most common genodermatoses were; ichthyosis 83 (31.9%) neurofibromatosis 74 (28.5%) and epidermolysis bullosa 25 (9.65), regarding the frequency of other genodermatoses were illustrated in (table-1)

Table-1: Distribution of sample according to the most common disease

Genodermatosis	Patients	
	No	Percent%
Ichthyosis	83	31.9
Neurofibromatosis	74	28.5
Epidermolysis Bullosa	25	9.6
Palmoplanter Keratoderma	23	8.8
Xeroderma Pigmentosum	19	7.3
Tuber Sclerosis	12	4.62
Darier Disease	6	2.3
Ectodermal Dysplasia	4	1.54
Pachyonychia Congenita	3	1.15
Pseudoxanthoma Elasticum	2	0.77
Familial Peeling Syndrome	2	0.77
Incontinentia Pigmenti	2	0.77
Crest Syndrme	2	0.77
Cowden Syndrme.	1	0.38
Hopp Syndrome	1	0.38
Dyschromatosis Uneversalis	1	0.38

From the 83 patients with Icthyiosis, (56.1 %) of patients presented as ichthyosis vulgaris, (20.5%) as lamellar ichthiosis , (6%) as non bullos ichthyosiform erythroderma, (2.4%) as Netherton syndrome , (1.2 %)as Sjogrens-Larsson syndrome and (1.2%) as x – linked recessive ichthyosis (figure-2)

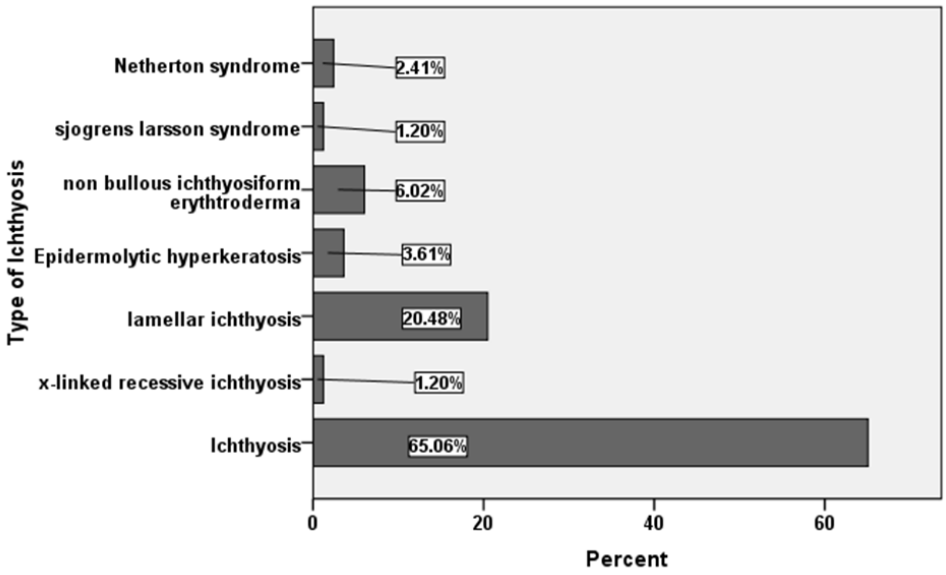

Figure-2: distribution of Icthyiosis patients according to the types.

(56%) of cases with Epidermolysis bullosa had Epidermolysis bullosa simplex, (24%) had junctional epidermolysis bullosa and (20%) had dystrophic epidermolysis bullosa (figure-3).

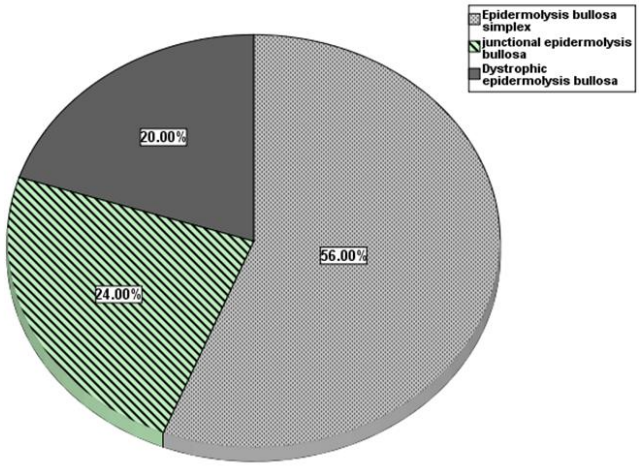

Figure-3: Epidermolysis bullosa subtypes

The family history was positive in 52% of patients, from those patients with positive family history; (66.27%) had ichthyosis, (33.78 %) had neurofibromatosis, (86.96) with hereditary palmoplantar keratoderma, 100% had mal de melda and tylosis, 36% with epidermolysis bullosa, 55.56% had epidermolysis bullosa simplex, 33.33% had dystrophic epidermolysis bullosa, 11% had junctional epidermolysis bullosa. 100% had peeling syndrome, pachyonychia congenita, and ectodermal dysplasia. 33.3% had Darier disease, 84% had xeroderma pigmentosum, 50% had pseudoxanthoma elasticum

Family history was not recorded in patients with incontinentia pigmenti, crest syndrome, cowden syndrome, Hopp syndrome and dyschromatosis universalis. Regarding the consanguinity, it was positive in 152 (58.5%) patients of the total number of patients. In ichthyosis was positive in 69.9% of patients , in epidermolysis bullosa was positive in 76%, epidermolysis bullosa simplex was positive 78.57%, in hereditary palmoplantar keratoderma was positive in 87%, in neurofibromatosis was positive in 37.84%, xeroderma pigmentosum was positive in 63.16%, 33% in Dariers disease , 50%i in ectodermal dysplasia , 100% in familial peeling syndrome and in incontinentia pigmenti (table-2) Consanguinity was not recorded in crest syndrome , pseudoxanthoma elasticum, Hopp syndrome and pachyonychia congenital.

Table-2: percent of positive family history & history of consanguinity within each diagnosis:

Genodermatosis (Total No. Of Patients)	F/H Percent (%)	Consanguinity Percent (%)
Ichthyosis (83)	66.27 %	69.88 %
Neurofibromatosis (74)	33.78 %	37.84 %
Epidermolysis Bullosa (25)	36 %	76 %
Palmoplanter Keratoderma (23)	86.96 %	86.96 %
Xeroderma Pigmentosum (19)	84.21 %	63.16 %
Tuber Sclerosis (12)	16.67 %	50 %
Darier Disease (6)	33.33 %	33.33 %
Ectodermal Dysplasia (4)	100 %	50 %
Pachyonychia Congenita (3)	100 %	0.00 %
Pseudoxanthoma Elasticum (2)	50 %	0.00 %
Familial Peeling Syndrome (2)	100 %	100 %
Incontinentia Pigmenti (2)	0.00 %	100 %
Cowden Syndrme (1)	0.00 %	100 %

IV. Discussion:

Available data suggest that genetic and congenital disorders are more common in Arab countries than in industrialized countries, several factors may contribute to the high prevalence of genetically determined disorders like high consanguinity rates. 25-60% of all marriages are consanguineous, the lack of public health measures directed at the prevention of congenital and genetic disorders with inadequate health care before and during pregnancy, and services for the prevention and control of genetic disorders are restricted by certain cultural, legal and religious limitations. In Libya many genetic diseases are recorded, our study will present the frequency of the genetic diseases registered in our genodermatosis's clinic in a period of six years with some details regarding clinical types, family history and history of consanguinity. From the 260 patients who attended our genodermatosis clinic between 2013 and 2020 ichthyosis was the most common diagnosis registered, as the study recorded 83 (31.9%) cases with ichthyosis which is similar to that recorded by Rabah M. Shawky et al in Egypt in 2012 **[27].** and it also corresponds to Haider R. AL-Hamami et al in Iraq in 2010**[28]**, where the rate was (36.88%) and (25.3%), respectively. On other hand, this percentage contrasted with Isadora Zago Miotto et al, in Brazil in 2020, where the ichthyosis form what they are attributed to (19.8%) **[29]**. On other hand, this percentage contrasted with Isadora Zago Miotto et al, in Brazil in 2020 **[29]**, where the ichthyosis form what they are attributed to (19.8%) **[29]**. Ichthyosis vulgaris constituted the commonest type in our study (56.15), as for Haider R. AL-Hamami et al in Iraq in 2010, it accounted for (42.9%) **[28]**. In contrast lamellar ichthyosis constituted the commonest type in Rabah M. Shawky et al study in Egypt in 2012 (34.8%) [28] followed by X linked ichthyosis (11.2%). Regarding Neurofibromatosis, it is noted that the rate in this study is 28.5%, which is twice with Isadora Zago Miotto et al study in Brazil in 2020 (14.8%) [29], and almost three times Haider R. AL-Hamami et al in Iraq in 2010 (9.6%) [28], and that all sample in the Libyan study were Neurofibromatosis type 1. Regarding Epidermolysis bullosa, this study recorded 25 (9.6%) cases somewhat close to Rabah M. Shawky et al study in Egypt in 2012 (16.9%) [27], and Isadora Zago Miotto et al study in Brazil in 2020 (19.7%) [29], it was observed that 16% of the cases were traced back to the city of Tarhuna. The commonest type of Epidermolysis bullosa was of the simplex (56%), while Junctional EB constitute 24% and dystrophic EB 20%, and this is inconsistent with Sawsan M Jalalah et al in Saudi Arabian 2005 **[30]**, where Junctional EB was the commonest type (53%), while Dystrophic EB constitute 33%, and EBS only accounted for 13.3%. This study showed the percentage of keratoderma (8.8%) corresponded almost completely with Haider R. AL-Hamami et al study in Iraq in 2010 (7.9%) **[28]**. 21% of the cases are from Alkhoms city, and 17%, from the amazig (Berber) ethnicity in the west mountain area. The rate of xeroderma pigmentosum was close between this study (7.3%) and Haider R. AL-Hamami et al study in Iraq in 2010 (4.81%) **[28],** it was noted that 26% of the cases belong to the Wershafana tribe. When this study was compared with Farah Sameem et al study in 2018 about the spectrum of genodermatosis in Muslim majority population of north India (128 cases) **[31]**, the results were very similar in many diseases (table-3)

Table-3: comparison between our study and Farah Sameem et al study

The disease	Our study		Farah Sameem et al study [40]	
	patients number	Percent (%)	Patients number	Percent (%)
Ichthyosis	83	31.9	30	33.59
Keratoderma	23	8.8	10	7.8
Xeroderma pigmentosum	19	7.3	4	3.8
Tuberous sclerosis	12	4.62	6	4.86
Cowden syndrome	1	0.38	1	0.78

About 52% of patients have positive family history of the same genetic disease, this percentage is significantly higher than its counterparts Haider R. AL-Hamami et al study in Iraq in 2010 (35%) and Farah

Sameem et al study in India (33.59%). In a study of hereditary ichthyosiform disorders from Saudi Arabia [32] (75%) had a positive family history, which is similar to our study (66.77%), while in Haider R. AL-Hamami et al study in Iraq in 2010 was 38.1%, but it was positive in 92.9% of patients in previous Iraqi study done by Hassan HA in 1997 [33]. In xeroderma pigmentosa, family history was noted in 84% of our cases, Haider R. AL-Hamami et al study in Iraq showed that family history was noted in 50% of cases only. Family history was not recorded in patients with incontinentia pigmenti and both cases which diagnosed as incontinentia pigmenti were female, that corresponds to X- linked dominant of the disease. During this work the consanguinity was recorded in 58.5% of cases and it is more obvious in disease of autosomal recessive inheritance as dystrophic EB in which all patients had positive consanguinity, because both parents were more likely to carry the same defective gene and express the disease in their children. In this study consanguinity was positive in 69.9% of patients with ichthyosis, it is close to Haider R. AL-Hamami et al study in Iraq (61.9%). Most of patients in our study were from a rural community which can be explained as consanguineous marriages are more common in closed communities leading to the clustering higher prevalence of genodermatosis in them. The similarity between the results of this study and the results of the Egyptian , Iraqi and Saudi studies is noted to some extent, and this can be explained due to the close genetics and close social behaviour such as inbreeding, the results of the Indian on the Muslim minority in India were interesting , as they were similar in some disease to our study , and this can be explained by the great role of inbreeding on genetic disease , as the proportion of inbreeding was high in the Indian study , as is case with our study . neurofibromatosis came second in our study, unlike the rest of the studies. this can be explained by the fact that our study included all ages, while the rest of the studies focused on children only.

V. Conclusion & Recommendations:

260 with different Genodermatoses were studied, the most common genodermatoses were; ichthyosis (31.9%), From the 83 patients with Ichthyosis, (56.1 %) of patients presented as ichthyosis vulgaris. (56%) of cases with Epidermolysis bullosa had Epidermolysis bullosa simplex. 21% of the cases of keratoderma from ALkhoms city, and 17% from amazig ethnicity. 26% of the cases of (XP) belong to the Wershafana tribe.

Strategies for the prevention of genodermatosis should include integration of community genetics into the primary healthcare system, education, and strengthening the existing specialised genetic service.

- This data can be gathered to establish the regional registries for the genodermatosis which can further contribute to the national registries.

Limitations: the limitations of our work are the small sample of patients, and the dependence on single centre registries.

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