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X-linked genodermatoses from diagnosis to tailored therapy

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Abstract

Background. Genodermatoses are rare heterogeneous genetic skin diseases with multiorgan involvement. They severely impair an individual's well-being and can also lead to early death.

Methods. During the progress of this review, we have implemented a targeted research approach, diligently choosing the most relevant and exemplary articles within the subject matter. Our method entailed a systematic exploration of the scientific literature to ensure a comprehensive and accurate compilation of the available sources.

Results. Among genodermatoses, X-linked ones are of particular importance and should always be considered when pediatric males are affected. Regardless of other syndromic forms without prevalence of skin symptoms, X-linked genodermatoses can be classified in three main groups: keratinization defects, pigmentation defects, and inflammatory skin diseases. Typical examples are dyskeratosis congenita, keratosis follicularis spinulosa decalvans, hypohidrotic ectodermal dysplasia, chondrodysplasia punctata, hypohidrotic ectodermal dysplasia, incontinentia pigmenti, chronic granulomatous disease, CHILD syndrome and ichthyosis. In this field, genetic diagnosis of the specific disease is important, also considering that numerous clinical trials of orphan drugs and genetic therapies are being proposed for these rare genetic diseases.

Conclusions. Thus, this chapter starts from clinical to molecular testing and ends with a review of all clinical trials on orphan drugs and gene therapy for genodermatoses. ***Clin Ter 2023; 174 Suppl. 2 (6):236-242 doi: 10.7417/CT.2023.2493***

Key words: *genodermatosis, X-linked, hyperkeratosis, gene therapy, genetic diagnosis, tailored therapy*

Introduction

Genodermatoses

Genodermatoses are a group of inherited skin disorders that are caused by genetic defects like mutations or deletions of one or multiple genes (1). Genodermatoses typically affect the skin, hair, nails and sometimes other organs of the body. Due to a wide amount of genetic variation, multiple types of genodermatoses exist like ichthyosis or xeroderma pigmentosum. Symptoms therefore vary widely depending on the specific condition. Common symptoms include dry, scaly, or thickened skin; blisters or sores; and abnormal hair or nails. In some cases, genodermatoses can also cause problems with the eyes, teeth or internal organs (1).

Genodermatoses can occur in people of all ages and races, but some conditions are more common in a certain population. For example, ichthyosis is more common in people of African descent while xeroderma pigmentosa is more common in people of Japanese descent (1).

X-linked genodermatoses

X-linked genodermatoses are a group of genodermatoses disorders where the genetic causal factors are located on the X chromosome (2). These disorders are called X-linked because they are caused by mutations on the X Chromosome, one of the two sex chromosomes. Since females have two X chromosomes and males have one X and one Y chromosomes, the way that X-linked disorders are inherited and expressed can be different between males and females. Typically, symptoms will be present in males whilst females who carry the mutation on one of their X chromosomes may be affected to a lesser degree or not at all, as the second X chromosome can compensate for the mutation (1). X-linked genodermatoses can be further classified in three main groups:

Keratinization defects

In this group, the genodermatoses in caused by abnormal development or metabolism of the protein keratin in the skin cells. Keratin is a protein that gives the skin strength and integrity and it is important for the formation of the skin's barrier function. When there is a defect in the process of keratinization, the skin can become dry, scaly and prone to infection. Treatment often involve creams and ointments on the skin (3).

Pigmentation defects

Pigmentation defects are caused by abnormal development or metabolism of the pigment melanin in the skin cells. Melanin is the pigment that gives color to the skin, hair and eyes and it is essential for the protection of the skin from harmful effects of ultraviolet (UV) radiation. When there is

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a defect in the process of pigmentation, the skin can become lighter or darker than normal, or have uneven patches of color. This can particularly be the case in women due to mosaic X-chromosome inactivation (4).

Inflammatory skin diseases

In this group, the skin disease is caused by an inflammation reaction of the skin. This can result in redness, itching and scaling leading to eczema, psoriasis or acne. However, these conditions are also dependent of environmental factors (5).

Examples of X-Linked genodermatoses

Dyskeratosis congenita

Dyskeratosis congenita, also known as Zinsser-Engman-Cole syndrome, is characterized by skin changes, nail dystrophy, and leukoplakia (white patches in the mouth). The disease can also be accompanied by more serious consequences like bone marrow failure, leading to insufficient blood cell production, and cancer. Dyskeratosis congenita can be inherited and is caused by mutations in genes involved in telomere maintenance that lead to telomere shortening. The disease is diagnosed based on symptoms and confirmed by genetic testing. 19 different genes are found to be involved in dyskeratosis congenita with 1 out of 5 of the pathogenic mutations found in *DKC1*, a gene encoding for dyskerin (6).

Keratosis follicularis Spinulosa decalvans

Spinulosa decalvans is a genodermatosis affecting the follicles of the hair and is characterized by scarring alopecia on the scalp, eyebrows and axillae. Being X-linked, it is predominantly present in men and rarely in women (7). The disorder is caused by mutations in the *MBTPS2* gene encoding an intramembrane zinc metalloprotease involved in sterol control of transcription and the ER stress response called the membrane bound transcription factor peptidase, site 2 (or S2P) (8).

Hypohidrotic ectodermal dysplasia

Hyophidrotic ectodermal dysplasia is an ectodermal disorder leading to abnormal development of skin, hair, nails, teeth and sweat glands before birth (9). Patients have fewer or non-functional sweat glands leading to a reduced ability to sweat (hypohidrosis). This can result is serious problems with body temperature control. Patients will have little to no hair and absent or malformed teeth. The disorder is also associated with distinctive facial features like thin lips, flattened nose bridge and a prominent forehead. The X-linked form is caused by genetic mutations in the *EDA* gene (10) which is responsible for crosstalk between the ectoderm and mesoderm during development.

Chondrodysplasia punctata

There are 4 types of chondrodysplasia punctata of which 2 are X-linked. The Gondradi-Hunermann type is caused by mutations in the EBP gene (11). Patients have a short stature, low nasal bridge and skin lesions. The Rhizomelic form is caused by mutations in the PEX7 gene and is characterized by short extremities, cataracts, ichthyosis and nasal hypoplasia. Patients will rarely survive past infancy. The X-linked recessive type is caused by mutations in the *ANOS1* gene whilst the X-linked dominant (also known as Happle syndrome) form is caused by defects in the *EBP* gene. X-linked chondrodysplasia punctata is a developmental disorder of bone and cartilage. The disease presents as spots in cartilage and near the end of bones on X-Rays. It mostly occurs in the bones of the toes, fingers and ankles. In addition, patients will have short stature and short tips of fingers and toes. Furthermore, the patients will have a flattened nose with a flattened nasal bridge and crescent shaped nostrils (11).

Incontinetia pigmenti

Incontinentia pigmenti is a condition that mainly effects the skin. During infancy, patients will have a blistering rash followed by wart-like skin growth (12). During childhood, the wart growths will become grey-brown patches that eventually evolve in lighter patches during adulthood. In addition to skin symptoms, patients will experience hair loss, small or missing teeth, fingernails and toenails abnormalities and eye abnormalities (13). The disorder is caused by mutations in the *IKBKG* gene encoding the NEMO protein, which protects the cell from TNF-alpha induced apoptosis (12).

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is an immunodeficiency disorder in which white bloods cells are unable to kill certain bacteria and fungi, making patients with CGD at a high risk for frequent bacterial and fungi infections leading to recurrent infections (14). In addition, patients may suffer from abscesses in their liver, spleen bones, lungs and skin as well as granulomas in the bowel and urinary tracts. The disease is caused by defects in the NADPH oxidase complex, an enzyme complex build up from different proteins from multiple genes. Being an X-linked disorder, hemizygous or heterozygous mutations in the p91-phox (*CYBB*) gene can lead to CGD (15,16).

CHILD syndrome

Congenital hemidysplasia with ichthyosiform erythroderma and limb defects, also known as CHILD syndrome, is a dominant X-linked condition leading to ipsilateral symptoms in multiple organs. All patients will have unilateral erythematous skin plaque with a midline demarcation from birth (17). In addition, patients will suffer from musculoskeletal problems like hypoplasia to agenesis, possibly leading to scoliosis. CHILD syndrome is caused by mutations in the *NSDHL* gene encoding the NAD(P)H steroid dehydrogenase-like protein. This protein is responsible for the dehydrogenases of 3beta-hydroxy sterols that is vital for the production of cholesterol (18). This leads to a shortage of cholesterol for proper formation of membranes and myelin around nerve fibers (19).

Ichthyosis

Patients with X-linked ichthyosis are characterized by dark brown scales and dryness of the skin (20). The symptoms are congenital and more often do not improve with age. The disorder results from mutations in the *STS* gene leading to steroid sulfatase deficiency (21). A comprehensive list of X-Linked genodermatoses can be found in Table 1.

Clinical and molecular testing

Genodermatoses, and more specifically X-linked genodermatoses, are a group of heterogeneous skin disorder that are very similar and often difficult to distinguish from each other. Due to the heterogeneity in onset and severity of symptoms, it remains difficult to diagnose the specific type of genodermatoses. In addition, these disorders can each be caused by a mutation in different genes or multiple genes. Successful treatment relies on the correct characterization and identification of the specific disorder to allow for a targeted treatment. Therefore, diagnosing the specific type of genodermatoses is pivotal.

Clinical testing

The clinical expression of genodermatoses is very indistinct with much variants in symptom expression making their genotype-phenotype correlation challenging to determine for the treating physician. In some cases, symptoms can start from birth while in other cases symptoms remain unnoticed until adulthood. All subgroups of genodermatoses were divided into subgroups by to their clinical manifestations (22). These subgroups included: ectodermal disorders; connective tissue disorders; epithelial adhesion disorders; keratinizing disorder; DNA repair disorders; progeroid disorder; pigmentary disorder; tumor predisposition disorder; nail disorder; hair disorder; developmental disorder; vascular disorder; immune disorder; metabolic disorder.

When a patient presents themselves with genodermatosis like symptoms, the first step for correct identification and diagnosis is to perform a detailed clinical examination in order to provide an accurate list of phenotypes. This should include potential phenotypes on the skin, hair, nails and teeth. The second step involves a detailed anamnesis as well as the medical history of a three-generation family pedigree in order to evaluate the mode of inheritance. Finally, it is often needed to perform laboratory testing to find the proper diagnosis (22).

Laboratory testing for genodermatoses includes histopathology, electron microscopy and immunofluorescence. Histopathology can be most helpful in cases such as Darier disease or incontinent pigmenti. Using histopathology, it is possible to visualize classical cellular manifestations or certain types of genodermatoses like apoptotic keratinocytes presenting with dark and fragmented nuclei in Darier disease (22).

Molecular testing

Next to clinical evaluation, molecular testing can provide pivotal information for the diagnosis of genodermatoses. Due to the boom in DNA technologies available to researchers, it was possible to identify genes associated with genodermatoses using genetic linkage analysis and positional cloning (23). Technologies like DNA sequencing and RNA profiling therefore make it possible to easily identify which gene is involved in patients skin disorder and ergo which type of skin disorder the patient has.

Next generation sequencing (NGS) allows for massive parallel sequencing of DNA to simultaneously sequence hundreds of genes (24). Using this technique, researchers can perform a whole exome sequencing (WES) on patient DNA. The whole exome contains all of a patient genes, therefore, WES data can reveal any mutation in any gene. Currently, the diagnostic rates of WES are estimated at 30-60% for all genodermatoses, making it a popular tool for diagnosis of genodermatoses (25). Certain subgroups of genodermatoses like epithelial adhesion disorders and keratinization disorders have an 80-100% average diagnostic rate using DNA sequencing (26).

In other cases, the DNA itself can remain healthy without any mutations while the gene expression levels have changes beyond healthy levels. Without any expression of the gene, a patient will in most cases have the same phenotypes as if the gene was mutated. Screening for levels of RNA can therefore be key in diagnosis genodermatoses. RNA-Sequencing can be used to identify, quantify and compare RNA expression levels in a patient. There are three types of changes to RNA that can be identified using RNA-seq. 1) Detecting changes in expression of certain genes outside of their physiological boundaries. This can be caused due to epigenetic or genetic changes to promoters or enhancers that regulate the gene's expression (27). 2) Detecting changes in splicing patters that lead to an aberrantly spliced gene due to changes in intronic

Table 1. X-Linked genodermatoses, OMIM number, causative gene, OMIM number.

X-Linked Disease	OMIM	Gene	OMIM
Dyskeratosis congenita	305000	DKC1	300126
Spinulosa decalvans	308800	MBTPS2	300294
Hypohidrotic ectodermal dysplasia	305100	EDA	300451
Chondrodysplasia punctata	302950	ANOS1 EBP	300836 300205
Incontinetia pigmenti	308300	IKBKG	300248
Chronic granulomatous disease	306400	CYBB	300481
CHILD syndrome	308050	NSDHL	300275
Ichthyosis	308100	STS	300747

sdgdsgv

DNA segments (28). 3) Detecting changes in gene expression due to an imbalance in allele-specific expression (29).

In addition to evaluating the gene expression levels of the patient, RNA-seq can be used to detect foreign gene expression. This way, researchers can detect the presence of viruses that can causes viral dermatoses (30).

Clinical trials on orphan drugs and gene therapy

The advent of new diagnostic tools like DNA and RNA sequencing has led to an increase in genodermatoses diagnoses. In many cases, these skin disorders markedly affect the patients' quality of life and can lead to an increase in cancer risk (31). Currently, 1/2000 people have a type of genodermatoses. For these people, treatment is limited to skin and wound care using topical oils and creams, surgery or pain and itch treatment (32). In addition, patients can learn how to manage their symptoms and how to avoid certain triggers that might evoke symptoms. As these treatments are needed life-long, it can be economically challenging for patients to adhere to the full treatment plan (32). Due to the advances of scientific research over the past 20 years, researchers are starting to unravel the molecular and genetic background of genodermatoses. Unraveling the underlying pathophysiology can lead to novel and more targeted and specific methods for the treatment of genodermatoses. There are 3 different types of approaches to treat genodermatoses.

Interfering in the pathophysiological pathways

In some genodermatoses, a certain pathway is over- or under-activated, leading to an aberrant cellular environment. For many cellular pathways, there already exist drugs to increase or decrease the activity of the pathway. Using these drugs, doctors can choose to target the aberrantly regulated pathway. For example, in neurofibromatosis 1 (NF1), the mitogen-activated protein kinase (MAPK) is overactive leading to the NF1 symptoms. Decreasing the MAPK pathway using MAPK inhibitors is therefore an attractive treatment option (33).

Targeting the inflammatory pathways

In many genodermatoses, the symptoms are in part caused by an exaggerated inflammatory reaction. These symptoms are most often treated by targeting hyperkeratosis and using anti-inflammatory creams based on corticosteroids (34). In recent years, doctors are opting for therapies targeting the inflammatory process like TNF-α inhibitors, antibodies or cytokines (35). These treatments were proven to successfully reduce inflammation levels, alleviating symptoms.

Restoration of the underlying gene or protein defect

In some cases, genodermatoses is caused by a DNA defect like mutations, deletions or insertions that lead to a complete loss of that gene. As genes are transcribed into RNA, which later translates into proteins, loss of a gene due to mutations will downstream lead to a loss of the protein encoded by the gene. The pathophysiology of the specific genodermatoses will in that case be caused by the loss of the protein from the cellular environment. Restoring the gene or replenishing the protein will in that case result in a restoration of the defects caused by the absence of the protein. This can be achieved in multiple ways. First, protein therapy aims to replace the lost protein by providing the protein to the cells. This protein can be made in a lab and administered to the cells by in injections or drugs. For example, researchers were able to cure a mice model for dystrophic EB, a genodermatosis due to missing type 7 collagen (C7), by providing C7 by injection. The collagen is able to reach the skin and for anchoring fibrils at the dermo-epidermal junction, thereby performing their natural function and restoring the disorder (36). Protein therapy can often be challenging as the protein needs to be supplied in physiological levels as too little or too much protein could disrupt the physiological balance. In addition, the protein often needs to be administered at specific times, for example, some conditions are caused by defects during embryonic development. In these cases, suppling the protein will only have a positive effect during development. Secondly, Cell therapy can be used to restore the loss of a protein by administering health cells that can make this protein. For example, loss of collagen type 7, which made by fibroblasts, can be restored by providing allogeneic fibroblasts of a health donor. These cells can settle within the host patient and naturally produce C7 and thereby restore the disorder (37). Lastly, Gene therapy is a novel option to replace or restore the defect gene to restore the disorder (38). Given that all genodermatoses have a genetic defect or predisposition, principally, all genodermatoses could benefit from gene therapy. In Gene therapy, doctors can provide DNA, RNA or gene editing tools inside the cells of a patient and thereby restore the gene defect. These gene therapies can be distributed inside a patient by used non-integrating viral vectors or lipid or polymeric nanoparticles. However, there are still many hurdles to overcome for gene therapy to be safe and effective. Different kind of gene therapies are currently being tested and used. 1) Gene insertion: with gene insertion, researchers and doctors will supply a healthy copy of the mutated gene to the cells. This healthy copy can live outside the genome and replace the defective, mutated, gene (39). 2) Gene editing: instead of replacing the defective gene, gene editing aims to restore the naturally present gene by modifying or restoring the gene in the genome itself. This can be achieved by a variety of molecular tools like zinc finger nucleases (ZNFs), transcription-activator like effector nucleases (TALEN) and clustered regularly interspaced short palindromic repeats (CRISPR/Cas9) (40). These tools are able to make precise cuts in the genome that can be repaired by supplying a repair template via homology directed repair. This repair template contains the healthy/normal DNA of the mutated DNA causing the disorder. 3) RNA-based therapy: contrary to the previous techniques that aim to restore the defective DNA, RNA-based therapy aims to provide healthy levels of RNA that can naturally be transcribed into protein to restore to protein deficiency (41). In other cases, different types of RNA can be exogenously suppled that can interfere with splicing, transcription or transport of other genes thereby regulating overall gene expression in the cell. RNA-based techniques included: small interfering RNAs (si-RNA), antisense oligonucleotides (AONs), spliceome-mediated RNA trans-splicing (SMaRT) and micro RNAs (miRNAs) (41).

Genetic skin disease itching

Many of the genetic (X-linked) skin diseases involve some form of itching that has a negative impact on the patient's quality of life. A new clinical trial at the children's hospital of Chicago aims to evaluate the treatment of dupilumab on improving itch for patients with genetic inflammatory skin disorders (NCT05649098). The study has enrolled 30 participants and has started on February 1st, 2023. The study is scheduled to complete on February 1st, 2026.

Dyskeratosis congenita

Treatment for dyskeratosis congenita often involves stem cell therapy. To prepare the bone marrow for stem cell transplantation, patients receive high dose of pre-transplantation radiation and chemotherapy. This can often be intolerable for some patients, lead to side effects and result in slow recovery of blood counts. A new study evaluated if lower dose chemotherapy and radiation followed by stem cell transplantation is effective for patients with dyskeratosis congenita (NCT00455312). Researchers created a new nonmyeloablative conditioning regimen and tested it on 6 patients (42). Five of the six patients successfully engrafted the donor cells. After 26.5 months, four out of the six patients are alive. Thereby they conclude that the novel nonmyeloablative conditioning regimen is successful in prepare patients to receive stem cell therapy and can lead to successful engraftment of the stem cells without cause adverse events as occurs in the normal conditioning regimen (42).

Hypohidrotic ectodermal dysplasia

Hypohidrotic ectodermal dysplasia affects several ectodermal structures which leads to an impaired sweat glands, teeth development, and meibomian glands. This disorder is caused by the absence of ectodysplasin A (EDA) during development. Therefore, recent therapeutic approaches aim to replace this protein with synthetic proteins. In 2018, Schneider et al. administered fusion protein Fc-EDA prenatally to the amniotic cavities of three fetuses from two different pregnancies. In both cases, sweat glands, meibomian glands and teeth developed normally compared to (43). Currently, a new study aims to administer EDA immediately after birth to restore normal development (NCT01775462).

Another study aims to evaluate the efficacy of ER004, a first-in-class protein replacement molecule designed to perform a high-affinity binding to the endogenous EDA1 receptor (NCT04980638). When bound to the receptor, ER004 activates the EDA/NF_KB pathway to trigger normal development. This protein replacement clinical trial aims to evaluate the efficacy and safety of intra-amniotic ER004 administrations as a treatment option for patients with X-linked hypohidrotic ectodermal dysplasia.

Chronic granulomatous disease

X-linked chronic granulomatous disease (X-CGD) is caused by a defect in phagocytic cells ability to produce reactive oxygen species due to a mutation in the gp91phox subunit of NADPH oxidase. Currently, the treatment option of choice Is an allogenic hematopoietic stem cell transplantation to restore the ability of the body to naturally produce phagocytic cells. However, this treatment is subject to immunological rejection from the host. Therefore, a new clinical trial at the University Hospital of Frankfurt aims to treat with gene-corrected autologous CD34+ cells by using a SIN gammaretroviral vector for an *ex-vivo* gene therapy (NCT01906541). 5 participants were enrolled in the trial. From these patients, CD34+ cells will be extracted and cultured. These cells carry a mutation in the gp91phox gene that will be replaced by ex-vivo gene therapy before returning the corrected cells back inside the patient's body. As these cells are originating from the patient, they will likely not be rejected when reinserting. Similarly, a new study at the Children Hospital of Paris, France, aims to restore patients CD34+ cells with lentiviral transduction of the XCGD gene (NCT02757911). 3 participants are enrolled in this study which is set to end on June 2024.

These clinical trials have a large potential for success. Previously, Donald B Kohn et al. (2020) reported on the result of 2 clinical trials (NCT02234934 / NCT01855685) in which patients with hematopoietic stem cells receives ex vivo lentiviral gene therapy (44). After 12 months, 6 of the 7 patients showed 16 to 46% oxidase-positive neutrophils. These patients had no new X-CDG related infections and have been able to stop x-CDG antibiotics (44).

CHILD syndrome

Patients with CHILD syndrome suffer from congenital ichthyosis, erythroderma, and hyperkeratosis. The treatment of these conditions often involves systemic retinoids which may cause dose dependent adverse events. Recently, researchers made a novel topical isotretinoin ointment formulation to treat congenital ichthyosis (45). The formulation termed PAT-001 is patented for this use. In total, 19 patients enrolled in a clinical trial to test the safety and efficacy of PAT-001. In total, seven patients discontinued the trial and in total 28 adverse events occurred over 14 patients. However, scaling was significantly reduced in the treated group. More testing is required to make a proper cost/benefit analysis to outweigh the adverse events against the improved scaling.

Ichthyosis

X-linked ichthyosis is mainly characterized by hyperkeratosis and widespread scaling treated with oils and ointments or systemic retinoids. A new randomized, double-blind study evaluated the effect of TMB-001, a novel topical isotretinoin ointment on hyperkeratosis and scaling (NCT04154293) (46). In total, 33 patients enrolled in the study of which 11 received a 0.05% and 10 a 0.1% TMB-001 ointment treatment. Researchers found that TMB-001 demonstrated significant improvements to the patients' skin after 12 weeks of treatment. Furthermore, TMB-001 0.05% was more effective than 0.1%.

Another double blind, randomized control trial evaluated the effect of oral vitamin D on patients with congenital ichthyosis compared to a control group receiving acitretin treatment (47). Eleven patients received 2000 IU vitamin D a day for 24 weeks. Patients treated with oral vitamin D showed a significant decrease in the visual index for ichthyosis severity and area severity index after 12 weeks of treatment. However, this effect was not visual after 24 weeks (47).

Conclusion

Genetic testing is widely used in the diagnosis of X-linked genodermatoses and should always be considered after clinical diagnosis, especially when pediatric males are affected. Indeed, identifying the underlying genetic basis of these diseases will allow the development of gene therapies targeting the specific mutated genes. Considering the wide knowledge of the genetic basis of genodermatoses, more in vivo genetic therapy trials should be initiated, in order to provide patients with the best tailored treatment option.

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Conflict of Interest

Authors declare no conflict of interest.

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