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GENES AND PHENOTYPES INVOLVED IN AUTOSOMAL RECESSIVE ICHTHYOSIS: A CLINICAL AND GENETICAL REVIEW



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Abstract

Ichthyosis is a large heterogeneous group of genetic anomalies of skin which are distinguished by either distribution or quality of scaling and hyperkeratosis, also may contain other extra cutaneous and dermatologic involvement. These anomalies are due to gene sequence variants often linked in skin barrier formation. Inherited ichthyoses can be of either two forms; non syndromic and syndromic forms. Non syndromic ichthyoses only have phenotypic expression causing effect to skin. Non syndromic ichthyoses consists of autosomal recessive congenital ichthyoses, X-linked ichthyoses, ichthyoses vulgaris. Keratinopathic ichthyoses and other forms. This review emphasis on updates of all types of non-syndromic ichthyoses. This review figures out the molecular pathways and phenotype/ genotype associations. Autosomal recessive congenital ichthyoses can be of either three major phenotypes (lamellar ichthyoses, congenital ichthyosiform erythroderma and harlequin ichthyoses) more over, and be three of the minor subtypes (acral self-healing collodion baby, self-healing collodion baby and bathing suit ichthyoses). Keratinopathic ichthyoses are caused due to keratin genes sequence variant so are termed Keratinopathic ichthyoses. For diagnoses and discovery of ichthyoses genetic causes, the next generation sequencing is considered the influential tool. This paper reviews the recent pathomechanisms for the non-syndromic ichthyoses and explains the future perspectives.

Keywords: Autosomal Recessive, Ichthyoses, Skin, Genes

INTRODUCTION

Ichthyosis is an inherited genetic deformation characterized by cornification of skin. It may be inherited as autosomal recessive, X linked and autosomal dominant fashion. Clinically ichthyosis is characterized by scaling of skin, which may sometimes be associated with non-cutaneous and cutaneous malformations including palmoplantar keratoderma, recurrent infections, erythroderma and hypohidrosis (1). Ichthyosis may be caused by more than fifty genes sequence variant, it degrades the intra-cellular lipid biosynthesis pathway, DNA repair, adhesion and desquamation and also many other pathways. Each feature interrupted barrier function, even many pathways included pathogenesis (2). clinical malformations, mode of genetically inheritance of a consensus classification system for ichthyosis have been established based on the pathophysiology which is established by (3). Additionally, based on oji classification, ichthyosis can be classified into two main types; non syndromic and syndromic one, the non-syndromic ichthyosis form has cutaneous features while the syndromic form has cutaneous plus extra associated organ deformation.

NON-SYNDROMIC ICHTHYOSSES

The non-syndromic type of inheritance, molecular involvement and the rate of inheritance, the non-syndromic ichthyosis is classified into four classes or groups: (1) common ichthyoses, (2) keratinopathic ichthyosis, (3) autosomal recessive ichthyoses (ARCI) and other forms including erythrokeratoderma (4).

COMMON ICHTHYOSSES

Ichthyoses vulgaris (IV) and x linked recessive ichthyoses are classified as common ichthyoses.

ICHTHYOSIS VULGARIS

The most common type of ichthyoses is known as ichthyoses vulgaris (MIM 147600) has almost 1 out of 250 births incidence rate (1). Moreover, the ichthyoses vulgaris clinical diagnoses feature includes, generalized xeroses characterized by rough and dry skin, mostly it occurs in abdomen, chest and the extensor region of extremities. In most of the times palmoplantar hyper linearity and keratosis are linked with IV. Ichthyoses vulgaris condition is semi dominantly inherited. The filaggrin gene variant causes the pathogenic condition (*FLG*; MIM 135940), in the differentiation of epidermis and skin barrier establishment, the *FLG* has an indispensable role (5). As for HGMD professional 2017.1, the ninety-three *FLG* pathogenic mutations have been found.

X-LINKED RECESSIVE ICHTHYOSIS

Recessive ichthyosis with X-linked has an (MIM 308100) incidence rate of 1/2000 to 1/6000 males throughout the world, which is assumed as second most type of ichthyoses occurring inherently (6). In young people, XLRI is characterized by huge polygonal XLRI is due to mutation of gene sulfatase (STS). The gene is localized on chromosome xp22.31. This gene is involved in the metabolism of cholesterol, androgen and estrogen (7). According to the report of HGMD professional 2017.1, sixty-eight mutations have been reported (mostly large deletion mutations) in STS which causes the pathogenesis of XLRI.

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSSES

Autosomal recessive congenital ichthyoses (ARCI) contains a huge number of cornification's inherited malformations of nearly incidence of 1/20000 births (8). ARCI is further classified into three subtypes, (1) lamellar ichthyoses (LI), (2) harlequin ichthyoses (HI), and (3) ichthyosiform erythroderma (CIE). Up till now, twelve genes pathogenic sequence variants have been linked with ARCI including transglutaminase1 (*TGM1*; MIM 190195) lipoxigenase (*ALOXE3*; MIM 607206), 12R-lipoxigenase (*ALOX12B*; MIM 603741), cytochrome p 450 family 4, sub family F, ATP binding cassette sub family a number 12 (*ABCA12*; MIM 607800) polypeptide 22 (*CYP22*; MIM 611495), NIPA like domain containing 4 (*NIPA4*; MIM 609383), lipase N (*LIPN*; MIM 623924), ceramide synthase 3 (*CERS3*; MIM 615276), short chain dehydrogenase /reductase family 9C member 7 (*SDR9C7*; MIM 609769), patatin like phospholipase domain containing protein 1

(*PNPLA1*; MIM612121), and suppression of tumorigenicity 14 (*ST14*; MIM676797) (9, 10). In ACRI allelic and locus significant heterogeneity exists.

LAMELLAR ICHTHYOSIS

Lamellar ichthyosis (MIM 242300) is categorized by palmoplantar keratoderma, thick and dark gray or brown scales on face, scalp, ectropion of eye lids, trunk, flexor areas, hypohidrosis, erythema and alopecia. Moreover, the infants are capsuled with collodion membrane by birth (11). Blepharitis, photophobia, abnormal dentation are other associated features of lamellar ichthyosis. Histology of skin patients with LI show a little number of parakeratotic cells and mildly thick or normal granular layer. In LI patients, the stratum corneum is thicker (11). In nine genes sequence variants have been reported with LI including *ALOX12B*, *ABCA12*, *ALOXE3*, *PNPLA1*, *TGM1*, *CYP4F22*, *CERS3* and *NIPA4*, of these genes, the *TGM1* is most frequently reported (4, 12). It encodes 817 amino acid protein called as transglutaminase-1, it is Ca^{2+} dependent enzyme, which plays an essential role in covering of cornified cell (13). In *TGM1* gene almost 180 different mutations have been recognized which marked the pathogenesis of ACRI as for HGMD professional 2017.1 accessed 20th June, 2017.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

Epidermolytic hyperkeratosis is the second name of congenital ichthyosiform erythroderma (CIE; MIM 113800). CIE inheritance is autosomal recessive pattern which is characterized by throughout body erythroderma and scaling and thus without the formation of blisters. Infants born are often covered with collodion membrane (14). Ectropion, keratoderma, ectropion and nail dystrophy are often linked with development of erythroderma and scaling. Skin patient with CIE shows minor acanthoses, irregular parakeratosis, hyperkeratosis and a usual or mildly thickened stratum granulosum (11). In pathogenesis of CIE the mutation of these genes have been implicated; *CERS3*, *ALOX12B*, *ABCA12*, *ALOXE3*, *NIPAL*, *LIPN*, *TGM1*, *CYP4F22* and *CERS3*.

HARLEQUIN ICHTHYOSIS

Harlequin ichthyosis (MIM 242500) is a dangerous form of ichthyosis, many a time, it is threatening to life. Genetically, HI clinical features are large, thick scales with harsh ectropion, flattened ear and ectropion. In uterus, the scarce skin development occurs, the hyperkeratosis of hair canal takes place at second trimester, and the epidermis of affected fetus typical ultra-structural lamellar granules are contemporarily developed (15). HI occurs due to null mutations in *ABCA12* gene. In epidermal keratinocyte lipid transporter, the *ABCA12* performs lipid transporter, this is degradation in *ABCA12* which leads to loss of lipid barrier in skin and may lead to HI (16). As for HGMD 2017.1 professional in *ABCA12* 112 different mutations are linked with ACRI.

KERATINOPATHIC ICHTHYOSIS

Keratinopathic ichthyoses (KI), is a large term that is used for many various types of ichthyoses, which occur due to different keratin cluster gene mutations. This type of

ichthyoses includes annular epidermatic ichthyoses (ACI) epidermolytic ichthyoses (EI), ichthyoses curth macklin (ICM), congenital reticular ichthyosiform erythrodermal, autosomal recessive epidermolytic ichthyoses, superficial epidermolytic ichthyfism (SEI), epidermolytic nevi (EN), and congenital reticular ichthyosiform erythroderma (CRIE). KI conditions are most of the times inherited with autosomal dominant pattern, whereas some autosomal recessive mutations are also known. Moreover, the mutations in *KRT2* (MIM60194), *KRT1* (MIM139350) and *KRT10* (MIM148080) are involved in the pathogenesis of keratinopathic ichthyoses (4). As for HGMD 2017.1 professional, 60 different mutations in *KRT1*, 60 in *KRT10* and 18 in *KRT2* have been linked with different forms of KI.

ERYTHROKERATODERMA

Erythrokeratodermas show minor kind of ichthyoses which is characterized by showing erythematous, hyperkeratotic skin plaques and showing of well demarcated. Moreover, erythrokeratoderma are clinically classified into two types; erythrokeratoderma variabilis (EKV; MIM 133200) and progressive symmetric erythrokeratoderma (PSEK; MIM 602036), both show overlapping of phenotypic features between EKV and PSEK. Up till now, five genes are known which causes erythrokeratoderma on gene sequence variability. These gene include gap junction protein beta 3 which encodes for connexin 31 (8) gap junction protein alpha encodes for connexin 43 (17), gap junction protein 4 encodes connexin 303 (18).connexin protein form the gap junctions, which are featured by two extracel, four luricrin trans-membrane (19).Cornified cell envelope main components is luricrin which is produced in the upper granular of epidermis (20). *KRT83* was firstly told to be as keratin type II expressed weakly in hair cortexed. Moreover, *KRT83* is expressed in whole body of rat and sheep. Recently, in progressive symmetric erythrokeratoderma *KRT83* is reported in a great number of Pakistani families (18). As for HGMD professional 2017.1 a total of twenty-one different mutations in *GJB4*, 103 in *GJB1*, 10 in *LOR* and 37 in *GJB3* have been reported so far.

GENES INVOLVED IN ICHTHYOSIS

ALOXE 3 AND ALOX12B

Both these genes are located on chromosome 17p13.1. The size of *ALOXE3* is 22.6 kb and the size of *ALOX12B* is 15kb both have 15 exons. Lipoygenase-3 is the protein produced by *ALOXE3* and 12(R)-lipoygenase is the protein produced by the *ALOX12B* (21). Both these genes are involved in metabolizing triglycerides, essential fatty acids, phospholipids and has a significant role in the formation of lipid barrier (22). In *ALOXE3* about 22 mutations are reported and in *ALOX12B* around 64 variants are reported. Abnormal lipid metabolism and incensement of skin fragility are due to a mutation in these genes (23).

ABCA12

It is involved in formation of lipid bilayer and it plays a role in the transportation of epidermal lipids in the upper layer of the epidermis. Anomalous barrier function and



Hyperkeratosis occurs due to changes in the protein of this gene (16, 24). The location of *ABCA12* is on chromosome 2q35. It contains 53 coding exons and its size is 206 kb (25). About 116 mutations have been reported in the *ABCA12* gene. Lamellar ichthyosis is also caused due to missense mutations in the *ABCA12* gene (24).

NIPAL4

About 18 reported mutations of this gene causes the irregular function of the skin barrier (26). *NIPAL4* gene is present on chromosome 5q33.3 and has 6 exons. The protein of this gene is called ichthyin and it occurs in the plasma membrane (16, 24). This gene expresses itself in the lungs, brain, and epidermis and its protein also facilitates the transport of magnesium. Ichthyin also plays role in the metabolism of lipid through lamellar granule's processing (27).

PNPLA1

PNPLA1 gene encodes the protein called human patatin-like phospholipases which contains 437 amino acids and it is mostly expressed in the upper layer of the epidermis. it plays a key role in the cytoskeleton, but its main function is not known. Recent studies have shown that it also has a role in lipid metabolism and lipid organization in the epidermal layer (28). This gene is located on chromosome 6p21.31 and contains 8 coding exons. It is important to note that some autosomal recessive congenital ichthyosis variants are also reported in this gene. When it is expressed in the skin epidermal keratinocytes then there it functions as an acyltransferase (29). In the catalytic domain of this gene, there is a very rare missense and non-sense mutation rate; therefore, it also impacts the lipid barrier of the epidermis (30). Up till now, 44 variants of the *PNPLA1* gene are reported which is responsible for inherited ichthyosis (29).

LIPN

Lipase family member N is the protein that is encoded by the *LIPN* and this protein is localized in the granular layer of the epidermis. It has a role in the *ABHD5* gene pathway and linked with triglyceride metabolism of the skin. *LIPN* gene is present at chromosome 10q23.31 and contains 9 coding exons. Variation of this gene causes about 5% mutation proportion of autosomal recessive congenital ichthyosis and about 1 mutation of the *LIPN* gene is involved in inherited ichthyosis (31). A 2 bp deletion mutation has been reported to cause a frameshift and premature termination of translation (32, 28)

CERS3

CERS3 gene is present at chromosomal location 15q26.3 and 143.9 kb is the size of this gene. Ceramide synthase 3 is the protein encoded by this gene. Four transcripts are produced by this gene which makes two isoforms, i.e. one of these transcripts as 14 exons in which 11 are coding exons and the second transcript contains 10 coding exons out of 13 exons. One of these ceramide synthases is very effective in the stratum granulosum and stratum corneum of the skin. A large fatty acyl chain is developed by this which is involved in the production of the long chain of ceramides which play a role in skin barrier

formation (33). Up till now, 8 variants have been reported which causes inherited ichthyosis (31).

CYP4F22

CYP4F22 gene encodes a protein of 531 amino acids called Cytochrome P450 4F22 and this protein belongs to Cytochromes P450 (CYP) superfamily of heme-thiolate enzymes. This protein has a vital role in the lipxygenase pathway and helps in lipid production and metabolism of lipid. Some of its mutations are involved in autosomal recessive congenital ichthyosis which has a phenotype of larger white greyscales and erythroderma (34). *CYP4F22* gene is present at chromosomal location 19p13.12 and has 12 coding exons. Up till now, 21 mutations of this gene are reported which are linked with ichthyosis (34).

TGM1

TGM1 gene is located on chromosome 14q12 and its size is 14,133 bp and has 15 exons (35). Glutamine gamma-glutamyl transferase K (transglutaminase K) is the protein that contains 831 amino acids (36). Transglutaminases are involved in the gathering of cell envelope precursor proteins which is important in the formation of cornified cell envelope (37). Variations in the *TGM1* were reported in self-healing collodion babies and in them, the activity of epidermal *TGM1* was eradicated (38). The *TGM1* gene is involved in the crosslinking of hydroxyceramide in cornified cell envelope (CCE) (29).

TGM1 is the main enzyme that is involved in the generation of Cornified Cell Envelope (CCE) that is linked with ichthyosis. CCE is a membrane having a thickness of 15nm and formed on the inner surface of stem cells during the process of epidermal keratinocyte differentiation (16, 24). *TGM1* also plays a role as a catalyst for isopeptide bond formation. *TGM1* interconnects hydroxyl ceramide to CCE and acts as an important component for the formation of the intercellular lipid layer in Stratum corneum (35, 39). *TGM1* mutations are involved in the deficiency of intercellular lipid layers. About 130 variants in the *TGM1* gene are reported which are responsible for autosomal recessive congenital ichthyosis. Up to the present time, 186 mutations are associated with *TGM1* which causes ichthyosis (29).

FILAGGRIN (FLG)

The *FLG* gene is located on chromosome 1q21 and contains 3 exons. Filaggrin is the protein encoded by the *FLG* gene and this protein is in the epidermal differentiation complex (EDC). Stratum corneum is the dead cell compartment that plays a role in skin barrier function. Stratum corneum is formed by EDC and EDC is involved in the terminal differentiation of the epidermis (40). The structural proteins called keratins are formed by Keratinocytes. The normal skin barrier is produced by the keratin network. Several types of ichthyosis are caused due to mutations in the genes of profilaggrin, filaggrin, and keratin. It is known that profilaggrin is formed by the Keratohyalin granules of the epidermis (41, 42). Up till now, 93 mutations are reported in the *FLG* gene which causes ichthyosis. Several types of null, frameshift and deletion mutations are found in the *FLG*

gene causing the formation of truncated profilaggrin peptides which results in atopic dermatitis and divergent skin disorders (18).

KERATIN CLUSTER

Keratins are hard and fibrous proteins that have some important physicochemical properties. Keratins combine to form a network of intermediate filaments that is present in keratinocytes. These keratinocytes mostly lie in hair, skin, and nail (43). Keratins are formed in epithelial cells of all vertebrates. Metabolism, integrity, and stability of epithelial cells depend upon keratins. Twenty-eight genes are recognized for Type I keratins (K9-K28; K31-K40) while 26 genes are recognized for type II keratins (K1-K8; K71-K86). Each one of these genes encodes a polypeptide (44). Type I keratins are located at chromosome 17p21 and type II keratins are located at 12q13. Keratin filaments contain type I and type II proteins in equal proportion, and both are expressed differentially in tissue with a definite pattern. Keratins differ from each other in polarity, charge, size and number and sequence of amino acid (45). Keratin 1 and Keratin 10 is expressed in the epidermis. Some keratins are commonly expressed in the cells of basal epidermis i.e. keratin 5 (type II) and keratin 14 (type I). Keratinocytes are involved in the secretion of Keratin 1 and keratinocytes are present at the soles of the feet and palms of the hands. 62 mutations are reported in *KRT1* while 18 mutations are reported in *KRT10* (46).

SDR9C7

SDRO gene contains 4 exons present on chromosome 12q13.3. SDRO may catalyze the metabolism of another class of nuclear receptor ligands, or may regulate metabolism by binding substrates or products, or by serving as a regulatory factor (47). To date 4 mutations have been found in *SDR9C7* involving ichthyoses.

SULT2B1

SULT2B1 gene located at chromosome 19q13.33 as two forms. *SULT2B1a*, encodes a protein of 350 amino acids, and the longer cDNA, *SULT2B1b*, encodes a 365-amino acid protein. The proteins differ only at their N termini (48) (Her et al., 1998). To date in ichthyosis 6 mutations have been identified in *SULT2B1*.

CONCLUSION

Skin is the outermost layer; accounting for 12-15% of the body weight and provide protection against many external factor. Skin may either be glabrous or hairy skin which is present all over the body except palms and soles. Ichthyosis is clinically and genetically heterogeneous group of mendellian disorders of cornification characterized by dry, thick, rough scales and cracking of the skin surface. Hyper keratinization and shedding of skin is caused by abnormal desquamation of stratum corneum. It can be inherited or acquired form. Based on inheritance pattern, hereditary ichthyosis can be X-linked, autosomal semi-dominant, dominant and recessive. Ichthyosis can be divided in syndromic and non-syndromic types depending upon involvement of extra cutaneous genetic anomalies. Syndromic type ichthyosis is found in association with defects in extra cutaneous tissues

like hair anomalies, prominent neurologic defects and fatal disease course whereas non syndromic types exhibit skin related symptoms only. Syndromic types of ichthyosis are further categorized into X linked ichthyosis syndromes and autosomal ichthyosis syndromes while non-syndromic ichthyosis are further divided into common ichthyosis, autosomal recessive congenital ichthyosis (ARCI) and keratinopathic ichthyosis. Advances in the field of molecular biology have enabled the researchers to understand various complex mechanisms that are involved in pathogenesis of skin and its appendages. Mechanism of pathogenesis of ichthyosis is suggested to be related to at least one of the three major components of stratum corneum including intercellular lipid layer, cornified cell envelop (CCE) and keratin-filaggrin degradation products filling the cytoplasm of cornified cells. There are multiple genes involved in ichthyosis for effective diagnosis of ichthyosis massive parallel technique is used. A large quantity of data can be generated using this methodological approach.

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