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Pathogenesis of horrifying rare genetic disorders in humans – A review

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Abstract
The identification of novel mutations causing genetic disease has seen more progress in the last few years than in the previous twenty. This increased body of research has resulted in a wealth of information regarding the pathogenesis of rare genetic diseases. In this review, we illustrate the underlying pathogenesis of few horrifying rare genetic diseases like Ectrodactyly, Proteus syndrome, Polymelia, Neurofibromatoses, Diprosopus, Anencephaly, Cutaneous horn, Harlequin ichthyosis and Cyclopia in humans.

Keywords: Pathogenesis, rare disease, genetic

1. Introduction
Diseases that affect less than 1/2000 individuals are referred to as rare; those with a prevalence lower than 1/50000 are referred to as ultra-rare. Rare genetic diseases are one of the most scientifically complex health challenges of our time. There are currently 7,000 known rare diseases, of which 80% are genetic origin and half of which affect children [1-2]. Rare diseases are characterized by diversity of symptoms that vary not only disease to disease but also from patient to patient affected by same disease. Rare diseases caused by altered functions of single genes can be chronically debilitating and life-limiting. Notwithstanding their severity, some rare diseases are compatible with a good quality of life if they are diagnosed early and optimally managed. Although the individual diseases are rare, they are collectively common, affecting millions of individuals worldwide [3]. Unfortunately, effective therapies for these diseases are themselves comparatively rare. Thus, in addition to the effects on patients and their families, these diseases have a tremendous cost for health care systems and societies. The number of rare genetic diseases is difficult to gauge precisely [4]. The rapid identification of genes that are associated with human disease has revolutionized the field of medical genetics, providing more accurate diagnostic, prognostic and potential therapeutic tools. In addition, an improved understanding of the molecular aetiology of genetic disorders is also altering our perception of disease transmission [5]. This review summarizes the pathogenesis of some horrifying rare genetic disorders affecting human.

2. Ectrodactyly
Split-hand/split-foot malformation (SHFM)/ ectrodactyly, also known as “lobster claw hand or Karsch Neugebauer syndrome” is a limb malformation involving the central rays of the autopod and presenting with syndactyly, median clefts of the hands and feet and aplasia/or hypoplasia of the phalanges, metacarpals and metatarsals. There is median cleft in the hand and feet due to the absence of the central digital rays, which gives the appearance of a lobster. First case of ectrodactyly was described in 1936 [6]. Ectrodactyly may be present alone, or may be part of a number of birth defects. Hand deformation alone is unlikely to affect health. Its incidence has been reported to be about 1 in 90,000 babies with no sex predeliction [7]. A number of factors complicate the identification of the genetic defects underlying human ectrodactyly: the limited number of families linked to each SHFM locus, the large number of morphogens involved in limb development, the complex interactions between these morphogens, the involvement of modifier genes, and the presumed involvement of multiple genes or long range regulatory elements in some cases of ectrodactyly [8]. Syndromes in which ectrodactyly is associated with other abnormalities can occur when two or more genes are affected by a chromosomal rearrangement. This explains the association of SHFM with other congenital anomalies in patients with deletions in *2q31* or *7q21*. In contrast, syndromic

ectrodactyly may also be the result of single gene defects. The most common and best known human SHFM syndrome is ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome, which is caused by missense mutations in the *TP63* gene. The patterns of multiple abnormalities in patients with *TP63* gene mutations allow the identification of specific domains within this gene that are most relevant for the limb phenotype [9-10]. The most common mode of inheritance is autosomal-dominant with reduced penetrance. Anticipation has been suggested in some families. Autosomal-recessive and X-linked forms occur more rarely and other cases of SHFM are caused by chromosomal deletions and duplications [9-11].

Fig 1: Foetus hand showing claw shaped deformity with absence of middle three fingers.

4. Proteus Syndrome

Proteus syndrome is a complex disorder consisting variably of disproportionate, asymmetric overgrowth of body parts, particularly involving the skeleton; cerebriform connective tissue nevi; epidermal nevi; vascular malformations; and dysregulated adipose tissue [12]. The estimated incidence is of less than 1 per 1,000.000 live births and represents a significant challenge to the pediatric and orthopedic surgeons in order to establish a diagnosis and to elaborate a management plan. It was diagnosed in two childrens and was designated Proteus Syndrome [13]. It is a complex hamartomatous disorder consisting of partial gigantism of the hands and /or feet, asymmetry of the limbs, plantar hyperplasia, hemiangiomas, lipomas, lymphangiomas, varicosities, verrucous epidermal nevi, macrocephally, cranial hyperostosis, long bone over growth3 and ocular manifestations [14-15]. The causative gene could not be mapped for decades until very recently, when Lindhurst *et al*. found a mosaic activating mutation in AKT1 by exome sequencing of DNA and a phosphorylation-specific antibody assay in 158 biopsy samples from 29 patients. Little is known about PS, and its rare occurrence presents a challenge in better understanding the condition. The discovery of the somatic activating mutation of AKT1 as the cause has opened a new horizon for research with respect to elucidating the pathophysiology, diagnosis, and management of this rare condition [16-17].

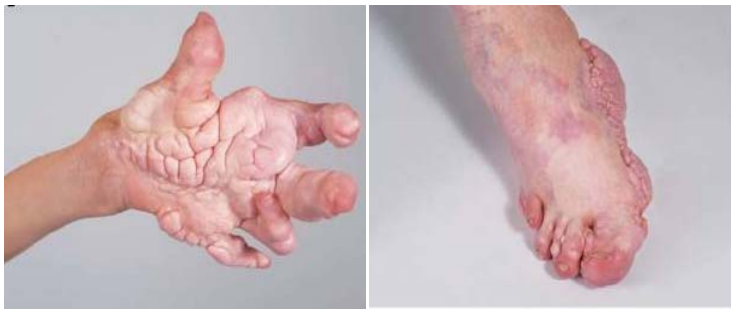

Fig 2, 3: Extensive cerebriform connective tissue nevus of palm and foot

3. Polymelia

Limb malformations occur in approximately 6 per 10,000 live births with 3.4 per 10,000 affecting the upper limb and 1.1 per 10,000 affecting the lower limb. Abnormalities of the limbs can be meromelia, amelia, phocomelia or polymelia. These defects are often associated with other birth defects involving the craniofacial, cardiac and genitourinary systems. Polymelia (supernumerary limbs) is an extremely uncommon congenital entity rarely reported in humans. The supernumerary limb can be either shrunken or deformed and can be attached to various regions of the body. Limb development is a very complex process involving precise gene regulation fundamental to normal growth. Limb development involves a very large number of genes [18]. One gene widely associated with the development of supernumerary limbs is the mouse mutant disorganization Ds gene, which is a semi dominant gene with variable penetrance in heterozygotes and lethality in homozygotes; 67% of heterozygotes have multiple defects and the rest have single defects, in which polymelia is prominent. In experiments with chick embryo, fibroblast growth factor-1(FBF-1) FGF-2, FGF-4, FGF-8 is able to stimulate development of additional limb. Radiologist plays a significant role in patients with polymelia to assess for additional congenital anomalies before surgical intervention. As only few reports are available regarding polymelia, more detailed study on it is needed [19-20].

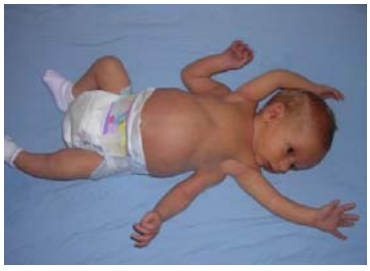

Fig 4: Child with polymelia

5. Neurofibromatoses

The neurofibromatoses (NF) are genetic disorders of the nervous system, which cause tumors to form on the covering of the nerves anywhere in the body at any time. Three distinct forms of NF have been identified 1) neurofibromatosis type 1 (NF1) 2) neurofibromatosis type 2 (NF2) 3) schwannomatosis. The tumors are generally non-cancerous. Neurofibromatosis affects both sexes and all ethnic groups. NF1 has an incidence rate of 1 in 4,000. Both NF2 and

Schwannomatosis have incidence rates of 1 in 40,000 [21]. Neurofibromatosis is an autosomal dominant disorder, which means only one copy of the affected gene is needed for the disorder to develop. Therefore, if only one parent has neurofibromatosis, his or her children have a 50% chance of developing the condition as well. The pathophysiology of neurofibromatosis (type 1) consists of the NF1 gene protein. This protein is a tumor suppressor and therefore serves as a signal regulator of cell proliferation and differentiation. A dysfunction of neurofibromin can affect regulation, and cause uncontrolled cell proliferation. Schwann cells in neurofibromas have a mutation in the NF1 alleles [22].

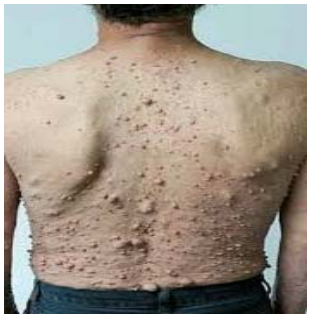

Fig 5: Man with neurofibromatosis

6. Diprosopus

Diprosopus also known as craniofacial duplication, Diprosopus is an extremely rare hereditary disorder in which parts (or all of the face) are duplicated. Diprosopus is an extremely rare form of congenital anomaly that results in partial or total duplication of the face. Several attempts have been made by several researchers to explain the mechanism that leads to craniofacial duplication. This mechanism resulting in two faces is considered to have occurred as a result of cranial bifurcation during neurulation of the notochord [23]. Two vertebral axes develop alongside the neural plates as a result of the bifurcation including neural crest derivatives. Facts from the literature also revealed that 0.4 percent of diprosopus is seen in conjoined twins. Another possibility is that there could be an increased production of sonic hedgehog (SHH), a protein which is essential for craniofacial patterning during fetal development; this has already been demonstrated in chicks by researchers in an experimental study [24].

Fig 6: Child born with diprosopus disorder

7. Anencephaly

Anencephaly is congenital absence of a major portion of the brain, skull and scalp. It results from failed closure of the anterior neuropore at 24-26 days post fertilization. In anencephaly the abnormality occurs in neurulation of the cranial part. Due to this the neural tissue is exposed and is not covered with the skull. The development of the cerebral hemispheres is also absent [25]. The incidence of anencephaly is 1:1000-1:20000. Epidemiology studies demonstrate variation in prevalence rates. The highest incidence is in Great Brittan and Irland, and the lowest is in Asia, Africa and South America. Anencephaly occurs 6 times more frequent in white than in blacks, females are more often affected than males [26]. Anencephaly, like other forms of neural tube defects (NTDs), generally follows a multifactorial pattern of transmission, with interaction of multiple genes as well as environmental factors, although neither the genes nor the environmental factors are well characterized. In some cases, anencephaly may be caused by a chromosome abnormality. The specific genes which cause the neural tube defects are not been identified still. One such gene methylene tetrahydrofolate reductase has been shown to be associated with the rise of neural tube defects. Thus, adding folic acid (vitamin B9) to the diets of women of childbearing age significantly decreases the incidence of neural tube defects [27].

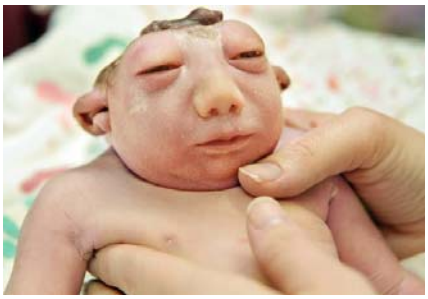

Fig 7: Child with anencephaly, low set ears and protruded eye ball

8. Cutaneous horn

Cutaneous horn is a clinical diagnosis referring to a conical projection of cornified material above the surface of the skin that resembles a miniature horn. Historically, it is also referred to by its Latin name, cornu cutaneum, and less commonly and more eponymously, as cornu cutaneum of Rokitansky [28]. The horn is composed of compacted keratin. The base of the horn may be flat, nodular, or crateriform. Cutaneous horns usually arise on sun-exposed skin but can occur even in sun-protected areas. Although these lesions can be found anywhere, the face and scalp account for 30% of all occurences. They are attributable to an array of benign (61.1%), premalignant (23.2%), and malignant (15.7%) lesions [29]. The pathogenesis of cutaneous horn is not fully understood. The horn itself is cornified debris that is of no clinical consequence. It is thought continuous stimulus may affect the formation of a cutaneous horn. Old age and abundant blood vessels at the base are also associated with cutaneous horn [30]. An array of benign lesions (seborrheic keratosis, viral warts, keratoacanthoma, trichilemmoma, epithelial hyperplasia, and more), premalignantconditions (actinic keratosis, arsenical keratosis, and Bowen's disease), and malignancies (squamous cell carcinoma, basal cell carcinoma, metastatic renal carcinoma, granular cell tumor, sebaceous carcinoma, and Kaposi's sarcoma) may be associated with cutaneous horns. Generally, these lesions present as isolated projections, arising in conjunction with actinic keratosis [31].

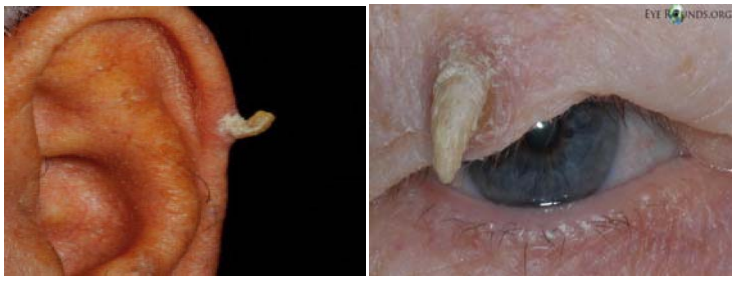

Fig 8, 9: Appearance of a cutaneous horn on the ear and eye lid.

9. Harlequin ichthyosis

Harlequin ichthyosis is a very rare and often fatal genetic skin disorder. Babies affected with Harlequin ichthyosis are born with extremely thick plates of skin separated with deep red cracks over their entire bodies. The incidence is calculated to be around 1 case in 300,000 births and approximately 200 cases of harlequin ichthyosis have been reported [32]. The known causative molecules underlying ichthyosis include ABCA12, lipoxygenase-3, 12R-lipoxygenase, CYP4F22, ichthyin and steroid sulfatase, all of which are thought to be related to the intercellular lipid layers. The major underlying genetic abnormality in harlequin ichthyosis is a mutation in the lipid-transporter gene ABCA12 on chromosome 2 [33]. A loss of functional ABCA12 protein disrupts the normal development of the epidermis, resulting in the hard, thick scales characteristic of harlequin ichthyosis [34]. Clinically, the harlequin babies may encounter dehydration, electrolyte imbalance, temperature malfunction and increasing sepsis risk because of severe skin damage. Therefore, affected neonates usually do not survive beyond first few days of life. High quality management of new born babies may improve survival. Introduction of oral retinoids and frequent application of emollients to improve barrier function is critical [35].

Fig 10: Baby with Harlequin ichthyosis

10. Cyclopia

Cyclopia (also cyclocephaly or synophthalmia) is a rare form of holoprosencephaly and is a congenital disorder (birth defect) characterized by the failure of the embryonic prosencephalon to properly divide the orbits of the eye into two cavities [36]. Exposure to drugs or to other potentially teratogenic environmental factors during organogenesis has been regarded as the basis of this anomaly. These factors were ionic radiation, contraceptives, viraemia plus corticosteroids and salicylates, rubella vaccine, antibiotics, and amidopyrine (Aminopyrine) [37]. Its incidence is 1 in 100 000 in newborns. Typically, the nose is either missing or replaced with a non-functioning nose in the form of a proboscis [38]. Sonic Hedgehog (SHH) Gene Regulator, named after the effects a mutation in the gene had on the forming embryo of fruit flies studied by scientists; a spiky appearance under a microscope, similar to that of its video game character namesake is involved in the separation of the single eye field into two bilateral fields. Although not proven, it is thought that SHH emitted from the prechordal plate suppresses Pax6 which causes the eye field to divide into two. If the SHH gene is mutated, the result is cyclopia, a single eye in the center of the face [39].

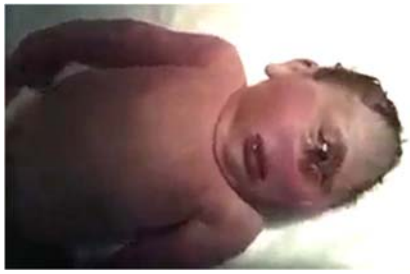

Fig 11: Newborn baby with cyclopia syndrome.

11. Conflicts of Interest

The authors declare no conflict of interest.

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