Mutation in Genes FBN1, AKT1, and LMNA: Marfan Syndrome, Proteus Syndrome, and Progeria Share Common Systemic Involvement

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Abstract

Genetic mutations are becoming more deleterious day by day. Mutations of Genes named FBN1, AKT1, LMNA result specific protein malfunction that in turn commonly cause Marfan syndrome, Proteus syndrome, and Progeria, respectively. Articles about these conditions have been reviewed in PubMed and Google scholar with a view to finding relevant clinical features. Precise keywords have been used in search for systemic involvement of FBN1, AKT1, and LMNA gene mutations. It has been found that Marfan syndrome, Proteus syndrome, and Progeria commonly affected musculo-skeletal system, cardiovascular system, eye, and nervous system. Not only all of them shared identical systemic involvement, but also caused several very specific anomalies in various parts of the body. In spite of having some individual signs and symptoms, the mutual manifestations were worth mentioning. Moreover, all the features of the mutations of all three responsible genes had been co-related and systemically mentioned in this review. There can be some mutual properties of the genes FBN1, AKT1, and LMNA or in their corresponding proteins that result in the same presentations. This study may progress vision of knowledge regarding risk factors, patho-physiology, and management of these conditions, and relation to other mutations.

Keywords: Genetic mutation; Marfan syndrome; Proteus syndrome; Progeria; Gene FBN1; Gene AKT1; Gene LMNA; Musculo-skeletal system; Cardiovascular system; Eye; Nervous system (Source: MeSH, NLM).

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Introduction

The haploid human genome consists of 3 billion nucleotides but changes in one single base pair can result in dramatic physiological malfunctions.[1] Mutations are changes in the genetic sequence at different levels that cause diversity among organisms.[2] This can be happened by way of a number of factors.

Mutation is common in all types of organisms which is chiefly classified in three types; deleterious mutation with harmful effect upon host, neutral mutation with no effect, and advantageous mutation for welfare of the organism. But, most of the non-neutral mutations are deleterious.[2-3]

If a deoxyribonucleic acid (DNA) repair mechanism fails, the physiological consequences of a mutation are quite inconstant, ranging from single cell death or cell carcinoma to hereditary genetic outcomes. Mutations in germline cells of human generally produce inheritable consequences, while mutation in somatic cells of human ordinarily only have outcomes affecting the individual in which the mutation occurs (National Council for Science and the Environment, Washington, DC. Available from: http://www.eoearth.org/view/article/159530/, updated 2014 April 10, cited 2014 April 18).

Every cell, in order to function properly, depends on thousands of proteins to function in the right places at the right times. Changes in DNA caused by mutation can cause errors in protein synthesis, creating partially or completely non-functional proteins which in combination ultimately could result in genetic disorders.[4]

Records in human mutation databases are increasing day by day.[5] Even about one hundred thousand diseases showed association with mutation of only 3,700 genes.[6] Around 300 new "inherited disease genes" (and about 10,000 new mutations) are added to the record book in a year.[7] The Human Gene Mutation Database (HGMD) is a complete assortment of germline modifications in nuclear genes containing over 141,000 mutations identified in more than 5,700 different genes up to June 2013.[8] The first genetic mutation was reported in the year 1977 in HGMD Professional database with a maximum entry of 13,490 in 2013. Among the entries Missense/Non-sense mutations are more than 82,000 (Human Gene Mutation Database. Available from: http://www.hgmd.cf.ac.uk/ac/hahaha.php, updated 2014 April 12, cited 2014 April 18).

Besides some common disorders, mutations sometimes report some rare diseases like progeria, Marfan syndrome (MFS), Mandibuloacral dysplasia (MAD), Loeys–Dietz syndrome, Wolff-Parkinson-White Syndrome, Ehlers–Danlos syndrome, Proteus syndrome, Cantu syndrome, etc. Some of them shows same prevalence pattern, some shows nearly same clinical features and presentations. But, in spite of knowing about affected proteins of mutation, the actual pathogenesis and course of the disease is not clear. Over a decade have passed after the completion of human genome project but the gene mutation diseases' treatment is still in a labyrinth. For a better treatment, pathogenesis should be discovered and to look through it, it is needed to track the effects of affected proteins which is reflects by common manifestations in different systems of the body.

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The reason for selecting these three genes is to study their little known pathophysiology. The documented similarities between them were wanted to compile in a review.

Search Strategy and Selection Criteria

A literature search was conducted using Google Scholar, PubMed (Medline), The Human Gene mutation Database, and Genetic Home of US national Library. Key word combinations included "Marfan syndrome clinical features", "Proteus syndrome features", "Progeria syndrome features", "Gene FBN1 mutation", "Gene AKT1 mutation", Gene LMNA mutation". One hundred thirty five articles were chosen for review. The inclusion criteria incorporated the articles on disease case reports, databases, review papers and original papers. The exclusion criteria were unavailability of any full article, unclear presentation, non-relevant study and reports of different languages other than English. The common features were assembled into this narrative review. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[9]

Gene FBN1, AKT1, LMNA and associated proteins

FBN1 gene is located on chromosome 15q15-21.3.[10] This gene is 200kb and divided into 65 exons.[11] It encodes fibrillin-1,[10] a large extracellular matrix glycoprotein which assembles in extracellular matrix. In this matrix, fibrillin-1 binds to other molecules of it and other proteins to form 10-12 nm threadlike filaments called microfibrils.[12] Microfibrils are main constituent of elastic fibers responsible for stretching and supporting many tissues of the body. It also store a protein called transforming growth factor beta (TGF-ß), a critical growth factor which helps in proliferation, differentiation, motility, and apoptosis of cells. Microfibrils help to regulate the availability of TGF-ß, which is inactivated when stored in microfibrils and activated when released (National Library of Medicine, NLM, Genetic - FBN1. Available from: http://ghr.nlm.nih.gov/gene/FBN1, updated 2014 April 12, cited 2014 April 18).

AKT1 is located on chromosome 14q32.32. It is also known as *PKB*, *RAC-PK*. This gene initiates for a protein called AKT1 kinase which is responsible for signaling in the cells for its growth, multiplication, stability and apoptosis (NLM, Genetic - AKT1. Available from: http://ghr.nlm.nih.gov/gene/AKT1, updated 2014 April 12, cited 2014 April 18).

In mouse, it is found that, during apoptosis, Akt is cleaved by caspases and mediates survival signals for protection against apoptosis.[12] Signaling involving *AKT1* kinase also appears to be vital for the usual growth and function of the nervous system. It has a role in cell-to-cell communication among neurons, neuronal survival, and the formation of memories. The AKT1 gene belongs to a class of genes known as oncogenes.[13]

The *LMNA* gene, also known as lamin A/C is located on the long (q) arm of chromosome 1 at position 22. More precisely, the *LMNA* gene is located from base pair 156,082,545 to base pair 156,140,088 on chromosome 1.[14,15] This gene translates some slightly diverse proteins called lamins; among them lamin A and lamin C are common in the most body cells. These proteins have an almost duplicate sequence of amino acids. The small difference in the sequence makes lamin A longer than lamin C due to encoded by an extra exon.[15] Lamins A and C are structural proteins called intermediate filament proteins that provide stability and strength to cells. Lamins A and C are scaffolding (supporting) components of the nuclear envelope. Specifically, these proteins are located in the nuclear lamina where it regulates the movement of molecules into and out of the nucleus. Between lamin A and C, only the lamin A protein must be processed from prelamin A before becoming part of the lamina (NLM, Genetic - LMNA. Available from: http://ghr.nlm.nih.gov/gene/LMNA, updated 2014 April 12, cited 2014 April 18).

Mutation of the Gene and diseases

Mutation in the Gene FBN1 causes MFS, Ectopia lentis, Shprintzen-Goldberg syndrome, and Hereditary aortic aneurysm. A mutation in the FBN1 gene has also been identified with Weill-Marchesani syndrome, stiff skin syndrome, neonatal MFS,[10,16] Juvenile idiopathic arthritis, and acromicric or geleophysic dysplasias.[17]

When mutation occurs in *AKT1* gene, it causes Proteus syndrome. *AKT1* gene is an oncogene which can create breast, ovarian and colorectal cancer after mutation and may have some association with schizophrenia (NLM, Genetic - AKT1. Available from: http://ghr.nlm.nih.gov/gene/AKT1, updated 2014 April 12, cited 2014 April 18). Mutation in gene AKT1 may also causes endometrial carcinoma,[18] bladder tumors,[19] squamous cell carcinoma of lung,[20] metastatic thyroid cancer,[21] hepatocellular carcinoma, and acute leukemia,[22] and many other tumors of the body.[33]

Mutations in the *LMNA* gene are related to a number of diseases, including Hutchinson-Gilford progeria syndrome (HGPS), limb girdle muscular dystrophy, familial partial lipodystrophy, Emery-Dreifuss muscular dystrophy, dilated cardiomyopathy, Charcot-Marie-Tooth disease. The mutated gene of lamin A that causes HGPS commonly known as progerin.[23,24] Loss of lipid level, type-2 Diabetes mellitus, Dispersed Leukomelanodermic Papules, mandibuloacral dysplasia, lethal restrictive dermopathy, and atypical progeroid syndrome (APS) are also result of mutation in LMNA gene.[128]

In latter sections, MFS due to FBN1 mutation, Proteus syndrome due to AKT1 mutation and Progeria syndrome due to LMNA mutation is going to be discussed for common systemic involvement.

Common systemic involvement of these gene mutations

Musculo-Skeletal system

The phenotypes of MFS caused by *FBN1* mutation, Proteus syndrome caused by *AKT1* mutation and Progeria caused by *LMNA* mutation commonly results musculo-skeletal system abnormality.

In MFS, most of the visible signs are related to the skeletal system. Persons may have dolichostenomelia, arachnodactyly, abnormal indentation or protrusion of the sternum, stooped shoulders, malocclusions,[25] abnormalities of the spine,[26] presence of osteopenia (mainly in Marfan children), inadequate bone acquisition.[28] The diagnosis of MFS relies on defined clinical criteria (Ghent nosology), outlined by international expert.[29] MFS causes the femoral head protruding into abnormally deep hip sockets (protrusio acetabuli).[25] Protrusio acetabuli is a criterion for the diagnosis of MFS. If acetabuli is protruded for long

time, it can cause anomaly in the hip joint and acetabular line.[19] MFS also shows vascular smooth muscle cell apoptosis.[30,31]

In Proteus syndrome, skeletal abnormalities are the most frequent findings.[35] Proteus syndrome shows megaspondylodysplasia,[32] and cranio-facial abnormalities.[33-35] Abnormal bony edges, bony invasions, joint immobility, and loss of overlying soft tissues have been reported in cases of it.[33,34] Manifestations of Proteus syndrome include large sized finger in association with permanent medial or lateral deflection of one or more fingers, fusion of the bones in fingers or toes, or webbing of the soft tissues between the digits.[35]

In this condition, overgrowth of muscle and abnormally large muscle group with asymmetric muscle development are found.[36] Some smooth Muscle shows hyperplasia.[37,38]

In Progeria caused by LMNA mutation, skeletal defects include severe osteolysis,[39] hypoplasia, dysplasia, and pathological fractures. It can cause severe alterations in osteogenesis, including craniofacial disproportion with a "plucked bird" appearance,[40,43] short dystrophic clavicles, and thin and high pitched voice that may also occur.[40,42,43] It also cause resorption of the clavicle,[41-43] microvascular inadequacy, matrix abnormalities, bony maldevelopment, abnormally broad metaphyses and epiphyses, avascular necrosis of the femoral head.[42] The patients also have an extremely aged appearance and the limbs are usually thin and may be associated with stiff joints, and coxa valga. They also demonstrate "horse riding" stance and wide based shuffling gait.[43] The ranges of motion for wrist, ankle, and hip rotation may decrease than normal.[41] There is chance of stooped shoulders, calcaneovalgus, genu valgum, kyphosis, or calcaneo varus.[41,43] The muscle strength is preserved.[41,44,45]

More specifically, MFS and Progeria both cause abnormal chest cavity where MFS can cause pectus excavatum or pectus carinatum,[25] and Progeria may cause pyriform thorax with tapering of ribs.[40-43] Osteopenia occurs in both of the cases which is axial or peripheral in MFS,[37] and generalized in progeria.[40-43] MFS also share pathological fracture and vascular smooth muscle cell defect with progeria.[28,31,40,44] On the other hand, Proteus syndrome and progeria both have dental abnormalities where Proteus syndrome may cause alveolar dental ridges,[35] and Progeria cause dental crowding with delayed teeth eruption.[41-43]

Some other regular features of musculo-skeletal system which are common in all these three mutations are discussed in the ***Table 1***.

Cardio-vascular system

The MFS, Proteus syndrome and Progeria commonly cause cardio-vascular system abnormalities.

In MFS, cardio-vascular systems, usually diagnosed in young age is associated with poor prognosis.[46] Cardiac arrhythmias, sudden cardiac death, endocarditis,[47-49] are also cardiovascular manifestations of the MFS. Mitral Valve Prolapse is indicated as a useful diagnostic tool.[47,50,51] The cardiovascular manifestations are the leading cause of death in MFS.[51] MFS can also cause dilatation of the main pulmonary artery (MPA), dysfunction of the myocardium due to microfibrillar defect,[51] abnormal reading on an electrocardiogram (ECG) but aortic wave reflection is not elevated in MFS.[51-52] Infantile MS presents high morbidity with mitral regurgitation and heart failure.[53] Clinical presentations of these manifestations comprise short breath, cardiac palpitations, abnormal heartbeats or angina pectoris with pain radiating to the back, shoulder, or arm.[52] Myocardial infarction and bacterial endocarditis are some cardiac causes of death.[54] In vascular system, there can be many types of defects in arterial wall including calcification. Rarely it shows axillary artery aneurysm.[55,56]

Proteus syndrome affects cardiac system less but sometimes it reports complex congenital heart disease and some myocardial abnormalities.[57-59] Multiple superficial, visceral and vascular abnormalities are present in Proteus syndrome.[60] Vascular malformations have also been reported in this case with variety of types. They grow proportionately with the patient: they never regress, but they can expand.[33] It can also cause cerebral vascular malformations,[61] vascular tumors, portwine stains (PWS), and venous anomalies (varicosities, prominent veins).[62]

Table 1. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Musculo-skeletal System.

Involvement of	Marfan syndrome [34,35,39]	Proteus syndrome [42-45,47]	Progeria [48-52,54]
Extremities	Long and slender limbs, finger, toes, wrists that grows disproportionally. Flat feet, Hammer toes.	Macrodactyly of hands & feet. Clinodactyly, Syndactyly, Polydactyly of fingers and toes.	Hypoplasia and pathology of arm, leg, finger, and toe. Narrow and thin shaft of femur and humerus. Resorption of terminal phalanges and dystrophic nails.
Spine	Abnormal curvature of spine (scoliosis), kyphoscoliosis and other abnormalities.	Vertebral dysplasia, asymmetry and enlargement.	Severe scoliosis and decreased spinal flexion.
Skull and facial	High palate, small jaw	Calvarial thickening, frontal bony prominence, macrocephaly, hyperostoses of the skull. Nasal bridge deformity, external auditory canal overgrowth.	Persistent open fontanelles, cranio-facial disproportion, short and sculptured nose, large bald head, small jaw.
Joint	Abnormal flexion, pain, early osteoarthritis.	Abnormal flexion	Avascular necrosis of joint bones, Hip dislocation.
Motion	Limited.	Limited.	Limited.
Muscle	Atrophy and hypoplasia.	Rarely. Atrophy may present in quadriceps femoris.	Sometimes atrophy.

In HGPS, the principal factor affecting mortality in individuals is cardiovascular disease. The description of the cardiovascular features of HGPS has proven to be quite consistent,[63] that include prominent atherosclerosis and calcification of coronary arteries and others. The coronary artery disease leads to ischemic changes in the myocardium, including well-defined infarcts. In addition, it may also cause narrowing of the small intramural arteries, which may contribute to myocardial fibrosis.[64] Chest x-rays shows cardiac enlargement and the electrocardiogram (ECG) shows right atrial hypertrophy sometimes.[65] Sonographic and ECG evidence of myocardial ischemia is not common initially, but after a few years, echocardiograms and carotid Doppler sonography may show hypertrophy of the intimal layer of the internal carotid artery. Atherosclerotic changes, tricuspid valves with increased echo texture, left and right atrial dilatation, calcific aortic stenosis, cardiomegaly, and hypercholesterolemia are also seen in progeria.[65,66] Death from cardiac complications at an average age of 14 years is usually preceded by angina pectoris and myocardial infarction,[66] caused by progressive atherosclerotic disease.[66] Children may die of myocardial infarction when they are found with diffuse loss of vascular smooth muscle and endothelial cells throughout their coronary arteries and replacement by fibrosis and adventitial thickening.[67] If an old man has typical HGPS, he shows refractory congestive heart failure due to arteriosclerotic heart disease and hypertension, and also has arteriosclerosis obliterans.[68] Sometimes loss of vascular smooth muscle cells (VSMCs) in the great vessels, veins, smaller arteries, and arterioles is seen in a case of progeria. There is spontaneous breaks in elastic structures,[63,67] and prominent adventitial fibrosis too.[69] Vascular atherosclerotic changes may cause subdural hemorrhage leading to death in some cases. Small collagen fibrils in the atherosclerotic intima and media with extensive loss of mural smooth muscle cells in the aorta are also reported.[70] Progeria can cause cerebral infarction and renal infarction.[62]

More specifically, MFS and Progeria both cause mitral valve calcification and increased echo texture.[51,63-65] MFS also cause mitral valve prolapse, regurgitation, fluttering of mitral leaflet,[47] and severe rheumatic mitral stenosis.[49] MFS and Proteus syndrome also share ventricular hypertrophy and dysfunction,[50,51,65] systolic and diastolic abnormality,[51,66] cardiac murmur, angina pectoris, congestive cardiac failure and myocardial infarction in common.[52,54,66] On the other hand, Proteus syndrome and Progeria both can cause thickening of myocardial septum,[59,65] cardiomyopathy, myocardial fibrosis and mass,[59,66] and abnormality in vascular endothelium.[33,63,67]

Some other regular features of cardio-vascular system which are common in all these three mutations are discussed in the ***Table 2***.

Eye

The MFS, Proteus syndrome and HGPS commonly affect eye.

In MFS, eye complications such as lens dislocation or ectopia lentis occur in more than half the people who have MFS, earlier in women,[73] and in some cases it is progressive (Mayo Clinic - MFS. Available from: http://www.mayoclinic.org/diseases-conditions/marfan-syndrome/basics/complications/con-20025944, updated 2014 April 07, cited 2014 April 18).[71,72] Glaucoma is also common at a younger age which can damage the optic nerve.[74,75] Sometimes MFS reports phthisis bulbi, bilateral or unilateral blindness.[74-76] The another ocular abnormality is enlargement of the globe, presumably caused by stretching of the tunica scleralis, and the zonular fibers.[71] Some studies suggest prevalence of retinal detachment and some suggest prevalence of ectopia lentis. This variation recommend other genotype–phenotype relationships exist which may account for differences in ocular manifestations of MFS.[73]

The ocular manifestations of a Proteus syndrome are due to severe maldevelopment and malfunction of the neuroretina. Epibulbar tumors are recorded most commonly,[76] while periorbital exostoses are infrequent,[77,81] extraocular tendons and posterior segment involvement can be seen in a case of Proteus syndrome presenting with vertical strabismus secondary to a fibrous tumor within the superior oblique tendon.[78,79] Sometimes myopia associates with mild calcific band, abnormal vitreous structure, vitreous hemorrhage, and a resolved serous retinal detachment in a patient of Proteus syndrome.[81] The oncogene of Proteus syndrome may show some overgrowth syndromes in eyes.[81] Sometimes epibulbar cystic lesions with nodular gliosis are also reported in this condition.[81]

In Progeria, loss of eye brows and eye lashes with prominent eyes is common in the early childhood.[43,83] Eyelid retractions, lagophthalmos, superior sulcus deformity, upper lid lag in down gaze, and poor pupillary dilatation are also reported. In the HGPS, eyes look prominent (pseudoproptosis) probably due to lid retraction, although there is no true proptosis. Superior sulcus deformity may also occur due to lipodystrophy of the orbital fat. Patients with HGPS do not develop other ocular features associated with aging, such as presbyopia, arcus senilis or age-related macular degeneration. Other rare ocular

Table 2. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Cardio-vascular System.

Traits	Marfan syndrome [56,60,64,65]	Proteus syndrome [66-68,71]	Progeria [72-75,77,79]
Aorta	Aortic aneurysm, regurgitation, Aortic rupture, stiffness, dissection. Dilation of ascending aorta	Aortic malformation	Atherosclerosis of aorta, dilated ascending aorta, thickening and calcification of aortic valve, loss of vascular smooth muscle cell in descending aorta.
Heart conduction	Arrhythmia	Thickening of myocardial septum may affect conduction.	ECG shows giant P waves
Contractile dysfunction	Present	Thickening of myocardial septum may affect contraction.	Present
Hyperplasia of arterial wall	Seen	Seen	Seen

manifestations of the HGP syndrome are bands of skin running from the upper lid to the cornea, senile ectropion, ptosis with Marcus-jaw-winking phenomenon, dry-eye syndrome, and iridocorneal adhesions.[83-85]

More specifically, MFS and Proteus syndrome both cause optic nerve damage,[74,75] and the former can also cause hypoplasia and papilledema of optic nerve.[79,82] Proteus syndrome and Progeria both have features of nystagmus or nystagmoid movements.[76,83]

Some other regular features of eye which are common in all these three mutations are discussed in the ***Table 3***.

Nervous system

The MFS, Proteus syndrome and Progeria commonly cause nervous system abnormalities.

In MFS, the most common and classic neurological manifestations are cerebrovascular.[86,87] Patients with MFSmay have a subarachnoid hemorrhage or intracranial aneurysm,[88] and near total erosion of a pedicle. Dural ectasia can be added to the list of pleiotropic manifestations of the MFS.[89] There is probability of heterogeneous involvement of other components of Extra Cellular Matrix microfibrils at the basis of this cerebrospinal manifestation.[90,91] Dural ectasia with bone erosion which are often reported in this condition can be associated with severe postural headache secondary to spontaneous intracranial hypotension resulting from cerebrospinal fluid leaks caused by underlying fibrillinopathy.[91-93] It is recognized as a potential complication in children with MFS,[93] and also reported with severe back pain in adults.[94,95] When neural symptoms or findings do occur they may be related to stretching and traction mechanisms.[91]

Proteus syndrome often presents hemimegalencephaly with high incidence of other brain anomalies.[96,97] These include hypoplasia of the corpus callosum and crus cerebri, grey and white matter calcification and cortical migration/organisational disorders.[96] Neurologic sequelae caused by vertebral anomalies are reported too.[98,99] Proteus syndrome has evidence to develop pinealoblastoma, Dandy-Walker malformation, corpus callosal abnormalities, periventricular calcification, hypodense periventricular white matter, and mental deficiency. Hemimegalencephaly is not a finding in this entity; reported abnormalities include hydrocephalus, porencephaly, cerebral calcifications, and polymicrogyria. Additional Central Nervous System (CNS) findings are thought to be the sequelae of vascular dysplasia, and include infarcts, atrophy, porencephaly, and calcifications.[100] Some neurological defects like hydrocephaly, lissencephaly, partial agenesis of the corpus callosum are also reported with the Proteus syndrome.[101] It may cause paraspinal hamartoma.[99] Protuberance of the skull,[102] structural and functional asymmetry of the central nervous system,[103] hydrocephalus and mental retardation are also some features of proteus syndrome.[102] Epilepsy and ohtahara syndrome is diagnosed in children affected by Proteus syndrome associated with infantile spasms, myoclonia, and partial epilepsy in newborn infants.[97]

In HGPS, diffuse encephalopathy, and Pseudotumor cerebri has been reported.[41] Even a mild head injury can cause intracranial pathology in a progeria patient. Progressive atherosclerosis of intracranial vessels is responsible for formation of the hematomas in this condition.[104,105] In progeria, motor and mental development is normal, as are intelligence.[106] But there may be a low-frequency conductive hearing loss.[107]

There is chance of Peripheral neuropathy,[108] cerebrovascular disease of aging in this age related disease, progeria.[109]

More specifically, MFS and Progeria both may cause headache,[91-93,104] and do not have any mental retardation.[105,106] MFS and Proteus syndrome both have spinal cord involvement where MFS may cause spinal Cerebro-spinal Fuild (CSF) leaks, spinal arachnoid diverticula, trauma, and congenital enlargement of spinal canal,[90,91,94] and Proteus syndrome may cause spinal stenosis, paraspinal tumor, and spinal cord compression.[98,99] On the other hand, seizures in seen in both Proteus syndrome and Progeria.[100,102,104]

Some other regular features of nervous system which are common in all these three mutations are discussed in the ***Table 4***.

Not shared systemic phenotypes

MFS often presents spontaneous recurrent or bilateral pneumothorax,[110] congenital malformations,[111] pneumonia, bronchiectasis, emphysematous bullae, upper lobe fibrosis, aspergilloma and other lung related disorders.[110-114] Patients may have lower values of Forced Vital Capacity and Total Lung Capacity and other spirometric values,[115] with a decrease in carbon monoxide transfer factor, and lung elastic recoil.[115] Other Lesser known areas of involvement are renal and dermatologic.[111,117]

Table 3. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Eye.

Traits	Marfan syndrome [81-86]	Proteus syndrome [87,88,90-92]	Progeria [94,96]
Opthalmic anthropometric measures	Increased axial length	Overgrowth syndromes can cause length or distance abnormality	Reduced horizontal palpebral fissure length, inter pupillary distance, inner canthal distance and outer canthal distance.
Refractive errors	Myopia and astigmatism	High myopia	Myopia or hyperopia
Cornea	Unilateral corneal opacities, flat cornea	Keratopathy	Corneal dryness, opacities, clouding and keratopathy.
Retina	Detachment or tear in the retina	Abnormal retinal pigment, dysgenesia. Diffuse retinal disorganization and chorioretinal mass	Retinal arteriolar narrowing, tortuosity, Retinal angiosclerosis and retinopathies.
Cataract	Seen	Seen	Seen
Strabismus	Present	Present	Present

In proteus syndrome, Patients most commonly show bilateral ovarian serous cystadenomas, mesothelioma, and papillary carcinoma of the thyroid.[118] Connective tissue nevus and brownish epidermal nevus in various region,[33,119] benign and malignant tumors and hamartomas are also seen in proteus syndrome. Commonly encountered tumors include hemangiomas, lymphangiomas, lipomas, epithelial tumor of the female genital tract, testicular and paratesticular tumors.[119] Four types of abnormal fat may occur in Proteus syndrome: lipomas, lipohypoplasia, fatty overgrowth, and partial lipohyperplasia. There may be Fatty matter infiltration, Subependymal nodules, and Parenchymal distortion. Other rare tumors include Meningioma, Parotid monomorphic adenoma, Astrocytoma, Optic nerve tumor, Pinealoma, Breast intraductal papilloma, Leiomyoma, Endometrial carcinoma, and giant kidney cysts. Multiple tumors in the same patient are often seen in proteus syndrome,[33] with distal renal tubular acidosis and nephrocalcinosis, dilated and tortuous renal veins with possible calcifications.[120]

Progeria can cause low weight, vertical midline groove in the chin, sclerodermatous skin, reduced subcutaneous fat,[121] prominent superficial veins, dyspigmentation, and alopecia of skin.[122]

A progeria case may present some biochemical abnormalities like hypoaminoacidemia, hyperaminoaciduria, increased radioactive Iodine uptake in thyroid, and other abnormalities in blood.[123]

Progeria patients may be seen to sleep with open eyes, labial weakness, and nasal speech affecting speech fluency.[43] Localized glomerulosclerosis, tubular atrophy, mesengial matrix growth, papillary adenoma are shown in older cases.[124]

Vision of future research

The genes responsible for the three diseases are not known to interact, so the possibility of mutation in any of them affecting functions of the other two is quite unlikely. However, recent studies suggest that mutations in the penultimate exon of FBN1 (in the 3' terminus) give rise to a neomorphic phenotype leading to a condition known as Wiedemann-Rautenstrauch syndrome,[125] a rare disorder characterized by overlapping of the clinical manifestations of both marfan's syndrome and progeroid syndrome. It has been suggested that, this rare subgroup of MFS, comprised of congenital lipodystrophy, a neonatal progeroid appearance,[126] and a progressive clinical course with early lethality, should be referred to as marfanoid-progeroid syndrome.[127] Evidence of involvement of any mutation in the LMNA gene, the one associated classical progeria has not been unveiled till now.[125] Any association of mutation in the AKT1 gene with the aforementioned circumstances is yet to be explored.

Conclusion

Genetic mutation is day by day increasing entries in the disease directory and started threatening the mankind like never before. MFS, Proteus syndrome, and Progeria are one of the most recognized mutation related diseases caused by mutation of FBN1, AKT1, and LMNA genes correspondingly. If we go through the Clinical features and systemic involvements of these mutations, we can find common involvement of musculo-skeletal system, cardiovascular system, eye, and nervous system. In musculo-skeletal system, deviations of spinal curvature, abnormalities in the extremities, skull, and facial bones are reported in all the three mutations. All cause abnormal flexion and limited range of motion of joints. In cardiovascular system, all the three mutations have reported abnormality of the aorta and cardiac conductive system. Contractile dysfunction of heart and hyperplasia of arterial wall have been seen in common too. In case of eye, MFS, Proteus syndrome, and progeria share many clinical features. All cause cataract, strabismus, and refractive errors along with same kind of retinal and corneal abnormalities. These mutations also have described some common nervous system features where all cause meningeal abnormalities, neurovascular abnormalities, congenital and developmental abnormalities. Stroke has been seen in all the three cases too. Though the mentioned mutations have certain individual unique characteristics too, the outcomes indicate that there can be some relation among the proteins related to these mutations, or among the genes of which modification occurs. The results of this review will enrich the field of genetic research and medicine. Furthermore, this study can help to acknowledge the reported sign & symptoms of three diseases and inter-relation among them. Additionally, it is recommended to have more attention in this field.

Table 4. Common Features Found in Marfan Syndrome, Proteus Syndrome, and Progeria Involving Nervous System.

Traits	Marfan syndrome [97,98,100,102-107]	Proteus syndrome [111-113]	Progeria [50,116,118]
Neurovascular	Cerebral artery aneurysm, dissection, hemorrhage and ischemia.	Vascular dysplasia, infarction and hemorrhage	Transient ischemia, stenosis of cerebral, vertebral and basilar arteries, arteriosclerosis, atherosclerosis, Epidural hematoma
Stroke	Seen	Seen	Seen
Meninges	Dural ectasia, hernia of meninges or meningocele	Meningioma	Meningeal hematoma.
Congenital CNS abnormality	Present	Present	Present
Developmental CNS abnormality	Present	Present	Present

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