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A study of skeletal dysplasia in a selected cohort of Sri Lankan Patients

BY

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CERTIFICATION

I certify that the contents of this dissertation are my own work and that I have acknowledged the sources where relevant.

……

Signature of the candidate

This is to certify that the contents of this dissertation were supervised by the following supervisors:

…….

NAME OF SUPERVISOR

……. ……..

Dr Dulika Sumathipala

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ABSTRACT

BACK GROUND

Skeletal dysplasia is a large group of disorders with diverse manifestation and multiple aetiology. These disorders can be associated with variety of other systemic complications. There are many classifications according to the clinical, biochemical and radiological characteristics. The International classification and Nosology of genetic skeletal dysplasia 2010 revised version used to analyze the patients in this study. There were 456 disorders in 40 different groups.(1) Prevalence of skeletal dysplasia 1:5000 live births.(2)

In this study patients were assessed by clinically and radiologically to give an overview of skeletal dysplasia present in Sri Lanka.

METHODOLOGY

The patients were recruited from the Human Genetics Unit, Faculty of Medicine, University of Colombo, the National hospital of Sri Lanka (NHSL) and Lady Ridgway Hospital (LRH) in Colombo. Detailed medical history of each participant was obtained including family history up to three generations. The demographic parameters and consanguinity were also studied. The clinical characteristics were analyzed according to the classification given in the international Guild lines and classifications. Radiological assessment done by a experienced Consultant Radiologist.

RESULTS

There were total number of 42 patients with 17(40.5%) male patients and 25 female patients. According to the clinical and radiological criteria 9 patients (with Osteogenesis Imperfecta, short stature 17 patients, craniosynostosis 5 patients and 11 patient with the other types of skeletal dysplasia. Out of the seventeen patients with short stature 6 in the Achondroplasia group. Dysmorphic facial features seen in 35 patients, sixteen with thorasic anomalies, nine with fractures in long bones, developmental dysplasia of hip in 15 patients were observed. Eighteen patients were with cardiac malformations other than skeletal deformities. Two patients had hearing impairment and one presented with blindness. Ten patients were totally dependent and disabled , in that 6 patients with Osteogenesis Imperfecta.

Six patients were born to consanguineous parents (14.3%) and eight patients (19%) had affected family members. Twenty two patients (52.5%) from western province, including 12 from Colombo district and 10 from Gampaha district.

CONCLUSION

The Skeletal Dysplasia, although individually rare is an important group of disorders in clinical practice. The statistics showed the incidence keep increasing yearly. In this study sample patients presented with significant morbidities due to defects in bone formation, mineralization and linear growth. Skeletal Dysplasia in general can be grouped in many ways depending on clinical and radiological findings even when there is no specific diagnosis. This is the basic clinical approach we practiced to asses our sample. In a limited time at selected centers we observed diverse

groups of skeletal deformities. This indicates a need of a large scale assessment in the near future.

This is an era of micro and nano technology. The micro array should be the gold standard of the diagnosis. We would like to emphasize that the clinical and radiological assessment should go together with the molecular diagnosis to enhance the clinical practice. The advanced molecular diagnostics should be available within the reach of every clinician in the Globe. It will open a new chapter in genetic counseling, prenatal and preimplantaion genetic diagnostics and molecular pathway targeted therapeutics in the near future.

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1: INTRODUCTION

This dissertation gives a overview of clinical and radiological characteristics in a cohort of patients with skeletal dysplasia, presented to three tertiary care institutions during a period of 6 months. In the first chapter background, clinical characterization and aetiology of skeletal dysplasia were discussed. The first section described the overview of the disease with prevalence and pattern of inheritance. Second section gives a brief description of skeletal biology. The detailed account of skeletogenesis and skeletal dysplasia in the 3rd section. The 4th section described the molecular mechanism of skeletal patterning under three headings.

Second chapter described the national burden of skeletal dysplasia. In the 3rd chapter section one clinical characterization and involvement of skeletal components described in using medical terminology. Introduction of basic terminology with simple diagrams in section two of this chapter. In the 3rd section of this chapter described the common skeletal dysplasia according to the number of patients recruited under 4 major sub topics.

1.1: BACKGROUND

Skeletal dysplasia is a heterogeneous group of connective tissue disorders of developmental defects of the skeletal elements which start in utero at very early stage of life. This leads to formation of abnormal shape, size and density of bone and cartilage causing disability and disfiguring of variable extent.(3) Some may be lethal in utero. The estimated incidence of skeletal dysplasia is 2 to 5 per 10000 live births.(4) The disease may be present as an isolated case or an inherited manner. Autosomal dominant and autosomal recessive modes of inheritance are common. The manifestation of skeletal dysplasia is structural deformities of bone or fractures of the skull, chest, spine, pelvis, upper limb, lower limb, hand and feet.(5) Classification of skeletal dysplasia started 30 years ago and it has been modified several times since then according to their clinical, radiological, pathological and genetic aetiology. Based on

the criteria mentioned 456 different conditions were listed in 40 groups.(6) The international Nosology and classification of constitutional disorders of bone had its last revised version in 2010. Proper understanding of the development of skeleton in related to signaling genetic pathways is helpful in diagnosing skeletal dysplasia.

1.1.1: SKELETAL BIOLOGY

The human skeleton develops from three embryonic cell lineages. They consist of bone and cartilage tissues, constructed by chondrocytes and osteoblasts. In addition osteoclasts will contribute to their development after birth. The skeleton consists of 206 bones: 126 appendicular, 74 axial, and 6 ossicles. The functions of the skeleton are mechanical support of movement, protection of vital organs and a reservoir of blood and minerals. The skeleton has series of molecular mechanisms which determine the extent of longitudinal growth, the spatial restriction of extracellular matrix mineralization to bone, and the maintenance of a constant bone mass. These mechanisms determine the final location and the shape of the bone.(7)

1.1.2: SKELETOGENESIS AND SKELETAL DYSPLASIA

The patterning architecture of the skeleton during the development of the fetus determine the number, size and the shape of the future skeletal element.(2)The skeleton is derived from three embryonic cell lineages and migrates and proliferate to sites where skeletal elements will develop. The location of the initial skeletal formation will determine the particular

mesenchymal cell layer to develop the future bone and the cartilage. The lateral plate mesodermal cells develop the limb skeleton. Cranial neural crest cells migrate from the branchial arches to form the craniofacial skeleton. The axial skeleton is derived from paraxial mesoderm (somites).The skeletal morphogenesis can be divided into two major phases. The initial phase is the skeletal patterning which is controlled by major signaling pathways such as Wnts, Hedgehog, Bmps, Fgfs, and Notch/Delta. The second phase is cell fate determination, proliferation, deferentiation and maturation. A common progenitor cell (osteochondral progenitor) within the mesenchymal condensation will give rise to precursors of both the cartilage (chondrocytes) and bone(osteoblasts) .There are three types of chondrocytes cells in the growth plate : reserve or resting, proliferative and hypertrophic. (2) These chondrocytes undergo a program of proliferation, hypertrophy and degradation. Finally it is replaced by bone. By this mechanism the bones increase the length and the diameter. The osteoblasts directly forms the flat bones of the cranial vault and part of the clavicle and pubis by intramembraneous ossification.(2) The last phase of skeletogenesis is vascular invasion. In some regions of the craniofacial skeleton and the clavicle intramembraneous ossification will occur.(the mesenchymal cell condensations directly transformed the bone forming osteoblasts) The majority of the skeleton undergoes endochondral ossification The chondrocytes differentiation leads to form a framework of cartilage models(anlagen) and after vascularisation replaced by bone and bone marrow of future limbs. The skeletal growth and remodeling provide the functions of movement, the internal organ protection, haematopoeisis and also as an integral part of the endocrine system.

The pre and post patterning is controlled by the genes. Pattern formation and organogenesis were shared with signaling pathways and transcription factors. The cell fate determination, proliferation and maturation is controlled by various other mechanisms. The malfunctions of these developmental pathways give rise to disturbances in the patterning, growth and maintaining of skeletal components and its functions and give rise to various type of skeletal dysplasias , dysostosis and arthropathies. Mutation of early patterning genes that regulate the skeletogenesis cause dysostosis. These are cell to cell signaling molecules and transcription factors regulating cell migration, proliferation and fate determination . The disturbed function of the gene affect only the relevant skeletal element and the rest of the bone may not be affected. The abrogated morphogenesis can affect in all three major divisions of the skeleton : craniofacial, axial and appendicular . Dysostosis occur as a result of abnormalities of blastogenesis in first six weeks of embryonic life. This gives rise to defective bone formation and the defect is static throughout life(8). The genes and pathways active during skeletogenesis may involved in other developmental pathways as well. So when the gene is mutated in addition to the skeletal deformity, non skeletal anomalies can also be seen. The study of this phenomenon is known as pleiotropy. The mutations in the genes responsible for organogenesis can give rise to abnormalities in the skeletal element in a generalized way. This group of disorders can categorized as osteochondrodysplasias. In this group of disorders abnormalities are intrinsic to bone and cartilage . The phenotypic features of this group continue to evolve throughout life as a result of gene expression . So initially normal unaffected bone and joints may develop abnormalities later in life. Multiple bones from the axial and appendicular skeleton and bones which is formed by membranes and endochondral ossifications usually involved. (8) Under the groups of osteochondrodysplasias and

dysostosis there are more than 350 disorders of the skeleton identified. (9)The extra cellular matrix protein molecules also play a role in bone formation. Those proteins are formed by chondrocytes. The most prominent extra cellular matrix proteins are the collagens which associated as chains and form a triple helix structure. The helical structure undergoes post translational modifications before it become a extracellular matrix, and form a fibril by combining multiple triple helical chains. The collagen helixs may be composed of identical chains (homotrimeric) as in type II collagen. In collagen types I, IX, and XI , the collagen helixs formed with different collagen chains (heterotrimeric) (2). Collagens are expressed in a tissue specific manner and further classified by the structure they formed in the extracellular matrix. The most common varieties of collagens are the fibrillar types I, II, III, V and XI. The extensive cross-linking of collagens provide the mechanical strength in cartilage, bone and skin. The collagens with interrupted triple helixs : collagen types IX, XII, XIV and XVI, interact with fibrillar collagens and other extra cellular molecules : aggrecan, cartilage oligomeric matrix protein[COMP], decorin, fibulin and numerous other sulfated proteoglycans. There are non fibrillar short chain collagens : type VIII and X , and type X .Type X collagen expressed by hypertrophic chondrocytes during endochondral ossification and it is the most abundant type out of the two. The mutations of the genes encode these collagens leads to formation of various types of skeletal dysplasias.

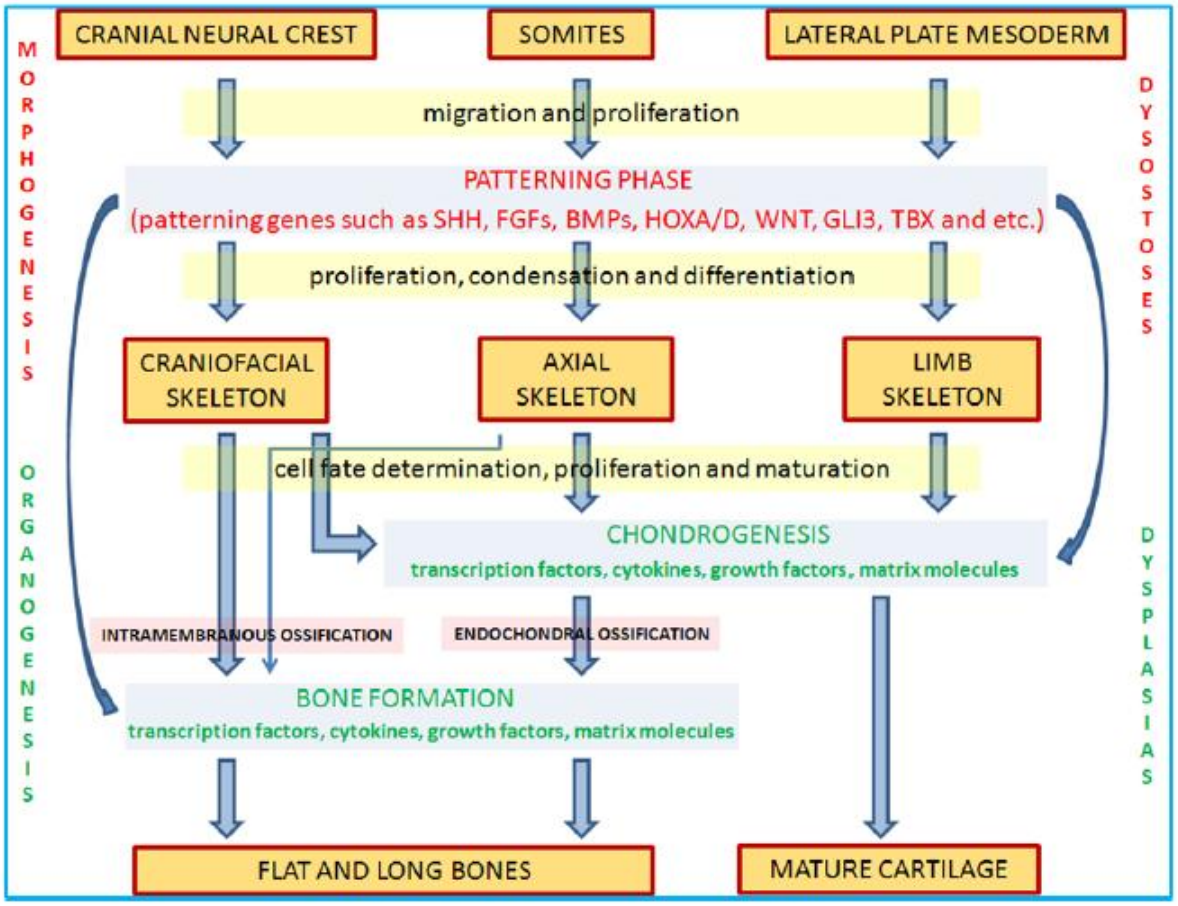


Figure1. Developmental processes involved in skeletal patterning and bone formation

(7)

1.1.3: MOLECULAR MECHANISM OF SKELETAL PATTERNING

1.1.3. a: Craniofacial Skeletal Patterning

Craniofacial skeletal patterning is mainly associated with neural crest cells from the branchial arches. This is under the tight control of signals between the cells of the neural crest and epithelial cells of the surface ectoderm, neural ectoderm or the endoderm.(7) The FGF signals from the ventral forebrain and pharyngeal endoderm pattern the pharyngeal skeleton. Then the surface ectoderm FGFs and BMPs do the frontonasal skeletal patterning.

1.1.3.b: Axial Skeletal Patterning

The segmentation of the paraxial presomatic mesoderm (PSM) and formation of epithelial blocks of segmented mesoderm (somites) on both sides of the neural tube and the underline notochord gives rise to axial skeletal patterning. Definitive patterning is occurs after the process of re-segmentation and anterior posterior fusion of two consecutive somite compartment. The formation of morphological boundaries separates the epithelial somites from PSM.

After the patterning, somites form the ventral sclerotome and dorsal Dermomyotome. These are the precursors of future vertebra, ribs, sternum and skeletal muscles. The sclerotome formation is determined by the *Shh*, produced in the notochord and the floor plate of the neural tube. These sclerotome cells express *Paxl.* The *Shh* inhibited by *Wnt* pathway signals coming from dorsal neural tube. Then the inhibition of sclerotome formation in the dorsal part of the PSM induces the formation of dermomyotome. Dermomyotome expresses the *Pax3.* This segmentation process is triggers the cyclical expression of genes in the Notch,Wnt and Fgf signaling pathways. All these processes are due to the expression of *Mesp2*.

The notch signaling pathway has an impact on skeletal development and skeletal dysplasias. This pathway consists of 5 ligands (Delta ligand 1, 3, 4, Jagged 1, 2) and four Notch receptors (Notch 1-4). The Notch receptor is cleaved after it binds to the ligand. The cleavation is done initially by tumor necrosis factor alpha conversion enzyme (TACE) and then by gamma secretase complex consist of Presenalin 1 and 2.The Notch intracellular domain (NICD) translocate to the nucleus and binds to the transcription factor recombination signal binding protein for immunoglobulin kappa J (RBPJK / CBF1/ RBPSUH or SUH). Then this complex

becomes a activation complex. The ultimate result is activation of expression of downstream target genes such as basis helix- loop- helix transcriptional repressors related to ing from Hairy enhancer of split (Hes 1, 5, 7) or to Hes – related with YRPW motif (Hey 1, 2 and L) to affect many cellular processes including cell proliferation and differentiation.(10) The downstream genes in the *Wnt*/beta- catenin canonical signaling pathway (*Wnt3a, Axin2, Nkd1 and Ripply 2*) having an interactions with Notch components. Finally the *Fgf8/ Wnt3a* and *RA/Raldh2* create the expression gradient and define the segmentation of paraxial presomitic mesoderm cells.(7) Mutations in the genes involved in the segmentation can cause abnormalities in the skeletal patterning. There are five major genes associated with congenital vertebral malformations in the man.*JAGGED1* and *NOTCH2* genes will cause Alagille syndrome and *DLL3, MESP2* and *LFNG* is associated with SCD. The genes that causing syndromes with multiple congenital defect, having involvements with defects in the vertebra :*CHD7* (CHARGE syndrome), *HOXD 13*(VATER/VACTERL syndrome), *SOX9* (Camphomelic dysplasia), *ACVR1*(Fibrodysplasia), *ROR2* (Robinow syndrome).(7)

1.1.3.c: Limb Patterning

The developing limb has three main zones : the proximal stylopod (it become humerus and femur), the middle zeugopod (which will develop as radius and ulna or tibia and fibula), the autopod (develop as carpal /tarsal / metacarpal / metatarsal bones and fingers and toes)(11). The limb patterning process of man is controlled by genetic signals in three main axes during embryonic development (7). The proximal – distal (PD) Starting from shoulders to the digit tips, anterior – posterior (AP) from the 1^{st} to the 5^{th} digits, dorsal – ventral (DV)from the back of the hand / feet to the palm / soles.(7) It also promote the differentiation of specific forelimb and hind limb structures. In embryonic life upper limb buds appear on the 26^{th} day and the lower limb

buds on the 28th day. The limb bud arising from the mesenchymal cells of the lateral mesodermal plate consisting of a mesenchymal core surrounded by ectoderm.The limb bud has three important centers: thickening of the distal boarder of the ectoderm form the apical ectodermal ridge (AER) the zone of polarizing activity (ZPA) and the non AER ectoderm .(7) The AER promote the rapid undifferentiated growth of its mesenchyme by its signaling pathways. The progress zone lies beneath the AER. The influence of the AER extend up to the adjacent cells of the progress zone and the proximal mesenchymal cells. The AER then start to differentiate into muscle and cartilage. The circumferential constriction of the limb bud become wrist and proximal constriction lead to form elbow. Then the joint inter zone and joint cavity formed. The apoptosis of AER create the fingers and toes. The *HOX* gene expressed in the intermediate mesoderm responsible for the position of the limb bud. The *HOX* genes are 39 in number and clusters in 4 separate groups. They consist of transcription factors important for body patterning.

The *HOX*A cluster is located in chromosome number 7, chromosome number 17 contained the *HOX*B cluster, *HOX*C cluster is on chromosome number 12 and *HOX*D cluster is on chromosome number 2.The *HOX* gene contain a Homeobox region of 180bp and encode the homeodomian and can bind DNA. The cascading genetic pathways are switching on by the protein transcription factors in the Homeobox genes. These homeodomian proteins act together with other transcription factors in the promoter region of downstream genes. Those promoter regions only activated if the correct combination of transcription factor present. This process is controlling the patterning of developing limb.(11)

Fgfs and Wnt ligands can cause ectopic limb development.Fgf10 mesenchymal expression can be induced by Wnt. Then Fgf10 with support of Bmp4 initiate Fgf8 expression and create a growth promoting mesenchymal ectodermal feedback loop between Fgf8 and the mesenchymal

Fgf10.(7) The major function of AER is to promote the proximal – distal outgrowth and patterning. The PD patterning is mediated by five Fgfs: Fgf8, Fgf4, Fgf2, Fgf9 and Fgf17.After the AER specification Fgf8 expression is distributed from anterior to posterior. The Fgf4, Fgf9 and Fgf17 activated in the posterior AER and during the progression of limb development expand to the anterior direction. The AER –Fgfs are essential for limb development. They also induce the distal cell identity by activating of *Hoxa* 11and *Hoxa*13. The presence of Fgf defendant distal fate specification of cells could create the zeugopod and autopod.

1.1.4: SKELETAL DYSPLASIA DISEASE BURDEN IN SRI LANKA

According to the statistics department, Ministry of Health publication in 2008 the morbidity of musculoskeletal and connective tissue diseases increased by number in each year.

Figure 2 : Causes of hospitalization in the year 2007

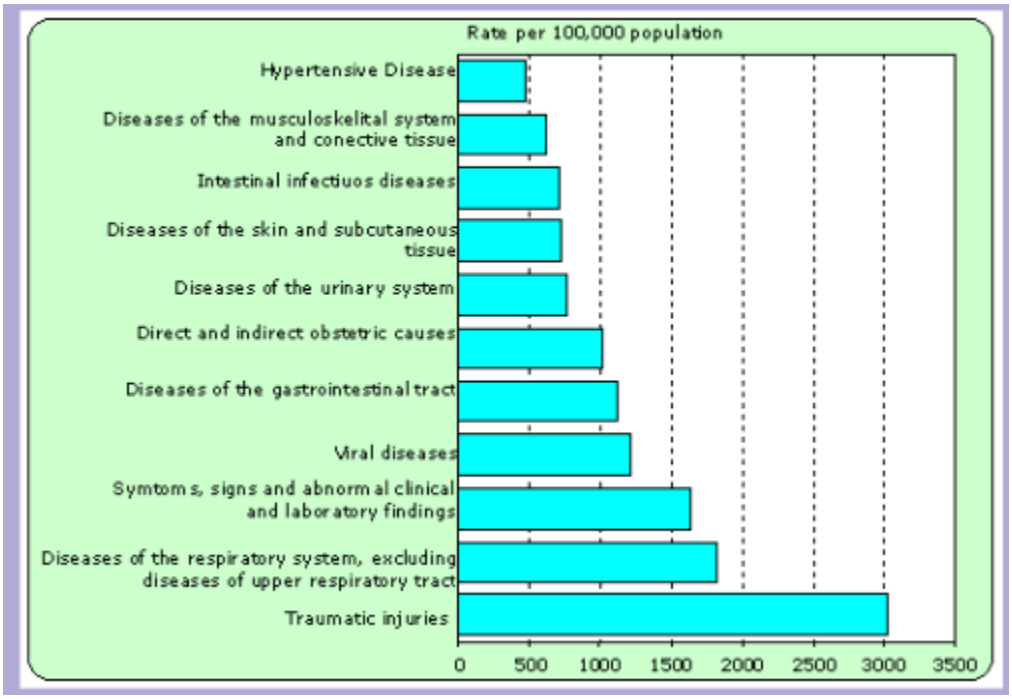


Table-1:Morbidity of musculoskeletal and connective tissue diseases from year 2005 to 2007(12)

Diseases of musculoskeletal and connective tissue	**2005**	**2006**	**2007**
Rate per 100,000 population	585.2	605.3	614.4
Percentage	3.4%	3.3%	3.3%

Even though the percentage of morbidity is not much changed, number of patients of musculoskeletal disorders was rising each year.

Table-2: Total hospital admissions due to musculoskeletal disorders

Year	**Musculoskeletal and connective tissue disorders**		**Congenital malformation and deformation**	
	Admissions	Deaths	Admissions	Deaths
2005	114976	115	11286	467
2006	120267	112	11905	538
2007	122905	31	12215	568

In this table total number of admissions with regards to musculoskeletal and connective tissue disorders and congenital malformation and deformation represent the category of skeletal dysplasia group. This showed rising of number of admissions each year. The total population of deformed patient not analyzed in this publication.

1.1.5: CLINICAL CHARACTERISTICS OF SKELETAL DYSPLASIA

The presenting feature of skeletal dysplasia may be,

i. Fracture
ii. Abnormalities in the skull
iii. Reduce limb length
iv. Disproportion of the limb
    a. Rhyzomelic -Proximal
    b. Mesomelic – middle
    c. Acromelic – distal
v. Deformities- Angulation and bowing
vi. Short stature with disproportion of the body (with large head or small thorax with short ribs)

The terminology of Skeletal Dysplasia established according to the predominantly affected part of the bone.

i. Epiphysis

Secondary ossification center located at each end of the long bones. (metacarpals and metatarsals only contain one epiphysis) Abnormalities lead to Spondyloepiphyseal dysplasia.

ii. Metaphysis

The growing area of bone close to epiphysis. If this area is affected it lead to form short stature.

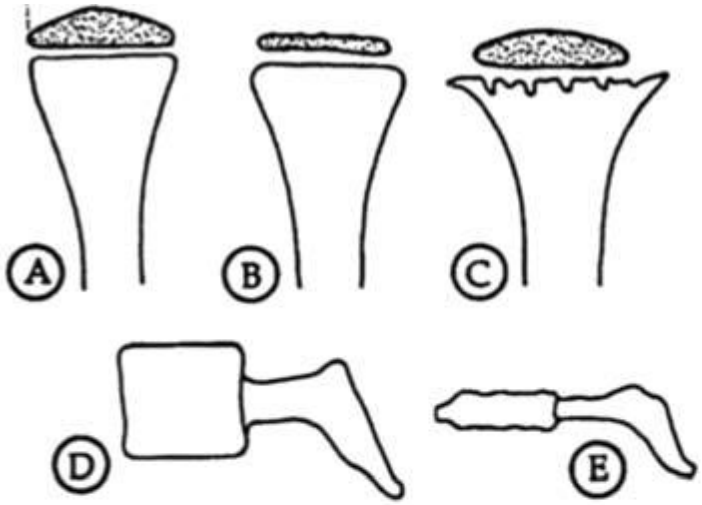
iii. Diaphysis

The shaft of the bone, it covered with the periosteum. Anomalies in this are lead to bone deformities and fractures E.g. .Osteogenesis imperfecta.

iv. Spondylo

Spinal column and vertebras belonged to this category and abnormalities lead to scoliosis and kyphosis.

Figure- 3 : Terminology of bone defects. .



Involvement	Disease Category
A+D	Normal
B+D	Epiphyseal dysplasia
C+D	Metaphyseal dysplasia
B+E	Spondyloepiphyseal dysplasia
C+E	Spondylometaphyseal dysplasia
B+C+E	Spondyloepimetaphyseal dysplasia

(13)

1.1.6: THE CLASSIFICATION AND NOMENCLATURE OF SKELETAL DYSPLASIA

The classification was based on the International Nosology and classification of genetic skeletal dysplasia 2010 revised version.(14)In this classification 456 conditions were included under 40 sub groups. This was based on the radiological, biochemical and molecular criteria. Among these conditions 316 disorders identified as associated with the mutations in one or more of 226 of known genes.

The key clinical features were taken from the OMIM and Gene Review and used as the deferentiation tools. All these clinical presentations, radiological features and the biochemical data used to get the final diagnosis and categorized according to the international classification.

Few known pathological terms used to describe the structural abnormalities.

1. Anomaly – Deviated appearance from normal structure
2. Amelia – Absent limbs
3. Clinodactyly – Involvement of fingers usually describe about the fifth finger
4. Dysplasia – Abnormality in formation
5. Dystrophy – Structural abnormality due to nutritional or metabolic cause.
6. Malformation – Primary structural defect due to failure of the normal development
7. Mesomelia – Shortening of fore arm/ shin
8. Polydactyly – Increased number of digits (pre axial / para axial)
9. Rhizomelia – Short proximal segment of the long bone (femur /humerous)
10. Syndactyly – Fused digits (by bone or soft tissue)
11. Syndrome – Multiple abnormality
12. Synostosis – Abnormal union of bone

Some clinical features were unique to the certain group of disorders. Therefore can be used as diagnostic indicators in certain instances.

1. Hemi atrophy of brain and mental retardation in craniosynostosis syndromes
2. Blindness or poor vision in osteopetrosis
3. Dyspropotionate large head in Achondroplasia
4. Clover leaf skull in Apert syndrome and Crouzon syndrome.
5. Radial ray defect in holt oram syndrome
6. Preaxial polydactyly in Noonans syndrome
7. Recurrent long bone fractures ,Wormian bones and blue sclera in Osteogenesis Imperfecta

1.1.7: THE GENETIC AETIOLOGY OF SKELETAL DYSPLASIA .

In this study individual testing was not performed as cost of the genetic tests were unaffordable. Known aetiology of each dysplasia was discussed below to gather the information of genetic aetiology of each group of disorders.

i. Chondrodysplasia group – Achondroplasia and Hypochondroplasia

This is due to mutation in the (*FGFR3*) Fibroblast growth factor receptor 3 gene

ii. Type II collagen group – Spondylometaphyseal dysplasia

Mutation of *COL2A1* gene.

iii. Filamin group – Larsen syndrome / Otopalatodigital syndrome - *FLNB* gene

iv. Short rib dysplasia group – Noonans syndrome

Mutations of one or more than one genes from *DYNC2H1, FFT* 80and *NEK1* results the Noonans syndrome

v. Increased bone density group – Osteopetrosis

Mutation of the *TC1RG1, CLCN7, OSTM1, RNAKL, RNAK, LRP5* genes manifests the osteopetrosis sub types.

vi. Osteogenesis Imperfecta and decreased bone density group – Osteogenesis Imperfecta sub types discussed in this group. Mutation of *COL1A1* and *COL1A2* genes known to cause these conditions

vii. Lysosomal storage disease with skeletal involvement (dysostosis multiplex). Mucopolysaccaroidosis sub types were discussed in this group. Mutations of one of the genes cause the disease: *IDA, IDS, HSS, NAGLU, GNS, GLB1*.

viii. Over growth syndromes with the skeletal involvements - Marfan syndrome caused by the mutation of *FBN1* or *FBN2* genes.

ix. Craniosynostosis syndromes discussed under this group. Mutation of *FGFR2* causes Apert syndrome, Craniosynostosis type II and Crouzon syndrome. The Saethre-Chotzen syndrome caused by the mutation of *TWIST1* gene.

x. Limb hypoplasia and reduction defects group. Holt- oram syndrome, Radial ray syndrome, Split hand foot malformation with long bone deficiency and femoral facial syndrome discussed under this category of disorders. Mutation of *TBX3, FBXW4* and *P63* known to cause these disorders.

xi. Polydactyly, Syndactyly triphalangism group. These disorders due to the mutation of *GLB, SHH, FGFR2, FBLN1, FGF10* genes. Isolated Syndactyly, polydactyly and split hand obstructive uropathy with spina bifida discussed under this group.

1.1.8: COMMON TYPES OF SKELETAL DYSPLASIA IN THIS STUDY GROUP

Categorization of the patients sample in to sub groups were done according to the international Nosology and Classification of Genetic skeletal dysplasia 2010 revised version.

Four sub groups were made depending on the total number of patients in each group.

i. Osteogenesis imperfecta

ii. Short stature

iii. Craniosynostosis

iv. Other types of skeletal dysplasias

1.1.8. i:Osteogenesis Imperfecta

Osteogenesis Imperfecta is a heritable condition of connective tissue. OI Categorized in to several sub types according to the aetiology clinical characteristics biochemical parameters and radiological assessments. Two classifications used in this study Sillence classification described OI type I-IV and additional classification for type V – XV.

OI is generally caused by a dominant mutation in the *COL1A1* or the *COL1A2* genes that encode type I collagen. (less collagen than normal and poorer quality than normal.) Less than 10 % of OI may be caused by recessive mutations in other genes in the collagen pathway. Mutations in the genes for prolyl 3-hydroxylase (*LEPRE1*) and for cartilage-associated protein (CRTAP) have been identified. OI Types V and VI do not have evidence of mutations in the type I collagen genes. OI is associated with fragile bones and it affects both bone quality and bone mass And also height, hearing, skin, blood vessels, muscles, tendons, and teeth may also be affected. OI is highly variable, ranging from a mild form with no deformity, normal stature to a perinataly lethal form.

A clinical criterion of diagnosis was based on clinical features given in the Gene Review and OMIM. Radiological criteria were obtained from RADIOPEDIA.org. Many different genes were identified in sub types of Osteogenesis Imperfecta. Genetic involvement of each type also summarized (table 4)

Table -3 : Radiological Classification of Osteogenesis Imperfecta (According to the classification given in the Radiopedia.org)

O I types	**Radiological features**
Type I	General bone fragility and increase the risk of fracture Normal stature or near normal stature,Loose joints, Minimal or absent bone deformity, Dentinogenesis Imperfecta
Type II	Many fractures and severe bone deformity
Type III	At birth - short and bowed limbs, small chest and soft calvarium, intra uterine fractures, healed fractures at birth, short stature, rotoscoliosis and vertebral compression fractures, popcorn appearance in metaphyses and ephiphyses, Dentinogenesis imperfecta and triangular face.
Type IV	Most fractures occur before puberty, short stature, mild to moderate bone deformity, triangular face and Dentinogenesis imperfecta
Type V	Hypertrophic calluses at fracture or surgical sites, calcification of the interosseus membrane between the radius and ulnar restrict the fore arm movements and may leads to dislocation of radial head.
Type VI	Bone mineralization defects
Type VII	Small skull with similar features of OI type IV

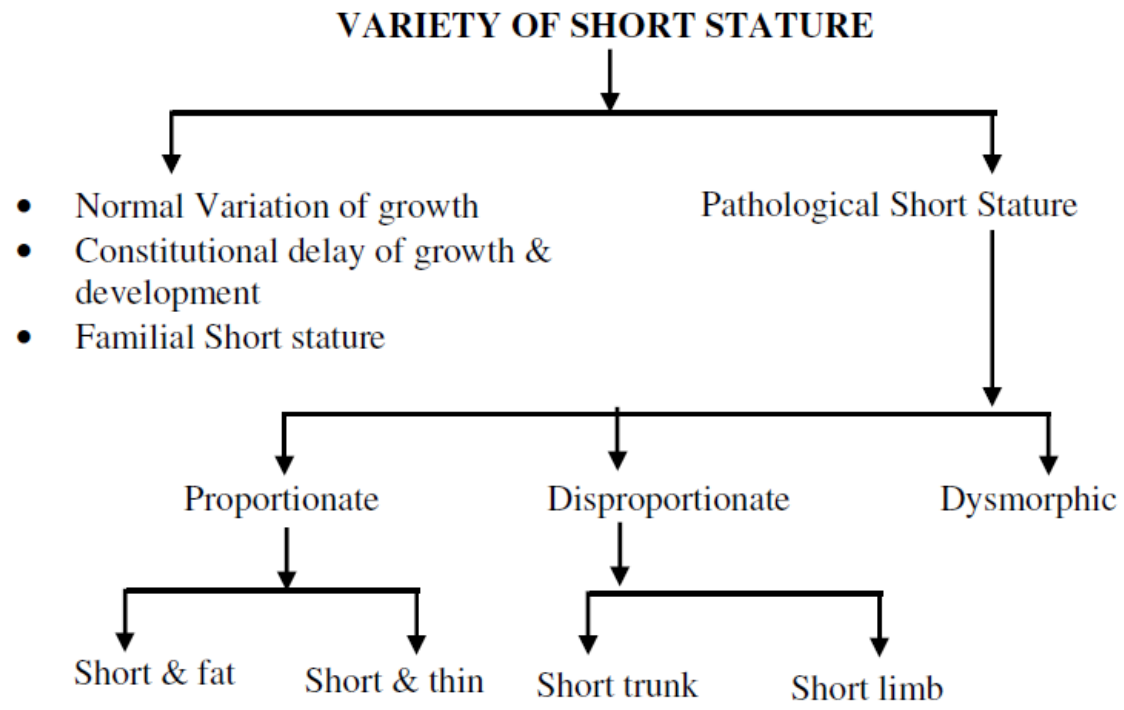
Table – 4 : Genetic classification of Osteogenesis Imperfecta (OMIM)

O I type	**Genes mutation**	**Location of the gene**	**Mode of inheritance**
Type I	Collagen 1, alpha -1 Polypeptide gene *COLIA*1	17q21.33	Autosomal Dominant
Type II	Collagen1, alpha – 1 polypeptide gene *COLIA1* Collagen 1, alpha-2 polypeptide gene *COLIA2*	17q21.33 7q21.3	Autosomal dominant
Type III	Collagen1, alpha – 1 polypeptide gene *COLIA1* Collagen 1, alpha-2 polypeptide gene *COLIA2*	17q21.33 7q21.3	Autosomal dominant
Type IV	Collagen1, alpha – 1 polypeptide gene *COLIA1* Collagen 1, alpha-2 polypeptide gene *COLIA2*	17q21.33 7q21.3	Autosomal dominant
Type V	Interferon – induced transmembrane protein 5 gene *IFITM5*	11p15.5	Autosomal dominant
Type VI	*SERPINF 1* gene	17p13.3	Autosomal recessive
Type VII	Cartilage – associated protein gene *CRTAP*	3p22.3	Autosomal recessive

1.1.8.ii: Short stature

Short stature is defined as height that is 2 standard deviation (SD) or more below the mean height for children of that sex and chronological age in a given population. The most common causes are familial (genetic) causes and constitutional delay of growth. Short stature can be classified according to many classifications.

Figure – 4 : General Classification of short stature(15)



Dispropotionate short stature can be subdivided depending on the most affected part of the body , short trunk group and short limbs group.Short limb group either rizomelic or mesomelic.

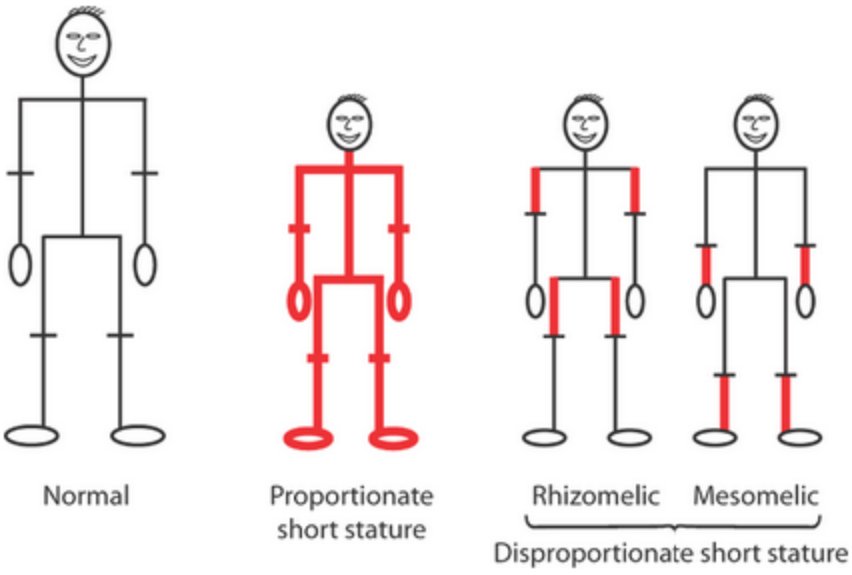


Figure 5 : Types of short stature according to propotionte of the body

Dispropotionate short stature

a. Endocrine - Hypothyroidism
b. Metabolic- Mucopolysaccaroidosis
c. Syndromic – Noonans syndrome
d. Skeletal dysplasia – Achondroplasia /Hypochondroplasia

Dyspropotionate short stature group can be either short limb group or having short trunk.

i. Short limbs
    a. Achondroplasia
    b. Hypochondroplasia
    c. Ostegenesis Imperfecta
    d. Metaphyseal chondrodysplasia
    e. Diastrophic dysplasia

ii. Short trunk
    a. Spondylo- ephiphyseal dysplasia
    b. Mucopolysaccaroidosis

Many types of skeletal dysplasias clinically manifest short stature. Achondroplasia , Hypochondroplasia, Spondyloepiphyseal dysplasia and Osteogenesis imperfecta identified as common skeletal problems that leads to short stature.

Some of the common metabolic causes such as Mucopolysaccaroidosis also discussed in this study.

1.1.8.iii: Craniosynostosis

Abnormalities of the cranial bones can be easily identified with the knowledge of normal neurocranial development. Cranial abnormalities mostly occur during the prenatal period .The neurocranium is devided into two parts as cavarium and the basicranium.The initial surrounding membraine derived from mesoderm and neural crest ectomesenchyme.(16) This is again subdevide into inner and outer ectomeninx. Outer ectomeninx devided into two layers as outer osteogenic layer and inner duramater.The osteogenic layer form the ossification centers and form

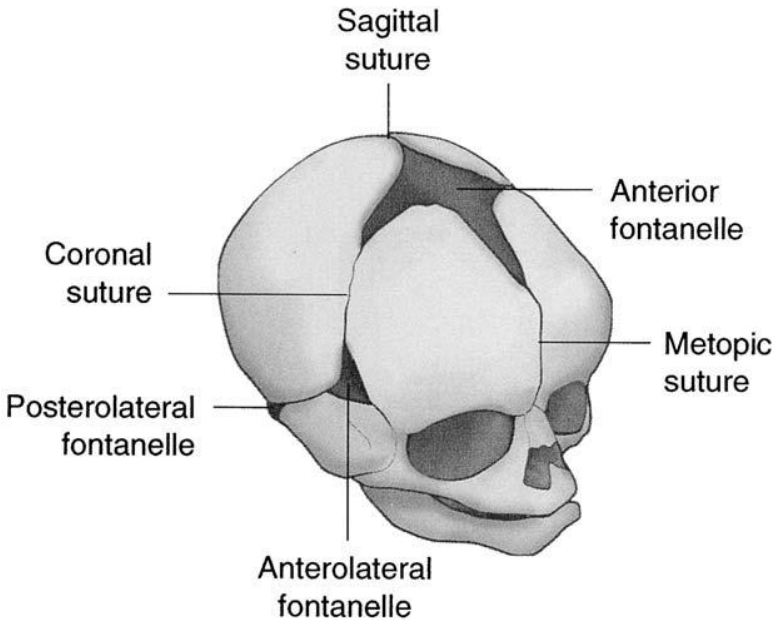
frontal, parietal, occipital and temporal bones.Interviening ares form sutures and fontenelles. Usually all the sutures has to fused at the end of the second year of life.

Defects in the ossification causes premature fusion of skull bones or craniosynostosis. This is a common developmental abnormality occur in 1:2500 births. (17)Genetic background of these disorders were related to mutation of several families of genes

i. Fibroblast Growth Factor Receptor genes -FGFR
ii. Transforming Growth Factor Beta genes – TGFB
iii. Eph/Ephrin Family of genes

There were about 11 genes regulate the pathways of suture development.

Figure 6: Cranial sutures(16)



Craniosynostosis can be categorized in to two major categories

a. Syndromic craniosynostosis
b. Nonsyndromic craniosynostosis

Syndromic craniosynostosis is associated with other systemic and functional malformations

This can be about 15% of the total craniosynostosis patients.(16)Some associated features such as hydrocephalous, increased intracranial pressure and Chiari malformations are common in syndromic craniosynostosis group of people. Common syndromes are Crouzon syndrome, Apert syndrome and Pfeiffer syndrome.

The simple non syndromic patient may have isolated involvement of cranial sutures : metopic, sagital and coronal sutures single or multiple suture.

a. Metopic suture

The metopic suture usually close just after birth. Premature closure of this suture causes trigonocephaly with midline ridge. Hypertelorism may occur if it is associated with frontonasal suture. Very rarely this can be associated with frontal lobe malformation and mental retardation.

b. Sagittal suture

The commonest form of craniosynostosis associated with Sagittal suture. The skull is appear as elongated with frontal bossing. A ridge can be palpable along the sagital suture and between the anterior fontenelle and junction of the lamboid sutures. The shape of the skull is called as scapocephally and Dolichocephaly. This type of craniosynostosis is commoner in males.(16) Associated brain malformations and mental retardation is rare .

c. Coronal suture

This type is more common in females. Usually unilateral. The bilateral coronal suture involvement always associated with a syndrome.(16) The unilateral coronal synostosis give the skull a characteristic appearance called plagiocephaly, it consist of

- Concave plattening of the forehead
- Elevated supraorbital margin on the affected side
- Frontal bossing of the opposite side.

X rays showing the characteristic harlequin sign. This deformity causes involvement of the supra orbital ridge and frontal bone and affect the position of the orbit. Orbital asymmetry can be observed. If not corrected by surgical treatment nasal bones also can be affected and nose may deviate to the unaffected side. Cheeks may become flat. This type is also associated with increased intracranial pressure and cerebral malformation. If the coronal suture involvement is bilateral it causes Brachycephaly with flat broad fore head.

d. Multi suture synostosis (Oxycephaly)

Head shape is short and narrow. Commonly associated with coronal and sagittal sutures. All of the sutures can also be affected resulting craniotelecephally. It is associated with high incidence of increased intracranial pressure and mental retardation.

In OMIM non syndromic Craniosynostosis has divided into sub categories , out of them common three sub types are going to describe in this study. (Appendix -4 - A) Depending on the involvement of the skull sutures.

Syndromic craniosynostosis also describes under 3 commonest syndromes.(appendix 4- B)

1.1.8.iv: Other Group Of Skeletal Dysplasia

The patients those who were not falling into above 3 major categories discussed under the topic of Other groups of skeletal dysplasia.In this broad category many diseases were presented one in each group. So we thought to discuss these diseases in common as we could not compare the features with one patient .

Some of the disoders in this category is rare in the general population ,as we came across being the tertiary level centers. So the general overview of the below mentioned disoders discussed with a available details of recruited patients

According to the international Nosology and Classification of genetic skeletal disorders these disoders discribed under many diferent categories.

1. Increased bone density group –Osteoprtrosis
2. Limb hypoplasia reduction group
    a. Holt – oram syndrome
    b. Radial Ray syndrome
    c. Femoral facial syndrome

d. Split hand foot malformation with long bone deficiency syndrome.

3. Polydactyly syndactyly group – polydactyly /syndactyly

4. Over growth with bone involement - Marfan syndrome

5. Filamin group related disorders - Larsen syndrome and otopalatodigital syndrome

1.1.8.iv-1:Ostepetrosis

Osteopetrosis is a rare single gene disorder causes osteoclasts failure and impairment of bone resorption. It may affect the H+ and Cl- transport system. This leads to enlargement of bone cavities and impairment of the bone marrow resulting abnormal hematological indices. Visual and hearing impairment occur due to compression of cranial nerves due to closure of bone foramina.(18)Affected individuals may present with osteoscelerosis, short stature malformation and brittle bone .According to the international Nosology and classification of genetic disorders of bone 2006 osteopetrosis falls in category 22 increased bone density group.(6)

This is a heterogeneous heritable condition .Inheritance can be autosomal dominant, recessive or X linked. Incidence rate is 1:100,000.(19)

Categorized into five major sub types according to the pattern of inheritance and severity.

Skeletal involvement is similar to all the sub types: increased bone density, diffuse focal scelerosis of varying severity, moderate defect at metaphysic, pathological fractures, osteomyelitis, dental abnormalities, tooth eruption defects and dental caries.(20)

A. .Type I .Autosomal recessive Osteopetrosis

a. classic type - gene TCIRG

b. Neuropathic - genes CLLN7/ OSTMI

c. ARO with renal tubular acidosis - Cabonic anhydrase II

Table 5 : sub categories of Autosomal recessive Osteopetrosis

Type	**Other features**	**severity**	**Onset**
A	Pancytopenia, hepatospleenomegaly, extramedullary heamatopoeisis, compression of cranial N II, VII and VIII , hydrocephalus, hypocalcaemia.	Severe	Perinatal
B	Similar to type a with associated retinal atrophy	Severe	Perinatal
C	Renal tubular acidosis, developmental delay, intracranial calcification, cranial nerve compression	moderate	Infancy

B. Type II - X- linked Osteopetrosis Lymphoedema, anhydrotic,ectodermal dysplasia and immunodeficiency.(OLEDAID)

Genes - IKBKG(NEMO)

Features- anhydrotic ectodermal dysplasia, Lymphoedema, immunodeficiency, recurrent infection . Onset in infancy and a severe form.

C. Type III - Intermediate Osteopetrosis (IRO)

Genes: CLCN7/PLEKHMI

Features: anaemia, extra medullary haematopoeisis, occasional optic nerve compression

Childhood onset and Mild to moderate disease

D. Type IV - Autosomal dominant Osteopetrosis(Albers- Schonberg disease)

Gene : CLCN7

Features : moderate haematological failure, cranial nerve compression

Childhood and adolescence onset , Mild to moderate disease

1.1.8.iv-4 : polydactyly ,Syndactyly group

Syndactyly occurs due to fusion of soft tissue of the finger or toe with or without bone involvement. This is due to absence of apoptosis.(21) Polydactyly referred as supernumerary digit or a part of a digit,. This could be ranging from duplication of a single digit to complete duplication of a limb. Polydactyly may be isolated or associated with a syndrome.

1.1.8.iv-5 : Filamin group

Otopalatodigital syndrome -Presented with cleft palate hearing loss. Occurs due to the mutation of *FLNA* gene

Larsen syndrome - Hip dislocation ,Talipes, nail anomalies Due to mutation of FLNB gene.

1.2: JUSTIFICATION

Skeletal dysplasis is a major course for disability and dependency in varying degree. Not only for the affected person, the family, society and last the country. Some of these patients with severe disability may end up in orphanages as the poverty of the parents unable to manage the consequences of skeletal dysplasia. The life expectancy varies with each disease and being no permanent cure it indeed a socioeconomic and health burden.

The publications of statistics department of Ministry of health showed there was a significant increase in the number of patient with skeletal deformities each year.(22) Even there was a less number compare to the other disease entities the extent and severity of each category, the duration of hospital stay and the cost of treatment are higher than most of other diseases .

To diagnose to a patient with skeletal deformity needs several investigations including biochemical and radiological as molecular genetics diagnostic tests were not within the reach of most clinicians.

This study gives a general idea about the common types and wide variety of uncommon types of skeletal dysplasias in Sri Lanka. We could mention the number of each category of disorders as frequency of occurrence because we included only the referred patients. The knowledge of phenotypic spectrum of the skeletal dysplasia would be useful in making management strategies at national level. The early diagnosis and intervention of the conditions may reduce the extent of disability and the cost of treatment. The Ministry of health could implement the genetic testing for at least the common types of skeletal dysplasias that would be beneficial for both the patients and the economy of the Nation. This may be a step to achieve the millennium development goals in year 2015 and beyond.

1.3: OBJECTIVES

Clinical and radiological characterization of skeletal dysplasia in a cohort of Sri Lankan patients.

2: METHODOLOGY

2.1: Ethical consideration

This study was approved by Ethics review committee of the Faculty of Medicine , University of Colombo, Sri Lanka.

The study was conducted according to the declaration of Helsinki (2008)This study has a social value as this describes the clinical and radiological manifestation of skeletal dysplasia in Sri Lankan territory . It also contributes towards knowledge in bone deformities present in Sri Lanka. This study has a scientific validity.

As mentioned in the objectives the aim of the study was to find out clinical phenotypic variation and radiological manifestation of patients with skeletal dysplasia.

This study was opened to all ethnic groups and all age groups of patients of both sex. Therefore this study had the fair participant selection. The consent was obtained in an ethical manner. When there was a language barrier appropriate translators from the medical field was used without breaking confidentiality.

Patients who volunteered for the study were also recruited after the informed consent. Those consent forms were prepared in all three languages and in cases where the patient could not read,

investigators verbally explained about the content of the form in simple understandable language to the participants. In the case of young children consent of the parents or guardian were obtained. When there was a patient with diminished mental capacity proxy consent was taken from the parent or from the guardian.

This was a descriptive study. Most of the patients were recruited from the referrals to the Human Genetics Unit, Department of Anatomy, Faculty of Medicine, University of Colombo. These referrals were from all over the Island as the only government institution in Sri Lanka for genetic services is the Human Genetics Unit. This clinic functions under various services including referrals for genetic testing, genetic counseling, experts opinion for managing patients with hereditary transmitted disorders, pre implantation genetic diagnostic testing and also a center of coordination for genetic testing from reference labs overseas. Apart from the direct referrals to the genetics unit, few recruited from two tertiary care hospitals: National hospital of Sri Lanka (NHSL) and Lady Ridgway Hospital (LRH) in Colombo with written permission of the responsible directors. As a tertiary care hospital NHSL was receiving patient from many parts of the country. Patients with skeletal dysplasia were mostly warded in surgical units including plastic surgery, neurosurgery and orthopedics units. From the LRH most patients were recruited from the university Unit and Orthopedic units. The Professorial Unit of LRH receives referrals from many parts of the country. Many patients with skeletal dysplasia had medical complications with the bone deformity. Few self referred patients were also included in the study.. This study sample consists of patients from many parts of the Island.

The study population comprised of 42 consecutive participants within the period of 1st of January to 30th of June 2014. The phenotypic spectrum described with the details of clinical examination and radiological features.

The participants were interviewed, examined and photographed by protecting the universally accepted patients rights' and human rights. Interviews were conducted in a private place where confidentiality could be assured. Patient were given an opportunity to participate with parent spouse or guardian as they wish. All the inquiries were done by the principle investigator unless there was a language barrier. In such situations the translators were used from the medical field. Patients were given enough time to clarify their questions before their participation to the study. Even after the consent and participation if there is any problem regarding the study to clarify they have been given the contact details of the principle investigator.

The data collection booklet was designed using a universally accepted format assuring the confidentiality of the patient and the data gathered. The identification page contained the patient's identification details .Once it was filed separately with the personal data being protected under lock and key by the principle investigator.

The electronic data base and charts only had the subjects case number and all the data bases and charts were password protected. These were the measures taken to minimize the loss of confidentiality of the participants.

Photographs were only taken from the subjects who gave informed written consent. The consent for the photographs were taken from the subject only for research purposes. Those photographs were primarily used to reevaluate the clinical features with the radiological findings by the principle investigator with the help of the expert consultant radiologist.

These measures were taken to improve the validity of the data. The photographic data were kept under appropriate security with the principle investigator

Even though the genetic testing was not performed the patients were given the overview of the condition with help of the history , pedigree, examination and biochemical and radiological investigation reports. When there was obvious correlation of the condition with the most probable aetiology and disease pattern patients were given disease specific counseling.

However they were indirectly also benefited by receiving the wide knowledge about the type of skeletal dysplasia they have for their future perspectives. In the field of clinical genetics the knowledge of the disease pattern of Sri Lanka may help to develop the advanced genetic tests focusing the common types of skeletal dysplasias.

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2.2 RECRUITMENT OF SUBJECTS

2.2.1 :STUDY POPULATION AND PLACE OF THE STUDY

The patients were recruited mainly from the referrals to the Human Genetics Unit, Department of Anatomy, Faculty of Medicine, University of Colombo since from 1st of January 2014 to 30th of June 2014. These referrals came from all over the Island as the unit is the only government institution in Sri Lanka for genetic services. This clinic manages referrals for genetic testing, genetic counseling, experts opinion for managing patients with hereditary transmitted disorders, pre implantation genetic diagnostic testing and also act as a center of coordination for genetic testing from reference labs overseas. Few patients were recruited from the two tertiary care hospitals: National hospital of Sri Lanka (NHSL) and Lady Ridgway Hospital (LRH) in

Colombo with written permission of the responsible directors .Out of the 42 patients 20 were recruited from the HGU,10 from NHSL and 12 from the LRH.

2.2.2: INCLUSION CRITERIA

patients with skeletal dysplasia (on clinical/radiological grounds)., adult patients who has clinical evidence of skeletal anomalies, patient who are presenting with dysmorphic features, patients who come with the other major anomalies with associated skeletal defects and syndromic patients with skeletal anomalies were included

All ethnic groups were included.

Patients who have given written informed consent or proxy consent were included.

2.2.3: EXCLUSION CRITERIA

Patients who were not Sri Lankans by decent, and those who did not give the written informed consent were not included.

2.2.4: REGISTRATION OF PATIENTS

Each person was registered in a registry by the principle investigator by issuing a case number. The details of each patient entered into the data base with that number. Data base consist of age, gender, geographical origin, clinical presentation family details consanguinity, and affected relatives. The radiological findings and relevant bio chemical data also included.

2.2.5: OBTAINING WRITTEN INFORMED CONSENT

Subjects or the parents or guardian in the case of children were given an information sheet with the details of the study and the consent form to read and sign before participating in the study. Questions they had regarding the study were discussed.. In case of minors (less than 18 years) consent was taken from guardians. In case of diminished cognition or psychiatric symptoms where informed consent cannot be obtained proxy consent was obtained from guardians. Knowing that they can withdraw their consent to participate the study at any time with no penalty or effect on medical care or loss of benefits they signed. Few parents did not give consent for the study. Some participants wanted to see the outcome of the study.

Those who signed the consent forms were recruited to the study by filling the data collection form. All participants were given the contact details of the Ethics Review Committee (ERC) and also of the principle investigator in case they needed to clarify any doubt about the study. This helped to impress them about the study and established a trust with our study team.

2.2.6: CLINICAL EVALUATION

It was done by describing the presenting age , age at initial diagnosis and severity of the disease. The bone deformity and fractures analyzed by an experienced consultant radiologist. Patients with congenital defects history was obtained from the participant or guardian. Patients were interviewed (in the presence of one or more family members who could give information on the family history) to work out the pedigrees. The pedigree was created including 3 generations with maximum possibility.. The demographic details, family history and clinical features of skeletal dysplasia were assessed. Examination of patients were done by the principle investigator a

MBBS qualified doctor. Clinical records were reviewed to obtain information about initial features, biochemical investigations and radiological features also used in diagnosis.

2.2.7: RADIOLOGICAL EVALUATION

The radiological evaluation done by experienced consultant radiologist by comparing the standard radiological manifestations with the features of the patient's X Rays. This was performed using standard radiological text books, online databases such as Radiopedia and OMIM, Gene reviews and review articles. The resources used were X Rays : Skull (AP/Lat), Neck (AP/Lat), Chest (PA/ Lat), Pelvis (AP/ Lat), X - Ray of femur, tibia, fibula and feet (AP/Lat), X-Ray of the humerous, ulnar , radius and hand(AP/ Lat), Ultra sound scans, CT scans, DEXA scan and MRI scans. Some patients didn't have the radiological records.. In such situation the details in clinical records were included. All the findings were reassessed with radiological findings of the supervisors.

2.2.8: CLASSIFICATION OF SKELETAL DYSPLASIA

Classification was done with the help of international Nosology and classification of skeletal dysplasia 2010 revised version. (14) Annexed in Appendix 1

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2.2.9: DATA COLLECTION AND STORAGE

At recruitment, study participants were personally interviewed by the principal investigator using a questionnaire to obtain demographic and clinical data.

The data collected were entered in to an electronic data base and also charts were made according to the standard diagnostic criteria in order to organize the data for analysis.. Personal data was kept separate from the database and not entered into the electronic database. The data entering was done according to the study number. The electronic database and the data tables were kept under the care of the principle investigator.

2.2.10: DATA ANALYSIS

The phenotypic variation in relation to gender, age group and ethnicity the standard version of SPSS statistics 17.0 license authorized wizard was used in appropriate places.

To find the mean values of age distribution and to create graphs the same software used .

3: RESULTS

3.1: Overview of the Results

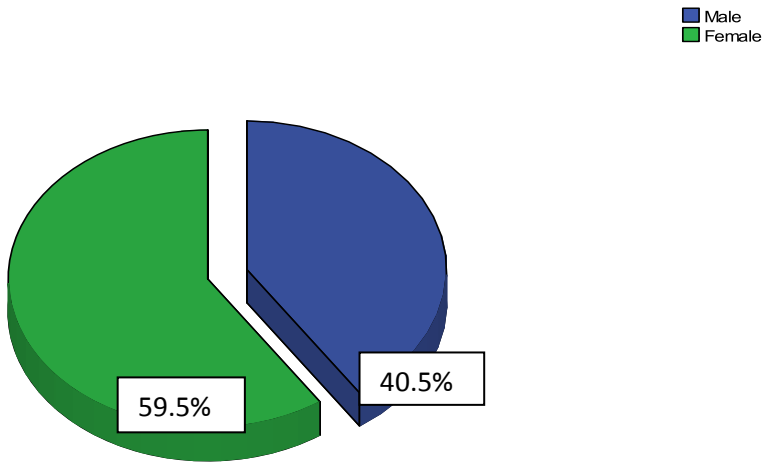
Sample size was 42. There were 17(40.5%) male patients and 25 female patients. Male to female ratio was 1:1.47.

Table -6 Gender distribution of the patients

	Number of patients	**Percentage**

Male	17	40.5%
Female	25	59.5%
Total	42	

Figure - 7 : Gender distribution of the patients



In this study 20 patients (47.6%) were within one to 10 years of age group .Eight patients with birth to one year old including 2 neonates and 6 infants. There were three female and one male patients over 30 years of age.

Table – 7 : Age and gender distribution of the total sample of patients

Age groups	**Male patients**	**% of male**	**Female Patients**	**% of Female**

Birth to 4 weeks	1	2.4%	1	2.4%
1 month to 1 year	2	4.8%	4	9.5%
1year to 10 year	9	21.4%	11	26.1%%
10 years to 20 years	4	7.1%	2	4.8%
20 years to 30 years	-	-	4	9.5%
30 years and above	1	2.4%	3	12.5%
Total	17		25	

Figure – 8 : Age distribution of patients

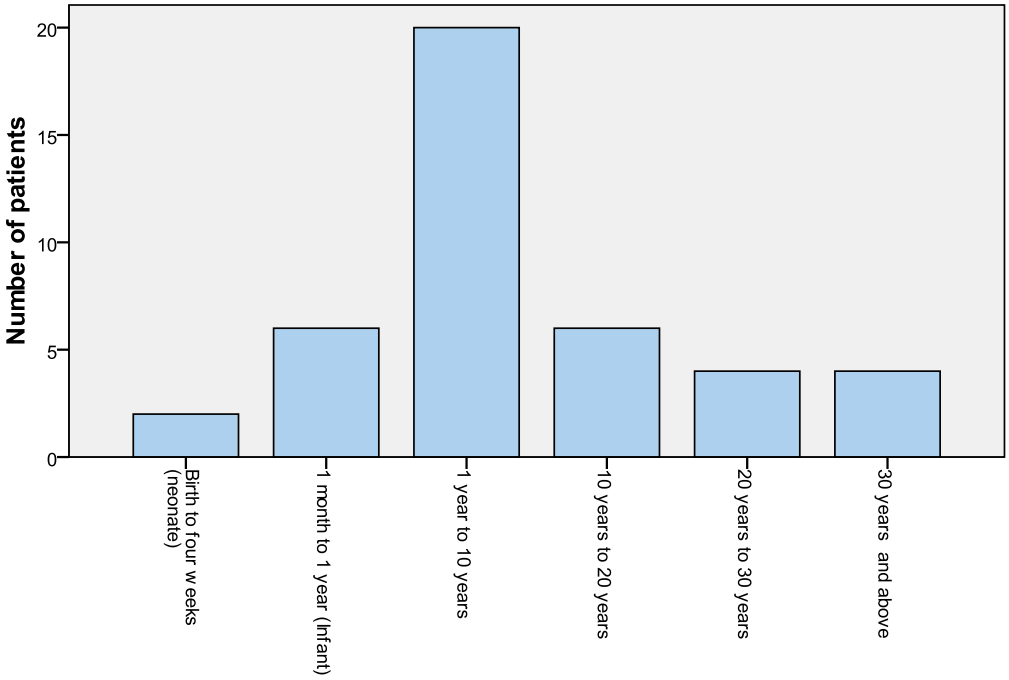
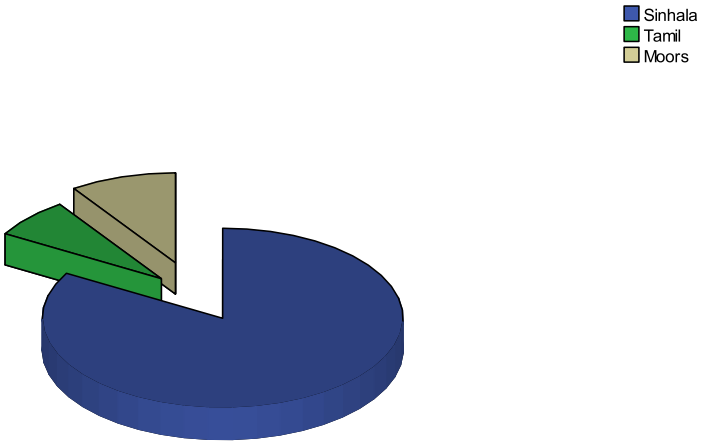


Figure -9 : distribution of Ethnicity in the sample of patient



Majority of patients in this study group were Sinhalese 35/42 (83.3%). Four Moors (9.5%) and 3 Tamils (7.1%)

Table - 8 : Geographical distribution of patients

District of Residance	Number of patients	Percentage of patients
Ampara	3	7.1%
Anurdhapura	1	2.4%
Badulla	1	2.4%
Colombo	12	28.6%
Gampaha	10	23.8%
Kalutara	3	7.1%
Kandy	2	4.8%
Kegalla	2	4.8%
Kurunegala	3	7.1%
Matara	1	2.4%
Nuwaraeliya	1	2.4%
Puttalam	1	2.4%
Ratnapura	1	2.4%
Vavuniya	1	2.4%

Twenty two patients (52.5%) from western province, including 12 from Colombo district and 10 from Gampaha district.

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Figure 10: Geographical variation of the patient sample

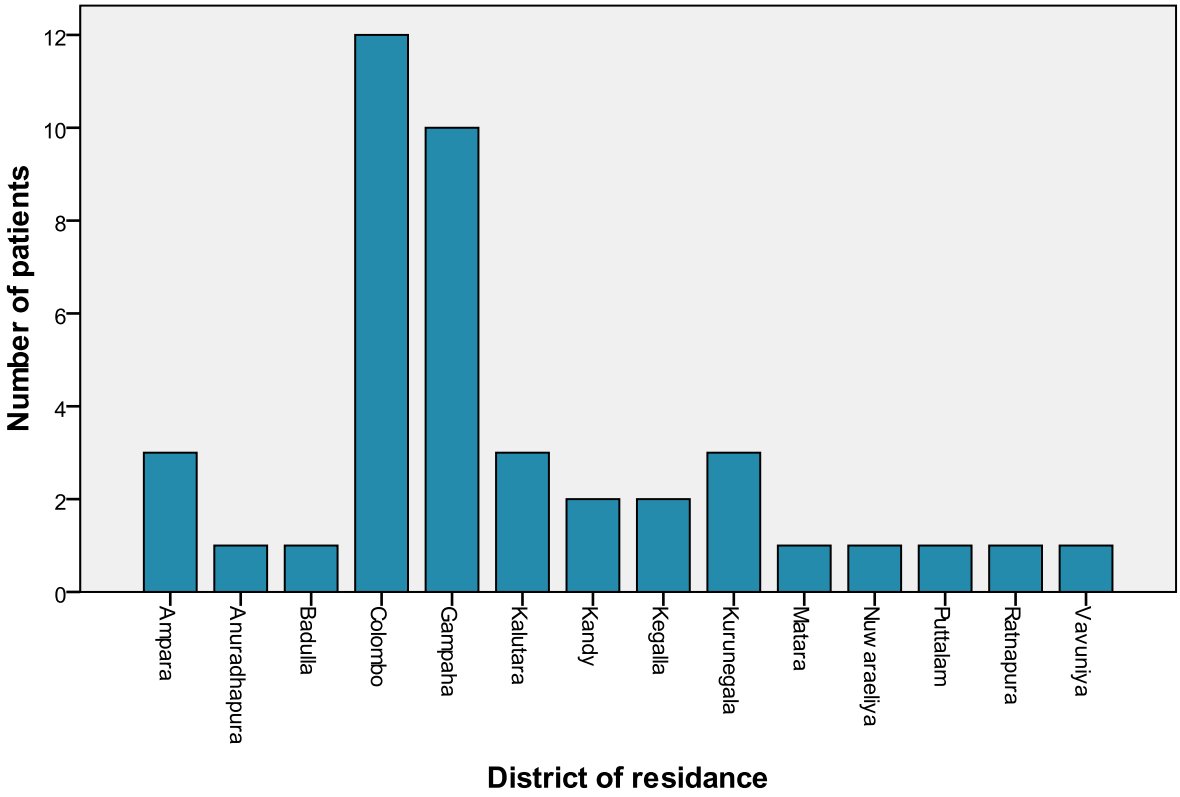


Table –9 : Number of patients and centers of recruitment

Place of Recruitment	Male	Female	Total	Percentage
LRH	5	5	10	23.8%
NHSL	1	4	5	11.9%
HGU	10	17	27	64.3%
	16	26	42	

These patients were recruited from three tertiary care center : Human genetics Unit (HGU) 27 (64.3%) , Lady Ridgway Hospital for Children (LRH) 10(23.8%) and The National Hospital of Sri Lanka (NHSL) 5 (11.9%)

Table -10 :Patients with Consanguinity and positive family history in the study sample

Category of patients	No of patients	Percentage
Patients with consanguinity	6	14.3%
Patients with positive family history	8	19%

Six patients (14.3%) were having consanguineous parents, and eight patients (19%) were having positive family history of affected 1st degree or 2nd degree relatives.

3.2 Diagnosis of the patients

According to the International Nosology and classification of skeletal dysplasia 2010 revised version (appendix 1) all 42 patient diagnosed and categorized based on the clinical, radiological and biochemical diagnostic criteria given in the OMIM and Gene Review.

Table - 11 : Serial numbers and sub categories of the diagnosis according to the international classification

Serial number	Disease category	No of pt	%
1	**FGFR3 Chondrodysplasia group**	10	23.8%
	A. Achondroplasia	7	16.6%
	B. **Hypochondroplasia**	3	7.1%
2	**Type 2 Collagen group and similar disorders**		
	A. Spondylometaphyseal Dysplasia	2	4.8%
7	**Filamin Group and related Disorders**	2	
	A. Larsen syndrome	1	2.4%
	B. Otopalatodigital syndrome	1	2,4%
9	**Short Ribs dysplasia Group**		
	A. Noonans Syndrome	2	4.8%
23	**Increased bone density group**		
	A. Osteopetrosis	1	2.4%
25	**Decreased bone density group**		
	A. Osteogenesis Imperfecta	9	21.4%
27	**Lysosomal storage disorders**	2	4.8%
	A. Mucopolysaccaroidosis type 2	1	2.4%
	B. Mucopolysaccaroidosis type 4	1	2.4%
30	**Overgrowth syndromes with skeletal involvements**		
	A. Marfan syndrome	1	2.4%
33	**Craniosynostosis Syndromes**	5	11.9%
	A. Apert syndrome	1	2.4%
	B. Craniosynostosis II	1	2.4%
	C. Saethre- Chotzen Syndrome	1	2.4%
	D. Crouzon Syndrome	2	4.8%
38	**Limb Hypoplasia reduction defects group**	5	11.9%
	A. Holt oram syndrome	1	2.4%
	B. Radial Ray Syndrome	2	4.8%
	C. Split Hand foot malformation with long bone deficiency	1	2.4%
	D. Femoral facial syndrome	1	
39	**Polydactyly Syndactyly group**	3	7.1%
	A. Syndactyly	2	4.8%
	B. Polydactyly	1	2.4%

In table 12 all 42 patients were subcategorized and summarized. Ten patients were belonged to *FGFR3* chondrodysplasia group(Gp -1) In that 6 were having features of Achondroplasia and 3 having features of Hypochondroplasia.

The second highest number of patients (9/ 42 – 21.4%) belonged to decreased bone density group (25^{th} Gp). Under this group patients with recurrent fractures included and sub types of Osteogenesis Imperfecta discussed. In increased bone density group (Gp-23) there was a child with Osteopetrosis.

Five patients were categorized in (Gp 33) Craniosynostosis syndromes. Two of them showed features of Crouzon syndrome, other three were with features of Apert syndrome, Craniosynostosis type II and Saethre- Chotzen syndrome.

There were 5 patients in Limb hypoplasia reduction defects group. (GP- 38) Two of them having categorized as Radial Ray syndrome. Other three were with the features of Holt Oram syndrome, femoral facial syndrome and split hand foot malformation with long bone deficiency.

Patient with malformed hand and feet were categorized under (Gp-39) Polydactyly Syndactyly group. One patient with Polydactyly, one with Syndactyly and one with split hand obstructive uropathy and spina bifida belongs to that group.

There were two Mucopolysaccaroidosis patient in (Gp-27) Lysosomal storage disease group.

Patient with Marfan syndrome was given the Over growth syndrome with skeletal involvement group.(Gp-30)

Under the type 2 collagen disorders group (Gp- 2) two patients with the features of Spondylometaphyseal dysplasia listed.

Filamin related disorders group.(Gp7) one patient with Larsen syndrome and other patient showed the features of Otopalatodigital syndrome.

As instructed in introduction and methodology this results categorized to 4 sub groups.

3.3 Sub Groups Of Skeletal Dysplasia

Table – 12 : Sub groups of the Skeletal dysplasia patients

Gender	Skeletal dysplasia total patients	Osteogenesis Imperfecta	Short stature	Craniosynostosis	Other types of skeletal dysplasia
Male	17	1	8	2	6
Female	25	8	9	3	5
Total number	42	9	17	5	11

3.3.1: Osteogenesis Imperfecta Group

Total number of patients were 9 (21.4%) including 8 females and one male.Two patients were diagnosed at birth. Age at onset of first symptom varies from birth to 37 years. Mean age of first symptom was 14 years. All the patient were presented with one or more fractures in the long bones.

Six patients were having short stature.8/9 presented with bone deformities. Blue sclera were noted in 5 (83.3% of OI patients) patients. Dental overcrowding and Dentinogenesis imperfecta noted in 6/9 patients.

Progressive hearing loss observed only in one patient. (11.1%). Positive family history of bone deformities in 3 patients out of three two patients were having family history of fractures.

Consanguineous marriages of parents noted in two patients, one 2nd degree consanguinity and one with the 3rd degree consanguinity.

Table – 13：Summary of the patient with fractures and bone deformities

Patient number	Current Age	Age at onset of first symptom	sex	Short stature	bone deformity	Blue sclera	Dentinogenesis imperfecta	Progressive hearing loss	Family history of fractures	Family history of bone deformity	Consanguinity
1	25	8y	F	Y	Y	Y	Y	No	No	No	No
2	13	9y	F	Y	Y	Y	Y	No	No	No	Yes
3	11y3m	6y	M	Y	Y	Y	Y	No	Y	Y	No
4	39	37y	F	No	Y	No	No	Y	No	No	No
5	36	33y	F	No	Y	No	No	No	No	No	No
6	1y11m	B	F	Y	Y	Y	Y	No	No	No	No
7	37	23y	F	No	No	No	No	No	No	Y	No
8	25	10y	F	Y	Y	No	Y	No	Y	Y	Yes
9	1y3m	B	F	Y	Y	Y	Y	No	No	No	No

Table - 14 :Number of Fractures and involvement of the long bone

Patient number	Total number of fractures	Fractures sites
1	4	Right Radius, Right Femur, Left neck of the Femur
2	6	Femur B/L ,Ulnar, Radius, Fibula B/L
3	4	Right tibia fibula ,right neck of the femur
4	2	Neck of the femur B/L
5	2	Neck of the femur B/L
6	8	B/L femur, B/L Humerous
7	3	Left ankle, neck of the Femur both sides
8	3	right femur, B/L Humerous
9	2	Right humerous ,Left femur

All the patients were having either unilateral or bilateral involvement of the femur. Patients who were presented at early age both upper and lower limb bones were involved.. In this study incidence of fracture neck of the femur and shaft of the femur were equally common.

. Fracture Humerous was presented in 3 patients. Tibial fracture was in two patients and Fracture radius and ulnar in one patient.

Table – 15 :Radiological features of Bone deformities in each patients with OI

study No.	Fractures	Radiological features
1	Right Radius, Right Femur, Left neck of the Femur	Severe osteopenia, carpal bone fusion, protrusio acetabuli
2	Ulnar, Radius, Fibula B/L	Scoliosis , kyphosis, excessive callus formation
3	Right tibia fibula ,right neck of the femur	Severe osteopenia, gracile bones popcorn calcification, AP bowing of long bones, cortical thinning
4	Left neck of the femur/right neck of the femur	Thin gracile long bones, diffuse osteoporosis
5	Neck of the femur B/L	Scoliosis ,kyphosis ,mild protrusio acetabuli ,low bone density, diffuse osteoporosis
6	B/L femur, B/L Humerous	Osteopenia, excessive callus formation, AP bowing, cortical thinning.
7	Left ankle, neck of the Femur left side	Osteopenia, Wormian bones in the skull
8	Skull vault thickening and sclerosis, fracture right femur	Sclerotic skull bones, absent carpal bones in the hands
9	Right humerous Left femur	Osteopenia ,cortical thinning, AP bowing of tibia and fibula

Table – 16: Assessment of clinical presentations of OI patients

Category	Number of patients	Percentage
Patients with fractures in the long bones	9	100%
OI with Blue Sclera	5	55.5%
Dentinogenesis Imperfecta	6	66.6%
OI with short stature	6	66.6%
Patient with impairment of hearing	1	11.1 %
Patient with bone deformities	8	88.8%

All the patients presented with fractures , and number of fractures varied from 2 fractures to 8 fractures involving the many sites of the long bones. Blue sclera was noted in 5 patients (55.5%) and Dentinogenesis imperfecta in 6 patients (66.6%). Six patient who was presented at early years had short stature. The patient who had the first fracture after 30 years had the average height. One patient out of nine were having progressive hearing loss (11.1%).

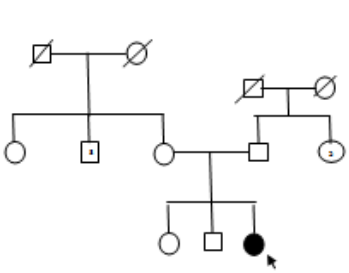
Table – 17 : Osteogenesis Imperfecta patients - other abnormalities and dependency

OI pt no	**Mobility /dependancy**	**Other systemic involvements**
1	Wheel chair	-
2	Wheel chair	Slightly dialated lateral ventricle of brain
3	Wheel chair	-
4	Disabled /walk with stick	-
5	Normal	-
6	Bed ridden	ASD /mild PS and mild TR
7	Normal	-
8	wheelchair	-
9	Bed ridden	Minor brain malformations

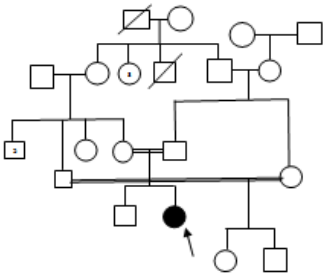
Disabilities were common with 7 /9 . Two patient were bed ridden and totally depended, 4/9 were wheel chair depended one was able walk with the support of stick and 2 did not have disabilities.

Two patients had minor brain abnormalities, one patient had a diagnosis of ASD.

Figure – 11 : Summary of pedigree of the patients with Osteogenesis Imperfecta



P- 1



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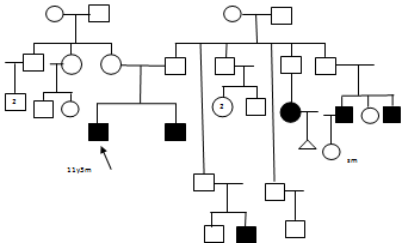

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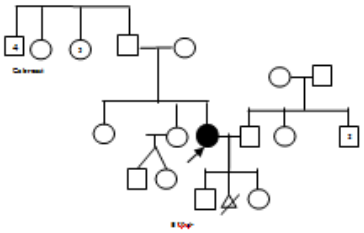

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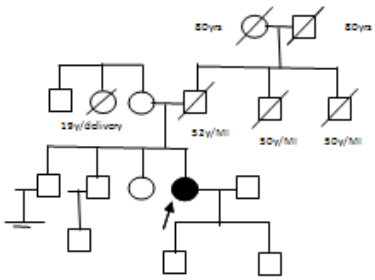

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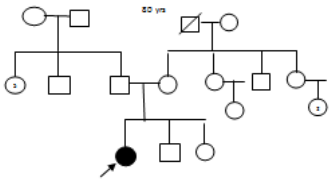

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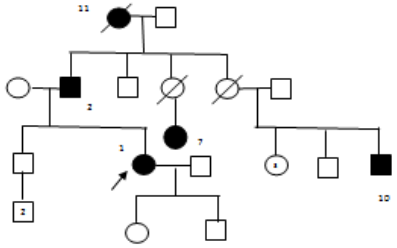

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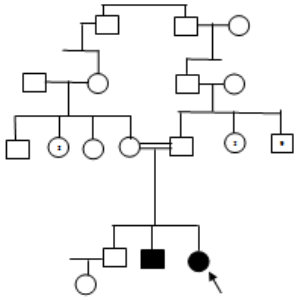

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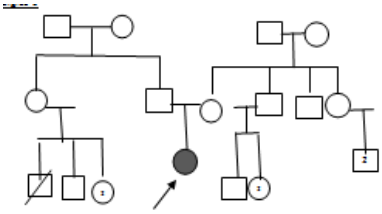

P - 9

P : denote patients study number

Table – 18 : Sub types of OI patients according to the history , clinical features and radiological characteristics

patient no	**Probable Diagnosis**	**Family history of similar conditions**			**Possible mode of inheritance**
		1st degree relatives	2nd degree relatives	3rd degree relatives	
1	OI type III	-	-	-	New mutation
2	OI type III	-	-	-	New mutation
3	OI type III	+	+	+	AD
4	OI type IV	-	-	-	New mutation
5	OI type IV	-	-	-	New mutation
6	OI type III	-	-	-	New mutation
7	OI type III	+	+	+	AD
8	OI type III	+	-	-	AR
9	OI type I	-	-	-	New mutation

Considering the history , examination and biochemical and radiological data and guidance from the supervisors and data bases we came to the final conclusion of diagnosis and possible mode of inheritance.

6/9 did not have family history or consanguinity. Three patients were having positive family history. 6/9 were severely affected and with features suggestive of OI type III.

Table – 19 : Geographical locations and place of recruitment

Patient No	**Geographical location (District)**	**Recruited from**
1	Gampaha	NHSL
2	Kurunegala	HGU
3	Kalutara	HGU
4	Colombo	HGU
5	Gampaha	HGU
6	Ampara	LRH
7	Gampaha	HGU
8	Kandy	HGU
9	Ampara	LRH

All patients were Sinhalese. They were from the different geographical locations. Three patients from Gampaha district and two were from Ampara. Rest of the patients represented the other districts.

Six patients were recruited from the HGU, and 2/9 were from LRH and 1 patient from NHSL.

3.3.2: Patients with short stature

Sixteen patient (38%) presented with short stature. This was basically divided into two groups as dyspropotionate short stature and proportionate short stature.

Ten patients (62.5% of short stature patents) belongs to the group of dyspropotionate short stature . In this 7/10 (43.75% of short stature patients)were Achondroplasia and other 3 (18.7% out of 16) were in Hypochondroplasia group.

Equal gender distribution. Mean age at presenting to the tertiary level medical care was 8 years.

Assessment of bone age was done in 3 patients ,two showed reduced bone age than the chronological age. One patient had normal bone age.

Table -20 : Overview of patient with short stature

	Current age of the patient	Bone age	Sex	Dyspropotionately short	Proportionately short	rhizomelia	mesomelia	Scoliosis	Lumbar lordosis	Bow legs (Genu varus)	Family history	Consanguinity
1	6y	N/A	M	-	yes	-	-	-	-	-	-	-
2	5y 10m	decreased	F	-	yes	-	-	-	-	-	-	-
3	26y	N/A	F	-	yes	+	+	+	-	-	-	-
4	2y9m	N/A	M	Y	-	+	+	+	+	+	-	-
5	1y9m	N/A	F	Y	-	+	+	-	-	+	+	-
6	2y3m	N/A	M	y	-	+	+	+	+	+	-	-
7	8m	N/A	F	Y	-	+	+	-	-	+	_	-
8	7y	Normal	F	Y	-	+	+	+	+	+	-	-
9	4y9m	N/A	M	y	-	+	+	+	+	+	-	+
10	14y	decreased	F	Y	-	+	+	-	+	+	-	-
11	4y	N/A	F	y	-	+	+	+	+	+	-	-
12	5m	N/A	M	y	-	+	+	+	+	+	-	-
13	31y	N/A	M	-	Y	-	-	-	-	-	-	+
14	12y	N/A	M	-	y	-	-	-	-	-	-	-
15	2m5d	N/A	F	Y	-	+	+	-	+	+	-	+
16	16y	N/A	M	-	Y	-	-	-	-	-	-	-

Table -21: Probable diagnosis, ethnicity and demography of patient with short stature

Patient number	Age	sex	ethnicity	Residence /district	Probable diagnosis	Referred from
1	6y	M	Tamil	Nuwaraeliya	Noonans syndrome	HGU
2	5y10m	F	Sinhalese	Gampaha	Spondylometaphyseal dysplasia	HGU
3	26 yrs	F	Sinhalese	Kalutara	Spondylometaphyseal dysplasia	HGU
4	2y9m	M	Sinhalese	Gampaha	Achondroplasia	HGU
5	1y9m	F	Tamil	Colombo	Hypochondroplasia	HGU
6	2y 3m	M	Sinhalese	Ampara	Achondroplasia	HGU
7	8m	F	Sinhalese	Ampara	Hypochondroplasia	HGU
8	7yr	F	Sinhalese	Colombo	Achondroplasia	HGU
9	4y9m	M	Sinhalese	Ampara	Achondroplasia	HGU
10	14y	F	Moor	Colombo	Hypochondroplasia	HGU
11	4y	F	Moor	Colombo	Achondroplasia	HGU
12	5m	M	Sinhalese	Gampaha	Achondroplasia	HGU
13	31y	M	Sinhalese	Kandy	Mucopolysaccaroidosis	HGU
14	12y	M	Tamil	Gampaha	Noonans syndrome	HGU
15	2d	F	Moor	Colombo	Achondroplasia	HGU
16	16y	M	Sinhalese	Matara	Mucopolysaccaroidosis	LRH

Table 22 : Radiological features of patient with short stature

Pt No	Clinical features	Radiological features	Diagnosis
1	Triangular shaped face, pectus carinatum, broad nasal bridge, epicanthal folds, telecanthus, high arched palate	B/L rib crowding, scoliosis of lumbar spine	Noonans syndrome
2	Normal face	Decreased bone age, delayed tooth eruption, short meta carpals, Brachydactyly	Spondylometaphyseal dysplasia
3	Synophrys , low set ears right hand 3rd finger is shorter than others ,upright 2nd,3rd, and 4th toes in both feet	B/L Short ulnar and radius, dislocated right elbow joint, Small chest, short ribs, anterior rib cuping.	Spondylometaphyseal dysplasia
4	Frontal bossing bowing of legs, normal hands	Champaign glass appearance of pelvic cavity, posterior scalloping of vertebral bodies.	Achondroplasia
5	Depressed nasal bridge , low set ears, micrognathia, cleft palate , normal hand	Posterior scalloping of lumbar vertebra, champaign glass appearance of pelvic cavity, lumbar lordosis, right side club foot, bilateral acetabular dysplasia	Hypochondroplasia
6	Large head, frontal bossing , mid face retrusion, trident hand, bow legs	Thoracolumbar kyphosis,rizomelic shortening of upper and lower limbs	Achondroplasia
7	Frontal bossing , dysmorphic facial features , normal hands	Absent ossification centers in the carpus, femoral ossification centers absent	Hypochondroplasia
8	Large head , frontal bossing trident hands bowing of legs	Posterior scalloping of vertebral bodies, dislocation of left elbow joint	Achondroplasia
9	Large head , dysmorphic facial features, trident hands	Posterior vertebral scalloping, thoracolumba kyphosis, champaign glass type pelvic inlet.	Achondroplasia
10	Large head, dysmorphic facial features, trident hands	Square shaped iliac bones, shortening of 1st metacarpals	Hypochondroplasia
11	Hyper pigmented skin, flat nasal bridge , low set ears, Short upper and lower limbs,	Dense and broad femur and humerous, femoral and tibial epiphysis not visualized, Thoracolumbar kyphoscoliosis	Achondroplasia
12	Triangular shaped face, mid face retrusion, Frontal	Narrowing of interpeduncular distance of lumbar spine,wide and	Achondroplasia

	bossing genu varus, Trident hand, dyspropotionate stature Limitation of elbow extension	short tubular bones (femur and humerous) with metaphyseal widening.	
13	Coarse facial features, pectus carinatum, widely spaced teeth, dental caries , hearing impairment, Hypermobility of joints.	Kyphoscoliosis	Mucopolysaccaroidosis type IV
14	Triangular shaped face, flat nasal bridge, high arched palate.Broad based gait, flat feet	Scoliosis , short metacarpals	Noonans syndrome
15	Large head, frontal bossing, mid face retrusion, Rhizomelic shortening of upper and lower limbs, genu vulgus, trident hand	Thoracolumbar kyphoscoliosis	Achondroplasia
16	Large head, broad nose, flat nasal bridge, short upper arm, fan shaped hands, macroglossia, ptosis, hearing loss, right inguinal hernia	Thoracolumbar kyphosis small flat iliac bone, 2^{nd} and 5^{th} metacarpal bones tapered, Epiphyseal dysplasia,	Mucopolysaccaroidosis type II

3.3.3:Patients with Craniosynostosis

Five patients (11.9%) in this study sample presented with Craniosynostosis. Two of them with Crouzon syndrome and others with Apert syndrome, Craniosynostosis type II and Saethre – Chotzen syndromes each.

Table – 23 :Summary of patient with feature of Craniosynostosis syndromes

Patient no	Age	sex	District	Involved area / skull suture	Diagnosis
1	2y5m	F	Kegalle	Sagital suture	Craniosynostosis type II
2	3y4m	M	Colombo	Metopic /frontal suture	Crouzon syndrome
3	3m10d	F	Ratnapura	Fronto parietal	Apert syndrome
4	11d	F	Gampaha	Metopic and sagital	Crouzon syndrome
5	11m	M	Colombo	Sagital suture	Saethre – Chotzen syndrome

Table- 24: Clinical and Radiological features of patients with Craniosynostosis

Pt no	consanguinity	Family history	Brain anomalies	Other system involvement
1	No	no	Superior sagital sinus thrombosis, premature fusion of sutures, hemiatrophy of left cerebral hemisphere.	Dysathria, normal fundus PFO in Heart
2	No	Yes 2nd degree relatives	Normal intelligence	Facial dysmorphism B/L undiscended testes
3	No	no	Microcephaly, prominent sub arachnoid space, small lateral ventricle. B/L diffuse gyral calcification, moderate cerebral atrophy.	Small osteum secondum ASD, PFO, Sub aortic VSD.
4	No	no	Fusion of metopic and sagital suture	Heart PFO
5	No	no	Fusion of sagital suture, ventriculomegaly	PDA small OS ASD

3.3.4:Other types of skeletal Dysplasia group

In this group 12 (28.5% of total patients) patient with 10 different disorders included .

Table - 25 : Other types of skeletal dysplasia - 12 cases with different clinical presentations.

Pt no	Age	sex	Ethnicity	Probable diagnosis	Residence /District
1	3y6m	M	Moor	Osteopetrosis	Kurunegala
2	1y2m	F	Sinhala	Syndactyly	Gampaha
3	17y	M	Sinhala	Marfan syndrome	Gampaha
4	4y10m	F	Sinhala	Talepes with femoral hypoplasia	Colombo
5	9m	F	Sinhala	Otopalatodigital syndrome	Gampaha
6	2y9m	M	Sinhala	Split hand foot syndrome with bone deficiency	Kalutara
7	7y5m	F	Sinhala	Larson syndrome	Kurunegala
8	5y3m	F	Sinhala	Holt oram syndrome	Nuwaraeliya
9	1y4m	M	Sinhala	Polydactyly	Gampaha
10	1y6m	M	Sinhala	Radial ray syndrome	Colombo
11	1/52	M	Sinhala	Radial Ray syndrome	Ratnapura
12	23y	F	Sinhala	Syndactyly	Anuradhapura

Table- 26 :Family history , consanguinity and associated other malformations of the Other types group patients

Patient no	Family history	Consanguinity	Skeletal involvement	Other system involvement	dependency
1	No	Yes	Diffuse osteosclerosis, cortical thickening	Facial dysmorphism, hydrocephalus ,blindness	Yes
2	Yes	No	Fusion of 3rd and 4th metacarpals	Facial dysmorphism	No
3	No	No	Pectus excavatum Scoliosis, prutrusio acetabuli, over crowding of teeth.	Myxomatous MVP trivial MR	No
4	No	No	B/L Talepes ,right hip dislocation	Meningomyelocele, nurogenic bladder, absent corpus callosum, hypotonia	Yes
5	No	No	Widely opened fontenelles, rib cupping, B/L short tibia and fibula	Facial dysmorphism, mild laryngomalasia	Yes
6	No	No	Absent left fore arm, palm and fingers. Absent right palm ,malformed digits in right side. Malformed rotated	Mild concentric LVH Inguinal hernia	Yes

			lower limbs		
7	No	No	Generalized osteoporosis, pectus carinatum, kyphoscoliosis, right hip dislocation, right radioulnar dysostosis,absent patella left side. trigonocephaly	Facial dysmorphism , right side microphthalmia Osteum secondum ASD, MVP and mild LVH	Yes
8	No	No	B/L absent radius, B/L hip joint laxity, malformed left shoulder,	Large osteum secondum ASD, deficient IVC, mild RPA stenosis at origin	Yes
9	No	No	Polydactyly B/L hand and feet, narrow chest, short ribs, short thickened tubular bones, genu vulgam nail dysplasia, delayed teeh eruption.	Facial dysmorphism, Partial AV canal defect, AV valve regurgitation, osteum secondum ASD	Yes
10	No	No	Bilateral fibular hemimelia, Angulation of both tibial bones, 3 metatarsals in right foot, 4 metatarsals in left foot, Left hand fused fingers and deformed.	Normal Ultra sound abdomen, hip and kidney	Yes
11	No	No	Facial asymmetry, hypoplastic thumb, absent left	Teralogy of Fallots, long segment pulmonary atresia,	yes

			radius	Osteum secondum ASD, dependant pulmonary circulation.	
12	No	No	Nail dystrophy, Syndactyly in both feet, 3rd,4thand fifth toes overlapped in both side, short toes, mild posterior scalloping of vertebral bodies and spina bifida of L5	Normal 2D ECHO, Small right kidney, mild hydronephrosis, mildly dialated pelvicaleceal system	No

As this study was conducted in the tertiary care centers this sample of patients were representing most of the district in the country. Twelve patient s (28.6%) from Colombo district , 10 /42 (23.8%) from Gampaha district. Three patient (7.1%) each from Kalutara , Ampara and Kurunegala. Rest of the patient each were from many different districts.

4 .DISCUSSION

Skeletal Dysplasia is a heterogeneous group of heritable condition resulting abnormalities in size, shape and density of the human skeleton.

The incidence of Skeletal Dysplasia is 2:10000 births.(23) The diagnostic approach of this group of disorders still based on clinical, biochemical and radiological data as genetic testing is out of reach to the majority of patients. So the better approach with detailed family history and through clinical examination is worth practicing as it is very helpful in the management and counseling of the patient and the parents.

From minor degree of skeletal malformation to major disability presentations showed the wide variability.

Our study was conducted in three tertiary care centers and we collected data from 42 patients with various types of skeletal disorders. The duration of data collection was 6 months.

This study does not reflect the disease pattern in Sri Lankan population as the small sample size and the collection done only in the selected places.

4.1 Demographic Data

Presentation of patient in this study is from throughout the country, but majority from Colombo (28.6%) and Gampaha district (23.8%). This may be due to high population index in those districts or the less distance to the centers we have selected. Reasonable prevalence in Ampara district as well. Rest of the districts patients were not commonly attended. Reason for less attendees may be due to financial problem for transport or may be the less interest about these incurable disorders.

4.2 :Age distribution

The time of skeletal manifestation of skeletal dysplasias were well recognized and defined. This knowledge is very helpful in Perinatal diagnosis of certain lethal and nonlethal disorders of bone. Achondroplasia and short limb dysplasias can be identified by ultrasound scan Hypochondroplasia usually evident 2 to 3 years after birth. The skeletal dysplasia due to Mucopolysaccaroidosis start to manifest the bone changes during puberty. Osteogenesis imperfecta certain types appear perinataly and some appear after 35 years of age.

Majority of this sample (20 patients / 26.1%) in between 1 year and 10 years of age. There were 2 neonates and 6 infants in this sample.

4.3:Gender Distribution

Generally there were no gender preponderance in skeletal dysplasia. With the possible inherent pattern of diseases this could be explained. Getting a detailed family history may give a clue of possible mode of inheritance. (24)If there is an affected family member in autosomal dominant mode of inherent there is a 50% chance of having a affected child. 25% chance with the autosomal recessive type. All the inherent mode have equal gender distribution. In X linked dominant type of inherent only the severity varies according to the gender. But in our study most disorders well known to inherit an autosomal dominant manner like Achondroplasia occurs in families without the affected member . Then the possibility of new mutation in the particular gene.

4.4 :Ethnicity

In our study population 83.3 % from Sinhalese people. This may be high population index of Sinhalese as they were the major. Tamil patients were 7.1% and Moors were 9.5%. Ethnicity is also a important parameter in certain diseases as they are common in some ethnic groups. Spondylo metaphyseal dysplasia with joint laxity was common in South African Afrikaner population.(24)

4.5 :Sub Groups Of Skeletal Dysplsia

4.5.1 :Osteogenesis imperfecta group

In this study 9/42 (21.4%) were belonged to reduced bone density group (OI) Consist of eight females and one male. A Canadian study in 2012 found equal gender distribution. (25) Indian study showed a higher presentation of male patients. (26)

The mean age of appearance of the first symptom was 14 years. Among them two patients were diagnosed at birth (22.3%) and 3 were above 35 years of age.

Facial dysmorphism seen in 3 female patients. Patients in figure- 3 One had asymmetrical triangular shaped face with frontal bossing and low set ears. The second patient(in picture B) had the cushionoid face with Hirsuitism and dry, coarse skin with pigmentation. (third patient didn’t give consent for photographs)

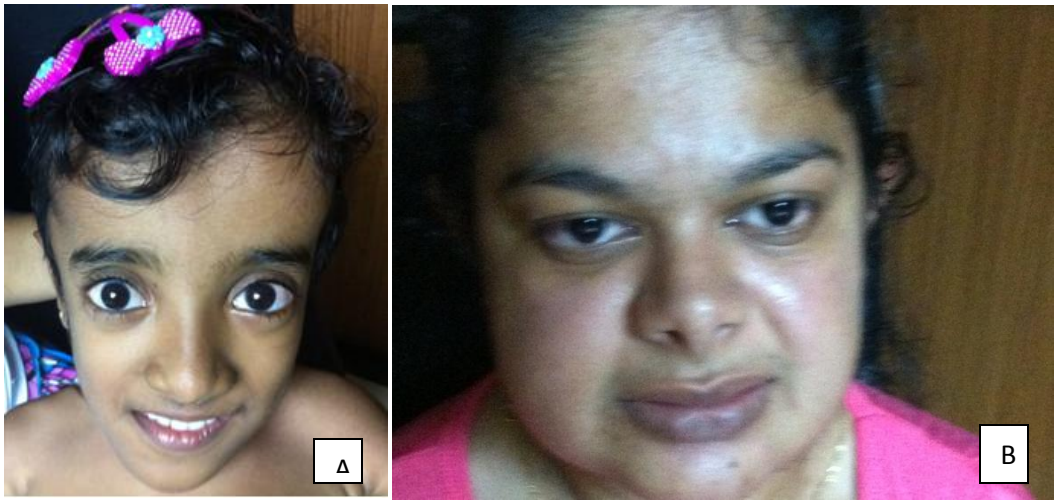

Figure – 12 : Facial features of two patients with OI : picture **A**. (patient no2)Asymmetrical triangular shaped face with frontal bossing, ptosis and low set ears **B. (**patient no-8) Cushinoid face with Hirsuitism, dry coarse skin, hyper pigmented patches

According to the diagnostic criteria these two patients belong to Osteogenesis imperfecta type III, but they showed variable phenotype. Both of them were born to consanguineous parents. Patient number 2 did not have affected family members. Patient number 8 was having affected brother elder to her, and wheel chair bound.

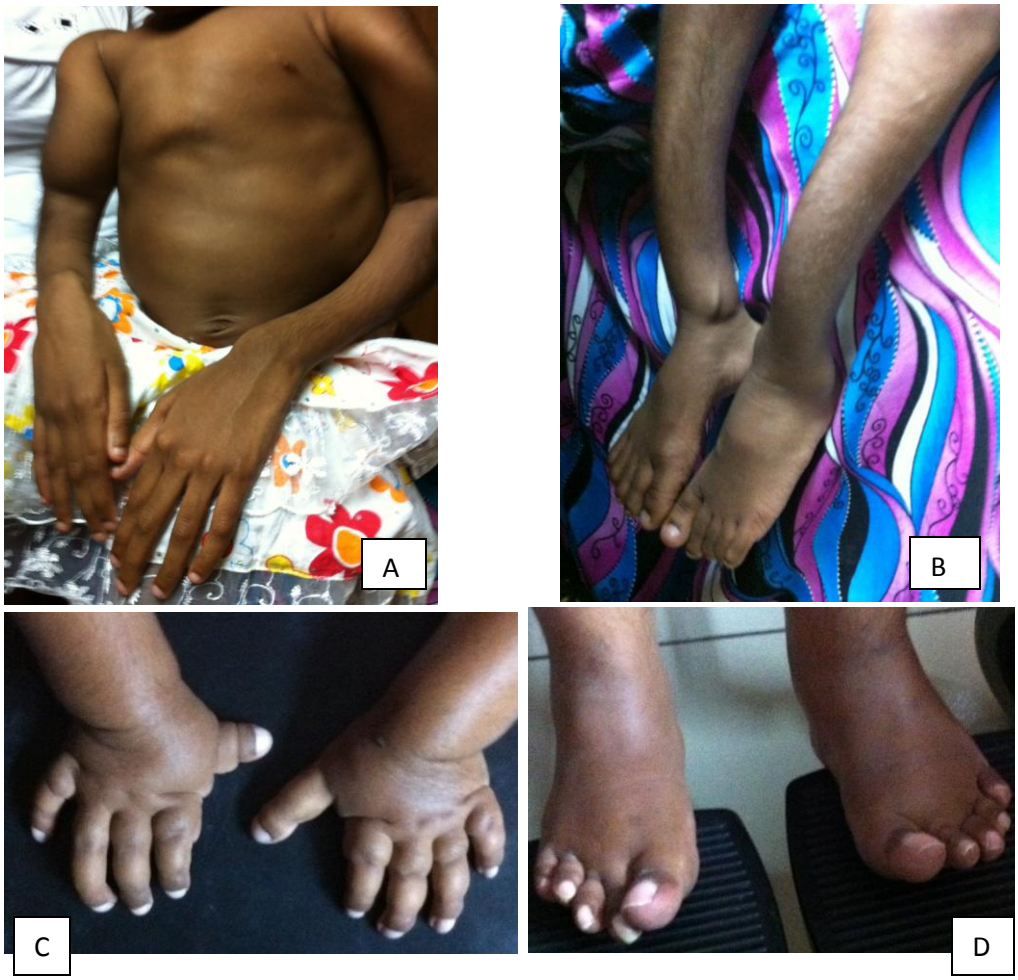

Figure –13 : Feature of hand and feet of patients with OI :Picture **A** and **B**.(patient no -20) Arachnodactyly , deformed upper and lower limb with anteroposterior bowing **C** and **D** (patient no-8) small hand and feet with absent carpal bones and overriding toes.

Three of the patients (33.3%) were having Arachnodactyly, two patients (22.2%) had short finger and small hands. Four of others(44.4%) had normal hands and feet.

Radiologically all the patient were having osteopenia in different degrees, multiple fractures and deformed bones.

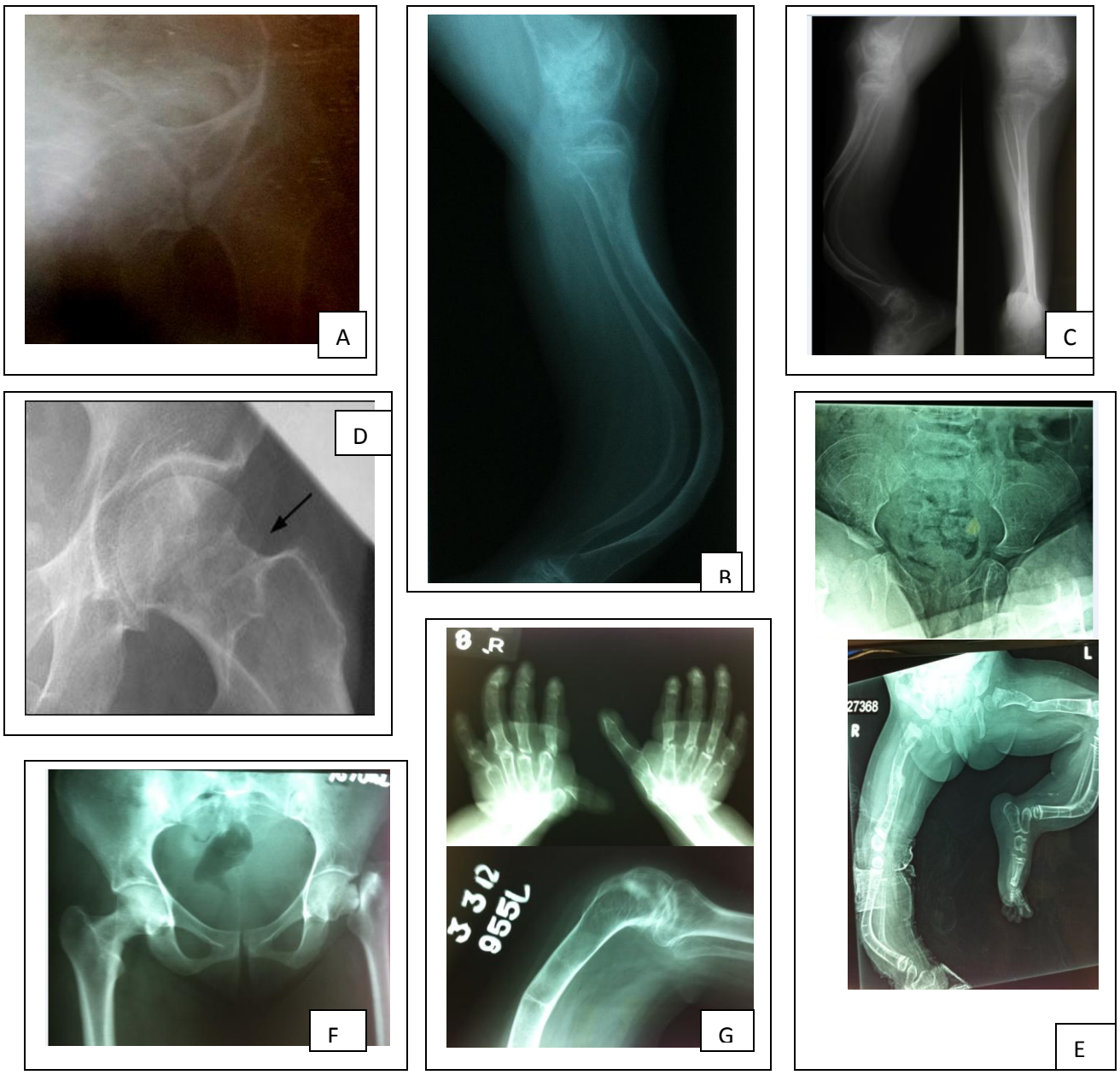

Figure 14 : Radiological features of patients with OI : **A (**Patient-1) Protrusio acetabuli, low bone density – OI type III : **B**(patient -2) Thin gracile bone with anteroposterior bowing OI type III : **C**(patient -3) Anteroposterior bowing and osteopenia OI type III : **D** (patient- 5) protrusio acetabuli and fracture neck of the femur extra capsular OI type IV : **E** (patient-6) low bone density with multiple fractures , the zebra lines in Iliac bones due to treatment OI type III : **F** (patient-7) disuse atrophy of Hip and fracture neck of the femur OI type I : **G** (patient -8) osteopenia, absent carpal bones, broad Metaphysis with mushroom like deformity OI type III.

All the patients presented with fractures. (100%) Numbers of fractures at the time of recruitment were varied from 2 to 8, mean number of fracture was 3.7. In 2007 India reported a higher number of fractures per individual and mean was 6.8.(26) All the patients were having fracture femur either unilateral or bilateral. Second commonest fracture was humerous.(33.3%) Wormian bones in the skull noted in one patient.(11.1%)

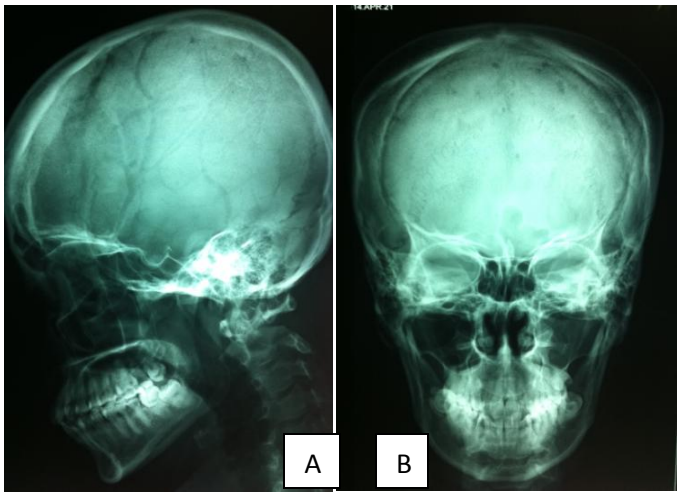

Figure 15 - : picture **A** and **B**(patient- 7) Wormian bones in the skull

Blue sclera was observed in 5 patients,(55.5%) Dentinogenesis imperfecta in 6 patients (66.6%)

One patient was having progressive hearing loss.(11.1%) A study done in Finland 2005 showed progressive hearing loss in 65.3% of patients . Found in all types of OI and the mean age at onset of hearing loss was 23.9 years. We could not calculate a mean age as we had only one case.(27)

Cardiac malformation diagnosed in one patient among the nine, and two were having minor cerebral malformations.

Seven out of nine were disabled and dependent, only two patient could perform the normal routine.

Consanguinity was found in 2 patients (22.2%), and family history of affected individuals noted in 3 patients.

The phenotypic variation we observed was difficult to correlate with the genetic mutation. Osteogenesis imperfecta type I to IV occurs as a result of mutation of genes of type one collagen.(COL1A1 and COL1A2) Mutation screening usually done with the widely used confirmation sensitive gel electrophoresis technique. (CSGE)The mutation could be a single nucleotide substitution or base insertion and deletion with missense type. The mutations alter the glycine codon in central exon of the gene which encode the protein region that form the collagen triple helix. Replacement of the guanine residue in glycine codon by different amino acid causes different phenotype of Osteogenesis imperfecta. Frequency of mutation can be vary. The correlation between triple helix glycine mutation and the phenotype is impossible. In between the mutation and phenotype nutritional and environmental factors which can change the features between individuals. (28)

4.5.2 :Short Stature

Sixteen patient (38%) presented with short stature. This was basically divided into two groups as dyspropotionate short stature and proportionate short stature.

Ten patients (62.5% of short stature patents) belongs to the group of dyspropotionate short stature . In this 6/10 (37.5% of short stature patients)were Achondroplasia and other 4 (25% out of 16) were in Hypochondroplasia group. Equal gender distribution. Mean age at presenting to the tertiary level medical care was 8 years.

Bone age was assessed in 3 patients ,two showed reduced bone age than the chronological age. One patient had normal bone age. Mid parental height was assessed. All the parents were having the average height.

Dyspropotionate short stature was common in this group of short stature patients. All the extremely short patients were having facial dysmorphism in varying degrees. This group consists of 7 Achondroplasia patients.

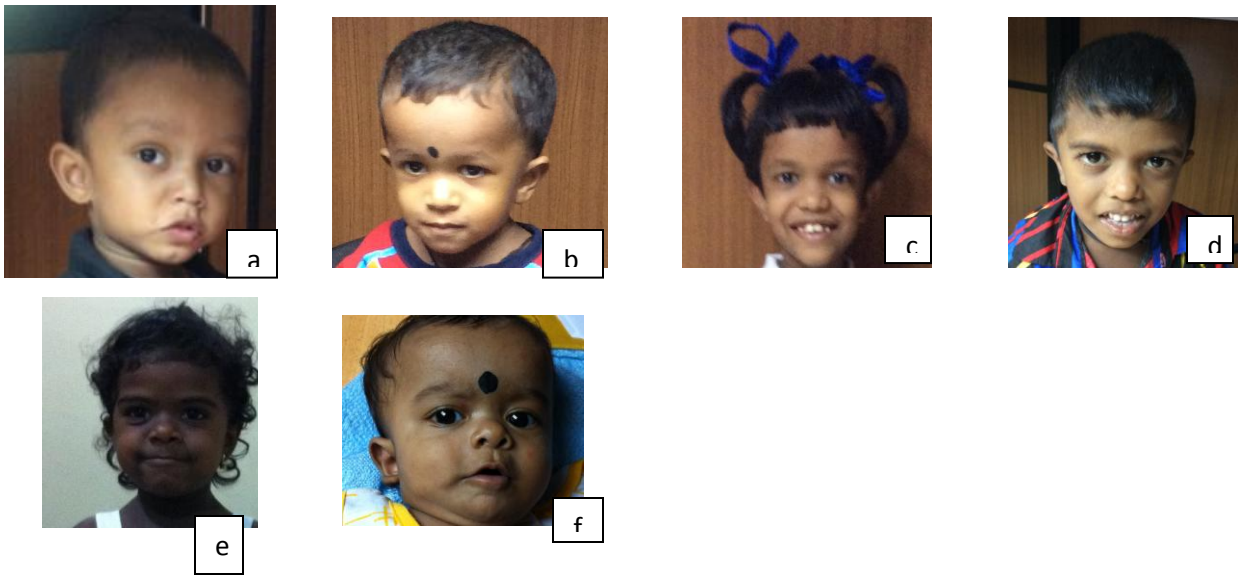

Figure 16 :Facial features of patient with Achondroplasia **a –f** Frontal bossing, low set years, mid facial retrusion flat nasal bridge and sunken eyes common to all the patients

All the patients with Achondroplasia share common radiological features such as Posterior scalloping of vertebral bodies, thoraco lumbar kyphoscoliosis and height well below the 3rd centile for age and sex.(standard growth parameters used to assess the patient – Appendix -2)

Assessment of growth is a complex, as many factors contribute to have a normal height. Normal variations of height mostly due to genetic factors. Environmental and nutritional factors may have impact on it. The genetic determinant usually polygenic. Many genetic variants commonly found in the population has small effect on height.(29) Reasent studies showed more than 500kb deletion and the copy number variants more than 4% may cause short stature.

The extreme of short stature probably due to single gene mutation. Eg: Achondroplasia. Number of other genetic conditions also causes growth retardation. Common causes were 3M syndromes .Intrauterine growth retardation, normal OFC at birth, prominent fore head, fleshy nose, full eye brows. Long filtrum, and pointed chin were common features. Radiologically gracile bones, small pelvic bones, broad thorax and thin ribs identified. Males were probably present with small testes and fertility problems.CUL7, OBSL1, CCDC8 genes identified as causative factors. These disorders inherited as autosomal recessive manner and common in consanguineous population.

4.5.3 : Craniosynostosis

The percentage of craniosynostosis in this study sample was 11.9% (5 patients)Among the patients with craniosynostosis 60% were females.(30) 50 % of patients were belong to non syndromic category.

Birth prevalence of Craniosynostosis is 4.3 per 10,000 births Environmental factors (intra uterine fetal head constraints) and genetic factors (single gene mutations, chromosome abnormalities and polygenic background) predispose to Craniosynostosis. Genetically determined Craniosynostosis mostly occur due to mutations in FGFR2, FGFR1, TWIST1, and EFNS1 genes and are characterized by autosomal dominant inheritance. More than half of the mutations of the above four genes occur in a denovo manner. (31)Craniosynostosis can be either syndromic or non syndromic. Syndromic Craniosynostosis is associated with multiple suture involvement and extracranial complications while nonsyndromic Craniosynostosis usually involves only a single suture.

We have one patient with Saethre-chotzen syndrome 2 patients with Crouzon syndrome, one with Apert syndrome . (32) Most non syndromic Craniosynostosis could be due to the mutation in FGFR3 gene.. With the knowledge of phenotypic features of the patient possible genetic origin can be identified .Craniosynostosis with facial dysmorphism usually associated with TWIST1 gene mutation. Saethre-Chotzen syndrome can be due to heterozygous mutation of the TWIST1 gene. The TWIST 1 gene located at chrome 7p21 region and position 19,121616 – 19, 123820 reverse strand .DNA sequence contains 2 Exones and the transcript length is 1669bp translated in to a 202 residue proteins. TWIST1 gene encode a transcription factor in basic Helix – Loop – Helix family (BHLH motif).The HLH (Helix – Loop – Helix) region of the motif is important for homo or hetero dimerization and the basic domain is necessary for binding of the dimer complex to a target DNA binding sequence. In the embryonic period of life TWIST1 is expressed in neural crest cells and essential for correct patterning of the neural tube and also proper migration of neural crest and head mesenchymal cells.(33, 34)The Saethre- Chotzen syndrome results because of the haploinsufficiency of TWIST1 gene due to many different

mutations including whole gene deletion, intragenic nonsense and frame shift mutations and missense substitutions. Missense substitutions mainly confined to BHLH motif that required for DNA binding and dimerization. Genotype- Phenotype correlations are not described in TWIST1 mutations but large deletions associated with learning disabilities. Missense mutations in C terminal twist box can be associated with non specific synostosis phenotype.(30) This syndrome was initially described by Saethre and Chotzen in the early part of 1930.(35) Saethre –Chotzen syndrome is autosomal dominantly inherited or can be sporadic (due to denovo mutations)(36)and shows high penetrance and variable expressivity.(37) Genetic heterogeneity is reported in Saethre- Chotzen syndrome . Other than TWIST gene there are at least two other genes :FGFR2, FGFR3 which are also involved in this syndrome.(38) The expression of the T WIST gene shows wide varience.(37) Craniosynostosis is also a variable feature. Those with large deletions in the region may have significant learning difficulties in addition to the typical features of the Saethre –Chotzen syndrome.(35) Wolfarm and his team has identified even with same mutation or deletion there are phenotypical variations in his sample of patients. The estimated prevalence of this syndrome was in between 1:25000 births and 1: 50000 births in 1998.(37)

The typical features of Saethre –Chotzen syndrome include facial asymmetry, low frontal hair line, hypertelorism, ptosis and small rounded ears. Characteristic skeletal involvement can also be seen :short stature, Craniosynostosis and radioulnar synostosis.(39) Limb anomalies include cutaneous Syndactyly, Brachydactyly and large broad toes. Many patients share common features even though the mutation occur in different genes.

The cytogenetic analysis is necessary to differentiate the conditions as the diagnosis is always complicated.

Therefore the usage of cytogenetic diagnostic tests for dysmorphism in early life helps to proceed with the effective fruitful family counseling and also beneficial in clinical management of affected neonate.

4.5.4 : Other types of skeletal dysplasia

We had 2 patients with Syndactyly (4%) in our sample and both of them were females. The commonest involvement as stated was 3rd web , these two were having both 3rd and 4th web involvements. Incidence of Syndactyly was 1 in 2000 to 2500 births.(40) in the population and frequency of affected males was twice in number than the females. The incidence of spina bifida occulta in the general population was about 10% to 24% . (41)We got one patient with Spina bifida occulta in our sample (2%)

Brief over view of other types of skeletal dysplasia given in table 25 in page 62.

Summarizing the study sample we have some interesting finding that may help to target the future studies of skeletal dysplasia in Sri Lanka.

Chest wall deformity with scoliosis in 16 patients out of 42 , it represented 38% of total sample.

18 patients (42.8%) were having cardiac malformation other than skeletal deformities.

Developmental deformities in the hip was common in the sample, we had 12 patients (28.5%) and six of them were unable to walk and wheel chair bound.

We came across one patient with bilateral optic nerve atrophy. He was blind since birth, and diagnosed to have osteopetrosis with increased bone density.

5.CONCLUSION

This study was conducted in patients with clinically obvious skeletal anomalies. During the period of 6 month starting from 1st of January to 30th of June 2014, collection of sample was done in 3 tertiary level centers in Colombo of Sri Lanka. Following conclusions were made after a comprehensive analysis of the patients' data.

Diagnosis of skeletal dysplasia is not a simple task as they are heterogeneous and rare in clinical practice. The Clinical geneticist together with expertise in the field of Radiology, Obstetric and Pediatric could improve the accuracy of diagnosis of skeletal dysplasia. This will facilitate the comprehensive approach in counseling of the patients regarding the current situation and the expected prognosis.

Certain skeletal dysplasias can identified at birth. Some of them appear to be symptomatic later in life. The need of a molecular diagnosis is mandatory to identify the causative mutation. Patient with high probability of skeletal dysplasia can be screened with this novel technology before they acquire the symptoms.

Summarizing the given history and clinical data we observed few families having more than one affected children with the consanguinity in parents. Some patient had affected second degree relatives with skip (first degree relative)generation. Few patients with gross deformities had less severely affected members in the previous generations and they left unnoticed as disability was minor.

Some have given the history of recurrent pregnancy loss with abnormally formed fetuses. The positive family history, consanguinity and bad obstetric history had an impact on the skeletal disorders. The disease burden could be minimized by arriving the diagnosis at birth and take action to prevent recurrence in the same family. Screening should be provided before pregnancy to the patient with skeletal deformities, high risk couples with family history of skeletal dysplasia and the consanguineous parents with possible risk of autosomal recessive skeletal disorders.

6.LIMITATIONS

The study was conducted in a limited period of time with referred patients in three tertiary care centers. The initial presentation and patient with minor deformities were less in number. Most patients were having gross deformity and complicated presentation. The study sample is not representing the actual picture of prevalence as these centers getting referrals from the peripheral hospitals.

The patients with minor deformities usually not seeking medical advice. We couldn't recruit some of those patients as they didn't give their will for the participation. Consent for photographs was unable to obtained in few of the recruited patient. Taking measurements in very young, bed ridden and disabled patients were really difficult, but managed to get the last 0.25 cm.

Lack of radiological findings in recruited patient also a limitation. Most of the patients only had the X ray of the most affected part. The assessment of rest of the skeleton was neglected.

With regards to family history, the observers' description accepted most of the time as documented evidence of diagnosis of family members not available.

7.RECOMMENDATIONS AND FUTURE PROSPECTS

This is a highly potential area for the future research .Need national level population based studies with multidisciplinary approach. Ultimate aim is to maintain a National Skeletal Dysplasia Registry.

Develop a management strategy and treatment protocol for skeletal dysplasia patients.

Develop a low cost molecular diagnostic tool with high sensitivity and specificity for screening of pregnant women and asymptomatic person with increased risk of skeletal disorders.

Develop a Network with expertise in genetic field at national and international level and share knowledge in cases with uncertain diagnosis.

Implement a Stem cell based therapeutic options in future.

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APPENDIX 1

List of abbreviations

AER – apical ectodermal ridge

COL1A1 – collagen one alpha one

CRTAP cartilage associated protein

FGFR – Fibroblast growth factor receptor

OI – Osteogenesis Imperfecta

OMIM – On line Mendelian inheritance of Man

PSM - Para axial pre somatic mesoderm

SCS -Saethre Chotzen syndrome

TACE -tumor necrosing factor alpha converting enzyme

NICD – Notch intra cellular domain

9.Appendix 2.1.

Group	Skeletal dysplasia type	genes
1	**FGFR 3 Chondrodysplasia group** Thanatophoric Dysplasia type 1 Thanatophoric dysplasia type 2 Severe achondroplasia with developmental delay and acanthosis nigricans SADDAN Achondroplasia Hypochondroplasia Camptodactyly, tall stature and hearing loss syndrome (CATSHL) Hypochondroplasia like dysplasia	FGFR3
2	**Type 2 collagen group and similler disorders** Achondroplasia type 2 (Langer- Saldino) Platyspondylic dysplasia Torrance type Hypochondrogenesis Spondyloepiphyseal dysplasia congenita (SEDC) Kniest dysplasia Spondyloperipharal dysplasia Mild SED with premature onset arthrosis SED with metatarsal shortening Sticler syndrome type I Stikler like syndrome	COL2A1
3	**Type 11 collagen group** Stickler syndrome type2 Marshall syndrome Fibrochondrogenesis Otospondylomegaepiphyseal dysplasia OSMED recessive type Otospondylomegaepiphyseal dysplasia dominant type	COL11A1 COL11A2
4	**Sulfation disoders group** Achondrgenesis type 1B Atelosteogenesis type 2 MED AR type SEMD PAPSS2 type Chondro dysplasia with congenital joint dislocation type Ehlers –Danlos syndrome	DTDST PAPSS2 CHST3 SHST14
5	**Perlecan group**	PLC(HSPG2)
6	**Aggrecan group**	ACG1
7	**Filamin group and related dissorders** Otopalatodigital syndrome Larsen syndrome	 FLNA FLNB
8	**TRPV4 group**	TRPV4
9	**Short rib dysplasia group with or without polydactyly**	EVC1 IFT80
10	**Multiple epiphyseal dysplasia**	COMP

		COL9A1
11	**Metaphyseal dysplasia**	COL10A1 RMRP
12	**Spondylometaphyseal dysplasia (SMD)**	ACPS
13	**Spondylo epiphyseal dysplasia**	DYM SMARCAL1 DDR2
14	**Severe spondylodysplastic dysplasia**	TRIP11 SLC35D1
15	**Acromelic dysplasia**	TRPS1 IHH
16	**Acromesomelic dysplasia**	NPR2 GDFS BMPR1B
17	**Mesomelic and rizomesomelic dysplasia**	SHOX GPC6
18	**Bent bone dysplasia**	SOX9
19	**Slender bone dysplasia group**	CUL7 TBCE
20	**Dysplasia with multiple joint dyslocations**	CANT1
21	**Chondrodysplasia punctata group**	EPP ARSE NSDHL
22	**Neonatal osteosclerotic dysplasia group**	PTHR1 DHCR24 COL1A1
23	**Increased bone density group** **osteopetrosis**	FAM20C TCIRG1
24	**Increased bone density group with metaphyseal involvement**	TBXAS1 OPG SOST
25	**Osteogenesis imperfecta and decreased bone density group**	COL1A1 COL1A2 SP7
26	**Abnormal mineralization group**	PHEX PGF23
27	**Lysosomal storage disease with skeletal involvement group** **mucopolysaccharidosis**	IDA IDS
28	**Osteolysis group**	LMNA
29	**Disorganized development of skeletal component group**	EXT1 EXT2
30	**Over growth syndromes with skeletal involvement group** **Marfan syndrome**	FBN1 FBN2
31	**Genetic inflammatory rheumatoid like osteoarthropathies**	WISP3
32	**Cleidocranial dysplasia and isolated cranial ossification defect group**	RUNX2 MSX2
33		

Appendix - 2 .1.1

Classification of Osteogenesis Imperfecta sub types.

OSTEOGENESIS IMPERFECTA, TYPE I OMIM number :166200

Autosomal dominant inheritance Normal to near normal stature Height often shorter than unaffected family members. Hearing loss, progressive conductive and or sensorineural, during adulthood. Otosclerosis Blue sclerae Normal teeth (in most patients) Dentinogenesis imperfecta (rare) Varying degree of multiple fractures Opalescent teeth (rare) Mitral valve prolapse. Mild osteopenia Varying degree of multiple fractures Wormian bones Biconcave flattened vertebrae Occasio Easy bruisability nal femoral bowing Mild joint Hypermobility. Thin skin Onset of fracture usually when child begins to walk Fracture frequency constant through childhood, decreases after puberty Fractures often heal without deformity Fracture frequency increases after menopause and in men ages 60-80 Caused by mutation in the collagen I, alpha-1 polypeptide gene (*COL1A1*)

OSTEOGENESIS IMPERFECTA, TYPE II OMIM no:166210

Autosomal dominant Short limb dwarfism Low birth weight Blue sclerae Beaked nose Congestive heart failure Pulmonary insufficiency ,Beaded ribs Numerous multiple fractures present at birth Wormian bones Soft calvaria Absent calvarial mineralization Large fontanellesPlatyspondyly Hi Tibial bowing ps usually flexed and abducted (frog-leg position) Flattened acetabulae and iliac wings Broad crumpled long bones Telescoped femur Thin skin, Nonimmune hydrops Premature birth Perinatal lethal Survival greater than one year rare Gonadal and somatic mosaicism reported in parent Ultrasound detection in second trimester of pregnancy. Caused by mutation in the collagen I, alpha-1 polypeptide gene (*COL1A1*) and mutation in the collagen I, alpha-2 polypeptide gene (*COL1A2)*

OSTEOGENESIS IMPERFECTA, TYPE III OMIM no : 259420

Autosomal dominant Short limb dwarfism recognizable at birth Adult height 92-108 cm Triangular face Frontal bossing Micrognathia Hearing loss Blue sclerae at birth becoming normal with age. Dentinogenesis imperfecta (both primary and secondary teeth), pulmonary hypertension ,Thin gracile ribs, Severe, generalized osteoporosis, Multiple fractures present at birth, Wormian bones, Large anterior fontenelle, Undermineralized calvarium Scoliosis, Kyphosis, Codfish vertebrae, Protrusio acetabuli, Long bone deformity evident at birth or in the

first 2 years of life, Bowing of limbs due to multiple fractures, Thin gracile long bones, Tibial bowing, Short deformed femurs, Evidence of in utero fracture Popcorn" calcification Basilar impression Some mutations have been found in homozygosity and the phenotype is more severe than that of the heterozygous parents Caused by mutation in the collagen I, alpha-1 polypeptide gene (*COL1A1)* and the collagen I, alpha-2 polypeptide gene (*COL1A2*)

OSTEOGENESIS IMPERFECTA, TYPE IV OMIM no : 166220

Autosomal dominant Short stature, often below 5th percentile Hearing loss Otosclerosis Normal-greyish sclerae Pale blue sclerae (10% of the cases) Dentinogenesis imperfecta Mild-moderate skeletal deformity, Varying degree of multiple fractures, Wormian bones, Scoliosis, Kyphosis Biconcave flattened vertebrae, Femoral bowing present at birth, straightening with time Bowed limbs due to multiple fractures, Often identified in newborn period, Fractures can occur in utero, during labor and delivery, or in newborn period, Fractures occur in first few months, then decrease in frequency and then occur with ambulation, Fractures decrease after puberty but increase after menopause. Caused by mutation in the collagen I, alpha-1 polypeptide gene (*COL1A1*) and mutation in the collagen I, alpha-2 polypeptide gene (*COL1A2*)

OSTEOGENESIS IMPERFECTA, TYPE V OMIM number : 610967

Autosomal dominant Short stature (childhood) Birth length normal Birth weight normal Normal sclerae Normal teeth , Moderate to severe bone fragility, Moderately deforming osteogenesis imperfecta , Varying degree of multiple fractures , Decreased bone mineral density , Wormian bones , Biconcave vertebrae, Wedge-shaped vertebrae, Flattened vertebrae, Irregular, meshlike matrix lamellae in the histology of the iliac crest, Limited pronation/supination of forearm, Anterior dislocation of radial head, Calcified interosseous membrane (forearms), Elevated serum alkaline phosphatase during hyperplastic callus formation Increased urinary collagen type I N-telopeptide excretion (NTx) during hyperplastic callus formation, Caused by mutation in the interferon-induced transmembrane protein 5 gene (*IFITM5*)

OSTEOGENESIS IMPERFECTA, TYPE VI OMIM no : 613982

No intrauterine fractures and normal birth length and weight .No fractures at birth. Fractures appear between ages 4 and 18 months. frequent fractures than patients with OI type IV, leads to long bone deformity. Ligamentous laxity,. Sclerae were white or faintly blue, normal teeth . Radiologic findings: long bone deformity, coxa vara, and protrusio acetabuli, vertebrae wedge-shaped or biconcave. vertebral compression fractures. Wormian bones of the skull were absent. Lumbar spine bone mineral density (aBMD) was low (similar OI type IV) .severe osteopenia, bulbous metaphyses, and severe limb deformity. Histology of iliac bone with distinctive 'fish-scale' pattern of the lamellae. hyperosteoidosis leads to defect in mineralization. biochemical bone markers within the reference range but serum alkaline phosphatase levels elevated. short stature and wheelchair bound. Causative factor is a homozygous truncating mutation in the *SERPINF1* gene.

OSTEOGENESIS IMPERFECTA, TYPE VII OMIM number : 610682

Autosomal recessive Normal birth length Short stature (adult) Normal birth weight, Large open anterior fontanelle Open sutures Round face Long philtrum Normal hearing Normal hearing Proptosis Bluish sclerae No dentinogenesis imperfecta Absent pulmonary artery Hypoplastic pulmonary veins Narrow chest Narrow chest Pectus excavatum, Multiple rib fractures, Multiple rib fractures, Hydronephrosis, Multiple fractures present at birth ,Moderate-severe bone fragility Osteopenia Wormian bones Poorly ossified calvaria Vertebral compression fractures Scoliosis, Coxa vara, Protrusio acetabulae, Rhizomelia , Micromelia Externally rotated/abducted legs Osteopenic long bones Crumpled long bones, Undertubulation (lack of diaphyseal modeling) Bowed lower limbs, Term delivery, Breech presentation, Multiple fractures present at birth, Death in infancy secondary to respiratory, insufficiency/pneumonia Fracture frequency decreased post puberty. Caused by mutation in the cartilage-associated protein gene (*CRTAP*)

Appendix 2.2 .2 Classification of short stature

A Primary growth disorders

A1 Clinically defined syndromes
- Turner syndrome
- Cornelia de Lange syndrome
- DiDeorge syndrome (velocardiofacial syndrome)
- Down syndrome
- Noonan syndrome
- Prader-Willi-Labhart syndrome
- Von Recklinghausen's disease (neurofibromatosis type 1)
- Silver-Russell syndrome

A2 Small for gestational age with failure of catch-up growth
- IGF-I deficiency, IGF resistance
- Due to known cause, e.g. prenatal infections, drugs, smoking, alcohol
- Idiopathic

A3 Skeletal dysplasias
- Achondroplasia
- Hypochondroplasia
- Dyschondrosteosis (Leri-Weill and other defects in the SHOX gene)
- Osteogenesis imperfecta I–VI
- Mucopolysaccharidosis (type IH, IS, II–VII)
- Mucolipidosis (type II and III)

A4 Dysplasias with defective mineralization

B Secondary growth disorders

B1 Insufficient nutrient intake (malnutrition)

B2 Disorders in organ systems
- Cardiac disorders
- Pulmonary disorders, e.g. cystic fibrosis
- Liver disorders
- Intestinal disorders, e.g. Crohn's disease, malabsorption syndromes
- Short bowel syndrome
- Renal disorders, e.g. Fanconi syndrome, renal acidosis
- Chronic anemia

B3 Growth hormone deficiency (secondary IGF-I deficiency)
- Idiopathic
- Genetic (HESX1, PROP1, POU1F1, LHX3, LHX4, GHRHR, GH)
- Associated with syndromes or cerebral or facial malformations, e.g. septo-optic dysplasia, empty sella syndrome
- Associated with prenatal infections, e.g. rubella
- Acquired (craniopharyngioma, other pituitary tumors, e.g. germinoma, hamartoma)
- Head trauma
- Central nervous system infections
- Granulomatous diseases, e.g. histiocytosis

B4 Other disorders of the growth hormone-IGF axis (primary IGF-I deficiency and resistance)
- Bioinactive growth hormone
- Abnormalities of the growth hormone receptor (growth hormone insensitivity syndrome, Laron syndrome)
- Abnormalities of GH signal transduction, e.g. STAT5B defect
- ALS (acid-labile subunit) deficiency
- IGF-I deficiency
- IGF resistance (IGF1R defects, postreceptor defects)

B5 Other endocrine disorders
- Cushing syndrome
- Hypothyroidism
- Leprechaunism
- Diabetes mellitus (poorly controlled)
- Short adult stature caused by accelerated bone maturation, e.g. precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, exogenous estrogens or androgens

B6 Metabolic disorders
- Disorders of calcium and phosphorus metabolism
- Disorders of carbohydrate metabolism
- Disorders of lipid metabolism
- Disorders of protein metabolism

B7 Psychosocial
- Emotional deprivation
- Anorexia nervosa
- Depression

B8 Iatrogenic
- Systemic glucocorticoid therapy
- Local glucocorticoid therapy (inhalation, intestinal, other)
- Other medication
- Treatment of childhood malignancy
- Total body irradiation
- Chemotherapy
- Other specified iatrogenic causes

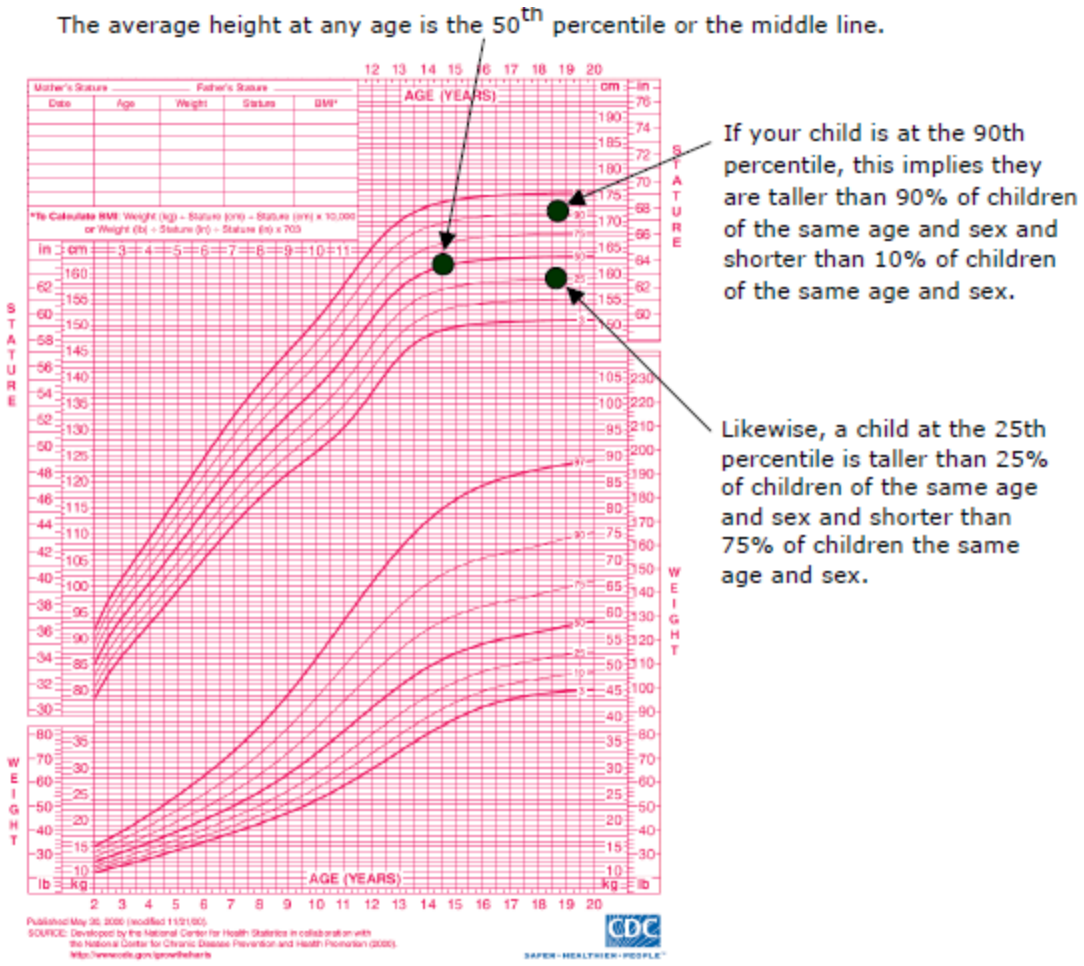
C Idiopathic short stature

C1 Familial (idiopathic) short stature

C2 Non-familial (idiopathic) short stature

Classification according to the ESPE classification [19].

Standard Growth charts used to assess the height of the child with short stature



Standard formulae used to calculate the mid parental height(42)

Mid-parental height for boys = (Mother's height + father's height)/2 + 6.5 cm ± 8 cm
Mid-parental height for girls = (Mother's height + father's height)/2 – 6.5 cm ± 8 cm.
The target height is plotted

Appendix 2 .2.3 a and B Analysis of craniosynostosis OMIM

Commonly used clinical genetic classifications

Diagnostic Category	Name of Disorder	Cause
Isolated craniosynostosis	Morphologically described	Unknown, uterine constraint, or FGFR3 mutation
Syndromic Craniosynostosis	Antler-Bixler syndrome	Unknown
	Apert's syndrome	Usually one of two mutations in FGFR2
	Baere-Stevenson syndrome	Mutation in GFGR2 or FGFR3
	Bailler-Gerold syndrome	Mutation in TWIST heterogenous
	Carpenter's syndrome	Unknown
	Craniofrontonasal dysplasia	Unknown gene at Xp22
	Crouzon's syndrome	Numerous different mutations at FGFR2
	Crouzonomesodermoskeletal syndrome	Mutation in FGFR3
	Jackson-Weiss syndrome	Mutation in FGFR2
	Muenke's syndrome	Mutation in FGFR3
	Pfeiffer's syndrome	Mutation in FGFR1 or numerous mutations in FGFR2
	Saethre-Chotzen syndrome	Mutation in TWIST
	Shprintzen-Goldberg syndrome	Mutation in FBFN1

Non syndromic craniosynostosis Appendix 2.2.3- A

CRANIOSYNOTOSIS I OMIM : 123100

Beaten copper appearance of the skull. Dolichocephaly , Oxycephaly or scapocephaly. Autosomal dominant inheritance.

CRANIOSYNOSTOSIS II OMIM: 604757

Skull malformations included forehead retrusion, frontal bossing, turribrachycephaly, and the Kleeblattschaedel deformity (cloverleaf skull anomaly; trilobular skull with craniosynostosis). myopic or hyperopic. May or may not have a seizure disorder. Intelligence was normal. No hand or foot abnormalities . In radiographic examination short first metatarsals.

CRANIOSYNOSTOSIS III OMIM : 615314

Autosomal dominant, Low anterior hairline Minor ear anomalies Strabismus Blepharoptosis , Malocclusion of teeth class I/II, Coronal synostosis, unilateral or bilateral Sagittal synostosis, Transverse

palmar crease , Brachydactyly, Hallux valgus, Syndactyly between adjacent toes, Low anterior hairline, learning disability, Developmental delay , Prominent ventricles in brain, Prominent CSF spaces, Agenesis of corpus callosum, partial or complete, Caused by mutation in the transcription factor-12 gene (TCF12)

Syndromic craniosynostosis Appendix2. 2.3- B

1. Crouzon syndrome OMIM : 123500

Craniosynostosis ,brachycephally, frontal bossing, maxillary hypoplasia, mandibular prognathism , conductive hearing loss, Atretic external auditory canals, optic atrophy , shallow orbit, proptosis , hypertelorism, strabismus, exposure conjunctivitis, poor vision , parrot like nose,lateral palatal swelling , dental over crowding, sleep apnea, craniosynostosis of coronal sagittal and lamboid sutures. Calcification of stylohyoid ligament, cervical spine abnormalities, mental retardation, occasional seizures, Caused by mutations in the fibroblast growth factor receptor 2 gene (FGFR2)

2. Apert syndrome OMIM:101200

Autosomal dominant inheritance, Deceleration of linear growth during childhood, Normal birth weight, Normal birth length, acrobrachycephaly, large fontenelle, high broad fore head, flat face , mid face hypoplasia, mandibular prognathism ,hearing loss, Choanal stenosis or atresia , shallow orbit, hypertelorism, down slanting palpreble fissures, proptosis, Depressed nasal bridge, cleft palate, malocclusion of teeth, delayed dental eruption, Hydronephrosis in the kidney, Craniosynostosis (coronal), jugular foraminal stenosis. Cervical vertebrae fusion, usually at C5 to C6, Synostosis of radius and humerous, Fusion of carpal bones, especially capitate and hamate, Symmetric osseous and/or cutaneous syndactyly of hands, Broad distal phalanx of thumb, polydactyly, Single nail common to digits 2 to 4, variable mental retardation, Agenesis of the corpus callosum, Ventriculomegaly, absent septum pelucidum, limbic malformations, chiari I malformations, hydrocephalus, caused by mutation in the fibroblast growth factor receptor 2 gene (FGFR2)

3. Pfeiffer syndrome OMIM :101600

Autosomal dominant , Clover-leaf skull ,Maxillary hypoplasia, Mandibular prognathism, shallow orbit,hypertelorism, downslanting palpebral fissures, proptosis, strabismus, small nose, low nasal bridge, cloanal atresia or stenosis, high arched palate, dental overcrowding, laringotracheomalasia, craniosynostosis of coronal and sagital sutures, radio humeral synostosis of elbow, partial Syndactyly of fingers and toes, broad great toe, hydrocephalus, Arnold chiari malformation, caused by mutation

in the fibroblast growth factor receptor-1 gene (FGFR1) and fibroblast growth factor receptor-2 gene (FGFR2).

Appendix 2.2.4 : Other types of craniosynostosis

Absent Radius syndromes (OMIM)

1. Radial Ray Hypoplasia with Choanal Atresia :OMIM 179270

Autosomal dominant, Flat nasal bridge, choanal stenosis, Hypoplastic thumb, hypoplastic fore arm muscles.

2. Hemifacial microsomia with Radial defects :OMIM 141400

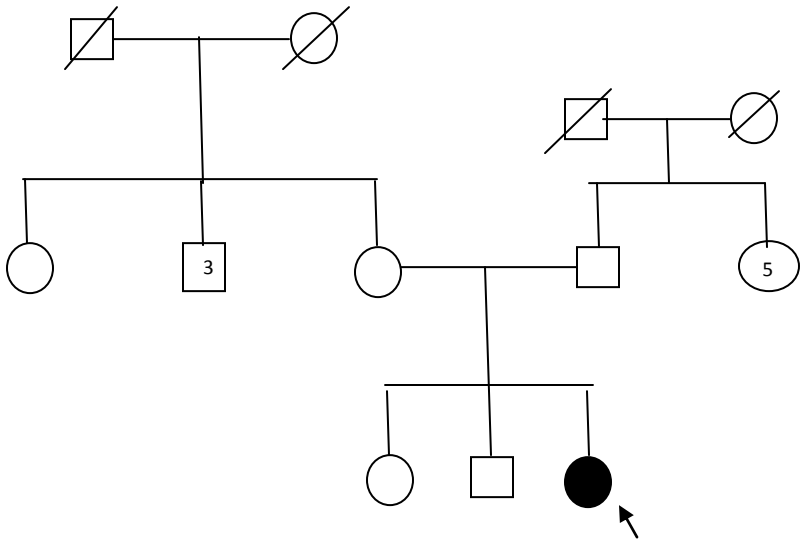
Radial limb defects, Thumb defects, oral cleft, hemifacial microsomia, skin tags at mandibular angle, short mandibular ramus, conductive hearing loss, external auditory canal atresia, multiple peri auricular ear tags and pits.

3. Duane-Radial Ray Syndrome : OMIM 607323

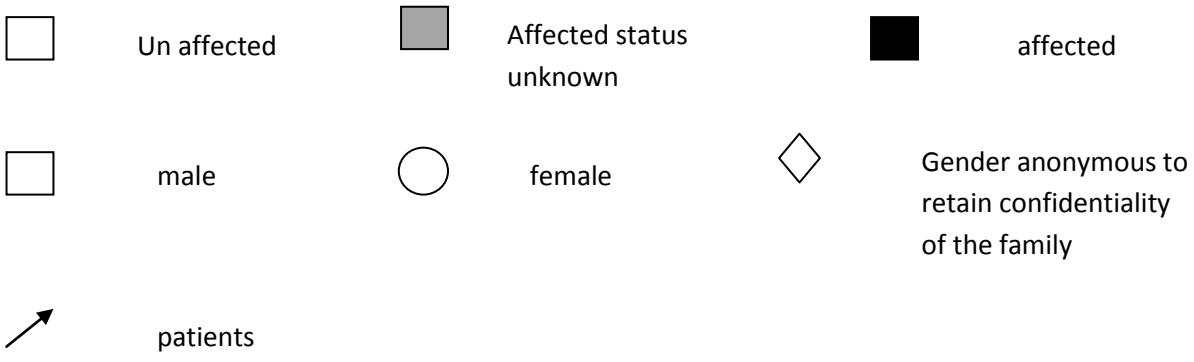
Facial asymmetry, deafness, fused cervical vertebra, scoliosis, spina bifida occulta, hypoplastic or absent radius, absent metacarpals, Syndactyly or polydactyly and flat feet. This is due to the mutation of sal – like 4 gene (*SALL4*)

Appendix -2.2.5

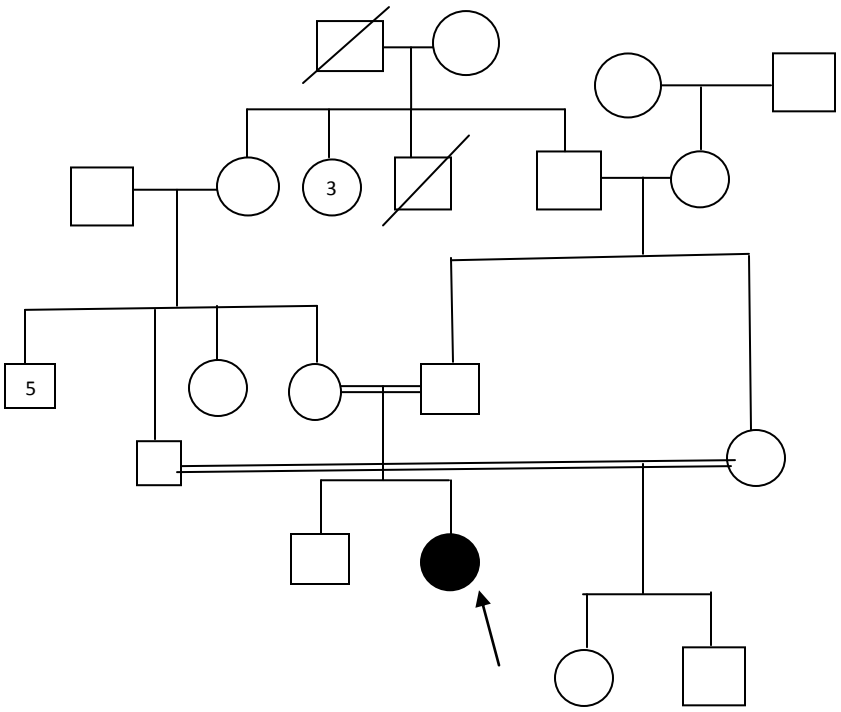
Pedigrees of Sub category Osteogenesis Imperfecta



Pedigree – 1 Patient number 1 of Osteogenesis Imperfecta (case1)



Pedigree 2



Pedigree 2 – Patient number 2 of Osteogenesis Imperfecta (case-3)

Un affected

Affected status unknown

affected

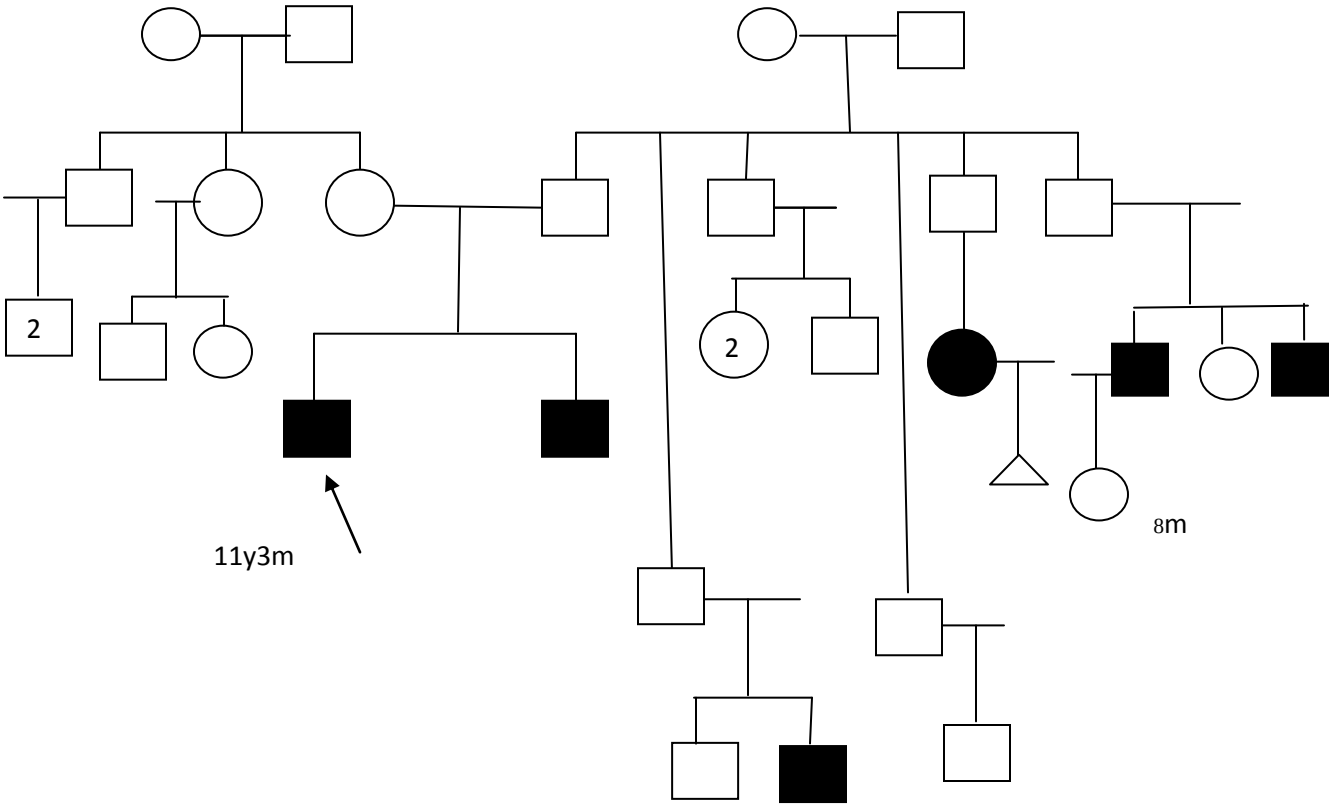
male

female

Gender anonymous to retain confidentiality of the family

patients

Pedigree 3



Pedigree 3 –Patient number 3of Osteogenesis Imperfecta (case-5)

Un affected

Affected status unknown

affected

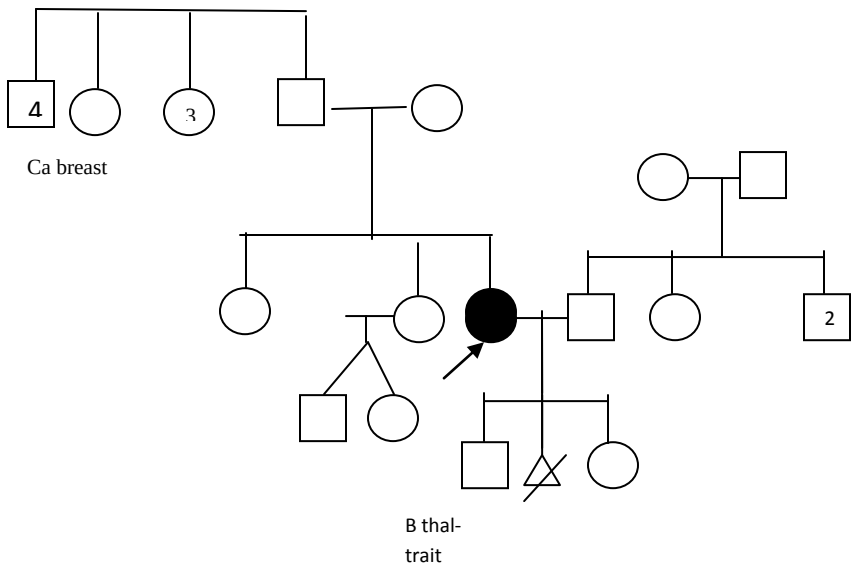
male

female

Gender anonymous to retain confidentiality of the family

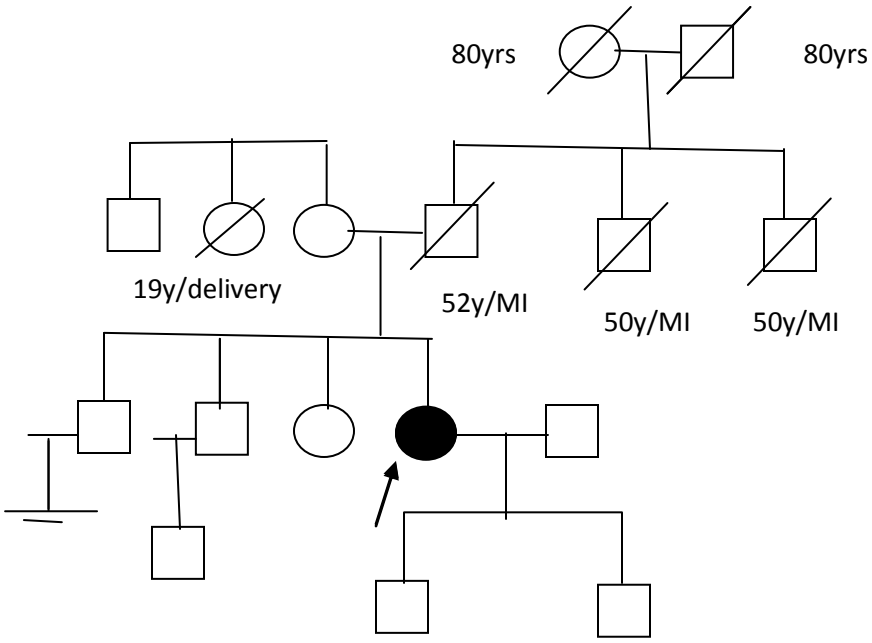
patients

Pedigree - 4

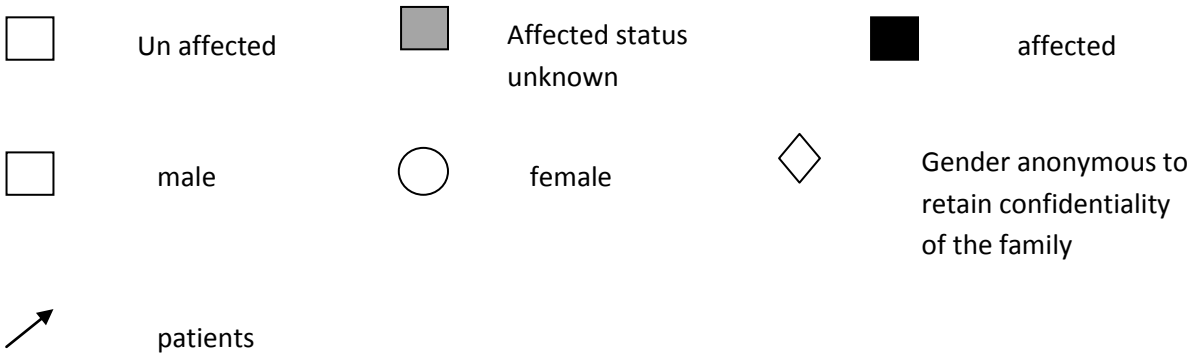


Pedigree 4 – Patient number 4 of Osteogenesis Imperfecta (case 18)

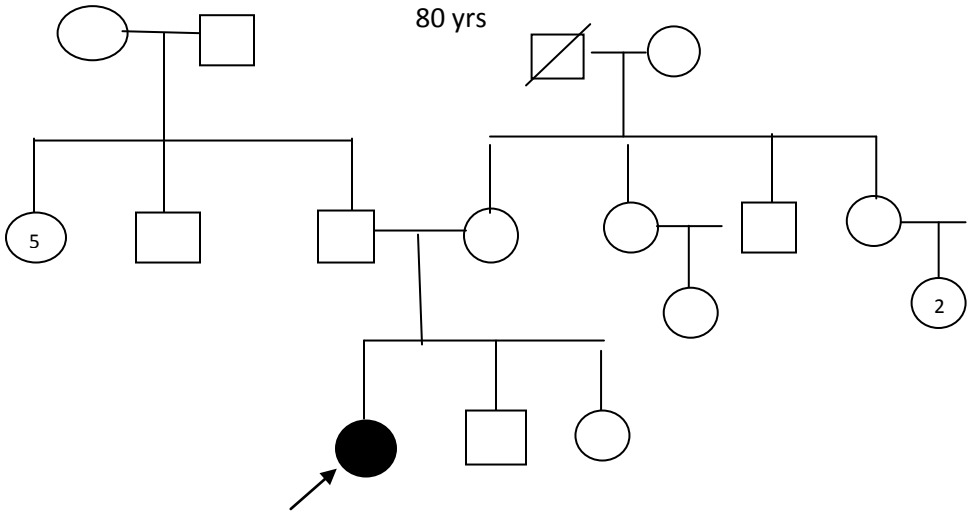
Pedigree 5



Pedigree -5 Patient number 5 in Osteogenesis Imperfecta (case -19)

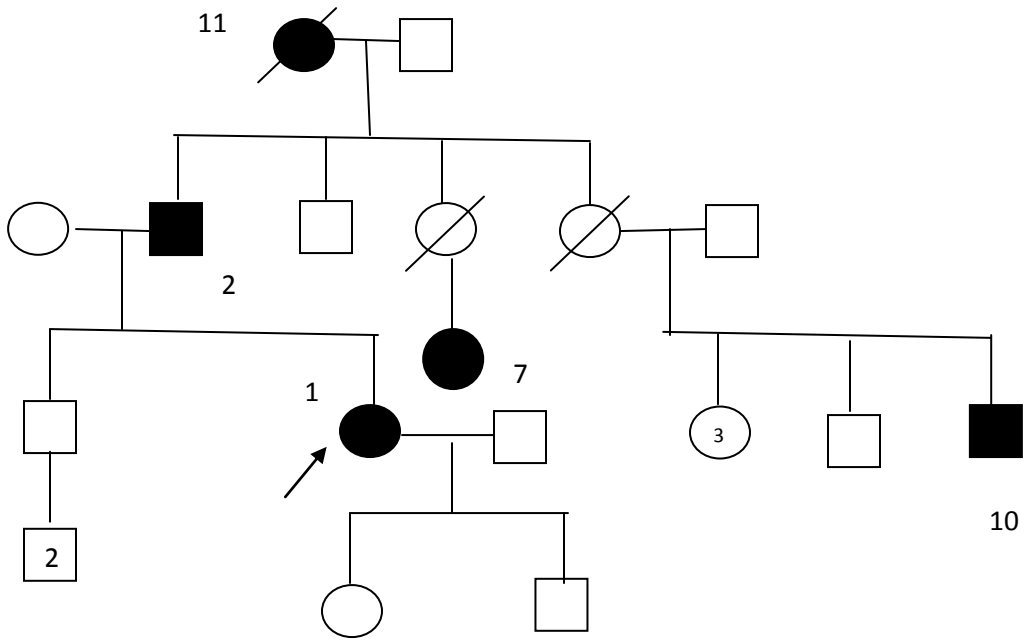


Pedigree 6



Pedigree 6 - Patient number 6 of Osteogenesis Imperfecta (case 22)

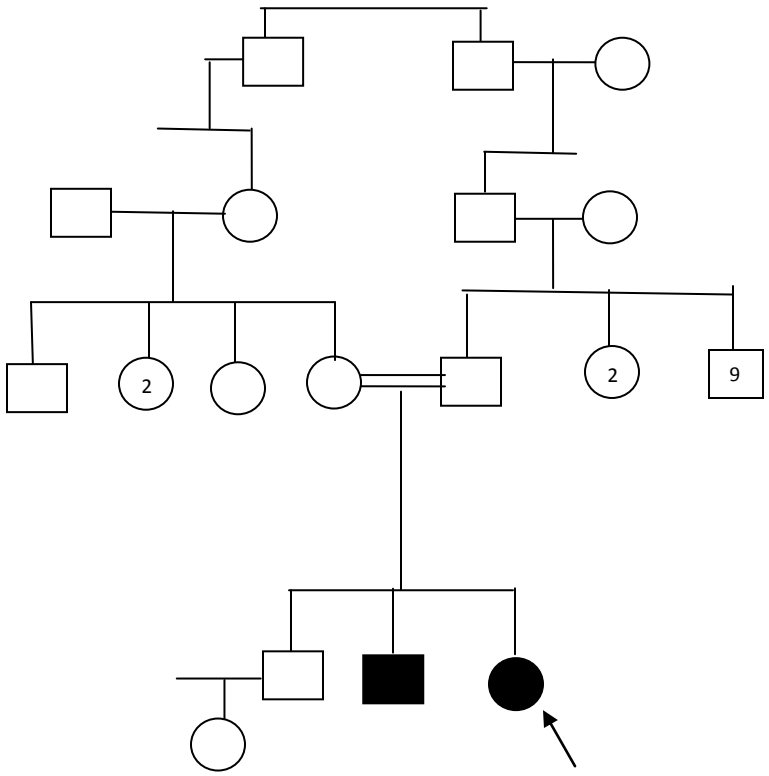
Pedigree- 7



Pedigree- 7 - Patient number 7 of Osteogenesis Imperfecta (case 23)

1: patient
2: patient's father :Started bowing of both lower limbs at the age of 55years . Now 68 years of age both legs are deformed and thoracolumba kyphoscoliosis
7 : patient's 1st cousin she had fractures with minor trauma and short stature.
10: Patient's 1st cousin : started bone deformities at the age of 30 years, he was 48 years at the time of history taking having bowing of both lower limbs and fractures of femur in both lower limbs.
11: paternal grandmother who died at the age of 80 years. She was having short stature, bowing of both lower limbs and fractures of the neck of the femur both sides.

Pedigree - 8



Pedigree –8 Patient number 8 of Osteogenesis Imperfecta (case -30)

Un affected

Affected status unknown

affected

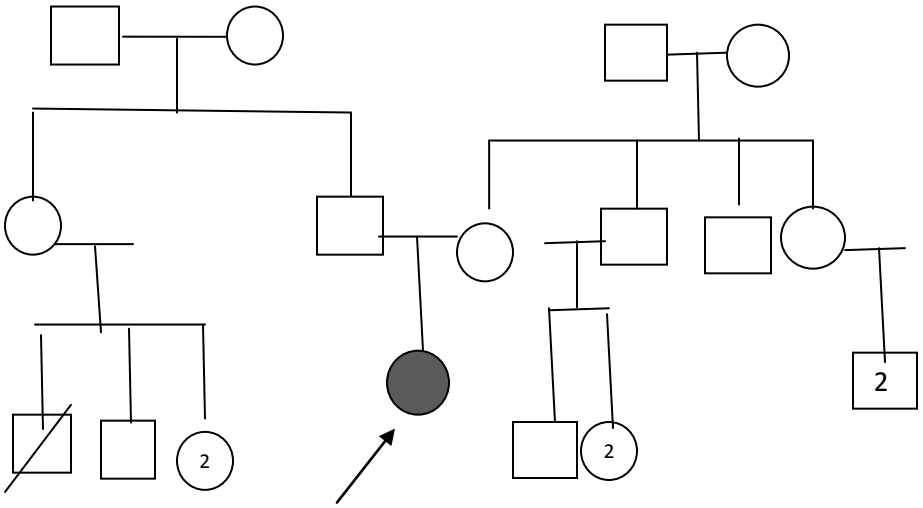
male

female

Gender anonymous to retain confidentiality of the family

patients

Pedigree 9



Pedigree 9 Patient number 9 of Osteogenesis Imperfecta (case -37)

Un affected

Affected status unknown

affected

male

female

Gender anonymous to retain confidentiality of the family

APPENDIX 3 DOCUMENT USED IN SUBJECT RECRUITMENT

தகவல் பத்திரம்

இலங்கையில் எலும்புகளில் ஏற்படும் இயல்புப்பிறழ்ந்த வளர்ச்சி நோயினால் பாதிக்கப்பட்டுள்ள நோயாளிகளிளிருந்து தெரிவுசெய்யப்பட்ட பெருங்குழுவில் இந்நோயைப் பற்றிய ஒரு ஆய்வு

மனித மரபியல் பிரிவு, கொழும்பு மருத்துவ பீடத்தில் மருத்துவ மரபியல் முதுநிலைக கல்வி மாணவியாக இருக்கும் Dr. திலினா D. வணிகசேகர ஆகிய நான் இந்த ஆய்வை மேற்கொள்கிறேன். "இலங்கையில் எலும்புகளில் ஏற்படும் இயல்புப்பிறழ்ந்த வளர்ச்சி நோயினால் பாதிக்கப்பட்டுள்ள நோயாளிகளிளிருந்து தெரிவுசெய்யப்பட்ட பெருங்குழுவில் இந்நோயைப் பற்றிய ஒரு ஆய்வு" எனும் தலைப்பில் நடைபெறும் இந்த ஆய்வில் பங்குபெற உங்களையும் அழைக்கிறேன்.

ஆய்வுக் குழு அங்கத்தவர்கள்

Dr. உதாரி லியனகே (சிரேஷ்ட மேற்பார்வயாளர்) - விரிவுரையாளர், உடற்கூறியல் பிரிவு, மருத்துவ பீடம், கொழும்பு பல்கலைக்கழகம்.

பேராசிரியர். வஜிர H.W. திசாநாயக (மேற்பார்வையாளர்) - பேராசிரியர், உடற்கூறியல் பிரிவு, மருத்துவ பீடம், கொழும்பு பல்கலைக்கழகம்.

பேராசிரியர்.றொஹான் W. ஜயசேகர (மேற்பார்வையாளர்) - பேராசிரியர், மனித மரபியல் பிரிவு, மருத்துவ பீடம், கொழும்பு பல்கலைக்கழகம்.

Dr. திலினா D. வணிகசேகர (சிரேஷ்ட ஆய்வாளர்) - மருத்துவ மரபியல் முதுநிலைக் கல்வி மாணவி மருத்துவ பீடம், கொழும்பு பல்கலைக்கழகம்.

இந்த ஆய்வின் குறிக்கோள்

எலும்புப் பிறழ்வின் மருத்துவ மற்றும் கதிரியக்கத் தோற்றப்பாடுகளை விவரிப்பதும் இந்நோயின் மரபியல் நோய்க் காரணிகளை நிர்ணயிப்பதுமே இந்த ஆய்வினுடைய நோக்கமாகும்.

தன்னார்வ பங்கேற்ப்பு

இந்த ஆய்வில் பங்குபற்றுவதோ அல்லது பங்குபற்றாமல் இருப்பதோ உங்களுடைய தனிப்பட்ட முடிவாகும்.முன்னர் நீங்கள் இவ் ஆய்வில் பங்குபெற சம்மதம் தெரிவித்திருந்தாலும், எவ்வேளையிலும் உங்களால் இந்த ஆய்விலிருந்து அறிவித்தலுடன் விலகிக்கொள்ள முடியும். மேலும் நீங்கள் விலகிக்கொண்டாலொ அல்லது பங்குபெற்றாவிட்டாலோ, அது உங்களுக்கு வழங்கப்படும் மருத்துவ சிகிச்சையையோ அதன் தரத்தையோ பாதிக்காது.

ஆய்வின் காலம், செயல்முறை மற்றும் பங்குபெறுவோரின் கடமைகள்.

இந்த ஆய்வானது கிட்டத்தட்ட ஆறு மாதங்கள் வரை நடைபெறும். இவ் ஆய்வில் பங்குபெற சம்மதம் தெரிவித்த பின்னர், நாங்கள் உங்களுடன் நேர்கண்டு கதைத்து, உங்களை பரிசோதித்து, உங்களது மருத்துவ பதிவுகளை பார்வையிடுவதோடு உங்களது பேச்சு மற்றும் நடையையும் வீடியோ பதிவு செய்ய விரும்புகிறோம். இந்த தகவல்களை அறிவியல் ஆய்விதழில் வெளியிட உங்களது சம்மதம் எங்களுக்குத் தேவை. நாங்கள் உங்களது பெயரையோ அல்லது வேறு அடையாளம் காட்டக்கூடிய தகவல்களையோ வெளியிடுவதை தவிர்ப்போம். மேலும் தங்களிடமிருந்து 5 ml இரத்தம் எடுப்பதற்கும் உங்களது சம்மதம் தேவைப்படுகிறது.

கிடைக்கக்கூடிய நன்மைகள்

இந்த ஆய்வில் பங்குபெற்றுவதன் மூலம் உங்களுக்கு ஏற்பட்டுள்ள எலும்புப் பிறழ்விற்கு காரணமான மரபியல் குறைபாடுகளை அடையாளம் கண்டு கொள்ள **முடியும். மேலும் இந்த ஆய்வின் மூலம் எலும்புப் பிறழ்வினால் பாதிக்கப்பட்டுள்ள இலங்கையர்களைப் பற்றிய அறிவு எமக்குக் கிடைக்கும். இவர்களிடையே காணப்படும் பொதுவான மரபியல் குறைபாடுகளை**

கண்டறியும் போது, இந்த நோயாளிகளுக்குப் பொருத்தமான கருத்துரை மற்றும் அறிவுரையை எங்களுக்கு வழங்கக்கூடியதாக இருக்கும். மேலும் இந்த அறிவின் மூலம் விழிப்புணர்ச்சி மற்றும் இந்நோய்த் தடுப்பு முறைகளைப் பற்றி பயனுள்ள ஒரு கருத்துரைத் திட்டத்தை வடிவமைக்க முடியும்.

அபாயங்கள், தீங்குகள் மற்றும் உபாதைகள்.

எலும்புப் பிறழ்வை உண்டாக்கும் மரபியல் குறைபாட்டினை கண்டறியும் பரிசோதனைகளுக்காக கிட்டத்தட்ட 5 ml இரத்தம் உங்களிடமிருந்து எடுக்கப்படும். இந்த செயல்முறை சிலவேளைகளில் சிறு வலியையோ உபாதையையோ உண்டாக்கலாம். இரத்தம் எடுப்பதால் ஊசி குத்தும் இடத்தில் சிறு சிராய்ப்பு மற்றும் தொற்று ஏற்படக்கூடிய சாத்தியங்கள் உண்டு. பயிற்றுவிக்கபபட்ட ஒருவரால் , கிருமி அற்ற நிலையில் இரத்தம் எடுக்கப்படும் போது இந்த அபாயங்கள் குறைக்கப்படும்.

செலவு ஈடுகள்

இந்த ஆய்வில் பங்கு பெறுவதற்கு எந்தவித செலவும் ஈடுசெய்யப்பட மாட்டாது. இருப்பினும், சோதனை முடிவுகள் எழுத்துமூலம் தரப்படும்.

இரகசியத்தன்மை

பெறப்படும் எல்லாத்தகவல்களும் இரகசியமாக பேணப்படுவதோடு, உங்களையோ அல்லது உங்களது குடும்பத்தையோ அடையாளம் காடும் வகையில் ஒருபோதும் வெளியிடப்படமாட்டாது. தகவல் சேகரிப்புப் புத்தகம் பெறப்படும் தகவல்களின் இரகசியத்தன்மையை பேணும் வகையில் வடிவமைக்கப்பட்டிருக்கும். தகவல்களைக் கொண்டிருக்கும் இலத்திரனியல் தரவுத்தளம், பங்குபற்றியவர்களின் எண்ணிக்கையை மாத்திரமே கொண்டிருக்கும். மேலும் இத்தகவல்களைக் கொண்டிருக்கும் கணணி கடவுச்சொல் பாதுகாப்பு உள்ளதாக இருக்கும். உங்களது அனுமதி இல்லாமல், தங்களது தகவல்கள் உங்களை அடையாளம் காட்டும் வகையில் பொது மக்களுக்கு முன்னிலைப்படுத்தப்படவோ வெளியிடப்படவோ மாட்டாது.

பங்கு நிறுத்தம்

நீங்கள் இந்த ஆய்விலிருந்து காரணங்கள் எதுவும் கூறாமல், தண்டங்களோ அல்லது மருத்துவ பராமரிப்பில் பாதிப்புகளோ இல்லாமல் எவ்வேளையிலும் விலகிக்கொள்ள முடியும். நீங்கள் விலகிக்கொள்வதாக முடிவெடுத்தால்,தயவு செய்து எங்களுக்கு விரைவில் தெரிவிக்கவும். இருப்பினும், ஆய்வு முடிவுகள் பிரசுரிக்கப்பட்ட பின்னரோ அல்லது பிரசுரிக்க அனுப்பிய பின்னரோ உங்களால் இந்த ஆய்விலிருந்து விலகிக்கொள்ள முடியாது.

<u>விளக்கம்</u>

செய்யப்படும் பரிசோதனைகள்/செயல்முறைகள் பற்றி விளக்கமோ அல்லது தகவல்களோ வேண்டுமெனின் தயவுசெய்து பின்வரும் நபர்களிடம் 011- 2689 545 / 0712272882 எனும் தொலைபேசி இலக்கத்தினூடாக தொடர்பு கொண்டு கேட்டறிந்து கொள்ளவும்:

Dr. திலினா D. ணிகசேகரவ

மருத்துவ மரபியல் முதுநிலைக் கல்வி மாணவி

மனித மரபியல் பிரிவு,

மருத்துவ பீடம்,

கொழும்பு.

Dr. உதாரி லியனகே

விரிவுரையாளர்,

உடற்கூறியல் பிரிவு,

மருத்துவ பீடம்,

கொழும்பு.

INFORMATION SHEET

A STUDY OF SKELETAL DYSPLASIA IN A SELECTED COHORT OF SRI LANKAN PATIENTS

This study is conducted by me, Dr Thilina Wanigasekera, an MSc student in Clinical Genetics in the Human Genetics Unit, Faculty of Medicine, Colombo. I would like to invite you to take part in the research study titled "A STUDY OF SKELETAL DYSPLASIA IN A SELECTED COHORT OF SRI LANKAN PATIENTS " conducted by myself and my research team.

Members of our research team

Dr Udari Liyanage (Principle Supervisor) - Lecturer, Department of Anatomy, Faculty of Medicine University of Colombo.

Prof. Vajira H W Dissanayake (Supervisor) - Professor ,Department of Anatomy, Faculty of Medicine, University of Colombo.

Prof. Rohan W. Jayasekera (Supervisor) - Professor , Human Genetics Unit, Faculty of Medicine ,Colombo.

Dr Thilina D. Wanigasekera (Principle Investigator) Msc student in Clinical Genetics ,Faculty of Medicine Colombo.

1.**Purpose of the study**

The purpose of the study is to describe the clinical and radiological phenotypic features of Skeletal Dysplasia and to determine the genetic aetiology.

2.**Voluntary participation**

Your participation in this study is voluntary. You are free to not participate at all or to withdraw from the study at any time despite consenting to take part earlier. There will be no loss of medical care or any other available treatment for your illness or condition to which you are otherwise entitled. If you decide not to participate you may withdraw from the study at any time by informing us.

3.**Duration, procedures of the study and participant's responsibilities**

The study will be conducted over six months . We require your permission to ask you questions, examine you, have access to your medical records, and video records of your photographs relevant for diagnosis of the particular disease condition. We also need your permission to publish the data collected in a scientific journal. We will not mention your name or any other identifiable information about you when we publish the results. We also need to take 5ml of venous blood from you to do the genetic test.

4.**Potential benefits**

Participation in this study will help you to know the genetic defect that has made you to develop the Skeletal Dysplasia. This will contribute the advancement of knowledge of Skeletal Dysplasia in Sri Lankan patients . Identifying the common genetic defects causing Skeletal Dysplasia in Sri Lankan patients will help to design effective genetic counseling programs and tests to improve the awareness and prevention.

5.**Risks, hazards and discomforts**

Blood will be drawn to detect the genetic defect causing Skeletal Dysplasia. Approximately 5ml of blood will be taken for testing from you. The risk for you by participating in the study is the risk of pain, bruising and infection at the needle prick site. These will be minimized by performing blood drawing under aseptic conditions by trained phlebotomist.

6.Reimbursements

There will be no reimbursement for participating in the study, but you will be given a copy of the molecular genetic test results.

7.Confidentiality

Confidentiality of all records is guaranteed and no information by which you can be identified will be released or published. The data collection booklet is designed to ensure confidentiality of information gathered. The electronic database containing the data will have only the subject study number and the database and the computer containing the database would be password protected. These data will never be used in such a way that you could be identified in anyway in any public presentation or publication without your express permission.

8.Termination of study participation

You may withdraw your consent to participate in this study at any time, with no penalty or effect on medical care or loss of benefits. Please notify us as soon as you decide to withdraw your consent. However it will not be possible for you to withdraw once the results are sent for publication or once the results are published

9.Clarification

If you have questions about any of the tests / procedures or information please feel free to ask any of the persons listed below by calling 011 2689 545/0712272882

Dr Thilina Wanigasekera

MSc Student

Human Genetics Unit

Faculty of Medicine

Colombo

Dr. Udari Liyanage

Lecturer

Department of Anatomy

Faculty of Medicine

Colombo

තොරතුරු පත්‍රිකාව

ශ්‍රී ලාංකිය රෝගීන් අතර පවතින අස්ථි විකෘතිතා සම්බන්ධව සිදුකරන විස්තරාත්මක අධ්‍යයනය

කොළඹ වෛද්‍ය පීඨයේ ප්‍රවේණි විද්‍යා අංශයේ පශ්චාත් උපාධියක් හදාරන වෛද්‍ය තිලිනා වනිගසේකර වන මම ඇතුළු අනෙකුත් පරීක්ෂණ සමාජිකයන් විසින් කරනු ලබන ඉහත සඳහන් පරීක්ෂණයට සහභාගි වීම සඳහා ඔබ හට ආරාධනා කිරීමට අප කැමැත්තෙමු.

අපගේ පර්යේෂණ කණ්ඩායමේ සාමාජිකයින් වනුයේ

- වෛද්‍ය උදාරි ලියනගේ (ප්‍රධාන අධීක්ෂක) - කොළඹ විශ්ව විද්‍යාලයේ වෛද්‍ය පීඨයේ කාය ව්‍යවච්ඡේද ඒකකයට සම්බන්ධ කථිකාචාර්යවරියකි.
- මහාචාර්ය වජිර එච්. ඩබ්ලිව්. දිසානායක (ප්‍රධාන අධීක්ෂක) - කොළඹ විශ්ව විද්‍යාලයේ වෛද්‍ය පීඨයේ මානව ප්‍රවේණි විද්‍යා ඒකකයට සම්බන්ධ මහාචාර්යවරයෙකි.

- මහාචාර්ය රොහාන් ඩබ්ලිව්. ජයසේකර (අධික්ෂක) - කොළඹ විශ්ව විද්‍යාලයේ වෛද්‍ය පීඨයේ මානව ප්‍රවේණි විද්‍යා ඒකකයට සම්බන්ධ මහාචාර්යවරයෙකි.
- වෛද්‍ය තිලිනා ඩී. වනිගසේකර - (ප්‍රධාන පරීක්ෂකවරිය) - කොළඹ විශ්ව විද්‍යාලයේ වෛද්‍ය පීඨයේ ප්‍රවේණි විද්‍යා ඒකකයට සම්බන්ධ පශ්චාත් උපාධි අපේක්ෂකවරියකි.

01. මෙම අධ්‍යයනයේ අරමුණ

මෙම පර්යේෂණයේ ප්‍රධාන අරමුණ වනුයේ ඝායනික රෝග ලක්ෂණ" X කිරණ පරීක්ෂණ සහ ප්‍රවේණි රෝග විනිශ්චය අනුසාරයෙන් ශ්‍රී ලාංකිය රෝගීන් අතර පවතින අස්ථි විකෘතිතා පිළිබඳ විස්තර කිරීමය.

02. ස්වේච්ඡා සහභාගිත්වය

මෙම අධ්‍යයනය සඳහා ඔබගේ සහභාගිත්වය ඔබගේ කැමැත්තෙන්ම සිදු කරන්නකි. මෙම අධ්‍යයනය සඳහා සහභාගි නොවීමට ඔබට පුර්ණ අයිතිය ඇති අතර සහභාගි වීමට කලින් කැමැත්ත ප්‍රකාශ කර තිබුනද ඕනෑම අවස්ථාවක අප හට දැනුම් දී ඔබට අධ්‍යයනය නිමා කිරීමට පුර්ණ අයිතිය ඇත. එමගින් ඔබට ලබා දෙන වෛද්‍ය ප්‍රතිකාර සඳහා කිසිදු බලපෑමක් ඇති නොවේ.

03. කාල සීමාව" පර්යේෂණයේ ක්‍රියා පිළිවෙල සහ සහභාගිවන්නන්ගේ වගකීම

මෙම පර්යේෂණය මාස 6 කාලයක් තුල සිදු කරනු ලැබේ. ඔබගෙන් ප්‍රශ්න ඇසීමට" ඔබව පරීක්ෂා කිරීමට" ඔබගේ වෛද්‍ය වාර්තා පිරික්සීමට සහ අවශ්‍ය විටක රෝග විනිශ්චය සඳහා ඔබගේ ජායාරූපයක් ගැනීමටද අප හට ඔබගේ අවසරය අවශ්‍ය වේ. තවද ජාන පරීක්ෂණ සඳහා මි.ලි.5ක රුධිර සාම්පලයක් ඔබගෙන් අපට අවශ්‍ය වේ. මේ සියලු අවශතා සඳහා පර්යේෂණ කාල සීමාව ඇතුලතදී ඔබ එක් වරක් පමණක් අප ආයතනය වෙත පැමිණීම සෑහේ' තව ද අප විසින් කරනු ලබන පර්යේෂණයේ දත්ත විද්‍යාත්මක සඟරාවක වල කිරීම සඳහා ද ඔබගේ අවසරය අවශ්‍ය වේ.
මෙම ප්‍රතිවල පල කිරීමේදී ඔබගේ නම හෝ ඔබව හඳුනාගත හැකි අන්දමේ වෙනයම් තොරතුරක් හෝ අප විසින් සපයන්නේ නැත.

04. මින් ලද හැකි ප්‍රතිලාභ

මෙම පරීක්ෂණයට සහභාගිවීමෙන් ඔබට කුමන වර්ගයේ අස්ථි විකෘතිතාවක් ඇති වී ඇත්දැයි දැනගත හැකිය. එයට අමතරව මෙම පර්යේෂණයට සහභාගි වන රෝගියාගේ පවුලේ සාමාජිකයන්ට සහ ඥාතීන්ට අස්ථි විකෘතිතා සහ සංකූලතා අවදානම නිර්ණය කර ගත හැකිය. තවද ඔබගේ ප්‍රතිවල සම්බන්ධයෙන් උපදේශනය නොමිලේ ලබා ගත හැකිය. මෙම පර්යේෂණය අස්ථි විකෘතිතා සම්බන්ධව ශ්‍රී ලංකික ජනතාව අතර පවතින දැනුම තවත් වැඩි කර ගැනීමට උපකාරීවේ.

05.අවදානම් තොරතුරු සහ අපහසුතා

අස්වි විකෘතිතා සහිත රෝගීන්ගේ ජානමය වෙනස්වීම සොයා ගැනීම සඳහා පර්යේෂණ වලදි උපයෝගි කරගැනීමට ඔබගේ කැමැත්ත මත රුධිර සාම්පලයක් ලබා ගැනීමට සිදුවේ. මෙම රුධිර සාම්පලය ලබා ගැනීමේදි ඔබට යම් අපහසුතාවයක් ඇති විය හැක. කලාතුරකින් රුධිර සාම්පලය ලබා දීමේදි එන්නත් කටුව නිසා යම් තැල්මක් එම ස්ථානයේ හට ගත හැක. මෙම තත්වයන් අවම කර ගැනීම සඳහා රුධිර සාම්පලය ලබා ගැනීම" සියලුම ආරක්ෂිත තත්වයන් යටතේ පළපුරුදු හෙද නිලධාරිනියක් මගින් සිදු කරනු ලැබේ.

05. දීමනා

ඔබ මෙම අධ්‍යයනයට සහභාගී වීම වෙනුවෙන් ඔබට දීමනාවක් නොලැබේ. එහෙත් ඔබට ඔබගේ රෝගය පිළිබඳ වාර්තාවක් ලබා දෙනු ඇත.

06. රහසිගත බව

සියළුම තොරතුරු සහිත වාර්තාවන් සහ අධ්‍යයනය මගින් ලබා ගන්නා දත්තයන්ගේ රහස්‍යභාවය තහවුරු කරන අතර" ඔබගේ අනන්‍යතාවය හඳුනාගත හැකි ආකාරයේ කිසිවක් ඔබගේ කැමැත්තකින් තොරව හෙළි කිරීමක් හෝ ප්‍රකාශයට පත් කිරීමක් සිදු කරනු නොලැබේ. දත්ත එකතු කිරීමේ පත්‍රිකාව සකසා ඇත්තේද ඔබගේ රහස්‍යභාවය තහවුරු කෙරෙන අයුරිනි. විද්‍යාත්මක සඟරාවක මෙම පර්යේෂණ වාර්තා වල කිරීමට අවශ්‍ය වූ විටද කිසිදු අයුරකින් ඔබගේ අනන්‍යතාවය හෙළි නොවන අයුරින් අපි එය පල කරන්නෙමු.

07. අධ්‍යයනයට සහභාගිවීම නැවැත්වීම

අධ්‍යයනයට සහභාගිවීමට දුන් කැමැත්ත ඉවත් කර ගැනීම අධ්‍යයනයේ කුමන හෝ අධිකරයකදි සිදු කිරීමට ඔබට හැක. එසේ සිදු කරන්නේ නම් එම තීරණය ගත් විගසම ඒ බව අපහට කරුණාකර දැනුම් දෙන්න. නමුත් එකතු කර ගන්නා ලද දත්ත ප්‍රකාශයට පත් කිරීමෙන් පසුව ඔබට අධ්‍යයනයෙන් ඉවත් වීමට නොහැක.

08. වැඩිදුර තොරතුරු

ඔබට මෙම ක්‍රියා පටිපාටින් පිළිබඳ කිසියම් ප්‍රශ්නයක් ඇත්නම් හෝ වැඩිදුර තොරතුර අවශ්‍ය වේ නම් කරුණාකර පහත සඳහන් වෛද්‍යවරුන් අමතන්න.

වෛද්‍ය තිලිනා ඩී. වනිගසේකර" පශ්චාත් උපාධි අපේක්ෂිකා මානව ප්‍රවේණි විද්‍යා අංශය
වෛද්‍ය පීඨය - කොළඹ
දු.අ. 0112689545/ 0712272882

වෛද්‍ය උදාරී ලියනගේ " කවිකාචාර්ය කාය ව්‍යවච්ඡේද අංශය"
වෛද්‍ය පීඨය - කොළඹ
දු.අ.

CONSENT FORM

A STUDY OF SKELETAL DYSPLASIA IN A SELECTED COHORT OF SRI LANKAN PATIENTS.

To be completed by the participant/guardian

The participant/ guardian should complete the whole of this sheet himself/herself.

1. Have you read the information sheet? (Please keep a copy for yourself) YES/NO

2. Have you had an opportunity to discuss this study and ask any questions?
YES/NO

3. Have you had satisfactory answers to all your questions? YES/NO

4. Have you received enough information about the study? YES/NO

5. Who explained the study to you? ……

6. Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your medical care?
YES/NO

7. Sections of your medical notes, including those held by the investigators relating to your participation in this study may be examined by other research assistants. All personal details will

be treated as STRICTLY CONFIDENTIAL. Do you give your permission for these individuals to have access to your /your child's records?

YES/NO

8. Do you give permission for video recording? YES / NO

9. Do you agree to have leftover blood samples to be stored for future research into Skeletal Dysplasia?

YES/NO

10. Do you agree for the samples to be sent abroad? YES/NO

10. Have you had sufficient time to come to your decision?
YES/NO

11. Do you agree to take part in this study? YES/NO

Participants'/ Guardian's signature:……..…….Date……

Name (BLOCK CAPITALS):…… …….

To be completed by the investigator

I have explained the study to the above volunteer and he/ she has indicated her willingness to take part.

Signature of investigator:……...……..Date……..…….

Name (BLOCK CAPITALS):…….

leue;a; m%ldY lsÍfï m;%h

Y%S ,dxlSh frda.skaa w;r mj;sk wiaÓ úlD;s;d ïïnkaOj isÿlrkq ,nk úia;rd;aul wOHhkh'

a. iyNd.Sjkakka$ Ndrlrejka úiska msrùu i|ydh'

fuu m;%h iyNd.Sjkakka$ Ndrlrejka úiska muKla ms<s;=re iemhsu l< hq;=h'

1. Tn f;dr;=re m;%sldj lshjqfha o @

^lreKdlr f;dr;=re m;%sldfõ msgm;la Tn ,nd.kak&

Tõ $keye

2. fuu wOHhkh ïïnkaOj idlÉPd lsÍug yd ta ms<sn|j m%Yak weiSug Tng wjia:djla ,enqKdo@

Tõ $keye

3. Tnf.a m%Yak i|yd i;=gqodhl ms<s;=re ,enqKdo@

Tõ $keye

4. fuu wOHhkh ïïnkaOj iEysulg m;aúh yels ;rï wjfndaOhla ,enqKdo@

Tõ $keye

5. fuu wOHhkh ïïnkaOfhka Tng meyeÈ,s lrk ,oafoa ljqreka úiskao@

……

6. lsisÿ lreKq oelaùulska f;drj" wjYH TskEu úgl oS fuu wOHhkfhka bj;a ùug Tn yg $ Tnf.a orejd yg yelshdj we;s nj iy thska Tnf.a$ Tnf.a orejdf.a bÈß ffjoH m%;sldr i|yd n,fkdmdk nj;a meyeÈ,s jqjdo@

Tõ $keye

7. Tnf.a$ Tnf.a orejdf.a ffjoH jd¾;d iy m¾fhaIK o;a; fuu wOHhkh ïïnkaO idudðlhska úiska wOHhkh lrKq we;' ish,q jd¾;d iy o;a;j, rdyiHNdjh rlskq ,efi" Tnf.aa$ Tnf.a orejdf.a ffjoH jd¾;d wOHhkh i|yd wkque;sh fokafkao@q'

Tõ $keye

8. fuu wOHkfha lghq;= i|yd Tnf.a $ Tfi orejdf.a cdhdrEm .eksugTn wjir fokafkao@

Tõ $keye

9. w;sßla; reêr idñm, fjk;a cdkuh wOHkhka i|yd fhdod .eksug wkque;sh fokafkao@

Tõ $keye

10. reêr iñm, fjk;a rgl oS mrsCId lrKq ,nkjdg tlÕo@

Tõ $keye

11. fuu wOHhkhg iyNd.sùu i|yd ;srKhlg t<ôug Tng wjYH muK ld,hla ,enqKdo@

Tõ $keye

12. Tn fuu wOHkhg iyNd.s úug tlÕ fjkjdo@

Tõ $keye

iyNd.Sjkakkaf.a $ Ndrlrejkaf.a w;aik…… Èkh……
ku (……..……
b. m¾fhaIl úiska msÍu i|ydh'

fuu wOHhkh iïnkaO lreKq ud úiska wOHhkhg iafjÉPdfjka iyNd.Sjkakka yg meyeÈ,s lrk ,oS' Tyq $ wE úiska fuu wOHhkhg iyNd.s ùug leue;a; m%ldY lrk ,oS'
m¾fhaIlf.aa w;aik…… Èkh……..
ku (……

ஒப்புதல் படிவம்

இலங்கையில் எலும்புகளில் ஏற்படும் இயல்புப்பிறழ்ந்த வளர்ச்சி நோயினால் பாதிக்கப்பட்டுள்ள நோயாளிகளிலிருந்து தெரிவுசெய்யப்பட்ட பெருங்குழுவில் இந்நோயைப் பற்றிய ஒரு ஆய்வு

பகுதி A (பங்குபற்றுபவர் அல்லது பாதுகாவலரினால் பூரணப்படுத்தப்பட வேண்டும்)

(முழு படிவமும் பங்குபற்றுபவரினால்/ பாதுகாவலரினால் நிரப்பப்பட வேண்டும்.

1. இந்த ஆய்வை பற்றிய தகவல்களை முழுமையாக வாசித்து தெளிவாக விளங்கிகொண்டீரா? (தயவுசெய்து இந்த தகவல் படிவத்தின் ஒரு பிரதியை நீங்கள் வைத்திருக்கவும்) ஆம்/ இல்லை

2. இந்த ஆய்வை பற்றி கலந்துரையாட அல்லது கேள்வி கேட்க உங்களுக்கு சந்தர்ப்பம் கிடைத்ததா? ஆம்/ இல்லை

3. உங்கள் எல்லாக் கேள்விகளுக்கும் திருப்திகரமான பதில்கள் கிடைத்தனவா? ஆம்/ இல்லை

4. இந்த ஆய்வைப் பற்றி போதுமான தகவல்கள் கிடைத்ததா? ஆம்/ இல்லை

5. இந்த ஆய்வைப் பற்றி உங்களுக்கு விளக்கமளித்தது யார்? .....

6. எந்தவித காரணங்களும் தெரிவிக்காமலும் அல்லது உங்களுக்கு அளிக்கப்படும் மருத்துவ சிகிச்சையில் எவ்வித பாதிப்பு ஏற்படாமலும் உங்களால் இந்த ஆய்விலிருந்து எந்நேரமும் விலகிக்கொள்ள முடியும் என்பதை புரிந்துகொண்டுள்ளீரா? ஆம்/ இல்லை

7. உங்களது மருத்துவப் பதிவுகள், பரிசோதனை அறிக்கைகள் மற்றும் தனிப்பட்ட விவரங்கள் இந்த ஆய்வில் பங்குபெற்றும் மற்றைய ஆராய்ச்சியாளர்களினால்

சிலநேரங்களில் ஆய்வு செய்யப்படலாம். அனைத்து தனிப்பட்ட விவரங்களும் நிச்சயமாக ரகசியமாக பேணப்படும். இந்த ஆய்வாளர்கள் இத்தகவல்களை உபயோகிக்க நீங்கள் அனுமதிக்கின்றீர்களா? ஆம்/ இல்லை

8. உங்களை வீடியோ பதிவு செய்ய உடன்படுகின்றீர்களா? ஆம்/ இல்லை

9. மீதமுள்ள இரத்த மாதிரிகளை எதிர்கால ஆய்வுகளுக்கு பயன்படுத்த அனுமதிகின்றீர்களா? ஆம்/ இல்லை

10. உங்கள் இரத்த மாதிரியை பரிசோதனைகளுக்காக வெளிநாடுகளுக்கு அனுப்ப சம்மதிக்கின்றீர்களா? ஆம்/இல்லை

11. நீங்கள் உங்கள் முடிவுக்கு வர போதுமான நேரம் இருந்ததா? ஆம்/ இல்லை

12. இந்த ஆய்வில் பங்குபெற்ற சம்மதிக்கின்றீர்களா? ஆம்/ இல்லை

பங்கேற்பவர்/பாதுகாவலரின் கையொப்பம் :.....திகதி:.....

பெயர் (ஆங்கில பெரிய எழுத்துக்களில்) :

.....

<u>பகுதி B (ஆய்வாளரினால் பூரணப்படுத்தப்பட வேண்டும்):</u>

இந்த ஆய்வை பற்றி மேலே குறிப்பிடப்பட்டுள்ளவருக்கு விளக்கியுள்ளேன். மற்றும் இவர் இந்த ஆய்வில் பங்குபெற்ற தன்னார்வத்துடன் சம்மதம் தெரிவித்துள்ளார்.

ஆய்வாளரின் கையொப்பம் :.....திகதி:.....

பெயர் (ஆங்கில பெரிய எழுத்துக்களில்) :

....

01126895

Subject Study Number					-		

Data Collection Form

Study of skeletal Dysplasia in a selected cohort of Sri Lankan Patients.

Name of subject ……..

Date of birth ……/……/……

Age ……

Address ……

……

Telephone number
(Home) ……

(Mobile) ……

Email ……

Referring Physician ……

Date of Referral ……

Hospital ……**Ward:** ……..

Clinic No/ BHT No ……

Genetic Test requested ……

Indication ……

Data Protection and Confidentiality

After completion of this page, ensure that the subject study number is entered on **all pages** of this booklet. Then detach this page and store separately from the remainder of the booklet.

Subject Study Number					-		

Date of entry to study Date on consent form

		-			-				

		-			-				

1.2 Age of the patient.

1.1Date of birth

1.3 Sex 1.4 Ethnicity 1.5 Height in centimetres.

1.6 Weight (kg) 1.6 OFC 1.7 Bone Age

2. Diagnosis (if available)

3.Reason for referral

3.1 FAMILY PEDIGREE

Draw the family pedigree indicating all illnesses present, document abortions/still births as well.

I
II
III
IV

Consanguinity : Yes / No

Subject Study Number					-		

3.2Additional pedigree information

Location in pedigree	**Clinical or other information**

4.0 Investigation Reports

4.1 Biochemical Tests done/ not done – Please attach a photocopy of the report

Date	**Test**	**Result / conclusion**

Subject Study Number					-		

4.2 Genetic tests done / not done - Please attach a photocopy of the report

Date	**Test**	**Result / Conclusion**

4.3Radiological Evidance

X-Rays	**View**	**Findings**	**Date taken**
Skull X-Ray			
Neck X-Ray			
Chest X-Ray			
Spinal X-Ray			
Upper limb			

Lower limb			

Subject Study Number						-		

X-Rays	**View**	**Findings**	**Date taken**
X-Ray of the hand			
X-ray of the foot			
Other			

5.0 Type of Skeletal dysplasia(6)

Age at diagnosis	**Type of Skeletal dysplasia**	**Yes**	**No**	**Other**
	1.Achondroplasia group (FGFR3)			
	2.Type 2 Collagen Group			
	3.Type 11 Collagen Group			
	4.Sulphation Disorders Group			
	5.Perlecan Group			

	6.Filamin Group			
	7.Short Rib Dysplasia (with /without Polydactyly)			

Subject Study Number					-		

Age at diagnosis	**Type of Skeletal dysplasia**	**Yes**	**No**	**Other**
	8.Multiple Ephiphysial Dysplasia and Pseudochondroplasia Group			
	9.Metaphysial Dysplasia Group			
	10.Spondylo Metaphysial Dysplasia Group			
	11.Spondylo Epi (Meta)Physial Dysplasia Group			
	12. Spondylo Metaphysial Dysplasia Group			
	13.moderate Spondylo Metaphysial Dysplasia Group			
	14.Acromelic Dysplasia Group			
	15.Acromesomelic Dysplasia Group			
	16. Mesomelic and Rhizo - mesomelic Dysplasia Group			
	17.Bent Bones Dysplasia Group			
	18.Slender Bone Dysplasia Group			
	19.Dysplasia with Multiple Joint Dislocation Group			
	20.Chondrodysplasia Punctata Group			

	21.Neonatal Osteosclerotic Group			
	22.Increased Bone Density without Modification of Bone Shape Group			
	23. .Increased Bone Density with Metaphysial and Diaphysial involvement Group			

Subject Study Number					-		

Age at diagnosis	**Type of Skeletal dysplasia**	**Yes**	**No**	**Other**
	24.Decreased Bone Dencity Group			
	25.Defective Mineralization Group			
	26.Dysostosis Multiplex Group (associated with lysosomal storage disease)			
	27.Osteolysis Group			
	28.Diorganized development of skeletal component Group			
	29.Cledocranial Dysplasia Group			
	30.Craniosynostosis syndromes and other cranial ossification disorders Group			
	31..Dysostosis with predominant craniofacial involvement Group			
	32. Dysostosis with predominant vertebral and costal involvement Group			
	33.Patellar Dysostosis Group			
	34.Brachydactylies			
	35.Limb hypoplasia – Reduction defects Group			
	36.Polydactyly, Syndactyly –			

	triphalangism Group			
	37.Defects in joint formation and synostosis Group			

Subject Study Number					-		

6.0 **Assessment of the involved area**

Area involved	**Yes**	**No**	**Other**
1. Skull **2. Thorax** **3. Spine** **4. Pelvis** **5. Upper limb** **6. Lower limb** **7. Other**			

Subject Study Number					-		

6.1Assessment of the skull

Type of Defect	**Yes**	**No**	**Other**
1Microcephaly			
2.Macrocephaly			
3.Dolicocephaly			
4.Scaphocephaly			
5.Acrocephaly			
6.Brachycephaly			
7.Oxycephaly			
8.Turricephaly			
9.Plagiocephaly			
10.Kleeblattschadel			

11.Craniofacial dysostosis			
12.Other			

Subject Study Number					-		

6.2 Assessment of the Thorax (43)

Area involved	**Yes**	**No**	**Other**
2.2 Thorax(43) **2.2.1 Type I** **Pectus Carinatum** **Pectus Excavatum** **2.2.2. Type II** **Costal abnormalities** **2.2.3. Type III** **Chondrocostal Abnormalities** **2.2.4. Type IV** **Sternal Abnormalities** **2.2.5 Type V** **Clavicular- Sternal Abnormalities** **2.2.6 Other**			

Subject Study Number					-		

6.3. Assessment of the spine

Deformity	**Yes**	**No**	**Other**
Scoliosis			
Kyphosis			
Lordosis			
Spina bifida			
Osteogenesis Imperfecta			
Other			

6.4Assessment of the pelvis

Type of deformity	**Yes**	**No**	**Other**
Dislocation of hip			
Deformed pelvis			

Other			

Subject Study Number					-		

6.5.1 Assessment of the upper limbs

Defect	**Yes**	**No**	**Other**
Complete absence of upper limb			
Absence of upper arm and fore arm with hand present			
Absence of both fore arm and hand			
Absence of hand and fingers			
Short upper limb			
Other			

6.5.2 Other structural defects in the upper limbs(44)

Deformity	**Yes**	**No**	**Other**

I.Faliure of part Formation **a. Transverse** **b. Longitudinal** **I . Phocomelia** **Ii . Radial** **iii. Central** **iv .Ulnar**			

Subject Study Number					-			

Deformity	Yes	No	Other
Cleft Hand **Ulnar Club Hand** **Radial Club Hand** **II. Failure of Differentiation** **a. Synostosis** **b. Dislocation of Radial Head** **c. Symphalangism** **d. Syndactyly** **e. Contractures** **1.soft tissues** **a. Pterygium** **b. Congenital Trigger** **c. Abcenc e of Extensors** **d. Hypoplastic thumb** **e. Adducted Thumb** **f. retroflexible Thumb** **g.. camptodactyly** **h.Withered Hand**			

2.Bones **a. Clinodactyly** **b. Kirner** **c. Delta Phalanges** **III. Duplication** **a. Thumb** **b. TriPhalangism / Hyperphalangism** **c. Polydactyly Mirror Hand**			

Subject Study Number					-		

Deformity	**Yes**	**No**	**Other**
IV. Over Growth **a. Limb** **b. Macrodactyly** **c. Undergrowth** **V. Constriction Band Syndrome** **VI. Generalized skeletal abnormalities** **VII. Other**			

6.6.1 Assessment of lower limb deformities

Defects	**Yes**	**No**	**Other**
Complete absence of lower limb			

Absence of thigh and lower leg with foot present			
Absence of both lower leg and foot			
Absence of foot and toes			
Short lower limb			
Other			

Subject Study Number					-		

6.6.2 Assessment of other lower limb deformities(45)

Defect	**yes**	**No**	**Other**
Club Foot			
Congenital vertical talus			
Curly toes			
Flat feet			
Metatarsus adductus			
Other			

6.6.3Toe Abnormalities(45)

Toe Abnormalities	Yes	No	Other
6.1 Congenital Hallus Varus			
6.2 Polydactyly			
6.3 Syndactyly			
6.4 Macrodactyly			
6.5 5th Toe Contracture Angulations			
6.6 Other			

Subject Study Number					-		

7.1 Involvement of other systems

Date at diagnosis	System	Test	Description	Other
	1.Brain/locomotorsystem			
	2.Respiratory system			
	3.cardiac /circulatory system			
	4.Renal involvement			

	5. Genitourinary system **6.Other**			

8.0 Mental retardation present/absent

Subject Study Number					-		

Patient Date

		-			-				

K/EDTA vial

Label	Volume	Storage	Comments
1. **2.**	**1.** **2.**	**1.** **2.**	

<u>COMMENTS</u>

Record reasons for missing data and any additional relevant comments. ENSURE THAT ANONYMITY IS PRESERVED.

The booklet should be signed when ALL available data have been entered and cross checked with relevant data recorded elsewhere in this booklet.

Signed……. **Date……**

Investigator/Research Assistant