Chapter 3
Review of literature
Skeletal dysplasias are the heterogeneous groups of disorders of bone and cartilage. These hereditary disorders principally impact morphogenesis, development, and growth of the skeleton. Their clinical manifestations include short stature, abnormal body proportions and/or limb shape, deformity, and various complications. Currently, there are 436 well-described conditions with 364 causative genes classified under 42 groups [1]. Of these various groups, a small sub set is with arthropathy as a primary manifestation. These monogenic arthropathies are caused by alterations of genes encoding proteins that play an important role in osteochondrogenesis. Common well-defined arthropathies are listed in Table 3.1. Other than these well-defined arthropathies, there are also a few conditions, where the genetic etiology is unidentified like Mseleni joint disease and Handigodu joint disease.

Of the various well-defined inherited arthropathies, we could evaluate progressive pseudorheumatoid dysplasia, multicentric osteolysis, nodulosis and arthropathy, hyaline fibromatosis syndrome and hyperphosphatemic familial tumoral calcinosis in our study population.

3.1 Progressive pseudorheumatoid dysplasia

Progressive pseudorheumatoid dysplasia (MIM #208230) is an autosomal recessive skeletal disorder of childhood that affects the joints and the spine. Progressive pseudorheumatoid dysplasia (PPRD) was first described by Wynne-Davies et al., in 1982 as spondylo-epiphyseal dysplasia (SED) tarda with progressive arthropathy[2] and almost simultaneously by Spranger et al., as progressive pseudorheumatoid arthritis of childhood [3, 4]. The term progressive pseudorheumatoid dysplasia was given by the international working group on constitutional diseases of bone in the classification of osteochondrodysplasias [5]. The 2015 nosology and classification of
genetic skeletal disorders uses the term ‘progressive pseudorheumatoid dysplasia (PPRD; SED with progressive arthropathy)’ and groups it under group 31: genetic inflammatory/rheumatoid-like osteoarthropathies [1]. It also finds a mention in group 13: spondylo-epi-(meta)-physeal dysplasias (SEMD).

Table 3.1: Common well characterized inherited arthropathies with known genetic etiology

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>OMIM Number</th>
<th>Inheritance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stickler syndrome type 1</td>
<td>COL2A1</td>
<td>108300</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Stickler syndrome type 2</td>
<td>COL11A1</td>
<td>604841</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Stickler syndrome type 3</td>
<td>COL11A2</td>
<td>184840</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Stickler syndrome type 4</td>
<td>COL9A1</td>
<td>614134</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Familial digital arthropathy with brachydactyly</td>
<td>TRPV4</td>
<td>606835</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Hypertrophic osteoarthropathy</td>
<td>HPGD</td>
<td>259100</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Multicentric osteolysis, Nodulosis and arthropathy (MONA)</td>
<td>MMP2</td>
<td>259600</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>
Multicentric carpal-tarsal osteolysis with and without nephropathy  

Progressive pseudorheumatoid dysplasia  

Chronic infantile neurologic cutaneous articular syndrome  

Sterile multifocal osteomyelitis, periostitis, and pustulosis  

Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anaemia  

Hyperphosphatemic familial tumoral calcinosis  

Infantile systemic hyalinosis/Juvenile hyaline fibromatosis (ISH/JHF)  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>OMIM</th>
<th>Inheritance</th>
</tr>
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<tbody>
<tr>
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<td>MAFB</td>
<td>166300</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Progressive pseudorheumatoid dysplasia</td>
<td>WISP3</td>
<td>208230</td>
<td>Autosomal recessive</td>
</tr>
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<td>Chronic infantile neurologic cutaneous articular syndrome</td>
<td>NLRP3</td>
<td>607115</td>
<td>Autosomal dominant</td>
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<tr>
<td>Sterile multifocal osteomyelitis, periostitis, and pustulosis</td>
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<td>612852</td>
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<tr>
<td>Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anaemia</td>
<td>LPIN2</td>
<td>609628</td>
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</tr>
<tr>
<td>Hyperphosphatemic familial tumoral calcinosis</td>
<td>GALNT3/FGF23/KL</td>
<td>211900</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Infantile systemic hyalinosis/Juvenile hyaline fibromatosis (ISH/JHF)</td>
<td>ANTXR2</td>
<td>236490</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

The prevalence of PPD has been estimated as one per million in the United Kingdom (prevalence category of <1-9/1,000,000). However, the disease may be significantly underdiagnosed due to the overlap of the clinical features with juvenile idiopathic arthritis [2]. This disorder is more prevalent in the Mediterranean region because of the high consanguinity rate [6, 7]. A handful of cases have been published from this region covering different countries like Kuwait, Lebanon, Iran, Jordan, Saudi Arabia, Syria, Palestine and Morocco [6, 8-13]. The studies on various populations indicate that PPD is more frequent in endogamic communities [12].

Progressive pseudorheumatoid dysplasia is an early onset childhood disorder. The affected patients are normal at birth without any signs and symptoms. The general
age of the onset of symptoms in almost all the cases is below eight years whereas at a few instances it has occurred in adolescence too [2, 14]. The age of onset of PPD varies between 1 and 13 years [12, 14]. The initial signs of the disorder in majority of the cases are gait abnormalities and muscular weakness leading to easy fatigability [15]. Pain is an inconsistent feature. These early signs are followed by joint swellings and vague joint pain, which starts in small joints of hands and gradually develops in all the major joints like knees, hip, wrists, and elbows. However, redness is usually absent over swollen joints and tenderness is either absent or disproportionately minimal as compared to the stiffness; pain is often manifests at hip joints probably indicating the consequences of a diseased hip joint. Flexion and extension contractures slowly develop and lead to restricted mobility of the joints.

Affected individuals show normal stature in the initial stages of life but as the disease progresses, they do not show age appropriate height gain. The adult height in most of the instances is less than third centile and is often in the range of 4 to 5 SD below the mean [2, 9]. This can be explained partly by flexion deformities at hips, knees and spine deformities like kyphoscoliosis and lordosis. However, three affected individuals of the same family, diagnosed as PPD, were reported with a normal adult height [16]. The deformities of knee joints often manifest as genu varum or genu valgum. PPD involves multiple joints. The most frequently affected joints are small joints of hands followed by hips, knees, elbows, and wrists. Joints of feet, ankles and shoulders show occasional involvement [2, 11]. Contractures at small joints of fingers lead to camptodactyly. The joint deformities in hands are first noted in proximal interphalangeal joints followed by distal interphalangeal joints. Decreased mobility of the neck was observed in a few cases. This generalized bone and cartilage dysplasia
shows no other extra skeletal manifestations. These patients have normal cognition, facial dysmorphism is usually not observed.

Radiologically PPD represents unique signs that include epiphyseal dysplasia, platyspondyly and often metaphyseal changes [15]. It is one of the skeletal dysplasia that demonstrates enlarged epiphyses, decreased joint space, and mild to severe metaphyseal irregularities. Metaphases may be wider and margins irregular. The radiographs of joints show enlarged epiphyses, widened metaphyses, narrow or absent joint spaces, irregular articular surfaces and diffuse osteoporosis. Small joints of hands and feet show proximal interphalangeal joint swellings in early infancy followed by distal joint abnormalities. Spine radiographs in affected individuals show several changes. Irregularities in the ossification of vertebral end plates and flattened vertebral bodies are observed in all the cases of PPD [11]. Scoliosis and/ or kyphosis are noted in majority of the cases whereas lumbar lordosis is observed very rarely. Platyspondyly associated with anterior beaking, which is more apparent in later stages of life, is a prominent feature in older children. Narrow or loss of intervertebral disc spaces is also noticeable in the spine radiographs. The key features observed in radiographs of pelvis are enlarged and flattened capital femoral head along with short and wide femoral neck. The joint deformities in the hips lead to coxa vara. Broadened ilia and irregular acetabular roofs are also observed.

In 1998, El-Shanti and colleagues localized the PPD locus to 12.9cM critical region on chromosome 6q by linkage studies in an inbred Jordanian family [7]. Later in the same year Fischer and colleagues narrowed the PPD locus to a 3cM interval on chromosome 6q22 by linkage studies on three families with different ethnicities [17]. In 1999, Hurvitz and colleagues further narrowed down it to 2 cM interval with the help of 10 additional families and WISP3 gene (Wnt1-inducible signaling pathway
protein 3) was identified as the candidate gene for PPD in the two genes present in the 2 cM interval on the chromosome 6q22 [10]. They identified nine WISP3 mutations in eight unrelated families confirming it as causal gene for PPD.

The WISP3 gene consists of five exons that encode a 354-amino acid protein of ~40 kDa molecular weight. The WISP3 protein encodes five functional domains: peptide signal sequence (1-16 amino acids), insulin-like growth factor binding proteins (IGF-BP) like domain (46-116 amino acids), von Willebrand factor type C (vWC) repeat domain (119-180 amino acids), thrombospondin type I domain (206-253 amino acids) and cysteine knot domain (264-346 amino acids), which approximately corresponds to each exon [10, 18]. The WISP3 is a member of the CCN (connective tissue growth factor/cysteine-rich61/nephroblastoma overexpressed) family of growth factors [19]. WISP3 is attributed to CCN family of extracellular matrix associated proteins because of the high sequence homology. The CCN family proteins are multifunctional proteins that regulate cell migration, adhesion, cell proliferation, differentiation, and survival in connective tissues [20]. The WISP3 expresses predominantly in mesenchymal cells (synoviocytes and chondrocytes) [10]. It also shows an expression in tissues of kidney, testis, placenta, ovary, prostate and small intestine [19]. The in vitro studies on chondrocyte cell lines indicated that the WISP3 protein regulates the collagen II and aggrecan expression by the activation of SOX9 transcription factors [20]. The WISP3 plays a major role in cartilage homeostasis by inhibiting the cell proliferation and promoting precursor cell differentiation of chondrocytes [21]. The WISP3 expression is very much reduced in the chondrocytes of PPD patients [22]. Mutant articular chondrocytes with very low levels of WISP3 expression show increased proliferation rate, increased cell viability and decreased apoptosis in PPD patients suggesting that they are in immature and hyper-
proliferative state [22]. This helps in explaining the enlarged metaphyses in PPD patients. Mutant WISP3 protein shows abnormal aggregation in the cytoplasm and cell membrane of the chondrocyte cells [21]. As the mutant WISP3 protein delays intracellular collagen synthesis and inhibits extracellular collagen secretion, the cartilage flexibility in PPD patients diminishes. However, the role of WISP3 in cartilage homeostasis and the pathophysiology of PPD are not yet completely understood. The most frequently modified amino acid throughout the protein is cysteine. The WISP3 protein contains 34 highly conserved cysteine residues. Alterations at these cysteine residues results in pathogenicity by altering the protein structure and function. Fifteen mutations affecting twelve cysteine residues are reported.

Since the identification of WISP3 as the causative gene for progressive pseudorheumatoid dysplasia in 1999 [10], ~49 mutations have been reported from 118 families. These pathogenic sequence variations have been reported in all the exons and some introns of the gene. Most of the variations are deletions (16, 43%) and missense mutations (15; 31%), followed by nonsense (8; 16%), splice site mutations (7; 14%), duplications (5; 10%) and complex variation like indels (1; 2%) variants. Even though all the exons show mutations, exon 2 and exon 4 (14 variants each) are involved more frequently followed by exon 5 (11 variants). Four variants are reported in exon 3 and three variants in exon 1. Truncating mutations either by substitutions or insertions or deletions leading to changes in the frame constitute 61% of the pathogenic variations. The mutation, p.(Cys52*) is the most frequently observed mutation worldwide (34 families). Complex variation i.e., deletion of two nucleotides followed by insertion of a single nucleotide (c.621_622delAAinsT) is reported in one case [15]. So far three polymorphisms have been reported in the
literature: p.(Gln56His), p.(Gly83Glu) and p.(Gln269Gln) [10, 12, 15]. The polymorphism p.(Gly83Glu) shows the segregation with the common mutation p.(Cys52*). One far intronic mutation has been reported in the intron 1, which causes an insertion of 131 base pairs between the exons 1 and 2. Like most of the monogenic disorders, specific mutations were carried often by ethnic populations due to founder effect [12]. No specific genotype phenotype correlation was established as the severity of the disease in patients did not vary with the mutations [15, 23].

At present, no specific therapy is available for children with PPD. Treatment is mainly symptomatic. Anti-inflammatory medications including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and immunosuppressive drugs have a limited role in the treatment of PPD [24]. Pain due to secondary osteoarthritis may respond to NSAIDs. Timely correction of skeletal abnormalities limits the disability in childhood and adolescence [25]. These orthopedic problems in progressive pseudorheumatoid dysplasia include angular deformities of lower limbs, progressive stiffness of large and small joints, early arthropathy of the joints, progressive stiffness, and deformities of spine. The main principles of orthopedic management of PPD were: correction of joint deformities, restoring normal alignment of lower limbs, maintenance of joint mobility, pain relief in severe arthritis, correction of deformities of spine and spinal stenosis [25].
**Figure 3.1:** A schematic representation of all the mutations observed in WISP3 from literature. Truncating variants are represented in red, missense variants in green and splice variants in blue. Coding exons are marked below the domain structure of WISP3 protein.
3.2 Multicentric osteolysis, nodulosis and arthropathy

Multicentric osteolysis nodulosis and arthropathy is an osteolytic bone disorder characterized by progressive osteolysis and arthropathy. Osteolytic bone disorders (also known as idiopathic osteolysis, vanishing bone syndrome, or disappearing bone disease) are a group of genetic conditions characterized by rapid bone resorption leading to loss of bone and/or joint erosion. Since the initial description of massive osteolysis by Jackson [26], several osteolytic conditions have been described under different terminology [27-33]. In 1969, Torg et al. described a syndrome demonstrating autosomal recessive inheritance with moderate osteolysis of carpal and tarsal bones, wide metacarpals and metatarsals, swelling of digits, joint contractures with subcutaneous nodules [34]. Later in the same year Winchester et al. described a related disorder with generalized osteoporosis, progressive osteolysis confined to carpal and tarsal bones, joint contractures, short stature, coarse facies, corneal opacities, gum hypertrophy and electrocardiographic changes [35]. This condition was reported as a new type of mucopolysaccharidosis syndrome with radiographic features resembling those of rheumatoid arthritis. Next, Hollister et al. described thick and leathery skin with hyperpigmentation and hirsutism as a feature of this syndrome [36]. They also proposed Winchester syndrome as a non-lysosomal connective tissue disorder, since its initial assumption as a mucopolysaccharidosis had no further evidence. Subsequently, one more family with Torg syndrome and five families with Winchester syndrome were reported until the year 2000 [37-41].

In the year 2000, Al-Mayouf et al. described ten cases from six unrelated consanguineous families of Saudi Arabian origin with coarse facies, hirsutism, painful hands, generalized osteoporosis and severe osteolysis of carpal and tarsal bones [42].
Despite the phenotypic overlap with Torg syndrome, they proposed it to represent a novel phenotype viz., Nodulosis, Arthropathy and Osteolysis (NAO) syndrome. Al Aqeel and colleagues described further six similar cases from a Saudi kindred [43], followed by identification of MMP2 (Matrix metalloproteinase 2 gene on 16p12.2 as the candidate gene by Martignetti et al. [44]. They identified two homozygous pathogenic sequence variations in the gene in two families by haplotype analysis of homozygous by descent microsatellite markers. In 2005, an Italian patient was described to have Winchester syndrome with a pathogenic variation in the MMP2 gene [45]. The next year, Rouzier et al. described the case originally reported by Lambert et al. [46] as Winchester syndrome and reported a mutation in MMP2 gene [47]. Soon, Zankl et al. reported a Torg syndrome patient with compound heterozygous MMP2 mutations and proposed that all three syndromes viz., Torg syndrome, Winchester syndrome, and NAO syndrome are allelic disorders [48]. They suggested the name Torg-Winchester syndrome for these disorders and considered it a continuum of the same spectrum. The 2006 revision of Nosology and Classification of Genetic Skeletal Disorders, described them as a single disorder, Torg-Winchester syndrome including NAO syndrome [49] and the same continued in the 2010 and 2015 nosology and classification of genetic skeletal disorders [1, 50].

In the current classification, group 28: osteolysis group has 9 conditions: familial expansile osteolysis (MIM #174810; RANK), mandibuloacral dysplasia type A (MIM #248370; LMNA), mandibuloacral dysplasia type B (MIM #608612; ZMPSTE24), progeria, Hutchinson–Gilford type (MIM # 176670; LMNA), Hajdu–Cheney syndrome (MIM #102500), multicentric carpal-tarsal osteolysis with and without nephropathy (MIM #166300; MAFB), and lipomembranous osteodystrophy with
leukoencephalopathy (MIM #221770; TREM2 and TYROBP) along with Torg–
Winchester syndrome (MIM #259600, MMP2).

However, recently the molecular analysis of cultured fibroblasts of originally defined
patients with Winchester syndrome, reported by Winchester et al., revealed the
mutations in the MT1-MMP gene, suggesting it as an independent condition [51].
Based on this Evans et al. stated that the misdiagnosis of two cases of MONA as
Winchester syndrome led to this misconception of allelic disorders. The phenotypic
variability along with the progressive changes of the symptoms might have added to
the misperception of this disorder.

Torg syndrome and Nodulosis, Arthropathy and Osteolysis (NAO) syndromes are
together now referred to as Multicentric Osteolysis Nodulosis and Arthropathy
(MONA, MIM #259600) which is likely to be widely accepted term for all the
phenotypes caused by mutations in MMP2 gene. Winchester syndrome (MIM
#277950) is being designated as a separate entity with similar features as MONA
with the absence of subcutaneous nodules with mutations in MT1-MMP gene. The
major manifestations of MONA syndrome are generalized osteolysis (remarkably of
carpal and tarsal bones) and the symptoms associated with arthropathy viz.,
progressive joint contractures, joint swelling and joint pain [42, 52, 53]. Other clinical
manifestations are subcutaneous nodules on palmar and plantar surfaces, coarse
facies, corneal clouding, hyperpigmentation of skin and cardiac involvement.

The MMP2 gene has 13 exons and encodes a 660-amino acid protein weighing ~72
kDa. It encodes matrix metalloproteinase-2 enzyme, also known as gelatinase. The
MMP2 protein consists of multiple functional domains viz., signal peptide (1-29
amino acids), pro peptide domain (43-97 amino acids), catalytic domain (118-446
amino acids) and hemopexin domain (475-518, 520-563, 568-615, 617-660 amino
The catalytic domain harboring three inserts of fibronectin type 2 repeats (233-274, 291-332, 349-390 amino acids) is the most conserved domain. The cysteine motif (Pro100-Arg-Cys-Gly-Asn-Pro-Asp106) of the pro MMP2 binds with the catalytic zinc ion and plays a role in maintaining the latent state of pro-MMP2 [55]. Hemopexin domain is the binding site for tissue inhibitors of metalloproteinases (TIMPs) and shows the structure of a four-blade propeller fold [54, 56]. The pro MMP2 and TIMP2 complex interacts with 2 membrane-type MMP (MT1-MMP) molecules for activation of the gelatinase on the cell surface forming the proMMP-2 activation complex [57]. The gelatinase enzyme is one of the specialized proteinases that are traditionally known to catalyze the breakdown of specific subsets of extracellular matrix. Recent literature also defines its crucial role in cell attachment, proliferation, differentiation, and apoptosis [58]. The MMP2 deficient mice were initially shown to be phenotypically normal as against the MT1-MMP (activator protein of pro MMP2) null mice, which expressed a phenotype similar to MONA [59]. However, the recent evidence demonstrates the attenuated form of MONA in the mice models of MMP2 null mice with abnormal development of craniofacial structures, arthropathy and decreased bone mineral density. The loss of MMP2 enzyme activity has been shown to affect the osteoblast and osteoclast growth significantly [58]. The MMP2 also regulates the activity of TGFβ1 and thus plays a role in bone formation and homeostasis [45, 60].

In MMP2 gene 17 inactivating mutations have been reported in 31 cases from 16 families [44, 45, 47, 48, 52, 53, 61-67] (LOVD MMP2 database). The families have been reported from India, Saudi Arabia, Egypt, Turkey, and Italy, Morocco, South America, Brazil, Algeria and Korea. All the subjects showed homozygous mutations, except two affected patients [48, 67]. Most of the mutations of the MMP2 gene lead
to loss of gelatinolytic activity of matrix metalloproteinase-2 enzyme [53]. Ten of
these are missense mutations, three are nonsense mutations, three are small
deletions and one is a splice site variant. So far the variation, p.Arg101His is the only
variation which has been observed in two different families (from Saudi Arabia and
South America), while the remaining are the private mutations. Only two families
reported compound heterozygous pathogenic variants (p.Arg101His/p.Gly454Alafs*44; p.(Ser396Arg)/p.(Tyr425Ser)) suggesting this
syndrome is extremely rare and is often precipitated by consanguinity[48, 67].
At present, there is no specific therapy for this condition. Bisphosphonates have been
tried by two groups but did not benefit the affected children to a significant extent
[61, 68]. Steroids and immunosuppressant drugs have been used without much
benefit and are best avoided given their side effects [42, 48, 52, 65, 66]. There is no
data on the benefit of analgesics either. Currently, the care is supportive at best.
Physical therapy may slow the rate of development of contractures and prolong
mobility. However, there is paucity of data on natural history and life expectancy of
the condition. The oldest patient reported in literature is 43 years [53]. More studies
and long-term follow-ups are necessary in this regard.
Figure 3.2: A schematic representation of all the mutations observed in the MMP2 from literature. Truncating variants are represented in red, missense variants in green and splice variants in blue. Coding exons are marked below the domain structure of the MMP2 protein.
3.3 Hyaline fibromatosis syndrome:

Hyaline fibromatosis syndrome (MIM #228600) is a unifying term for the arthropathic disorders, Infantile systemic hyalinosis (ISH), and Juvenile hyaline fibromatosis (JHF). Though initially considered separate disorders after the identification of causative gene, both ISH and JHF are regarded as the variants of the same disorder [69, 70]. Hyaline fibromatosis syndrome is an autosomal recessive inherited syndrome caused due to the mutations in the gene anthroxin toxin receptor 2 (ANTXR2) [71, 72]. Both the conditions show multiple skin lesions including subcutaneous nodules in the scalp and pearly papules in the perioral, perinasal and perianal regions along with progressive painful joint contractures [73]. Other features include gingival hypertrophy, short stature, osteopenia, osteolytic lesions, along with hyperpigmentation over joint prominences. This disorder is mainly characterized by the deposition of amorphous hyaline material in the skin and internal organs [74]. However, the findings of histopathological examinations are indistinguishable in both these forms. Though the condition was described in all types of populations, Al-Mayouf et al. reported that it is more prevalent among Saudi Arabia and Arab population [75]. This may be due to the high consanguinity rates observed in those populations.

Infantile systemic hyalinosis has been considered a severe form of the condition with early onset and lethality in early childhood [74]. The main clinical features of ISH include progressive joint contractures with pain, diffusely thickened skin, pearly papules, hyperpigmentation over the bony prominences, gingival hypertrophy, osteoporosis, susceptibility to fractures, recurrent diarrhea, and failure to thrive [73]. However, Juvenile hyaline fibromatosis is the milder form with less pronounced phenotypic features in the affected individuals [76]. The main clinical features of JHF
include papulonodular skin lesions, soft tissue masses, flexion contractures of the joints, gingival hypertrophy, and osteolytic lesions [70].

This condition was first described in 1873 by Murray as ‘molluscum fibrosum’ [77]. Later Puretic et al. reported mesenchymal dysplasia in 1962, a novel connective tissue disorder with similar features. In the year 1964, Kitano et al. coined the term, juvenile hyaline fibromatosis for this condition [78]. However, Landing and Nadorra described ‘infantile systemic hyalinosis’ as a different condition from JHF in 1986 [79]. Subsequently, several publications reported these two conditions [73, 80]. In 2002, Rahman et al. localized the JHF gene to 7cM critical region on chromosome 4q21 by genome wide linkage studies in two families from Gujarat (India) [81]. The same study confirmed this critical region by studying additional three families of Turkey, Morocco and European origin, respectively. Later in the year 2003, the same research group and another research group identified the causative gene, capillary morphogenesis protein gene-2 (CMG2) in patients with ISH and JHF as well [71, 72]. They also suggested that ISH and JHF are allelic disorders. However, due to the discrepancies in the phenotypic features and survival rates of various reported patients, it is apparent the differentiation of ISH and JHF is not feasible [74]. In addition, a wide variety of terms has been used to describe these conditions. Considering all these, in 2009, Nofal et al. proposed the unifying term Hyaline Fibromatosis syndrome [69]. They also proposed a grading system for this condition to be graded as mild, moderate, and severe. Later Denadai et al. supported this unifying term stating that the ISH and JHF are different variants of the same disorder and modified the grading system [70]. This new grading system includes four grades with lethal as the most severe grade (Table 3.2).
**Table 3.2:** Proposed grading system of hyaline fibromatosis syndrome adopted from Denadai et al., 2012

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin and/or gingival involvement</th>
<th>Joint and/or bone involvement</th>
<th>Internal organ involvement with or without clinical manifestations</th>
<th>Severe clinical decompensation (organ failure and/or septicemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Mild)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 (Moderate)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 (Severe)</td>
<td>+</td>
<td>±</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>4 (Lethal)</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

±: manifestation can be present or not; Clinical manifestations = persistent diarrhea, and/or recurrent infections, and/or other except criteria 1 and 2.

CMG2 is also called as anthrax toxin receptor 2 (ANTXR2) which is a type I transmembrane glycoprotein of ~55 kDa [82]. The CMG2 is the main receptor of the anthrax toxin and present ubiquitously [83]. It is a 489 amino acid protein with a signal peptide, von Willebrand factor type A (vWA) domain, Ig-like domain, transmembrane helix and a cytoplasmic tail [83]. The ectodomain of CMG2 contains vWA domain through which it binds to lamin and collagen IV [84]. These proteins are induced in endothelial cell morphogenesis with the induction of CMG2. This suggests the role of CMG2 in basement-membrane matrix assembly and endothelial cell morphogenesis [70]. This also suggests that the hyaline material deposits between the endothelial cells in the affected individuals is may be due to the leakage of plasma components through the basement membrane to the perivascular space [72].
The loss of function mutations in *ANTXR2* are known to cause hyaline fibromatosis syndrome. Until date, approximately 38 mutations are identified in *ANTXR2* gene from ~15 studies. A variety of molecular variations is reported in *ANTXR2* gene, including gross deletions comprising exons, insertions, missense, and splice site variations [70, 85]. Of these different variants, c.1073_1074insC is the most common variant and c.1074delT is the second most common variant. Together these two variants constitute ~35% of total affected individuals. Haplotype analysis in two Iranian families revealed a founder effect for the variant, c.1074delT [86]. Since these two Iranian families are of different ethnic and language backgrounds and this mutation has been observed in a variety of populations, it is appropriate to propose that this deletion variant (c.1074delT) and the insertion variant (c.1073_1074insC) are in the hotspot region. Various studies also suggest the GC rich region encoding the proline residues (352-356; 358) in exon13 is the mutational hotspot region [87, 88]. Two mutation proven cases have been published from India [89-91]. The cases reported by Koonuru et al., and Lakkireddy et al., are probably the same case as they report identical twins with same mutation.

The pathogenic variants in the extracellular vWA domain were suggested to be associated with a severe phenotype and the mutations in the cytoplasmic domain with a milder phenotype [72]. However, this correlation is not always true suggesting other confounding factors such as environmental factors and modifying genes. The mutations in ectodomain leads to protein retention in endoplasmic reticulum due to the decreased folding efficiency [82]. Based on this a therapeutic approach has been proposed proteasome as the potential drug target in HFS [88]. The loss of function mutations in ectodomain lead to protein folding defects and resulting in the degradation of protein through proteasome. Thus, using proteasome inhibitors helps
in retention of the CMG2 protein subsequently elevating its levels. However, this rescue is more efficient in milder phenotypes and applicable for missense mutations present in exon 1 to exon7.

3.4 Hyperphosphatemic familial tumoral calcinosis:

Hyperphosphatemic familial tumoral calcinosis (HFTC, MIM #211900) is an extremely rare metabolic disorder, which shows autosomal recessive inheritance pattern. Hyperphosphatemic familial tumoral calcinosis (HFTC) and hyperostosis-hyperphosphatemia syndrome (HHS) are two different clinical presentations of the same disease [92]. HHS is characterized by recurrent long bone lesions with hyperostosis, whereas HFTC shows ectopic calcification around major joints. Elevated serum inorganic phosphate and 1, 25-dihydroxyvitamin D levels are common in both the conditions [93].

The GALNT3 gene encodes the protein glycosyltransferase, UDP-N-acetyl-a-D-galactosamine: polypeptide N-acetylgalactosaminyl transferase 3, which is required for the O-linked glycosylation of FGF23. HFTC is caused due to mutations in the GALNT3 which prevents O-linked glycosylation of FGF23 or recessive loss of function mutations of FGF23 or mutation in Klotho (KL) which is a cofactor required to activate FGF receptors or due to direct mutations in FGF23 [94-96]. Mutations in the GALNT3 and the FGF23 lead to the FGF23 deficiency whereas the mutations in KL lead to reduced activity of FGF23 [97-99]. These mutations disrupt phosphate homeostasis and results in abnormal bone mineralization [100].

Till date ~33 mutations have been identified in GALNT3 gene [101]. The p.(Arg162*) is the most common mutation, which is present in four families. Due to the occurrence of another mutation, p.(Arg162Gln) in the same location. Ichikawa et al.
suggested this region might be susceptible to the mutations [93]. There are seven reported $FGF23$ mutations, and only one report of the $KL$ mutation to date causing HFTC [93]. Surgical management and pharmacological treatment are the available options. However, the results of both the treatments are inconsistent [97].

3.5 Other rare inherited arthropathies

Stickler syndrome is a genetically heterogeneous connective tissue disorder. It is characterized by articular, ocular, orofacial and auditory manifestations. Stickler syndrome is classified based on the underlying genetic defect as type 1, 2, 3 and recessive type. Type 1 is caused due to the mutations in the collagen gene $COL2A1$ [102]. Type 2 is caused due to the mutations in $COL11A1$ gene [103]. Type 3 occurs due to the mutations in $COL11A2$ gene [104]. The recessive type of stickler syndrome is associated with the mutations in three genes: $COL9A1$, $COL9A2$, and $COL9A3$ [105-107]. However, the causality of $COL9A1$ and $COL9A3$ should be reasserted. Approximately 80% of the cases with the Stickler syndrome are of type 1 [108].

Familial digital arthropathy with brachydactyly (FDAB) occurs due to the mutations in Transient receptor potential cation channel, subfamily V, member 4 ($TRPV4$) gene [109]. It shows an autosomal dominant inherited pattern [110]. Until date, this condition is observed in only three affected families. The disease is characterized by osteoarthritis of interphalangeal joints in fingers and toes in first decade of life followed by brachydactyly. Interphalangeal, metacarpophalangeal, and metatarsophalangeal joints are the mainly affected joints with no other skeletal manifestations restricting the disorder to fingers and toes [110]. Three missense mutations in $TRPV4$ gene are associated with FDAB, they are p.Gly270Val, p.Arg271Pro, and p.Phe273Leu [109].
Multicentric carpal-tarsal osteolysis (MCTO) with and without nephropathy is an autosomal dominantly inherited disorder. MCTO is caused due to the mutations in MAFB (V-MAF musculoaponeurotic fibro sarcoma oncogene family, protein B) gene [111]. The disorder is clinically characterized by progressive osteolysis of carpal tarsal bones and usually manifest in the early childhood. The affected individuals may develop progressive renal failure at a later stage. Craniofacial abnormalities, intellectual disability, and involvement of other joints (ankles, wrists, and elbows) are also observed in some patients [111-113]. Till date, approximately fifteen missense mutations have been identified in the MAFB gene, which exhibits dominant negative pathogenicity [114].

Chronic infantile neurologic cutaneous articular syndrome or neonatal onset multisystem inflammatory disease (CINCA/NOMID) is a systemic auto inflammatory disease, which shows autosomal dominant inheritance pattern. It is caused due to the gain of function mutations in the gene cryopyrin (NLRP3) [115]. CINCA/NOMID is one of the cryopyrin-associated periodic syndrome (CAPS) conditions. This is the most severe condition of the three CAPS entities. It is characterized by a triad of symptoms: neonatal onset of cutaneous symptoms, chronic meningitis, and recurrent fever. Skeletal manifestations show chronic arthropathy, epiphyseal long bone ossification and osseous overgrowth which may be associated with contractures in some cases [116, 117]. According to the mutation database of auto inflammatory syndromes (Infevers) till date, approximately 143 mutations are identified in NLRP3 gene, which are affiliated with cryopyrin-associated periodic syndromes [118]. Approximately 50% of the patients affected with CINCA syndrome do not show NLRP3 gene mutations by conventional testing strategies [119]. This suggested the
involvement of somatic mosaicism, consequently, the somatic mutations have been observed in the germline mutation negative patients in the recent past [119, 120].

Sterile multifocal osteomyelitis, periostitis, and pustulosis is an autoinflammatory syndrome, which shows autosomal recessive inheritance pattern. It is caused due to the mutations in Interleukin-1-receptor antagonist (IL1RN) gene [121]. The symptoms of the disease appear in perinatal period as the systemic inflammation of skin and bone. Cutaneous manifestations include pustular rash and oral mucosal lesions. The skeletal changes include widening of ribs, periosteal reaction, osteolytic lesions, joint swelling, and cervical vertebral fusion [122]. The affected individuals show increased levels of inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). If untreated the disease follows a fatal course, however, the treatment with anakinra shows rapid improvement [115]. Until date, 5 mutations are reported in IL1RN gene of which p.Glu77* is the most common one [123].

Chronic recurrent multifocal osteomyelitis with congenital dyserythropoietic anemia is an autoinflammatory bone disorder caused due to the pathogenic homozygous variants in LPIN2 gene [124]. It is also called Majeed syndrome. It is characterized by chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia [125]. Onset of symptoms is usually within the first two years of life. The chronic recurrent multifocal osteomyelitis manifests as exacerbations and remissions consisting bone/joint pain, primarily large joint swellings and osteomyelitis at multiple sites [126, 127]. Joint contractures are often developed later in life. Other clinical symptoms include mild fever, failure to thrive, hepatosplenomegaly and cutaneous inflammations. Until date, 3 mutations; a splice variant (c.2327+1G>C), one deletion (c.540_541delAT), and one missense variant (p.(Ser734Leu)) reported in 3 families [128].
Other than the inherited arthropathies with known genetic etiology, there are also a few conditions, which are clinically characterized but the genetic basis is not yet identified. A few of them are Handigodu joint disease and Mseleni joint disease. Handigodu syndrome is endemic to Malnad region of Karnataka, India. Whereas, Mseleni syndrome is restricted to the northern Zululand population of South Africa. Handigodu joint disease (MIM 613343) is a spondylo epimetaphyseal dysplasia observed in the Malnad region of Karnataka [129]. In addition, it is predominantly restricted to the Chanangi and Chaluvadi communities. Since the syndrome was identified in the village Handigodu, it was named Handigodu joint disease or spondylo epimetaphyseal dysplasia, Handigodu type. The syndrome manifests as a late onset disorder with progressive degenerative osteoarthropathy of hip and spine [130]. However, the genetic etiology of this condition has not been discovered. Based on the anthropometric and radiological findings, this disorder has been classified into three distinct types:

Type 1: Primarily characterized by osteoarthritic changes of hip with pain, gait abnormalities, lumbar lordosis and normal or average height.

Type 2: The affected individuals show short trunk short stature with dysplastic changes observed in hip and spine. Platyspondyly was noted in these patients.

Type 3: A severe short stature due to severe spinal involvement. Apart from hip and spine, epiphyseal changes were also noted at knees, hands, and wrists.

However, all the types were noticed in the same families suggesting these types might be the variable expression of the phenotype [129].

Apart from the inherited arthropathies listed here, there are miscellaneous conditions like CACP syndrome (camptodactyly - arthropathy - coxa vara -
pericarditis), Myhre syndrome, Navajo familial neurogenic arthropathy and chondrocalcinosis with arthropathy as one of the clinical feature.