Al–Aqeel Sewairi syndrome, a new autosomal recessive disorder with multicentric osteolysis, nodulosis and arthropathy

The first genetic defect of matrix metalloproteinase 2 gene

Aida I. Al–Aqeel, MD, FRCP.

ABSTRACT

Objective: We report a distinctive autosomal recessive multicentric osteolysis in Saudi Arabian families with distal arthropathy of the metacarpal, metatarsal and interphalangeal joints, with ultimate progression to the proximal joints with decreased range of movements and deformities with ankylosis and generalized osteopenia. In addition, they had large, painful to touch palmar and plantar pads. Hirsutism and mild dysmorphic facial features including proptosis, a narrow nasal bridge, bulbous nose and micrognathia.

Methods: Using a genome-wide search for microsatellite markers from 11 members of the family from the Armed Forces Hospital and King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia, localized the disease gene to chromosome 16q12-21. Haplotype analysis with additional markers narrowed the critical region to 1.2cM and identified the matrix metalloproteinase 2 (MMP-2), (gelatinase A, collagenase type IV, EC 3.4.24.24) gene as a disease candidate at Mount Sinai School of Medicine, New York, United States of America in April 2000.

Results: Some affected individuals were homoallelic for a nonsense mutation (TCA>TAA) in codon 244 of exon 5, predicting the replacement of a tyrosine residue by a stop codon in the first fibronectin type II domain (Y244X). Other affected members had a missense mutation in exon 2 arginine 101-histidine (R101H) leading to no MMP-2 enzyme activity in serum or fibroblast or both of affected individuals. In other affected members, a non-pathogenic homoallelic GT transversion resulted in the substitution of an aspartate with a tyrosine residue in codon 210 of exon 4 (D210Y). The MMP-2-null mouse has no developmental defects, but are small, which may reflect genetic redundancy.

Conclusion: The discovery that deficiency of this well-characterized gelatinase/collagenase results in an inherited form of an osteolytic and arthritic disorder provides an invaluable insights for the understanding of osteolysis and arthritis and is the first genetic evidence that MMP2 deficiency is important in growth and development.

Table 1 - International skeletal dysplasia registry classification of the multicentric osteolyses.

<table>
<thead>
<tr>
<th>Types of multicentric osteolysis</th>
<th>Mode of inheritance</th>
<th>OMIM</th>
<th>Present at birth</th>
<th>Chromosomal locus</th>
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<tbody>
<tr>
<td><strong>Multicentric predominantly carpal and tarsal in the hand</strong></td>
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<tr>
<td>Multicentric carpal-tarsal osteolysis with and without nephropathy</td>
<td>AD</td>
<td>166300</td>
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<td>Shinohara carpal-tarsal osteolysis</td>
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<tr>
<td><strong>Multicentric predominantly carpal-tarsal and interphalangeal</strong></td>
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<tr>
<td>Francois syndrome</td>
<td>AR</td>
<td>221800</td>
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<td>Winchester syndrome</td>
<td>AR</td>
<td>277950</td>
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<tr>
<td>Torg syndrome</td>
<td>AR</td>
<td>259600</td>
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<tr>
<td>Whyte Hemingway carpal-tarsal phalangeal osteolyses</td>
<td>AD</td>
<td>-</td>
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<tr>
<td>Al-Aqeel Sewairi syndrome</td>
<td>AR</td>
<td>605156</td>
<td></td>
<td>16q12-21</td>
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<tr>
<td><strong>Predominantly distal phalanges</strong></td>
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<tr>
<td>Hadju-Cheney syndrome</td>
<td>AD</td>
<td>102500</td>
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<td>Giacci familial neurogenic acroosteolyses</td>
<td>AR</td>
<td>201300</td>
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<td></td>
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<tr>
<td>Mandulo acral syndrome</td>
<td>AR</td>
<td>-</td>
<td></td>
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<tr>
<td><strong>Predominantly involving diaphyses and metaphyses</strong></td>
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<tr>
<td>Familial expansible osteolysis</td>
<td>AD</td>
<td>174810</td>
<td>+</td>
<td>18p11.2-12.2pl21</td>
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<tr>
<td>Juvenile hyaline fibromatosis</td>
<td>AR</td>
<td>228600</td>
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OMIM - online mendelian inheritance in man, AR - autosomal recessive, AD - autosomal dominant
hands and feet which develop when these children start to walk and progressively increasing. Magnetic resonance imaging of these nodules shows rim enhancement near the margins, which suggest fibro collagenous nature\(^\text{14}\) (Figure 2) scarring with keloid formation was noted after the biopsy of these nodules. (Figure 1) Laboratory evaluations including complete blood count, serum chemistries, kidney, liver, bone, rheumatology panels, serum and urine metabolic studies including enzyme studies for Farber lipogranulomatosis were all normal.\(^\text{14,15}\)

Twenty-four hour urine collection for creatinine clearance, proteinuria and urinary electrolytes were normal with normal renal ultrasound and functional scan. Radiological evaluation of these children have revealed generalized osteopenia, fusiform swelling of fingers with hyperextension of metacarpal phalangeal joints and flexion of intraphalangeal joints, osteolysis of carpal and tarsal bones, which progressively lead to their destruction and metacarpal, metatarsal, phalangeal and interphalangeal joints with increasing age as well as ankylosis of the other joints, with cortical thinning, epiphyseal enlargement and loss of joint space with pelvic distortion\(^\text{13,14}\) (Figure 2). Joint biopsy reveals a normal synovium with no evidence of inflammation, while biopsy of the nodule showed fibrous fatty tissue.\(^\text{14}\) (Figures 3 & 4) Linkage analysis on genomic DNA from blood samples obtained after informed consent. Cell culture and zymography were carried out by standard procedures.\(^\text{16}\)

Results. Using polymerase chain reaction-based microsatellite markers, a genome wide search for homozygosity by descent was performed on 3 affected Saudi Arabian families. The disease gene was localized to chromosome 16q12, with a maximum lod score of 4.59 for marker D16S3253. Haplotype analysis narrowed the critical region to 13 cM interval between markers D16S3396 and GATA67G11. Further, haplotype analysis narrowed the critical region to 1.2 centimorgan (cM) region that spans the gene encoding MMP-2.\(^\text{16-18}\) In one family, all affected individual are homo allelic for a nonsense mutation (TCA→TAA) in codon 244 of exon 5 of the gene, predicting the replacement of tyrosine residue by a stop codon (Y244X).\(^\text{14,16-18}\) In the second family as G→A transition in codon 10 of exon 2, predicting the replacement of an arginine with histidine (R101H).\(^\text{15,16}\) In the third family no inactivating mutations were found in the exonic sequences of the gene, such mutation might be present in the promotor or intrinsic sequences.\(^\text{15,16}\) However, a non-pathogenic homoallelic G→T polymorphism resulted in the substitution of an aspartate with tyrosine residue (D210Y), which was also present in 50 unaffected members of the tribe;\(^\text{15,16}\) all affected members had no serum and fibroblastic MMP-2

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**Figure 1** - The clinical features showing (a) Index patient at 4 years. Note the bilateral proptosis, narrow nasal bridge, bulbous nose and small chin. (b) Fusiform swelling of fingers with flexion of interphalangeal joints and hyperextension of metacarpophalangeal joints. Note the hirsutism of the dorsum on the hand and arm. Keloid formation at the site of nodule biopsy. (c & d) Subcutaneous painful nodules at the palmar and plantar aspects of the hands and feet. (e) Another patient at the age of 20 years. Note the deformed hands, with elbows and wrists distorted with flexion of elbows and foreshortening of all fingers.
Al-Aqeel Sewairi syndrome, MONA, MMP-2 deficiency ...  

Figure 2 - Radiologic features showing (a) hands (index patient at 4-years), with osteopenia, fusiform swelling of fingers and osteolysis of the carpal, metacarpal, bones and interphalangeal joints. Note the proximal tapering, distal notching of the metacarpal bones, with severe cortical thinning and undermineralization with apparent increase in the caliber of the metacarpal bones. Shadowing by the subcutaneous palmar nodules is evident. Another patient at the age of 20-years. (b) Feet with complete chaotic destruction and loss of all tarsal bones, ankylosis of the ankle joint, metatarsal phalangeal joints, distal tapering of the metatarsals with loss of fifth digit and overlying tissue. Marked osteopenia with thickening of subcutaneous tissues over the tibia fibula. (c) Knees are markedly osteopenic with cortical thinning, epiphyseal enlargement, and reduced joint space. (d) Pelvis is markedly distorted, both hips are osteopenic, with irregularities of the femoral heads, protruding acetabula but no erosive changes. (e) Magnetic resonance imaging of the left foot (index patient), low signal intensity of the large subcutaneous nodules, with rim of enhancement extending all around the nodule in the immediate subcutaneous tissue on T2 sequences.

gelatinolytic activity, while parents, heterozygote siblings, had half-normal levels of MMP-2 activity (Figures 5 & 6).16-18

Discussion. Inherited multicentric, osteolysis, nodulosis and arthropathy ((MONA), nodulosis, arthropathy, osteolysis, idiopathic osteolysis-Saudi type, Al-Aqeel Sewairi Syndrome (OMIM # 605156)19 is a distinctive autosomal recessive multicentric osteolysis disorder in which crippling arthritis is associated with carpal and tarsal resorption, severe osteoporosis, distinctive facies, and palmar and plantar subcutaneous nodules. It was recently identified by 2 independent groups in eleven affected offspring of 6 consanguineous Saudi Arabian Families.13-15 Since the first description of the "vanishing bone" disease by Jackson,20 a number of clinically distinguished forms have been described.21 These disorders differ from each other in the mode of transmission, clinical features, and the extent and anatomical distribution of osteolysis.1,21 On these basis the International Skeletal Dysplasia Registry has classified them into four groups.2 (Table 1) The group with carpal, tarsal, and interphalangeal joint destruction include Torg (OMIM # 259600), Francois (OMIM # 221800), Winchester (OMIM # 277950), and Whyte Hemingway syndrome.2 It also includes MONA or Al-Aqeel Sewairi syndrome (OMIM # 605156),19 as the features of this syndrome overlap with many phenotypic features of these syndromes, mainly Torg.14 The matrix metalloproteinase (MMPs) also called matrixins, a family of zinc and calcium dependent and membrane, associated endopeptidase that are active at neutral Ph. Each member has specificity for a subset of extracellular matrix (ECM) molecules; collectively they catalyze the proteolysis of all components of ECM3 as well as other extracellular non-matrix proteins.22 The expression of most matrixins is transcriptionally regulated by growth factors, hormones, cytokines, and cellular transformation.23,24 To date 22 MMPs are identified.22,25

The development of a multicellular organism is dependent upon an ECM, which facilitates the organization of cells into more complex functional units: tissues and organs. The extracellular matrix is the glue that holds cells together, and provides
Figure 3 - Biopsy of the metacarpal phalangeal joint showing normal synovium with normal mesothelium.

Figure 4 - Biopsy of the nodule on the dorsum of the hand showing fibrofatty tissue.

Figure 5 - Gelatin zymography of control and affected serum samples. Lane 1, MMP2 and MMP9 zymography standards (Chemicon International); 2 serum from an unaffected, unrelated individual; 3-5, sera from unaffected parents and siblings; 6-10, sera from affected children. MMP - matrix metalloproteinase. (Source: Nature Genetics 2001; 28: 261-265)

Figure 6 - Gelatin zymography of control and patient fibroblast conditioned medium. Lane 1, mixture of MMP2 and MMP9 zymogram standards; 2, serum from unrelated, unaffected individual; 3 and 4, sera from 2 affected members. MMP - matrix metalloproteinase. (Source: Nature Genetics 2001; 28: 261-265)

Figure 7 - Matrix metalloproteinases regulation and extracellular matrix balance. MT - membrane type, MMPs - matrix metalloproteinases, TIMPS - tissue inhibitors metalloproteinases, TGF-β - transforming growth factor beta, ECM - extracellular matrix.
Matrix metalloproteinase participate in many normal biological processes (for example embryonic development, blastocyst implantation, organ morphogenesis, nerve growth, ovulation, cervical dilatation, postpartum uterine involution, endometrial cycling, hair follicle cycling, bone remodeling, wound healing, angiogenesis, apoptosis, for example) and pathological processes (for example arthritis, cancer, cardiovascular disease, nephritis, neurological disease, breakdown of blood brain barrier, periodontal disease, skin ulceration, gastric ulcer, corneal ulceration, fibrosis of the liver and lung). Matrix metalloproteinase are regulated at different levels. These MMPs are synthesized as pre pro-enzymes and secreted as active pro-MMPs in most cases. Which are activated by MT-MMPs (Membrane type matrix metalloproteinases). However, inhibition of MMPs is by endogenous tissue inhibitors (TIMPS). Currently, 4 of them are known. Membrane type (1)-MMP is a membrane associated matrix metalloproteinase that is highly expressed in osteocartilaginous and musculotendinous structure and may function as a pericellular activator of MMP-2 in atrimere complex with TIMP-2 and MMP-2. (Figure 7) MMP-2 is thought to regulate the activity of a critical growth factor, transforming growth factor-Beta (TGF-β). TGF-β-signaling mediates the coupling of the reciprocal activities of bone formation and resorption by influencing the maturation of osteocyte and enhancing the activity of osteoclasts. Physiologically TGF-β may coordinate osteoclast activity by recruiting osteoclasts to existing site of resorption. Pathologically TGF-β-induced osteoclast recruitment may be critical for expansion of primary and metastatic tumors in bone. Plasmin, elastase, MMP-9 and MMP-2 activates TGF-β by proteolytically cleaving the latent associated peptide, for example latent TGF-beta-binding protein (LTBP1) to produce 125-165-Kda fragment which is the physiological mechanism for the release of active TGF-β from ECM-bound stores. Lack of MMP-2 may therefore affect bone formation and homeostasis through modulating the level of active TGF-b. (Figure 7) The ECM remodeling is important for morphogenesis and homeostasis. The balancing act of ECM deposition and break down is very critical, therefore, MMP-2 deficiency leads to an imbalance between the breakdown and deposition of the ECM. Although MMP-2 null mice have no developmental defects (which may reflect genetic redundancy), mice with targeted inactivation of the MT1-MMP gene have many of the same features as people with multicentric osteolysis and arthritis syndrome. As the MT1-MMP activates MMP-2, it is not surprising that deficiency in either of these enzymes-albeit in different species can result in similar defects. Deficiency of MT1 in mice results in a decrease of collagen breakdown by fibroblasts in the skin and osteoblasts, a decrease in bone formation, and an increase in the number of osteoclasts (especially at ectopic sites). Tissue fibrosis may therefore be attributed to impaired function of fibroblasts, arthritis and osteolysis to increased osteoclastic activity; and craniofacial dysmorphism and osteopenia to impaired function of osteoblasts (Figure 7).

Where it is tempting to treat these disorders, there is no specific treatment available for the multicentric osteolysis. Our patients responded well to prednisolone 5-10 mg OD and methotrexate 5 mg q/weekly with improvement of their joints pain, contracture and nodulosis with normal growth while osteolysis did not improve but was non-progressive. Their osteopenia responded well to pamidronate 2 mg/kg 2 monthly infusions. However, some patients reported bone pain, which required them to discontinue the infusion. Other future treatment research strategies, for example targeted enzyme therapy with MMP-2 as MMP-2 deficiency is found in these patients, or the use of TGF-b as MMP-2 activates TGF-β, or the use of MT1-MMP or TIMP-2 as they activate MMP-2 in a trimeric complex are still to be explored. The discovery of this new disease entity represents the first hereditary disease resulting from MMP-2 deficiency and is the first genetic evidence that the proteolysis of the ECM mediates human growth and development.

References


