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REVIEW ARTICLE

Rare monogenetic syndromes in rheumatology practice

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Abstract The EULAR Executive Committee defined eight overall objectives for EULAR to achieve by 2012. The first of these objectives is to strengthen activities in areas that are currently less prioritized, such as non-inflammatory and orphan diseases. This study aims to increase awareness of rheumatologists towards rare hereditary musculoskeletal disorders, by describing their genetics, pathogenesis, and typical clinical and radiological features. We analyzed patient charts from the recent 5 years from the Rheumatology Outpatient Department of the University Erlangen-Nuremberg and of two rheumatologic practices, all joined in a regional network ("Rheumazentrum Erlangen") retrospectively for hereditary musculoskeletal disorders other than hemochromatosis, autoinflammatory syndromes, lysosomal storage diseases, and hypermobility syndromes. We were able to identify four patients with trichorhinophalangeal syndrome type I, multiple exostoses, Kirner's deformity, and osteopoikilosis. In addition, a PubMed and OMIM ("Online Mendelian Inheritance in Man") database search was carried out using these as key words and all relevant articles were reviewed for each of these diseases. Our findings show that rare hereditary musculoskeletal disorders occur in a routine rheumatological setting and that rheumatologists should know the clinical and radiological features of these diseases in order to adequately counsel the patient.

Keywords Dysostoses · Exostoses · Genetics · Osteopoikilosis

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Introduction

Genetic associations have been described for the majority of rheumatic diseases and in most cases this influence is characterized as multigenetic. In contrast, rheumatic diseases based on single gene mutations are usually rare, although there are exceptions like hereditary hemochromatosis [1]. Molecular genetics have markedly improved our knowledge about a number of monogenetic diseases that rheumatologists have to deal with in their daily practice. For example, major progress has been made in recognizing pathogenetic mechanisms and facilitating diagnosis of autoinflammatory disorders, lysosomal storage diseases, or hypermobility syndromes [2–4].

However, there are other monogenetic diseases, which can present diagnostic or therapeutic challenges to the rheumatologist. Several such patients have been seen over the last years in our university outpatient department and in private rheumatology practices joined in a regional network ("Rheumazentrum Erlangen"). In addition to these case reports, we present a review of the literature about monogenetic syndromes associated with musculoskeletal problems.

Trichorhinophalangeal syndrome type I

Case 1

A 36-year-old female patient of Central European descent complained about sudden pain attacks and burning sensations

in varying interphalangeal finger joints lasting for about 1 h. She had no morning stiffness, no pain or swelling of other joints, or any other symptoms of systemic rheumatic disease. With regard to her family history, she reported that her mother has "rheumatoid arthritis" and her father and sister have shortened distal phalanges of their thumbs.

Examination of the hands revealed no synovial joint swelling or tenderness, but an ulnar deviation of proximal interphalangeal joints, most prominent at digit II and III of both hands. Both terminal thumb phalanges appeared shortened (Fig. 1a, b). In addition, the patient had a pear-shaped nose, a long philtrum, thin hair, and diffuse alopecia (Fig. 2a, b).

Laboratory investigations were completely normal and did not show any signs of systemic inflammation. The radiographs of the hands showed cone-shaped epiphyses of proximal phalanges, shortened distal phalanges of both thumbs (Fig. 3a), shortened middle phalanges of fingers II–V (Fig. 3b), and ulnar deviation. No erosive bone changes were visible.

Pathogenesis and clinical features

Trichorhinophalangeal syndrome (TRPS) type I is an autosomal dominant disease caused by a mutation in the TRPS1 gene on chromosome 8 (8q24.12), which encodes a zinc finger protein which is a putative transcription factor [5]. Two related TRPSs have been described, type II is associated with mental retardation and type III is characterized by severe brachydactyly and growth retardation (<3 standard deviations). TRPS type II is a contiguous gene syndrome caused by a loss of functional copies not only of the TRPS1 gene but also the neighboring exostosin-1 gene (EXT-1, 8q24.11-q24.13) and therefore shares clinical features with multiple exostoses type I (see below) [6]. Reliable information about the prevalence of these diseases in the general population is not available.

The typical clinical features of TRPS type I are, as described in our case 1, the triad of a bulbous pear-shaped nose, thin and slow-growing scalp hair, sparse eyebrows and stubby hands with ulnar deviations of proximal interphalangeal joints. Characteristic radiological abnormalities are the cone-shaped epiphyses of proximal phalanges. In addition, there have been descriptions of short feet and metatarsal bones, micrognathia, hypoplastic mandible, winged scapulae, pectus carinatum, scoliosis, and hip dysplasia. Other reported manifestations include nail changes, diabetes, idiopathic hypoglycaemia, hypothyroidism, malformations of the ureter–bladder junction, renal and cardiac defects [6–10].

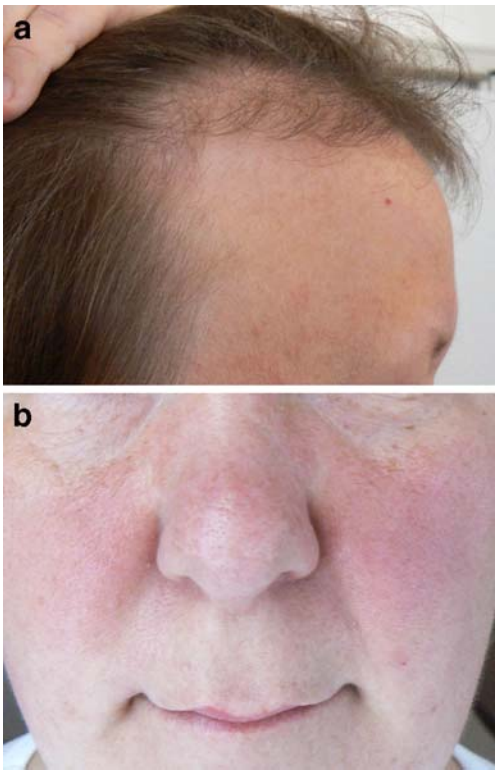


Fig. 2 **a** Sparse and thin hair and eyebrows in trichorhinophalangeal syndrome type I. **b** Bulbous pear-shaped nose and long philtrum in trichorhinophalangeal syndrome type I

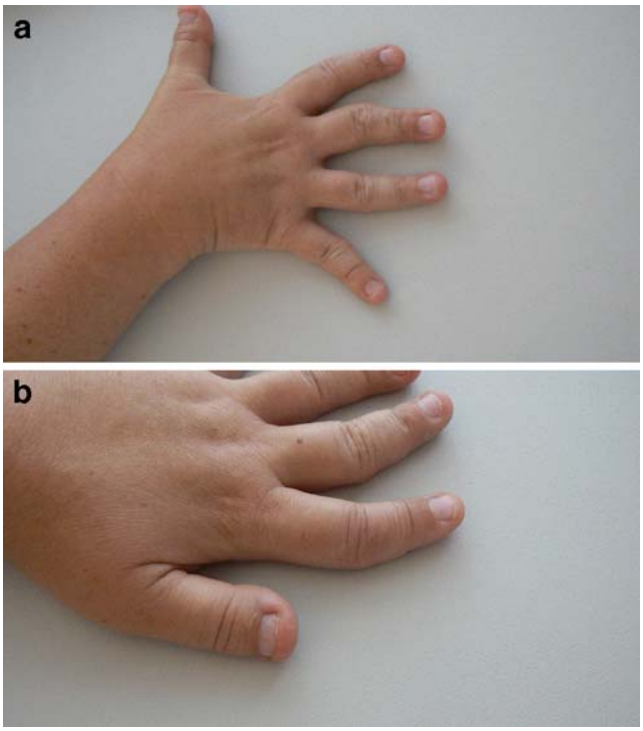


Fig. 1 **a** Ulnar deviation in proximal interphalangeal joints of fingers II and III in trichorhinophalangeal syndrome type I. **b** Shortening of terminal phalanx of the thumb in trichorhinophalangeal syndrome type I

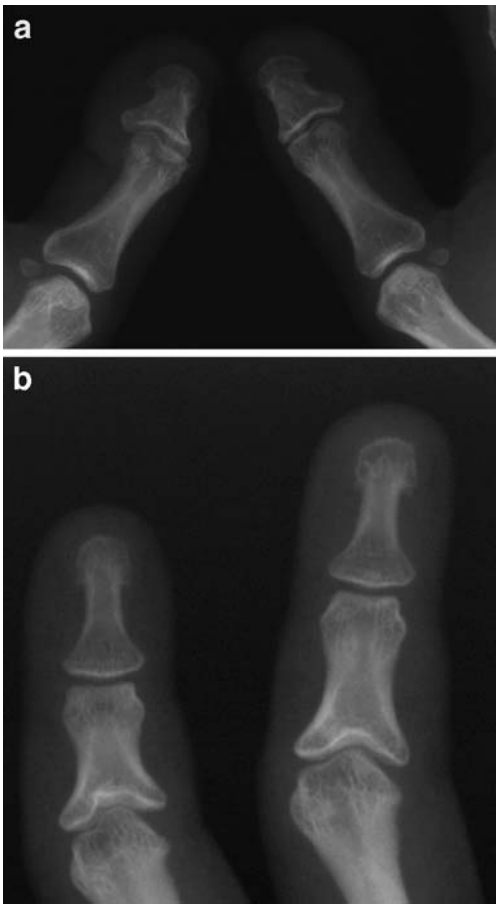


Fig. 3 **a** Radiograph of shortened thumbs in trichorhinophalangeal syndrome type I. **b** Cone shaped epiphyses in trichorhinophalangeal syndrome type I

Multiple exostoses (multiple osteochondromatosis)

Case 2

A 64-year-old woman of Central European descent presented with bony protuberances of the lateral side of the right knee, the lateral side of both ankles and the ulnar side of the right wrist, which were painful upon compression and had repeatedly caused episodes of tenosynovitis around wrist and ankle joints within the last 6 months. She reported that her 36-year-old son also has "bony spurs" and complains about similar problems. Further rheumatological examination revealed Heberden nodes of her distal interphalangeal joints of third and fourth fingers on both hands, but no clinical or laboratory sign of inflammatory rheumatic disease. Radiographs showed multiple exostoses at wrist, knee, and ankle joints, but no manifestation of any other rheumatic disorder (Figs. 4 and 5).

Pathogenesis and clinical features

In almost 90% of patients with multiple exostoses (syn. multiple osteochondromatosis) mutations in the tumor suppressor genes exostosin-1 (EXT-1; 8q24.11-q24.13) or exostosin-2 (EXT-2; 11p12-p11) have been described. These genes encode glycosyltransferases, which catalyze heparin sulfate polymerisation and thus play a crucial role in chondrocyte growth regulation and enchondral bone formation [11]. An additional rare defect involving yet another gene (EXT-3) has been described. Multiple exostoses are an autosomal dominant disorder with an estimated prevalence of 1:50,000.

Cartilaginous exostoses develop during childhood and cease to grow, when the epiphyseal growth plates close. The majority are located along the long bones of the extremities, predominantly around wrists, knees, and ankles; facial bones are not affected. The exostoses can vary in size and are frequently asymptomatic or cause only cosmetic deformities. However, they can also cause irritations of surrounding tissues such as bursae, tendons, nerves, or vessels and require surgical removal. The most important complication is a malignant transformation into chondrosarcoma, which occurs in up to 5% [12–14].

Kirner's deformity (dystelephalangy)

Case 3

A 15-year-old girl of Central European descent presented with progressive shortening of the distal phalanx of the

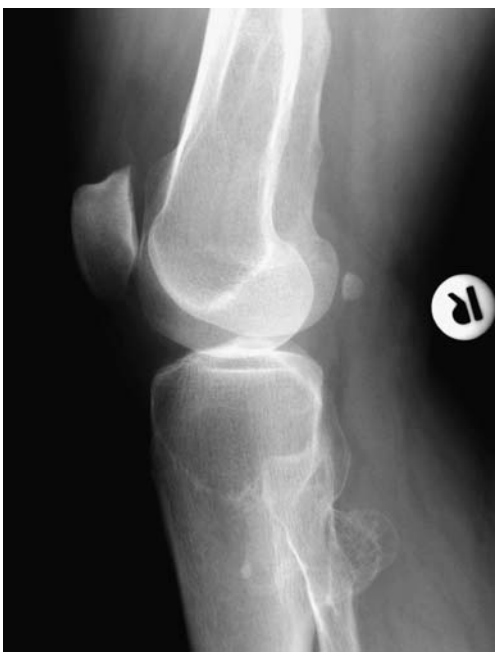


Fig. 4 Cartilaginous exostosis of the knee

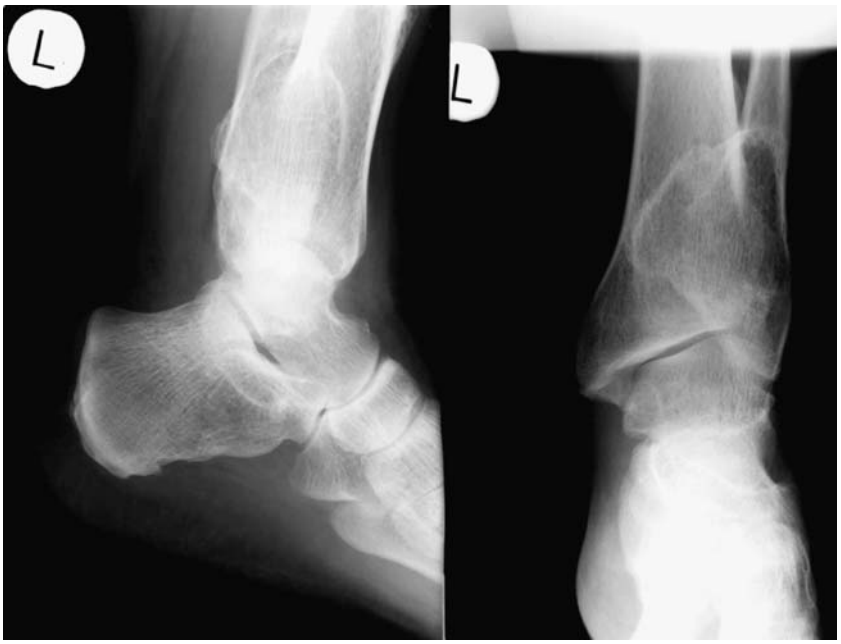


Fig. 5 Cartilaginous exostosis of the ankle

right fifth finger, which was painless but with infrequent episodes of hyperemia and swelling of the whole fifth finger persisting for up to 2 days (Fig. 6). No other signs or symptoms of an inflammatory rheumatic disease were present. No related problems were reported in her family history.

Laboratory tests were normal except for antinuclear antibodies at a low titer of 1:40 and a granular fluorescence on Hep2 cells. No antibodies against any nucleoproteins could be identified by ELISA technique. Anterior–posterior and lateral radiographs of the right fifth finger showed a dysmorphic hypoplastic phalanx with dorsal bending of the epiphysis (Fig. 7a, b). The left fifth finger was completely normal.

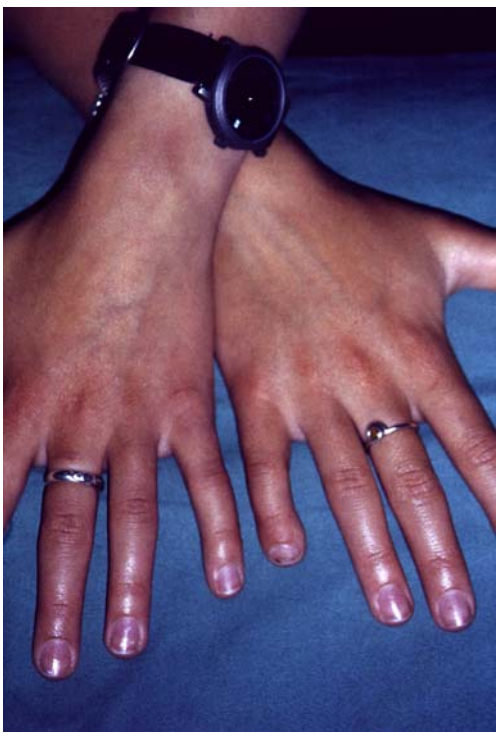


Fig. 6 Unilateral shortening of the little finger (Kirner's deformity)

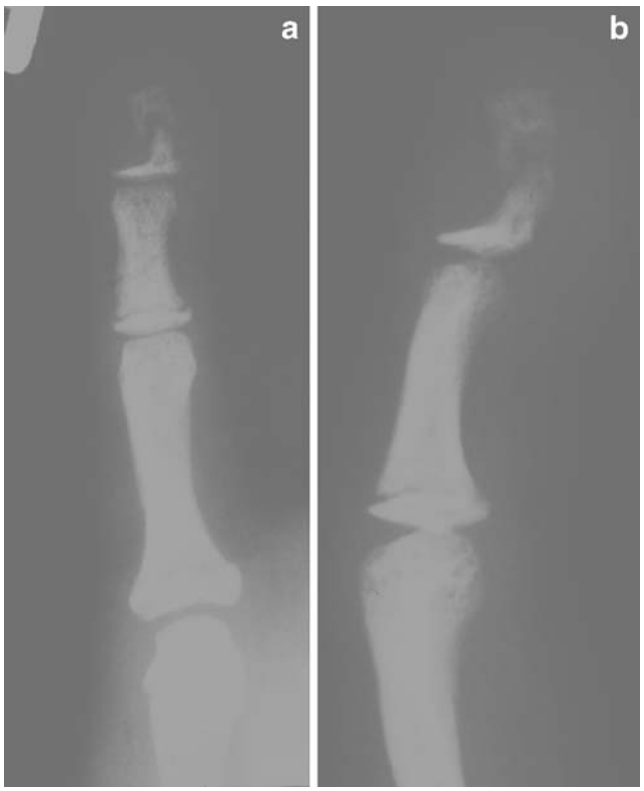


Fig. 7 **a** Radiograph of fifth finger in Kirner's deformity (a. p. view). **b** Radiograph of fifth finger in Kirner's deformity (lateral view)

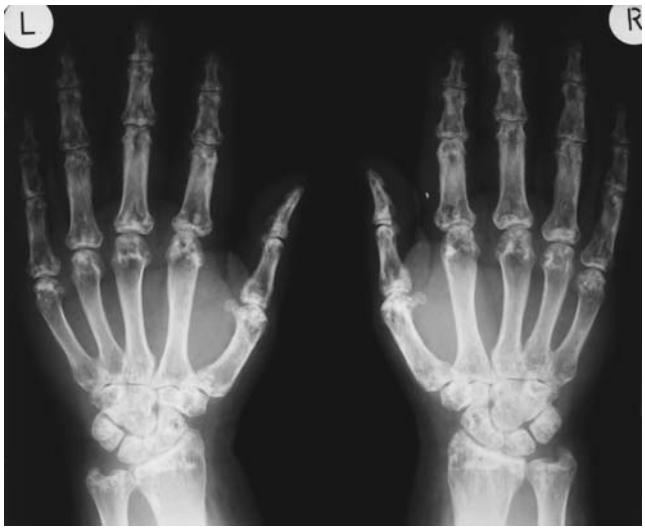


Fig. 8 Radiograph of hands in osteopoikilosis

Pathogenesis and clinical features

The underlying genetic defect of Kirner's deformity or dystelephalangy is not known. There have been reports of autosomal dominant inheritance but also numerous spontaneous cases without any family history. An analysis of 16,326 patients, who had undergone hand X-ray examinations, led to a detection of nine cases, which means a prevalence of 0.055% for this preselected patient population [15].

Kirner's deformity usually manifests between 8 and 14 years of age, female to male ratio is 2:1. Characteristic manifestation is a painless swelling or radial-volar curving of the terminal phalanx of the fifth finger. Bilateral and unilateral involvement has been described equally. The prognosis is good und usually there is no treatment necessary [15–17]. In our patient, the deformity has not progressed over the last 4 years, is not painful, and has not caused any functional limitations.

Osteopoikilosis

Case 4

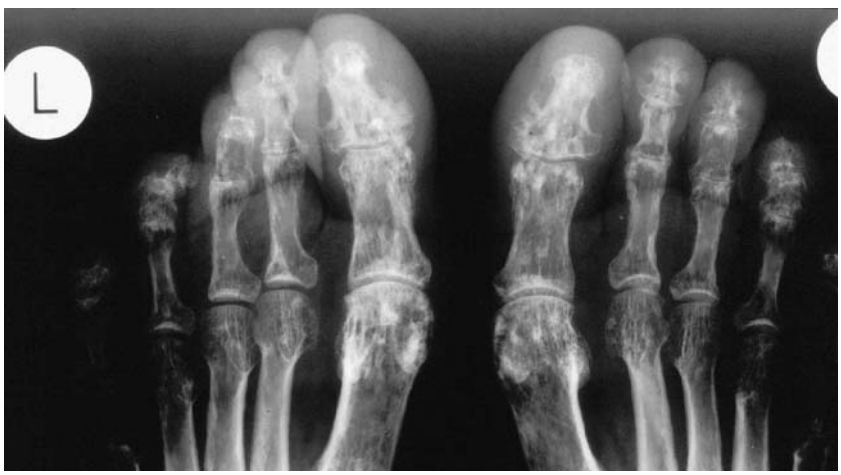
A 58-year-old patient of Mediterranean (Greek) descent was referred to us from the Department of Surgery, where an X-ray of the foot had been taken because of minor trauma. This radiograph revealed multiple small, variably shaped radiodensities especially in the small bones of fingers and toes (Figs. 8 and 9). He did not complain about bone or joint pain, nor did he have any skin lesions. There were no other signs or laboratory changes of an inflammatory rheumatic disease.

Pathogenesis and clinical features

Recently, a loss of function mutations in the LEMD3 gene has been identified as the cause for osteopoikilosis lesions. LEMD3 encodes an inner nuclear membrane protein, which apparently plays a role in bone morphogenetic protein signaling [18]. In relation to osteopoikilosis and also associated to LEMD3 mutation, dermatofibrotic lesions (Buschke-Ollendorff syndrome) may be present. Inheritance is autosomal dominant, spontaneous cases without family history of occurrence, and prevalence is estimated to be as high as 1:50,000.

Osteopoikilosis is a sclerosing bone dysplasia, characterized by multiple oval spots of radiodensities within the trabecular bone, most prominent in bones of fingers and toes, less frequent in the axial skeleton. Typically the patients are asymptomatic and the lesions are detected accidentally. However, in 15% to 20%, mild bone or joint pain may be seen. Therapy usually is not necessary. Another "flowing" pattern of hyperostoses of the cortex of tubular bones, termed melorheostosis, has also been linked to LEMD3 mutations. The reason for the variations in the pattern of osteosclerotic changes with this genetic background remains unclear [18–21].

Fig. 9 Radiograph of toes in osteopoikilosis



Discussion

In early 2007, the EULAR Executive Committee defined eight overall objectives for EULAR to achieve by 2012. The first of these objectives is to strengthen activities in areas that are currently less prioritized, such as non-inflammatory and orphan diseases. Among those orphan diseases in a routine rheumatology setting are several genetic disorders, which are associated with musculoskeletal problems. Over the last years molecular genetics have made enormous progress to

Table 1 Monogenetic disorders in rheumatology practice

Disease	OMIM number	Gene locus	Genetic defect	Musculoskeletal manifestations	Therapy
Autoinflammatory diseases (periodic fever syndromes)					
Familial Mediterranean fever	#249100	16p13	MEFV, Pyrin (marenostrin)	Monarthritis, myalgias	Colchicin, anakinra, TNF-blockers
TNF-receptor-associated periodic syndrome (TRAPS)	#142680	12p13.2	TNF receptor 1	Monarthritis, localized myalgia	Steroids, TNF-blockers, (anakinra)
Hyper-IgD syndrome	#260920	12q24	MVK, Mevalonate kinase	Polyarthralgia	Anakinra, (TNF-blockers)
Cryopyrin-associated periodic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, CINCA/NOMID syndrome)	#120100 #191900 #607115	1q44	CIAS1 (NLRP3) Cryopyrin	Deforming arthritis	Anakinra
Lysosomal storage diseases					
Fabry disease (angiokeratoma corporis diffusum)	#301500	Xq22	Alpha-galactosidase A	Severe periodic pain in distal extremities	Enzyme replacement therapy
Gaucher disease type I	#230800	1q21	Glukocerebrosidase	Bone pain and deformity, monarthritis, avascular necrosis	Enzyme replacement therapy
Mucopolysaccharidosis I—type Scheie (Scheie syndrome)	#607016	4p16.3	Iduronidase	Joint contractures, carpal tunnel syndrome, dysostosis multiplex, hip dysplasia	Enzyme replacement therapy
Pompe disease (glycogen storage disease II)	#232300	17q25.2-q25.3	Acid alpha-1, 4-glucosidase	Muscle weakness	Enzyme replacement therapy
Hypermobility syndromes					
Marfan syndrome	#154700	15q21.1	FBN1, fibrillin-1	Hypermobility, arachnodactyly, premature osteoarthritis	–
Ehlers-Danlos syndrome type III	#130020	6p21.3 2q31	TNXB, tenascin X COL3A1, collagen III	Hypermobility, recurrent joint dislocations, premature osteoarthritis	–
Miscellaneous					
Trichorhinophalangeal syndrome type I	#190350	8q24.12	TRPS1, zinc finger protein	Brachydactyly, intermittent pain in PIP-joints, ulnar deviation in PIP-joints, cone shaped epiphyses	–
Multiple hereditary exostoses (multiple osteochondromatosis)	#133700	8q24.11-q24-13	EXT-1, exostosin-1	Cartilaginous exostoses in proximity to epiphyseal growth plates, can cause irritation to bursae, tendons, nerves, vessels	Surgery
	#133701	11p12-p11	EXT-2, exostosin-2 (glycosyltransferases, catalyzing heparan sulfate)	Cave—malignant transformation	
	%600209	19p	EXT-3, exostosin-3		
Kirner's deformity (dystelephalangy)	%128000	Not known	Not known	Uni- or bilateral shortening or deformity of the distal phalanx of 5th finger, usually painless	-
Osteopoikilosis	#166700	12q14	LEMD3, inner nuclear membrane protein	Multiple small osteosklerotic areas predominantly in small bones of fingers and toes, in up to 20% bone or joint pain	-

define the underlying gene mutations and understand pathogenetic mechanisms in many of these diseases. Therefore, this article is intended to increase awareness and knowledge about bone and joint problems in selected monogenetic diseases among rheumatologists.

The genetic disorders, which recently received the most attention by rheumatologists are autoinflammatory syndromes (periodic fever syndromes), lysosomal storage diseases, and hypermobility syndromes (Table 1). The unveiling of the genetic background of periodic fever syndromes has markedly increased our knowledge of inflammatory pathomechanisms, such as the role of the inflammasome, which are not only relevant for this group of disease, but also play a role in Still´s disease, Behçets disease, or crystal-induced arthritides [22, 23].

Another group of genetic disorders, which has become interesting for clinical rheumatologists over the last few years, is that of lysosomal storage diseases. The reason for this is the availability of enzyme replacement therapies that have considerable influence on the disease course, which makes early diagnosis and onset of therapy a crucial factor. Because musculoskeletal symptoms are frequent and because of early signs of lysosomal storage disorders, rheumatologists play a key role in determining the overall outcome for the individual patient. Therefore, they should be familiar with the typical symptom constellations of these diseases [3, 24]. The characteristics of those storage diseases, for which enzyme replacement therapies are available, are listed in Table 1.

Hypermobility has long been a very heterogenous and ill-defined group of disorders. With the help of genetic analysis, defined disease entities can be characterized and the individual risk for cardiovascular or musculoskeletal complications can be assessed [4].

This leaves a miscellaneous group of less well-known monogenetic bone and joint diseases, which can be encountered in a rheumatologic practice. In order to better serve physicians to diagnose these, we presented a case of each disease and reviewed genetics, pathogenesis, and clinical presentation systematically. All patients have been seen by rheumatologists within a local network ("Rheumazentrum Erlangen") over the last few years. OMIM ("Online Mendelian Inheritance in Man") number, the current knowledge about location and type of the genetic defect, and musculoskeletal manifestations are all listed in Table 1. Although there are no therapies available for these disorders, a correct diagnosis by the rheumatologist is required for informing the patient about the benign nature of the disease, such as in trichorhinophalangeal syndrome type I, osteopoikilosis, and Kirner's deformity, for monitoring for complications (e.g., malignant transformation in multiple exostoses) and for genetic counseling.

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G. Schett: none

B. Manger: BM has received consultation fees from Genzyme Deutschland GmbH.

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