



# Genetic Disorders in Pediatric Rheumatology Clinic: When to Suspect, and Why?

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## Abstract

Just under a decade ago, most children with genetic disorders received a phenotypic diagnosis, often by atlas matching. With advances in genomics (decoding of human genome, easy availability of genetic testing, and reduction in cost of tests), genotypic diagnosis is now a reality. Genetic diseases can lead to non-inflammatory arthritis that can mimic juvenile idiopathic arthritis (JIA). A small but growing number (as newer genes are discovered) of genetic diseases are being diagnosed in children with a seemingly inflammatory musculoskeletal diseases or connective tissue diseases. A high index of suspicion by the pediatrician is most important for early diagnosis of these genetic disorders. In a busy outpatient clinic, it is the atypical presentation of a disease in a child that suggests a possibility of underlying genetic autoinflammatory or autoimmune disease. Correct diagnosis helps the physician, child, parent, and community.

**Keywords** Genetic disorders · Pediatric rheumatology · Non-inflammatory arthropathy · Musculoskeletal pain

## Introduction

Prolonged/recurrent pyrexia, limb pains, joint pain/swelling, muscle weakness, abnormal gait, recurrent oral ulcers, rashes and bony or subcutaneous swellings are common complaints that present to the rheumatology clinic. The essential diseases which the rheumatologist treats, narrow down mostly to those which are recognized as autoimmune or autoinflammatory e.g., juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM) and vasculitides. However, a patient does not announce a label of any of these diseases and therefore several prefer the term ‘musculoskeletal medicine clinic’ to ‘rheumatology clinic’ which expands the ambit to cover diseases beyond the inflammatory rheumatic diseases. This compounds matters since patients with above mentioned presenting or evolving features may have a genetic etiology.

It is therefore in the day’s work of a pediatric rheumatologist to pass these through a sieve and retain those that he/

she is responsible to manage and make referrals to other subspecialists for their expert care. The second sieve consists of identifying those with genetic etiology.

This article focuses on classifying genetic disorders that may be seen in a pediatric musculoskeletal (read as rheumatology) clinic and the features that may lead to their consideration in the differential diagnosis. It also highlights why it is relevant to identify such disorders. A summary table is illustrative of the various groups of diseases and their diversity (Table 1) [1–11]. The list is not exhaustive but illustrative. Table 2 attempts to classify some of these based on type of joint involvement, site or tissue of involvement and disease [12].

## Background

There are around 10,000 genetic diseases that have been reported affecting 6–8% of the general population [13]. There is scant data pertaining to the globally considered “rare diseases” in India, but around 7000 to 8000 rare disorders have been reported [14]. In authors’ series of 4000 patients, which were evaluated at the Pediatric Rheumatology Department between 2000 and 2022, approximately 200 (5%) patients were diagnosed with genetic disorders. Since these tests have

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**Table 1** Classification of common musculoskeletal presentation of genetic disorders based on etiology and pathogenesis

	INFLAMMATORY CONDITIONS	NON-INFLAMMATORY CONDITIONS
<b>CHROMOSOMAL DISORDERS</b>		
Trisomy 21 (Down syndrome)	JIA [1]	Early onset Perthes' disease [2], Atlanto axial dislocation
Turner syndrome	Polyarticular / Oligoarticular JIA [3]	
22 q 11 Deletion (Di George syndrome)	JIA [4]	
<b>MONOGENIC DISORDERS</b>		
A) Inborn Errors of Immunity (485 diseases) [5]		
(i) Combined Immunodeficiencies with syndromic features		Wiskott Aldrich Syndrome: Hemarthrosis Hyper IgE syndrome
(ii) Congenital defects of phagocyte number or function	X-linked chronic granulomatous disease (CGD): Serous non-infectious effusions [6]	
(iii) Predominantly antibody deficiencies	X-linked agammaglobulinemia (XLA): Septic arthritis, Osteomyelitis, Non-infectious joint inflammation [7] Common Variable Immunodeficiency (CVID) [8]	
(iv) Diseases of immune dysregulation	Very early onset inflammatory bowel disease: IL 10 deficiency, IL 10R deficiency	
(v) Autoinflammatory		
a) Interferonopathies	STING associated vasculopathy- Infantile onset (SAVI) COPA syndrome ADA2 deficiency Spondyloenchondro-dysplasia with immune dysregulation (SPENCD) Aicardi-Goutières syndrome (AGS)	
b) Inflammasomopathies	Familial Mediterranean fever (FMF) Mevalonate kinase deficiency (MVK deficiency) / Hyper IgD syndrome Familial cold autoinflammatory syndrome (FCAS) Muckle Wells syndrome (MWS) Neonatal-onset multisystem inflammatory disease/ Chronic infantile neurological cutaneous and articular syndrome (NOMID/ CINCA)	
c) Others	Blau syndrome TNF Receptor–Associated Periodic Syndrome (TRAPS) Deficiency of the interleukin-1 or 36–receptor antagonist (DIRA) / (DITRA) STAT3 gain of function mutation	
(vi) Autoimmune		
Complement deficiencies	Hereditary complement deficiency (Early onset lupus)	
B) HEMATOLOGIC		
Coagulopathies		Haemophilia
Hemoglobinopathies		Thalassemia, Sickle cell Disease
C) STORAGE DISORDERS		
		<b>Mucopolysaccharidosis</b> (Hurler, Scheie, Hunter, Morquio) <b>Sphingolipidoses</b> (Farber's, Fabry, Gaucher's)
D) NUTRITIONAL		
E) METABOLIC		
	Lesch- Nyhan syndrome (XLR) (Hyperuricemic arthritis) Hyperlipoproteinemia Type II (Familial Hypercholesterolemia) [9]	Rickets – Vitamin D dependent Type 1 (AR)

**Table 1** (continued)

	INFLAMMATORY CONDITIONS	NON-INFLAMMATORY CONDITIONS
F) OTHERS		Cystic fibrosis Neurofibromatosis (Scoliosis, Pseudoarthrosis, Limb overgrowth) Camptodactyly-arthropathy-coxa vara- pericarditis (CACP) syndrome Congenital insensitivity to pain with anhidrosis (CIPA) [10]
<b>POLYGENIC/ MULTIFACTORIAL DISORDERS</b>	JIA Systemic Lupus Erythematosus HLA B27 associated arthritis Psoriatic arthritis Celiac disease [11]	
<b>SOMATIC MUTATION DISORDERS</b>	Autoimmune lymphoproliferative syndromes (ALPS)	

*ADA2* Adenosine Deaminase 2, *AR* Autosomal Recessive, *COPA* Coatmer protein subunit alpha, *IgE* Immunoglobulin E, *IgD* Immunoglobulin D, *IL 10* Interleukin 10, *IL 10 R* Interleukin 10 receptor, *JIA* Juvenile Idiopathic Arthritis, *STAT3* Signal Transducer and Activator of Transcription 3, *XLR* X-linked recessive

become recently available, and due to direct referrals to other specialities like orthopaedics in cases of non-inflammatory skeletal arthropathies, this number is an underestimate.

India is aptly called the melting pot of genetic diversity. It is also home to inbreeding practices and founder mutations that have led to the accumulation of deleterious genetic variations causing high prevalence of autosomal recessive rare genetic diseases as compared to the other parts of the world [14, 15]. Several new diseases such as SHARPIN deficiency [16] and TBK1 deficiency [17] have even been discovered and reported for the first time from India.

Consanguineous marriages reported among the maternal and paternal first cousins are a frequent practice, and are more common in the southern states of Andhra Pradesh, Telangana, Tamil Nadu, and Karnataka [18]. There exists a significant relationship between consanguineous marriages and socio-economic variables [18]. There are around fifty-five endogamous populations in India. The common endogamous communities consist of the Vysya, Gujjars, Aggarwals, Kolis etc. [15, 19, 20]. Therefore, most relevant in the detection, presentation and education is to establish communication with the local communities.

**Table 2** Classification based on type of joint involvement and tissue of involvement [12]

HEREDITARY MUSCULOSKELETAL DISORDERS	
With Stiff joints	Beal's syndrome (Contractural arachnodactyly) Mucopolysaccharidosis Spondyloepiphyseal dysplasia congenita/ tarda, Multiple epiphyseal dysplasia Progressive Pseudo-rheumatoid arthropathy of childhood (PPAC)
With Swollen joints	Camptodactyly-arthropathy-coxa vara-pericarditis (CACP) Multicentric Osteolysis Nodulosis and Arthropathy (MONA)
With Hypermobile joints	Ehlers Danlos syndrome Marfan syndrome MPS IV (Morquio's syndrome)
With Bone involvement	Osteogenesis imperfecta Skeletal dysplasia: Achondroplasia, Hypochondroplasia Pachydermoperiostosis Familial Infantile Cortical Hyperostosis (Caffey's disease) Cammurati Engleman syndrome McCune-Albright syndrome Fibrous dysplasia Epiphyseal dysplasia (pseudo rheumatoid arthritis)
With Cartilage involvement	Diaphyseal aclasia
With Muscle involvement	Congenital Muscular disorders: Duchenne Muscular Dystrophy, Limb Girdle Dystrophy, Familial Periodic Paralysis

## When Do We Suspect a Genetic Disorder in a Rheumatology Clinic?

### 1. Known predisposing genetic condition

A 14-y-old boy with Down syndrome presented as an out-patient with complaints of a painful stiff neck after a fall while playing a contact sport. Recognizing that children with Down syndrome are prone to atlanto-axial dislocation, an X-ray cervical spine was requested. There was gross disruption of the normal alignment of the atlanto-occipital joint, with enlarged atlanto-axial interval, which was confirmed on further imaging, leading to a diagnosis of atlantoaxial dislocation.

Children with Down syndrome are also known to develop early onset Perthes disease [2] and have increased propensity to RF positive JIA [1]. Patients with Type 1 diabetes mellitus also have increased propensity to develop JIA as well as diabetic cheiroarthropathy causing flexion contractures [21]. These and many other disorders like Turner's syndrome, hemophilia etc. emphasize the importance of monitoring for evolution of musculoskeletal complaints in patients with known genetic disorders.

### 2. Consanguinity

A five-year-old boy presented with pallor, and hand foot syndrome with a sick look. Clinically, one would have considered a diagnosis of leukemia or sickle cell anemia. Further enquiry suggested that the child was the product of a consanguineous marriage and a resident of a geographic belt where sickle cell anemia was common. Hemoglobin electrophoresis confirmed the diagnosis of sickle cell anemia [22].

Rarer the gene frequency in the general population, greater is the importance of consanguinity when suspecting autosomal recessive diseases.

### 3. Family history

An eight-year-old boy was referred for evaluation of a swollen finger. Clinically the swelling was bony, and the imaging showed a non-ossifying fibroma. However, on evaluation of the family history, the mother had a large café au lait macule and further probing led to a history of the maternal uncle having been operated for a large lump on the scapula. A recall of the maternal uncle's histopathological record showed the mass to be a neurofibroma. This helped clinch the diagnosis of a bony manifestation of Neurofibromatosis.

This case emphasizes the importance of relevant family history in genetic disorders (autosomal recessive, where the sibling may be involved; X linked recessive, where the maternal uncle may be involved; autosomal dominant, where either parent may be involved).

### 4. Forme fruste

A 10-y-old boy was referred for a sub-acute onset of hip pain. On observation, the father had a tall stature and wore very thick glasses. The child did not have obvious features of Marfan syndrome. However, a 2D ECHO showed a mitral valve prolapse while radioimaging confirmed protrusio acetabuli. This is one of the commonest skeletal manifestations of Marfan syndrome [23].

This case brings to light that genetic diseases in their classic form may be easy to diagnose, but they may also frequently remain unrecognized in their incomplete or atypical state, known as the forme fruste. This calls for attention to the importance of recognition of the forme fruste of such diseases.

### 5. Multiple syndromic features

A four-year-old boy presented with a large swollen knee. He was found to have a waddling gait and the treating physician asked for muscle enzymes and an X-ray of the hip. On examination, there was no muscle weakness and muscle enzymes were normal. The X-ray showed coxa vara in both hips. This child also had a bent finger since infancy. All these features pointed to a clinical diagnosis of Camptodactyly-Arthropathy-Coxa Vara-Pericarditis (CACPV) syndrome.

Therefore, when a patient presents with multiple syndromic features besides musculoskeletal disease, it is important to consider that this could be a part of a syndrome rather than many isolated anomalies and the child should be evaluated for genetic disorders.

### 6. Disease with atypical/ nonspecific features with multiple multiorgan involvement

A three-year-old boy had been referred for evaluation of knee joint arthritis. Synovial biopsy performed previously was inconclusive. On enquiry, he had not grown well and there was history of recurrent acute otitis media, perineal abscesses and three episodes of pneumonia. Immunoglobulin levels were low and genetic testing confirmed a diagnosis of Bruton's or X-linked agammaglobulinemia.

Atypical and non-specific features, multiorgan involvement, recurrent or severe infections and failure to thrive should raise a suspicion of inborn errors of immunity. Arthritis can be a musculoskeletal manifestation of primary immunodeficiencies [24].

### 7. Early onset of known diseases known to start at later age

A one-year-old male child was labelled as a case of intra-uterine infection due to microcephaly, seizures, and delayed development. By two years of age, he developed a classic malar rash, a positive antinuclear antibody (ANA)

with positive anti-dsDNA along with hyperlipidemia. He was diagnosed to have Systemic Lupus Erythematosus. A Computerized tomography (CT) brain at this stage showed basal ganglia calcification. This raised the suspicion of Aicardi-Goutières syndrome (AGS), a form of monogenic lupus which was confirmed on whole exome sequencing.

SLE usually starts at an age beyond 6-8 y and therefore onset at an early age, should raise a suspicion for a monogenic cause. Similarly, a child with stroke at an early age could be a case of ADA2 mutation, which is a hereditary form of polyarteritis nodosa.

#### 8. Early onset disease with recurrent fever

A two-month-old girl presented with recurrent fever and urticarial rash. On follow up after a year, she had failure to thrive with swollen joints. Whole exome sequencing showed a mutation for Chronic Infantile Neurological, Cutaneous, Articular (CINCA) syndrome/Neonatal-Onset Multisystem Inflammatory Disease (NOMID), an autoinflammatory disease.

Periodic fevers that start at an early age include Familial Cold Autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and CINCA/NOMID. It is important to keep these in mind especially in patients presenting with early onset fever of which the cause has not been identified. These fevers usually present with rashes and are mistaken as viral exanthems despite the child being fully immunised. Recurrent rashes are not caused by viral infections. The converse is however not true. Some autosomal dominant genetic disorders (e.g., Marfan syndrome), and even recessive disorders (e.g., Familial Mediterranean Fever), may have an onset later in life.

#### 9. Prototypic clinical features

A six-year-old boy presented with complaints of large joint arthritis with painful red eyes. Ophthalmic examination confirmed uveitis. He also had sago granular skin rash. On examination, he had a large boggy knee joint swelling. The prototypic features of arthritis, uveitis and skin rash helped suspect the diagnosis of Blau syndrome, an early-onset sarcoidosis or hereditary juvenile-onset systemic granulomatosis, which was confirmed on genetic testing.

There are certain conditions that one must be aware of when there is classic combination of clinical features e.g., arthritis, uveitis and skin rash, is a classic triad of Blau syndrome.

#### 10. 'Refractory' diseases/ Remarkable symmetry

A 10-y-old girl had swellings of the metacarpophalangeal and proximal interphalangeal joints. This was interpreted as JIA by the treating doctor, and

immunomodulatory therapy was initiated. She was refractory to methotrexate and steroids. On retrospective evaluation, the previous medical records suggested normal acute phase reactants and there was no history of morning stiffness of the joints. The swellings appeared bony rather than articular. Radiologic evaluation led to a suspicion of an epiphyseal dysplasia. Considering her short stature, a lateral X-ray of the spine was requested. It showed platyspondyly and gene testing confirmed the diagnosis of spondyloepiphyseal dysplasia.

Patients are often mistaken to have an inflammatory arthritis but in hindsight, they have remarkable symmetry of the joints involved in addition to normal acute phase reactants and absent clinical features of inflammation. Epiphyseal dysplasias including multiple epiphyseal dysplasia (MED) and spondyloepiphyseal dysplasia (SED) belong to this category.

Thus, the above cases teach us when to suspect a genetic basis of disorders which may be seen in a rheumatology clinic (Table 3).

### Responsibility of the Rheumatologist

Genetics has made a late start in our country but has had a rapid catch up with contemporary techniques and increasing affordability. It is now therefore possible to offer a genotypic diagnosis in large number of cases. Pediatric rheumatologists thus need to update themselves regarding the usage and interpretation of genetic tests. A limited workforce with a priority diverted to common diseases, often makes this a challenge. It is of utmost importance to make every attempt for a phenotypic diagnosis before requesting a genetic test. This allows selection of the best test for evaluation. Obtaining unexpected reports and/or variants of uncertain significance unrelated to the suspected phenotype confuses both, the physician and the parent.

**Table 3** The 10 commandments: When to suspect a genetic disorder?

1	Known predisposing genetic condition
2	Consanguinity
3	Family History
4	Forme Fruste
5	Multiple syndromic features
6	Disease with atypical/ nonspecific features with multiple multiorgan involvement
7	Early onset of known disease/autoimmunity known to start at later age
8	Early onset disease with recurrent fever/rashes/serositis/eye changes etc
9	Prototypic clinical features
10	'Refractory' diseases / Remarkable symmetry

It is also an important responsibility to educate primary care practitioners when to suspect a genetic disorder to minimize diagnostic odysseys, which parents often face. This limits damage accrual. Provision of simplified multilingual explanation for parents and extended families is a particularly important task for the physician. Pre-conception counselling, and prenatal diagnosis with the help of genetic services (if available) also fall within the ambit of a pediatric rheumatologist.

Therapy of such disorders may be as cheap as colchicine or as expensive as maintenance intravenous immunoglobulin (IVIG) or biologics. It may be lifelong e.g., biologics, or permanently curative such as hematopoietic stem cell transplant, or be in evolution e.g., gene therapy, or even be at the various stages of trial. Monitoring of adverse effects due to these modalities/ diseases/ procedures is important. Hence, organ systems with a probability of getting affected should be regularly screened.

Unfortunately, there are several diseases for which no treatment is currently known or available. It is important to maintain a keen eye on websites such as [clinicaltrials.gov](http://clinicaltrials.gov) for monitoring therapeutic breakthroughs in the horizon and offer parents enrolment (if eligible) especially in situations where no management currently exists. This however is a tedious and lengthy process as it involves multiple layers of paperwork but can be extremely rewarding.

The reporting of these ultra-rare diseases in local and international journals can be academically satisfying. Contribution to global registries increases the pool for research and helps to bring India on the academic map. Indian Council of Medical Research (ICMR) guidelines however allow export of biological samples only for individual diagnostic purposes [25]. Protecting time for these special subgroups is thus of utmost relevance.

## Impact on Family and Caregivers

Rarity of disease, limited knowledge and limited resources are a devastating triad. Complex referral pathways lead to a delay in diagnosis and initiation of therapy. To be given a diagnosis of an ultra-rare disease, especially of an entity they do not comprehend, is usually shattering news. With several diseases which have been reported only in the last decade or so, limited awareness precludes even the medical community from providing evidence-based answers.

Denial and social self-isolation (Why me/ my child? What error did we commit?), broken marriages and alcoholism pose major social challenges. The monetary impact in terms of direct costs related to medical care and indirect costs due to loss of wages, employment or transport costs is another major burden. The cost of treatment (which is often ‘control rather than cure’ and thus lifelong) and fear of adverse effects

often diverts families to alternative medicines and poses another challenge for the healthcare providers. Above all, the family remains worried and uncertain about the future. Worries concerning schooling, education, longevity, marriage, employment, and the fate of the next born continue to plague their thoughts.

## Responsibility of the Country

Individually, musculoskeletal or rheumatological diseases may qualify as rare or ultra-rare in India but collectively they could constitute a large but unquantified number. The first responsibility of national associations is thus to build a national registry to understand the magnitude of the problem. Besides realizing the socio-economic burden, several such diseases could enter a revised version of the National Rare Disease Policy. First crafted in 2017, the revised version in 2021 is a step in the right direction. It makes several additions but has a slant towards neurodevelopmental, metabolic, and immunodeficiency disorders [25] and leaves ambiguous several diseases which come under the ambit of the rheumatologist under the addition ‘etc.’. This may make it difficult for parents and physicians to convince sanctioning authorities. The policy notably touches upon educational programs to reduce the load of such diseases and availability of drugs to treat such disorders and identifies centres of excellence where such care may be available.

A major shortfall however is the awareness and visibility of such benefits and dissemination of the policy amongst physicians, several of whom are even unaware of such a document. On a separate note, allowing for travel concessions and such benefits could help subsidize indirect costs. Currently the rail concession policy leaves many such patients excluded [26] while allowing concessions to children with hemophilia and thalassemia. Pediatric rheumatologist associations could help champion this cause to ministries and thus help families to reduce indirect and recurring travel costs for patients and their families.

## Responsibility of the Educational Institutions/Society

Children and young adults spend a third of their day at school or college. Many children with genetic musculoskeletal disorders are mentally normal and this fact should be exploited. It is pertinent to initiate and work towards developing vocational coaching appropriate to their abilities at school, career selection and sports. Educating lay persons and school authorities regarding these rare diseases is vital to integrate them into the mainstream. Body shaming due to deformity or drug (steroids) should be condemned. Recognizing that many of them may be immunocompromised due

to drug or disease and allowing them suitable concessions for doctor visits is another responsibility for a responsible educational institution.

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## Declarations

**Conflict of Interest** None.

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