

Orphan and rare diseases: Global prevalence in genomic era



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1. Introduction

Orphan and rare diseases present a significant healthcare challenge due to their low occurrence rates, often affecting less than 1 in 2,000 individuals in Europe. The scarcity of these conditions complicates research and treatment efforts, as pharmaceutical companies find it difficult in investment of resources and man power thus resulting in a lack of effective therapies (1).

However, with the advancements in genomics and personalized medicine, new opportunities have emerged for understanding and managing these diseases. Firms such as Orphanet and the National Organization for Rare Disorders (NORD) play vital roles in offering comprehensive support, information, and advocacy for individuals impacted by orphan and rare diseases. Orphanet serves as a European hub for rare disease and orphan drug information, furnishing detailed insights into disease classifications, associated genes, and clinical signs. Conversely, NORD provides a repository of rare disease data, along with avenues for financial and medical aid, as well as resources catering to patients, researchers, and healthcare providers in the world (2).

Both Orphanet and NORD emphasize the significance of raising awareness, conducting research, and extending support to tackle the distinctive challenges posed by orphan and rare diseases. Their collaborative efforts contribute to enhancing the visibility of these conditions within healthcare and research systems, thereby facilitating improved diagnosis, care, and treatment for affected individuals (2, 3).

Table 1. Examples of the orphan and rare diseases (2)

S. No.	Disease name	Onset of age
1.	Abdominal muscle deficiency syndrome	Antenatal, Neonatal
2	Abnormally invasive placenta	NA

3.	Absence of fingerprints-congenital milia syndrome	Childhood
4.	Angora hair nevus	Infancy, Neonatal
5.	Autoimmune hemolytic anemia	All ages
6.	Bacterial endocarditis	All ages
7.	Benign adult familial myoclonic epilepsy	All ages
8.	Bloom syndrome	Antenatal, Neonatal
9.	Body stalk anomaly	Infancy, Neonatal
10.	Bone necrosis	NA
11.	Cancer of penis	Elderly
12.	Carcinoma of vulva	NA
13.	Cardiogenital syndrome	Infancy, Neonatal
14.	Central core disease	Childhood
15.	Dancing eye-dancing feet syndrome	Childhood, Infancy
16.	Deep dermatophytosis	Adult, Childhood
17.	Dermal sinus tract	NA
18.	Disorder of sex development	NA
19.	Eating reflex epilepsy	NA

20.	Embryonal sarcoma of the liver	NA
21.	Enlarged parietal foramina	Antenatal, Neonatal
22.	Epidermal nevus syndrome	Infancy, Neonatal
23.	Familial amyloid nephropathy	All ages
24.	Familial joint instability syndrome	Adolescent, Childhood, Infancy
25.	Farmer's lung disease	NA
26.	Female infertility due to zona pellucida defect	Adult
27.	Generalized fetal edema	Antenatal
28.	Genetic gastro-esophageal disease	NA
29.	Genetic respiratory malformation	NA
30.	Hendra virus infection	All ages
31.	Hepatitis delta	All ages
32.	Hereditary gingival fibromatosis	All ages
33.	Idiopathic achalasia	All ages
34.	Immunoglobulin A nephropathy	NA
35.	Infantile spasms syndrome	Childhood, Infancy, Neonatal

36.	Juvenile polyarthritis	NA
37.	Jackson-Barr syndrome	NA
38.	Kosaki overgrowth syndrome	Infancy
39.	Kuskokwim syndrome	Childhood, Neonatal
40.	Kyasanur forest disease	All ages
41.	Lassa fever	All ages
42.	Lateral facial cleft	Antenatal, Neonatal
43.	Late-onset retinal degeneration	Adult, Elderly
44.	Lactotroph adenoma	Adolescent, Adult, Childhood, Elderly
45.	Localized pagetoid reticulosis	Adult
46.	Macroducty of hand, bilateral	NA
47.	Multiple acyl-CoA dehydrogenase deficiency	All ages
48.	Malformation of the cerebellar vermis	NA
49.	Male-limited precocious puberty	Childhood
50.	Mast syndrome	Adolescent, Adult, Childhood
51.	Nail anomaly	NA

52.	Nanophthalmos	Infancy, Neonatal
53.	Nasal dermoid cyst	NA
54..	Necrotizing enterocolitis	Neonatal
55.	Neurogenic sarcoma	Adolescent, Adult, Childhood, Elderly, Infancy
56.	Obesity due to congenital leptin deficiency	Childhood
57.	Hepatoportal sclerosis	All ages
58.	Oculocutaneous albinism	Neonatal
59.	Occupational allergic alveolitis	NA
60.	Oculoskeletodental syndrome	Adolescent, Adult, Childhood
61.	Oculodentodigital dysplasia	Infancy, Neonatal
62.	Oral submucous fibrosis	All ages
63.	Paget disease of the nipple	Adult
64.	Pulmonary arterial hypertension	All ages
65.	Pulmonary arterial hypertension associated with HIV infection	Adult
66.	Pancreatic cholera	All ages
67.	Papular mucinosis of infancy	NA

68.	Arterial duct anomaly	NA
69.	Periodic paralysis	NA
70.	Peruvian warts	NA
71.	Query fever	All ages
72.	defects of plectin	NA
73.	Question mark ear syndrome	Infancy, Neonatal
74.	Quantal squander syndrome	All ages
75.	defects of myofibrillar proteins	NA
76.	Radioulnar fusion	Childhood, Infancy
77.	Rajab-Spranger syndrome	Childhood
78.	Renin-angiotensin-aldosterone system-blocker-induced angioedema	Adult
79.	Rabies	All ages
80.	Riboflavin transporter deficiency	Adolescent,Adult Childhood, Infancy
81.	Ring chromosome 1 syndrome	Neonatal
82.	Renal nutcracker syndrome	Adult
83.	Russell-Weaver-Bull syndrome	Antenatal

84.	Salla disease	Infancy
85.	Salivary gland type cancer of the breast	Adult
86.	Sarcosinemia	All ages
87.	Transaldolase deficiency	Infancy, Neonatal
88.	Tropical pancreatitis	Childhood
89.	Teratogenic Pierre Robin syndrome	NA
90.	Unbalanced complete atrioventricular canal	NA
91.	Univentricular cardiopathy	NA
92.	Uveal melanoma	Adult
93.	Vulvar carcinoma	NA
94.	Vaginal atresia	Childhood
95.	Valley fever	All ages
96.	Vascular tumor with associated anomalies	NA
97.	Vitamin D dependent rickets type I	Infancy, Neonatal
98.	Vanishing testes syndrome	Neonatal
99.	Zika virus disease	All ages
100.	Zimmermann-Laband syndrome	Neonatal

2. Absence of fingerprints or congenital Milia syndrome

Congenital Milia disorder is a very uncommon hereditary disease that is distinguished by a unique set of symptoms. These symptoms include the absence of fingerprints on the hands and feet, the presence of blisters in new born, and the development of small white papules called milia, particularly on the face. This syndrome has been observed in two families, one of which has had members affected for three generations, totalling 13 individuals. Additionally, there is an unrelated person who also shows similar symptoms. Some individuals with this syndrome may also experience certain physical abnormalities, such as partial flexion contractures in their fingers and toes, as well as webbing between their toes. Some of the clinical features of the disease may include:

- Permanent finger flexion (camptodactyly)
- Skin rash
- Abnormal blistering
- Variations in skin thickness
- Reduced sweating (hypohidrosis)
- Unusual fingerprints
- Milia
- Amniotic constriction ring

However, the exact onset of these features remains unclear. Mutations in the SMARCD1 gene are linked to this syndrome, which follows an autosomal dominant inheritance pattern (4,5).

2.1 Prevalence of congenital Milia syndrome

The prevalence of Congenital Milia Syndrome, specifically the variant characterized by the absence of fingerprints, is extremely rare. Only about 10 families worldwide have been identified as affected by this disorder, indicating its rarity and the limited understanding of its incidence in the general population (5).

3. Query fever or infection due to *Coxiellaburnetii*

Q fever, also known as query fever, a widespread transmittable disease caused by a bacterium called *Coxiellaburnetii*. It is caused by both humans and animals. The name "Q" was chosen because the origin of the disease was initially uncertain. This condition primarily affects cattle, sheep, and goats, and humans usually contract it by inhaling dust that is contaminated by these animals. People at higher possibility of getting Q fever cover those who work in farming, veterinary, or have close contact with these animals. The symptoms of Q fever can vary from mild flu-like symptoms to cases with no symptoms at all. However, in severe cases, it can lead to chronic infections that affect important organs such as the heart, liver, lungs, and brain. This is particularly true for individuals with pre-existing heart valve issues or weakened immune systems. To diagnose Q fever, blood antibody tests are typically performed, and the treatment approach depends on the severity of the symptoms. Antibiotics are effective for severe or chronic cases. Preventive measures include disinfecting areas contaminated by the bacterium and maintaining thorough hand hygiene to minimize the risk of infection (6,7).

Some of the clinical features that may be observed in individuals with Q fever are as follows (6-9):

- **Fever:** One of the most commonly recognized symptoms is a high-grade fever (104°F or 40°C).
- **Flu-like symptoms:** Common flu-like symptoms include chills, sweats, fatigue, headache, soreness, nausea, vomiting, loss motion, and a dry cough.
- **Chest and abdominal pain:** Chest pain while breathing and abdominal pain can occur.
- **Pneumonia and hepatitis:** In severe cases, Q fever can lead to lung infection (pneumonia) or liver infection (hepatitis).

- **Chronic complications:** A small percentage (less than 5%) of infected individuals may form over a long time Q fever, which causes endocarditis and may cause symptoms like night sweats, fatigue, shortness of breath, weight loss, and swelling of the limbs.
- **Pregnancy complications:** Women infected with Q fever in pregnancy can be at risk of miscarriage, stillbirth, premature delivery, or giving birth to a low-weight just birth child.

3.1 Prevalence of query fever syndrome

The estimated regularity of Q fever in human serum samples in the Eastern Mediterranean region is 25.5%, with a wide range of 16.1% to 34.9% based on different studies. Specifically, studies conducted in Afghanistan found a prevalence rate of 34.4%, also with high variability (ranging from 0.0% to 76.8%). Other countries in the region such as Egypt, Iran, Iraq, Jordan, Lebanon, Oman, Pakistan, Saudi Arabia, Somalia, Sudan, Tunisia, and the United Arab Emirates had prevalence rates ranging from 15.8% to 59.1%, showing varying levels of heterogeneity. Overall, the popularity of Q fever in the Eastern Mediterranean region was reported to be 22.4% among humans, animal species, mites and ticks, and milk samples. These findings emphasize the significant presence of this fever in the region, especially among high-risk occupational groups and populations exposed to livestock (10).

4. Carcinoma of valva

Vulvar cancer, also known as carcinoma of the vulva, is a relatively uncommon type of cancer affecting the outer region of the female genitalia. Most cases, about 90%, are squamous cell carcinomas, originating from the thin, flat squamous cells that line the vulva. These cancers can develop from precancerous conditions like vulvar intraepithelial neoplasia (VIN), where untreated abnormal cell changes may progress to cancer. Risk factors for this infection is smoking, and certain skin conditions such as lichen sclerosus.

Typical symptoms of vulvar carcinoma include itching, burning, soreness, lumps, swelling, wart-like growths, changes in skin texture, and unusual discharge from vulvar lesions. Diagnosis usually entails a physical examination, colposcopy, and biopsy to confirm the presence of cancerous cells.

Treatment for vulvar carcinoma may include surgery, radiation therapy, chemotherapy, and immunotherapy, tailored to the cancer's stage and the individual patient's needs. Early detection and prompt treatment are crucial for effectively managing vulvar carcinoma and improving outcomes for those affected (11-13).

Some of the clinical features of the disease may include (13,14):

- **Itching:** It is the most frequent and persistent indication of vulvar cancer.
- **Bleeding, discharge, and pain:** Other common symptoms include bleeding, unusual discharge, painful urination, and pain.
- **Lump or mass:** The most noticeable sign of vulvar cancer is a lump or mass in the vulva, which may appear ulcerated, white, fleshy, or wart-like.
- **Skin changes:** Swollen lumps in the vulva that may be red, white, or dark brown can be a symptom.
- **Lymph node swelling:** Swollen or tender lymph nodes in the groin area can also indicate vulvar cancer.
- **Precancerous conditions:** Vulvar intraepithelial neoplasia (VIN), a precancerous condition, is a risk factor and can precede the development of vulvar cancer

4.1 Prevalence of carcinoma of vulva

Vulvar cancer is not very common, with about 2.5 cases per ten thousand women each year in the USA. The rates of this cancer and the number of deaths it causes vary a lot depending on a person's ethnicity. Non-Latino white women have the elevated rates of vulvar cancer compared to other groups of people (13).

5. Vanishing testes syndrome

Vanishing testes syndrome, or testicular regression syndrome (TRS), is a rare condition where a testis undergoes atrophy and disappears during foetal development. It's believed to stem from events like intrauterine or perinatal testicular torsion, vascular blockage, or hormonal imbalances. Key signs include the absence of a detectable testis during a physical exam, resulting in an apparently "empty" scrotum, and the presence of a closed-off spermatic cord, indicating early testicular formation. Biopsy often shows a fibrovascular nodule with specific cell types and calcification, with few cases retaining any testicular tissue. While there's a theoretical risk of cancer, no instances have been documented. TRS occurs in about 5% of cryptorchidism cases and makes up a significant portion of nonpalpable testis situations, surpassing complete testicular absence in this group (15-17).

5.1. Prevalence of vanishing testes

While vanishing testes syndrome is a relatively uncommon condition, it accounts for a significant proportion of cases with a nonpalpable testis, estimated to affect up to 1 in 1,250 males (18).

6. Alice in wonderland syndrome

Alice in Wonderland Syndrome (AIWS) is a odd neurological condition that causes deformation in how individuals perceive themselves and their surroundings. This can include seeing objects as larger or smaller than they really are, as well as feeling like their own body size has changed. The condition, titled after Lewis Carroll's "Alice's Adventures in Wonderland," is not contagious and mostly affects children and teenagers, but it can occur at any age. AIWS is often linked to migraines, infections like Epstein-Barr virus (EBV) and influenza, as well as seizures, strokes, mental health conditions, and certain medications or drugs. Despite its rarity, AIWS is estimated to affect up to 30% of teenagers, showing that it's more common in certain groups.

Symptoms of AIWS can be grouped into disturbances in how individuals perceive themselves, how they see things, or a combination of both. Self-perception disturbances involve altered perceptions of body size and shape, while visual perception disturbances affect how objects and spaces are viewed. These symptoms can be distressing and confusing, so accurate diagnosis and treatment are important.

Treating AIWS involves addressing the underlying causes, as there's no direct cure for the syndrome itself. This may include managing migraines, treating infections, controlling seizures, or adjusting medications. In some cases, reassurance alone may be enough, especially if symptoms are temporary and not causing significant distress. However, effectively managing chronic conditions like migraines or epilepsy may decrease the frequency and severity of AIWS symptoms (19,20).

7. Conclusion

In conclusion, the landscape of orphan and rare diseases presents a complex healthcare challenge due to their low occurrence rates and the resulting difficulties in research and treatment efforts. However, with the advent of genomics and personalized medicine, new avenues have emerged for understanding and managing these conditions. Organizations like Orphanet and NORD play pivotal roles in offering comprehensive support, information, and advocacy for individuals impacted by orphan and rare diseases. By emphasizing the importance of raising awareness, conducting research, and extending support, these organizations contribute significantly to improving the visibility of these conditions within healthcare and research systems. Ultimately, collaborative efforts in the field of orphan and rare diseases are essential for enhancing diagnosis, care, and treatment outcomes for affected individuals worldwide.

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