JOURNAL OF BIOMEDICINE AND BIOCHEMISTRY
Volume 4 Issue 4 (2025), pp. 89–96

REVIEW A R T I C A L

Journal JBB
Print ISSN:3006-0532
Online ISSN:2958-0528

Infantile Systemic Hyalinosis (ISH): A Comprehensive Review of Its Genetic Basis, Clinical Spectrum, and Therapeutic Challenges

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Received: 1 September 2025,
Revised: 22 October 2025,
Accepted: 10 December 2025,
DOI: 10.57238/jbb.2025.7432.1158

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ABSTRACT

Background: Infantile Systemic Hyalinosis (ISH) is a very rare and severe autosomal recessive disease, in which amorphous hyalineaceous material is deposited extensively in different tissues and presents a multisystemic clinical manifestation. This debilitating disease, based on a biallelic mutation of the ANTXR2 gene, is typically characterized by a course of infancy and progressive joint contractures, painful papules and macules on the skin, gingival hypertrophy, gastrointestinal dysfunction, and failure to thrive. Despite such melodies' effects on people who are affected and it is a poorly-known disease that has few known therapeutic options. This systematic literature review seeks to summarize the knowledge on ISH, including acrylic-based knowledge, genetic foundation, molecular pathophysiology, etc., various clinical expressions, diagnostic and treatment implementations. The study will be going to explore the specific characteristics that separate ISH and its allele Juvenile Hyaline Fibromatosis (JHF), which is a counterpart and speaks of the problems in diagnosis and early intervention, which is vital, through pooling together information based on the case reports and literature reviews in the short term. ISH is a strong reminder of how complicated rare things can be genetic disorders. Increased sensitization among health professionals, as well as Speedy and precise diagnosis, plays the utmost role in maximizing supportive care, enhancing the lives of the affected infants.

Keywords: Infantile Systemic Hyalinosis; ISH; ANTXR2; Hyaline Fibromatosis Syndrome; Genetic Disorder.

1. Introduction

Infantile Systemic Hyalinosis (ISH) is a very moderate and hereditary connective tissue disease. Genetic disorders are also a difficult disorder of the total fibromatosis[1]. The diffuse laying down of amorphous hyaline described it ISH, has disastrous effects as it causes the build-up of material in different parts of the body through different tissues multisystemic clinical manifestation that generally occurs during early infancy[2].The fact that the conditions are progressive and frequently fatal diseases highlights the necessity to understand said conditions, being able to comprehend rare genetic disorders and their drastic effect on their victims and their families[3].

ISH has a genetic nature of biallelic mutations in the ANTXR2 gene referred to as capillary morphogenesis gene 2 (CMG2)[4]. This is a gene coding a transmembrane protein that influences the critical role of extracellular matrix assembly in a profound manner, cellular adhesion.

The mutations of ANTXR2 impair the physiological role of this protein[5]. Resulting in unusual

buildup of hyaline material, which is collagen-rich and glycoproteins, dermally, gastrointestinal tract, muscles, lymph nodes, spleen, thyroid, adrenal, and adrenal glands[6]. ANTXR2, as the causative gene, has been identified and has given valuable clues on the molecular pathogenesis of ISH and its alleles. It is the counterpart of Juvenile Hyaline Fibromatosis (JHF)[7]. Both ISH and JHF are due to mutation of the same gene, and they have similarities; they are on opposite sides of a clinical spectrum, histologically similar to one another [8]. JHF is commonly associated with a less marked phenotype at later onset people to grow into adults[9]. On the contrary, ISH is marked with earlier severe and progressive progression and a high mortality rate, which, frequently, end in the first two years of life. There is a very high rate of death, mostly as a result of complications like repeated pneumonia and severe diarrhea[10].

Clinical manifestations of ISH are varied and comprise painful articular contractures, thick and hyperpigmented skin, and include papulo-nodular lesions, gingival hypertrophy, osteopenia and chronic diarrhea, protein-losing enteropathy, and repeated infections [11]. As critical as the genetic diagnostics have been developed, ISH remains a diagnostic is difficult diagnosis because of low prevalence and the inconsistency of its clinical manifestation[12]. Early and proper diagnosis plays an important role in the supportive management and genetic therapy for affected families[12]. At the same time, however, there are no particular curative treatments one may have against ISH, and mainly the management is geared toward mitigation of menacing symptoms and enhancing the life of the patients[13].

This review summarizes whatever has been known about Infantile Systemic Hyalinosis. The study will explore the genetic basis of the disease, review molecular processes that cause deposition of hyaline, describe the various clinical manifestations, describe the methods of diagnosis, and provide a summary of the current management strategies. Synthesizing data in recent case reports, it can be noted that the second five-year period will probably see the continuity of present-day political and institutional developments.

In the scientific literature through this paper, we will increase awareness of ISH in healthcare. Professionals make timely diagnoses and show the necessity of further research to develop more effective therapeutic measures with regard to this devastating condition. This paper aims to create awareness among clinicians and researchers, helping in diagnosing on time, and emphasizing the need for additional research to find effective methods of treatment in this disastrous hereditary disease.

1. Genetic Basis and Molecular Pathophysiology:

The basic root of ISH and JHF is in biallelic pathogenic mutations in the Gene ANTXR2, on chromosome 4q21. ANTXR2 gene, also called CMG2 (Capillary Morphogenesis Gene 2) is a transmembrane protein that is encoded by a gene; they plays a very important part in extracellular matrix (ECM) assembly and cell adhesion [14].

Particularly, ANTXR2 acts in the cell uptake of collagen VI, a major protein part of the ECM. ANTXR2 mutations cause a defective protein, which results in an ineffective protein an inappropriate processing, and breakdown of other ECM molecules[15], such as collagen VI Figure 1 and Figure 2 .

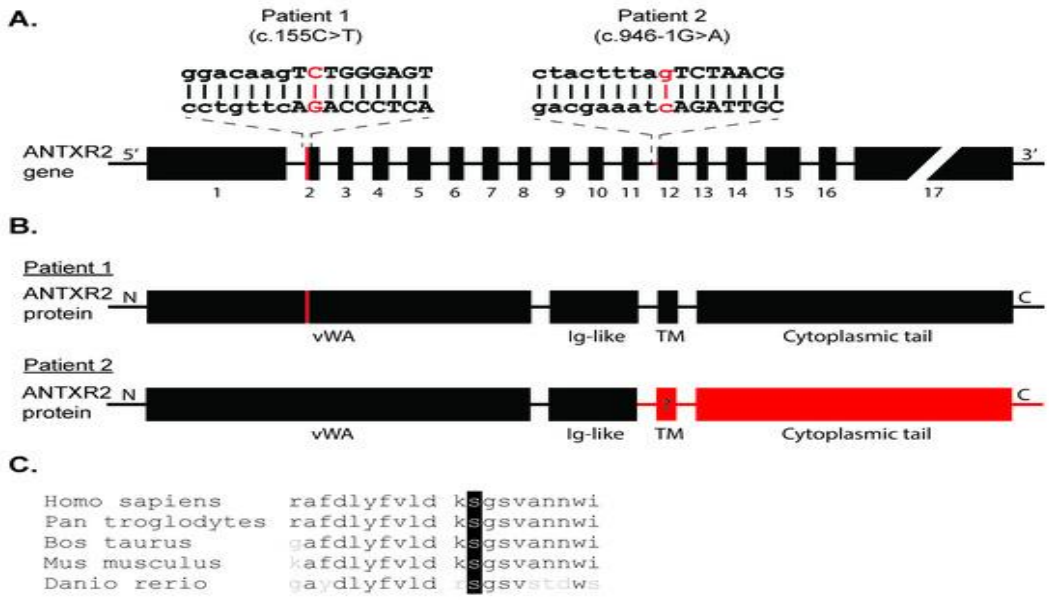

Figure 1. Infantile systemic hyalinosis is inherited in an autosomal recessive manner

This impairment causes the aberrant aggregation and deposition of amorphous eosinophilic hyaline in the different connective tissues all over the body [16]. The hyaline substance is highly concentrated in collagen VI, glycoprotein, and proteoglycans will gather in the papillary dermis, skeletal muscles, gastrointestinal tract and lymph spleen, spleen, thyroid, and adrenal glands. This worldwide deposition interferes with normal tissue architecture and its normalcy, which renders them a variety of clinical symptoms noted in ISH [17].

The phenotype of HFS is very severe, with the less severe one being JHF. The ISH, severe one, is commonly associated with the ANTXR2 type and localization mutation, and some mutations have stronger effects of loss of protein functionality and thereby a more serious clinical appearance [18].

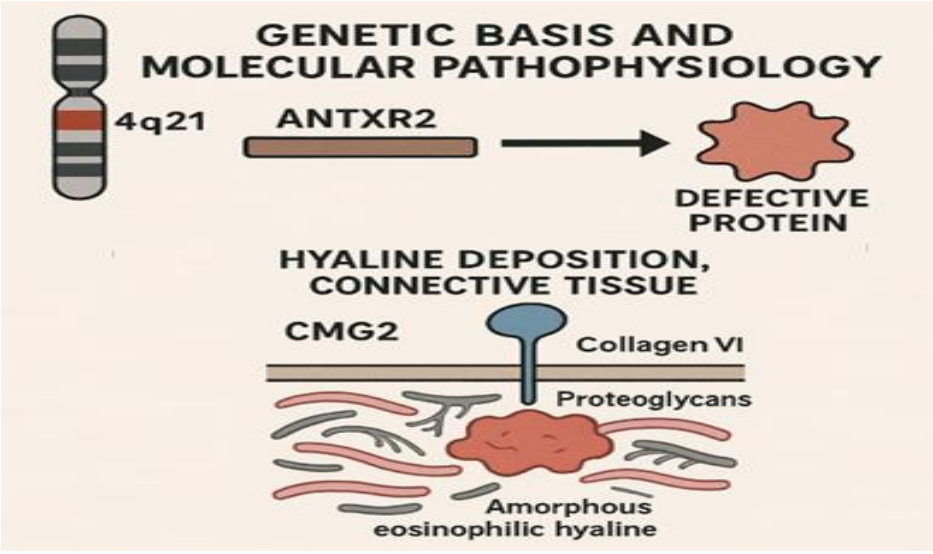

Figure 2. Genetic Basis and Molecular Pathophysiology

2. Clinical Manifestations:

ISH normally occurs during early infancy, and it may appear during birth or even during the first few months of life, and evolve very quickly and severely in the course of life. The multisystemic participation, because of the high occurrence of hyaline deposits, results in a constellation of typical symptoms and signs [19].

Musculoskeletal System: A very bad and handicapping character of ISH

The presence of progressive joint contractures is known as. Both of these contractures may influence large and small joints, which can cause severe pain and significant restriction of movements. The little handling can only worsen pain, and one can only imagine the amount of distress inflicted infant. Reduction in bone mineral density is also common, which is called generalized osteopenia, making bones sensitive and prone to breaking [20].

Dermatological: Skin is impaired in the majority of cases of ISH and may show a variety of characteristic lesions. These involve thickened and hyperpigmented skin, especially over bone protrusions and arthritis, and papulo-nodular eruptions. Pearly papules could be found on the face and the neck, as well as fleshy masses of the perianal form common. These skin conditions are usually painful, and they may hinder normal activities [21].

Gastrointestinal System: Gastrointestinal system involvement is a big contributor to:

- Mortality and morbidity of ISH. The infants who have been affected tend to develop serious, chronic absorptions due to diarrhea and protein-losing enteropathy, failing to thrive. This may lead to severe malnutrition and growth retardation as well, adding to the problems that these patients are having [22].
- Oral Manifestations: Gingival hypertrophy, Proliferation of gum tissue, also known as gingival hypertrophy regularly observed in ISH. This may tamper with oral hygiene and feeding to deficiency-related disorders and high rates of susceptibility to oral infections [23].
- Repeat Infections: Infants having ISH are highly prone to repeat infections, especially sepsis and respiratory infections. Probably, this vulnerability is caused by the increase in factors, a combination of which includes malnutrition, impaired immunity, and the systemic aspect of the disease [24].

3. Diagnosis:

ISH diagnosis is principally composed of a mixture of typical clinical features, abnormalities, histological abnormalities, and conclusive genetic examination of molecules. Given that a good index of suspicion is important in making the diagnosis of ISH, which has a rare and variable presentation early[25].

3.1 Clinical Suspicion:

The occurrence during early infancy of clinical manifestations which are typical of severe forms of the disease, or recurrent progressive loss of range of motion of the joints, especially in the legs, agonizing excoriations of the skin, hypertrophy of the gums, and grievous ISH should be suspected following gastrointestinal problems that cause the development of failure to thrive[26].

3.2 Histopathological Examination:

Skin Biopsy is a major diagnostic tool, light microscopy usually shows the deposition of eosinophilic, hyaline, amorphous c. Papillary dermis material. This substance is periodic acid-Schiff (PAS) positive it is believed to have glycoproteins and collagen [26].

Cells may be shown using electron microscopy, laden with fine fibrillary material and hypertrophic endoplasmic reticulum and Golgi apparatus. In case intestinal biopsies are carried out, they may show villous atrophy, increased edema, lymphangiectasia, and hyalinosis in cases of prominent gastrointestinal symptoms [26].

3.3 Radiographic Findings:

Skeletal radiographs usually reveal weaker bones in the form of generalized osteopenia, periosteal reaction, and lesions with a lucent appearance, especially in long bones and axial bones. There can be a rapid transit time in upper-gastrointestinal imaging studies[27].

3.4 Molecular Genetic Testing:

The clear diagnosis of ISH is confirmed by naming biallelic damaging variations in the ANTXR2 gene using molecular genetic testing. There may be single-gene testing, thought to multigene panels that incorporate ANTXR2 or whole genome sequencing, like exome sequencing. Genetic Testing plays an essential role during the diagnosis, as well as genetic counseling of affected families, so carrier testing can be done for at-risk family members, and prenatal testing in case of future pregnancies[28],see Figure 3.

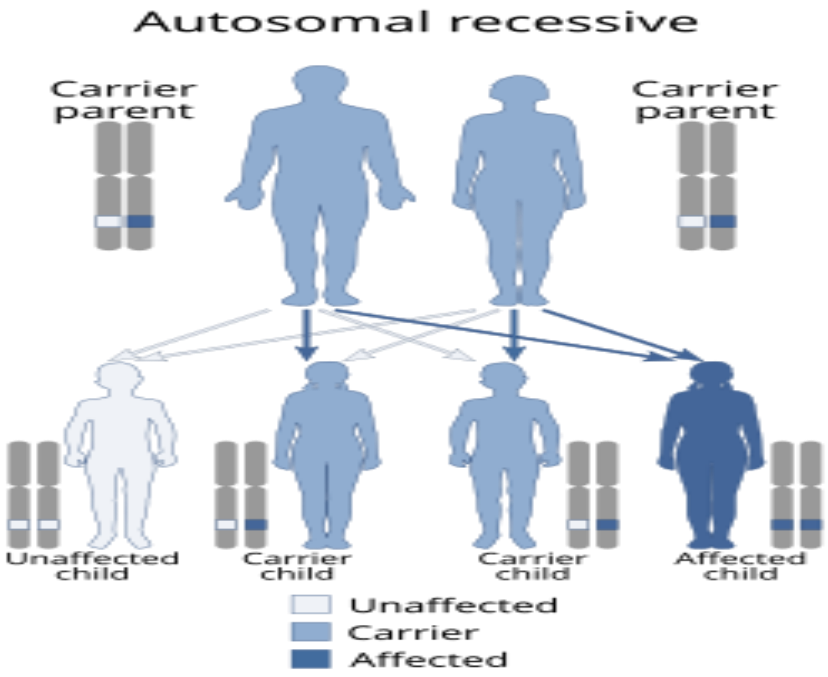

Figure 3. Molecular Genetic Testing

4. Management:

At present, no specific curative treatment is available against ISH, and its management is mostly based on a case-by-case basis, sympathetic in nature, and aimed at improving the symptoms, avoiding complications enhancing the living standards of the affected parties. Multidisciplinary strategy using physicians who specialize in pediatrics, genetics, gastroenterology, dermatology, and orthopedics. Treatment by doctors in pain management, physiotherapists, etc is necessary[29].

4.1 Nutritional Support:

Since the gastrointestinal involvement and failure were very severe, aggressive nutritional support was given. Aggressive nutritional support is vital in order to thrive. This can contain a nasogastric tube. They may need feeding, have gastrostomy wounds put in, or be tagged with parenteral nutrition to have enough to eat, regulate intakes of calories, and treatment of protein-losing enteropathy. The diets ought to be customized to help with malabsorption and lymphangiectasia[30].

4.2 Management of Pain:

Pain that is chronic and severe, especially of joints, Nursing, contractures, and handling, has to be managed properly. Nonsteroidal anti-inflammatory Pain may be controlled by using drugs (NSAIDs), opioids, and gabapentin. Discomfort can also be reduced by handling and splinting. One of the things cited is consultation with a It is usually helpful to have a pain management specialist[31].

4.3 Surgical Interventions:

Obstructing lesions of the airway or feeding could be operated need to be removed by surgery, though they tend to recur. Also, perianal masses may be resected. There are possible complications of endotracheal which anesthesiologists must know. Because of involvement in the face and the mouth, it can lead to intubation[32].

4.4 Support and Family Counseling:

Genetic counseling is important to families to help an affected child perceive the nature of the autosomal recessive mechanism of inheritance, various genetic risks, the risk of recurrence, and reproductive choice. Access and psychological support, brand promotions to patient advocacy groups, may also be a lifesaver when faced with the problems of the treatment of a genetic, lifelong, and debilitating condition[33].

2. Conclusion

ISH is a strong reminder of how complicated rare things can be genetic disorders. Increased sensitization among health professionals, as well as Speedy and precise diagnosis plays the utmost role in maximizing supportive care, enhancing the lives of the affected infants.

Moreover, there has been long-term research. The need for Florham Park is essential to unveil the complex molecular networks disrupted in ISH and to turn these realizations into progressive and efficient cures, providing a ray of hope to the families struggling to cope with this difficult condition.

Conflict of interest statement: The authors have no conflict of interest with respect to the publication of this article.

Ethical Consideration: The ethical committee approved the study at University of Jabir Ibn Hayyan, Al-Najaf Iraq

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How to cite this article
AlBayati MM, Abed WK, Hasan TH.Infantile Systemic Hyalinosis (ISH): A Comprehensive Review of Its Genetic Basis, Clinical Spectrum, and Therapeutic Challenges. Journal of Biomedicine and Biochemistry. 2025;4(4):89-96. doi: 10.57238/jbb.2025.7432.1158