

## CLINICAL REPORT

# Hyaline fibromatosis syndrome with a novel 4.41-kb deletion in *ANTXR2* gene: A case report and literature review

Yunqian Zhu<sup>1</sup> | Xiaonan Du<sup>2</sup> | Li Sun<sup>3</sup> | Huijun Wang<sup>4</sup>  | Dahui Wang<sup>5</sup> | Bingbing Wu<sup>4</sup> 

<sup>1</sup>Department of Neonatology, Children's Hospital of Fudan University, Shanghai, China

<sup>2</sup>Department of Neurology, Children's Hospital of Fudan University, Shanghai, China

<sup>3</sup>Department of Rheumatism, Children's Hospital of Fudan University, Shanghai, China

<sup>4</sup>Clinical Genetic Center, Children's Hospital of Fudan University, Shanghai, China

<sup>5</sup>Department of Orthopedics, Children's Hospital of Fudan University, Shanghai, China

## Correspondence

Dahui Wang, Department of Orthopedics, Children's Hospital of Fudan University, Shanghai, China. Email: [wangdahui@fudan.edu.cn](mailto:wangdahui@fudan.edu.cn)

Bingbing Wu, Key Laboratory of Birth Defects, Children's Hospital of Fudan University, National Children's Medical Center, 399 Wanyuan Road, Shanghai 201102, China.

Email: [081107271@fudan.edu.cn](mailto:081107271@fudan.edu.cn)

## Abstract

**Background:** Hyaline fibromatosis syndrome is a rare autosomal recessive disorder with *ANTXR2* mutations characterised by the accumulation of hyaline substances in tissues. We present a case with the severe form—infantile systemic hyalinosis (ISH)—with long survival and review the literature.

**Methods and results:** Trio-exome sequencing revealed compound heterozygous mutations, including a novel 4.41 kb deletion on 4q21.21 and the previously reported c.1294C > T mutation, in the *ANTXR2* gene. He was diagnosed with ISH and treated symptomatically. After follow-ups until 4 years of age, his recurrent respiratory infections and diarrhoea improved after one severe diarrhoea attack treated with intravenous gamma globulin. He is now awaiting surgical excision of gingival hypertrophy and joint contractures.

**Conclusion:** The novel gross deletion in *ANTXR2* enriches the genetic mutation spectrum of hyaline fibromatosis syndrome. The manifestation of decreased foetal movement, acute-infection attack or intravenous gamma globulin treatment may be associated with hyaline fibromatosis syndrome. A review of 116 reported cases reveals that missense mutations in the vWA domain are associated with joint symptoms, respiratory tract infection and diarrhoea, while frameshift mutations are associated with facial deformities and speech delays.

We have enriched the current knowledge of the clinical manifestations and genetic mutation spectrum of HFS.

## KEYWORDS

*ANTXR2*, hyaline fibromatosis syndrome, infantile systemic hyalinosis, juvenile hyaline fibromatosis

Yunqian Zhu and Xiaonan Du should be considered joint first author.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Molecular Genetics & Genomic Medicine* published by Wiley Periodicals LLC.

## 1 | INTRODUCTION

Hyaline fibromatosis syndrome (HFS) [MIN #22860] is an autosomal recessive condition characterised by the accumulation of hyalinising fibrosis. The disease-causing gene *ANTXR2* [MIM# 608041], also called *CMG2*, is located on chromosome 4q21 (Dowling et al., 2003; Hanks et al., 2003). The *ANTXR2* gene encodes a 55-kDa type I transmembrane protein, followed by an extracellular von Willebrand type A domain (vWA), an immunoglobulin-like (Ig-like) domain, a transmembrane (TM) domain and a cytosolic tail (Bell et al., 2001; Casas-Alba et al., 2018; Sun & Collier, 2010). There are four classes according to the identified mutations (Deuquet et al., 2012): Class I (missense mutations in the vWA domain), Class II (all other missense in exons 1–11), Class III (all frameshift and probably splicing mutations leading to deleterious effect) and Class IV (missense mutations in the cytosolic tail).

HFS is characterised by cutaneous nodules, pearly papules, perianal plaques, gingival hypertrophy, joint contracture with pain, intractable diarrhoea and recurrent infections (Casas-Alba et al., 2018), and has two forms: juvenile hyaline fibromatosis (JHF) and infantile systemic hyalinosis (ISH). JHF has a mild course and presents clinical features at 2–5 years with more prolonged survival (Çam et al., 2015). ISH is the life-threatening form associated with early onset in infants and early death within 2 years (Lu et al., 2016; Rahvar et al., 2016). HFS is classified into four grades according to the clinical manifestation: Grade 1 (mild) with skin or gingival involvement; Grade 2 (moderate) with joint or bone involvement; Grade 3 (severe) with recurrent infections, persistent diarrhoea or other symptoms; and Grade 4 (life-limiting) with organ failure and/or septicaemia (Denadai et al., 2012).

There is no radical treatment for HFS. Early surgical excision of subcutaneous nodules and gingival hypertrophy, methotrexate and steroids to improve range of motion, penicillamine to narrow skin lesions and non-steroidal anti-inflammatory drugs to relieve pain are the recommended clinical treatments (Denadai et al., 2012; Shieh et al., 2006; Urbina et al., 2004). Herein, we report a patient with ISH lived much longer than average with a gross deletion in exons 7–17 and a missense mutation of the *ANTXR2* gene.

## 2 | CASE REPORT

A Chinese male infant was born to healthy non-consanguineous parents. He was the second child and had no family history of ISH. His healthy older brother was 5 years old, and his mother had experienced two induced abortions. His mother was threatened with preterm

labour at 3 months of gestation and was treated with medication. Decreased foetal movement was observed during pregnancy. Foetal hydronephrosis was diagnosed by prenatal ultrasound screening. The boy was delivered by caesarean section after 38 weeks of gestation owing to oligohydramnios, premature rupture of membranes and intrauterine hypoxia. No hypoxia was observed after birth. When the child was 1-month-old, he developed increasingly restricted movement of his limbs. From 2.5 months, he began crying when he was moved. He presented with feeding problems and diarrhoea. Electromyography and magnetic resonance imaging of the head and lumbosacral vertebrae produced normal results. *SMA* gene was excluded before the visit.

The boy was referred to our clinic at 4 months with hypoactivity, hypotonia and sensitivity to passive movement. He had frontal bossing, a short nose, a depressed nasal bridge and presented with a papular skin rash on his hands (Figure 1a). He was diagnosed with myopathy due to hypoactivity and hypotonia. He had an increased serum alanine aminotransferase level (61 U/L, normal range: 0–40 U/L) and mild hyperkalaemia (5.57 mmol/L, normal range: 3.5–5.5 mmol/L). The levels of 2-ketoglutarate and citric acid increased owing to secondary changes in urine mass spectrometry. Tests for anti-dsDNA antibodies (dsDNA) were positive. The creatine kinase, serum creatinine, blood glucose, thyroid function, blood gas, coagulation function, syphilis antibody and blood tandem mass spectrometry data were normal. Hydronephrosis on the left side was diagnosed by ultrasound. Radiography revealed bilateral periosteal hyperplasia in the humerus, ulna, femur and tibia; a thickened cortex in the left clavicle; and a bony process at the upper end of the left radius (Figure 1d–g).

At 6 months, the infant developed flexion contractures in the elbow, hip, knee and ankle with swollen joints and body pain. One month later, hyperpigmentation over the bony prominences was observed (Figure 1b,c). He had experienced recurrent respiratory infections (one acute bronchitis and two upper respiratory tract infections) and one episode of diarrhoea. He was treated with antibiotics for infections and probiotics for diarrhoea. The subject's IgG level was 3.0 g/L (normal range: 3.7–8.3 g/L), CD3<sup>+</sup> was 57% (normal range: 64%–73%), CD8<sup>+</sup> was 23% (normal range: 24%–34%) and CD19<sup>+</sup> was 22% (normal range: 14%–21%). Separation of the renal pelvis, splenomegaly and patent ductus arteriosus was detected using ultrasound.

At 8 months, he failed to thrive with a weight of 7.0 kg (<2 SD). He could not raise his head or sit up unaided. Gingival hypertrophy was observed. His intelligence was similar to that of healthy children. Trio-exome sequencing (ES) was performed with the parents'



**FIGURE 1** A patient with infantile systemic hyalinosi at 8 months old (a–g) and 4 years old (h–o). (a) Papular skin rash on hands. (b and c) Hyperpigmentation over prominent of lateral malleolus. (d–g) Periosteal reaction in the humerus, ulna, femur and tibia. (h and i) Pearly papules around neck. (j and k) Cutaneous nodules and hyperpigmentation at chest and back. (l) Gingival hypertrophy. (m) Perianal plaques. (n and o) Joint contractures of feet.

informed consent. The data analysis was conducted using an in-house pipeline (Yang et al., 2019). ES revealed a NM:058172.5:c.1294C>T p.(R432X) nonsense mutation in exon 15 of the *ANTXR2* gene from the mother, which introduced a stop codon in 432 amino acids that generates a truncating protein. There was also a 4.41-kb deletion in 4q21.21 from the father, which predicted a premature stop codon in 215 amino acids generated by *ANTXR2* (Figure 2a). Sanger sequencing was performed to confirm the missense mutation (Figure 2b). Quantitative polymerase chain reaction (qPCR) was performed to identify the gross deletion (Figure 2c). The patient had a compound heterozygous mutation in *ANTXR2* (Figure 2d). Therefore, the diagnosis of ISH was confirmed.

At 2 years, he experienced recurrent acute bronchitis or pneumonia 3–5 times every year. Persistent diarrhoea with loose stool 6–7 times every day was developed. He was symptomatically treated with probiotics. At 3 years, he suffered from diarrhoea with severe dehydration, seizure and a coma. He was treated at hospital without any improvement. He was withdrawn from treatment and taken home according to his parents' will. After a 2-day coma at home, he woke up and recovered gradually. He was taken to the hospital and treated with intravenous gamma globulin (IVIg) due to his oedema, along with other symptomatic therapies. After this acute attack, his diarrhoea improved with well-formed stools 2–3 times

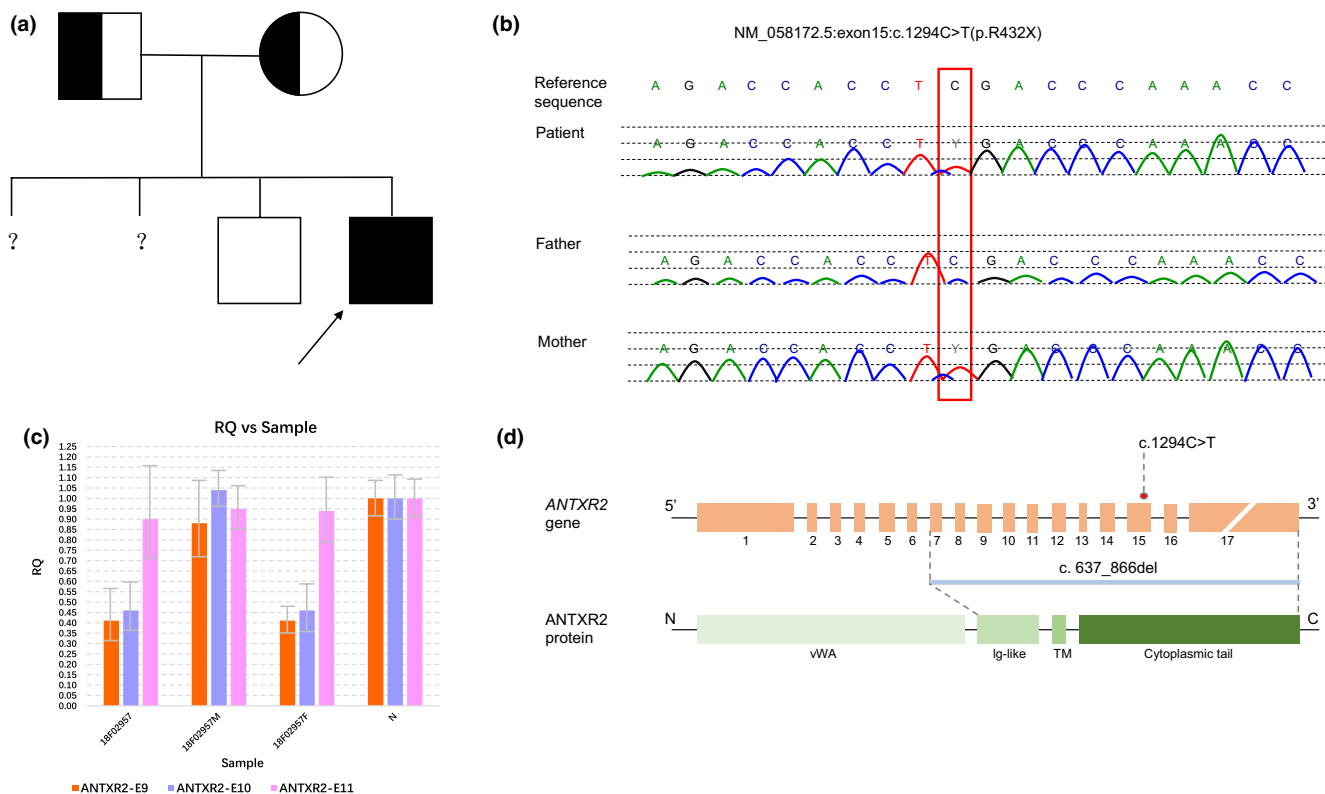
every day. He had a good appetite and rarely suffered from respiratory infections.

In the last follow-up at 4 years of age, his gingival hyperplasia led to facial deformity. Pearly papules around his neck, cutaneous nodules at his chest, back and right ear, hyperpigmentation at his abdomen and back with recurrent skin infections, and perianal plaques were observed (Figure 1h–m). His joint contractures had not progressed after 1 year of age (Figure 1n,o). He had a weight of 7.2 kg (<4 SD). He visited to our multidisciplinary treatment team and awaited surgical excision of gingival hypertrophy and joint contractures to relieve symptoms at his parents' wishes.

### 3 | DISCUSSION

Murray first reported a patient with HFS in 1873 (Murray, 1873). The disorder occurs most frequently in Turkish, Moroccan and Indian people owing to the high rate of consanguineous marriage (Casas-Alba et al., 2018; Chaudhry et al., 2021). HFS can be diagnosed based on clinical characteristics, together with histopathology or genetic sequencing. Early diagnosis is difficult without the typical phenotype.

Our patient presented with restricted movement with pain, hypoactivity and hypotonia. Thus, he was diagnosed with myopathy at our clinic. We then launched an



**FIGURE 2** Clinical presentation and molecular characterisation of infantile systemic hyalinosis family. (a) The family tree, with trio-exome sequencing for the proband (black arrow) and his parents. (b) The c.1294C>T mutation in exon 15 was confirmed by Sanger sequencing. (c) A 4.41 kb deletion on 4q21.21 was detected and confirmed by q-PCR. (d) Our patient with compound heterozygous mutations.

undiagnosed disease programme. Trio-ES was performed in his family; the pathogenic missense mutation in the *ANTXR2* gene from the mother was of concern. The discovery of one mutation was insufficient for a diagnosis of the autosomal recessive disorder. Therefore, we further analysed the sequencing data according to our in-house pipeline for copy number variation (CNV) detection (Qian et al., 2018). There was a 4.41-kb deletion in the *ANTXR2* gene from the father, which could not be detected by a routine next-generation sequencing pipeline. The deletion was confirmed by qPCR. According to the discussion in the multidisciplinary treatment team—which comprised representatives from the neurology department, psychiatry department, hepatology department and the centre for molecular medicine—ISH with compound heterozygous mutations of *ANTXR2* was diagnosed, and there was no indication for further biopsy. The clinical classification was Grade 3 in this patient. This is a case of gross deletion covering exons 7–17 of the *ANTXR2* gene. Therefore, molecular diagnosis is useful in patients without typical manifestations or biopsy results.

Our patient suffered from systemically involved persistent diarrhoea, recurrent infections and failure to thrive, which were consistent with the features of ISH.

Interestingly, his diarrhoea and infections greatly improved after acute severe diarrhoea with dehydration, seizure and a coma and treatment with IVIg and other symptomatic therapies. After that he had a good appetite. Such improvement in ISH after an acute attack has never been mentioned in other reported cases. Hanks (Hanks et al., 2003) found that ISH patients may experience less infections and pain in joints if they live longer than 1 year of age, but the causes of these changes are still unknown. Whether the acute attack of diarrhoea or the IVIg treatment are associated with these changes in our patient requires further study.

We searched the PubMed database for literature published from January 2000 to May 2021 using the keywords “hyaline fibromatosis syndrome,” “infantile systemic hyalinosis” or “juvenile hyaline fibromatosis” and “*ANTXR2*” or “*CMG2*” without language restrictions. In total, 49 articles reported 115 cases with clinical features and molecular diagnoses (Table S1). A total of 116 patients (including the case in the present study) were included for further analysis.

There were 81 of 116 patients reported the information of consanguineous or non-consanguineous parents. A total of 53 patients were born to consanguineous

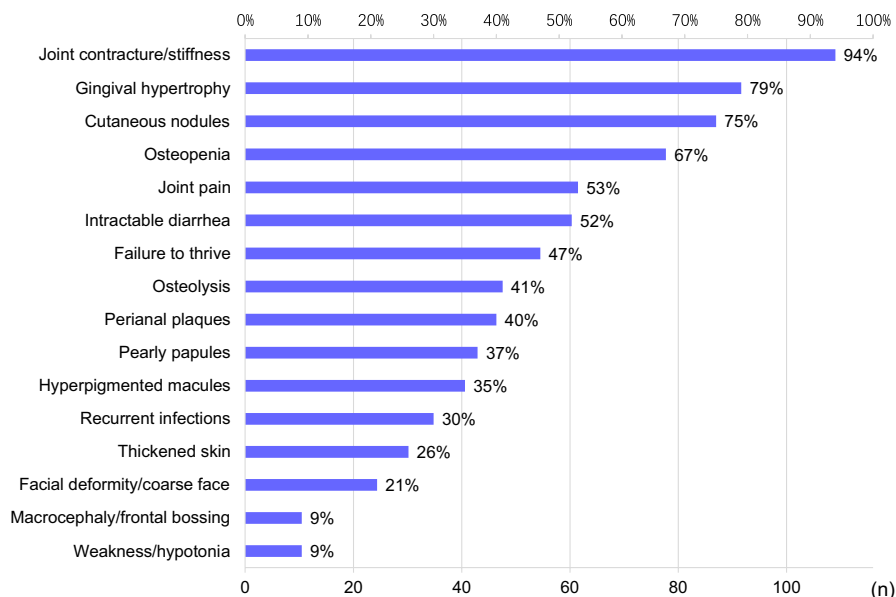
parents. Among 116 patients, the commonly observed symptoms were joint contracture or stiffness (94%, 109/116), gingival hypertrophy (79%, 92/116) and cutaneous nodules (75%, 87/116), followed by osteopenia (67%, 33/49), joint pain (53%, 61/116), intractable diarrhoea (52%, 60/116), failure to thrive (47%, 55/116), osteolysis (41%, 20/49), perianal plaques (40%, 46/116), pearly papules (37%, 43/116), hyperpigmentation (35%, 41/116), recurrent infections (30%, 35/116) and thickened skin (26%, 30/116). No intellectual disability was mentioned in any of the patients (Figure 3).

There are 61 mutations reported in *ANTXR2* up until May 2021 (The Human Gene Mutation Database). More than 75% of the mutations are homozygous, and less than 25% are heterozygous. Approximately half of the homozygous mutations were found to be deleterious. There are 73 of 116 patients with homozygous mutations. We therefore performed genotype–phenotype analysis of the 73 patients. We found that Class I (27%) and Class III mutations (63%) account for the majority. Patients with Class I mutations all suffer from joint contracture or joint stiffness (100%), much more than those with Class III (87%) and Class IV (50%). Gingival hypertrophy and nodules are more likely to be present in patients with Class IV mutations (100% and 100%) than those with Class I (65% and 70%) and Class III mutations (73.9% and 60.9%). Approximately half of the Class I cases were systemically involved (persistent diarrhoea, 55%; recurrent infections, 50%; failed to thrive, 45%), whereas the Class III cases had fewer recurrent infections (28%). Class I, II and III mutations harbour clinical classifications of Grade 2 to Grade 4, whereas Class IV mutations harbour Grade 1 to Grade 3. The age of onset is later in patients with Class III mutations (8 months)

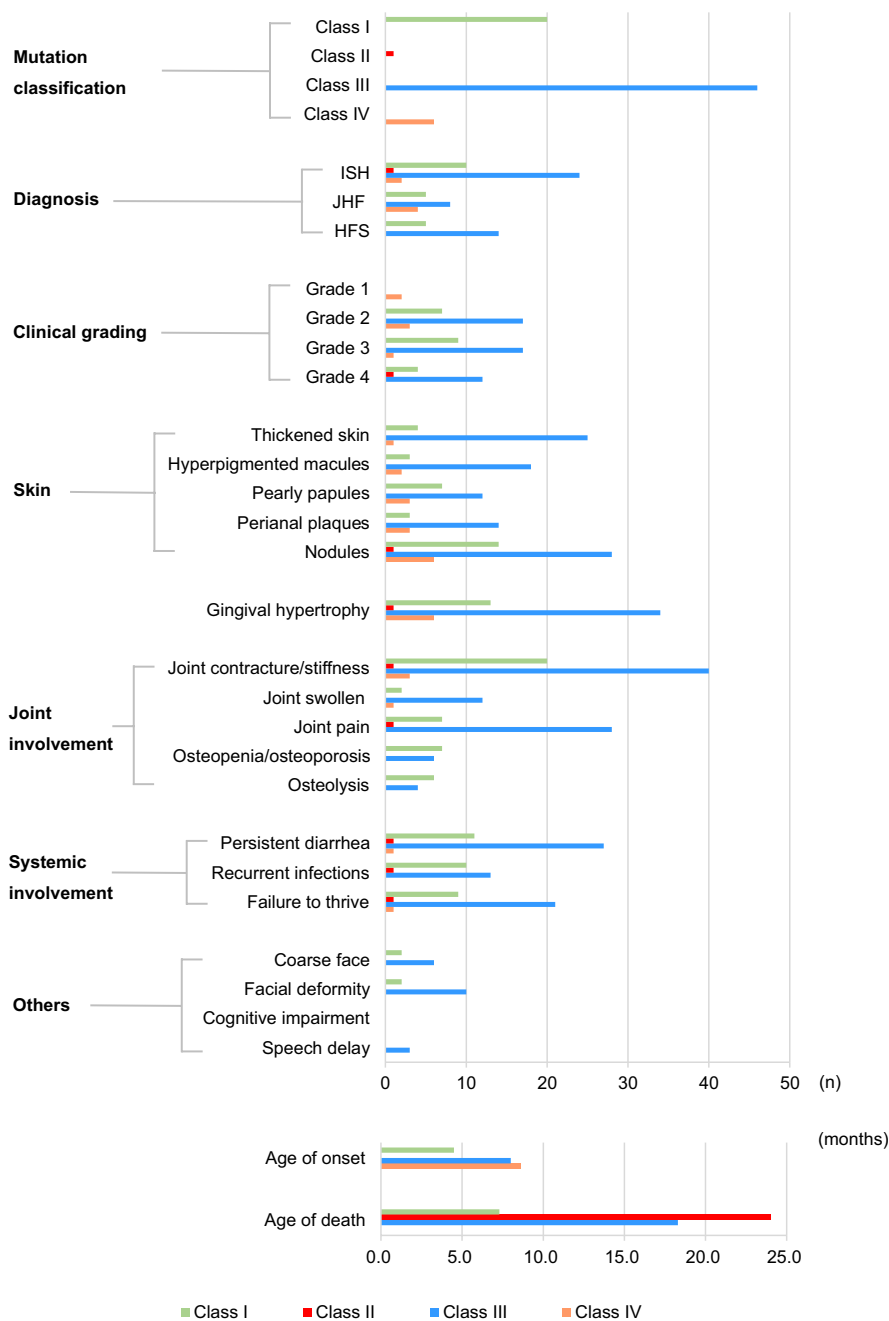
than that of patients with Class I (4 months) and Class II mutations (0 months). Consequently, we infer that Class III results in milder symptoms than Class I. Class II may produce the severest form owing to its earlier onset. Class IV mutation with relatively late-onset age produces the mildest form (Figure 4).

In our analysis, we found that facial deformities are overwhelmingly present in patients with Class III mutations (six low-set ears, four prominent ears, four depressed nasal bridge, three proptosis, two deep-set eyes, two a long face, one macrocephaly, one wide nasal bridge, one short nasal bridge, one prominent forehead) compared with other classes (one macrocephaly and one epicanthus in Class I mutations, and none in Class II and Class IV mutations). We therefore infer that Class III mutations may lead to facial deformities.

Cognitive impairment is rarely reported, which is in accordance with the belief that the *ANTXR2* gene is minimally expressed in the brain (Bell et al., 2001; Casas-Alba et al., 2018). To date, three cases of HFS with intellectual disabilities have been reported. One is a 5-year-old Turkish boy diagnosed with JHF without any genetic information (Çam et al., 2015), and the other two are Chinese twins diagnosed with ISH with compound heterozygous variants (Yang et al., 2021). Whether intellectual impairment in HFS is related to *ANTXR2* mutations remains unknown. Speech delay has been reported in the three cases. One was a JHF patient and two were twins diagnosed with ISH (Koonuru & Venugopal, 2015; Youssefian et al., 2017). Genetic testing revealed that these patients harboured Class III mutations. Therefore, we suggest that Class III mutations are associated with language difficulties. Additional case studies are needed for confirmation.



**FIGURE 3** The percentage of clinical manifestation in 116 patients diagnosed with hyaline fibromatosis syndrome.



**FIGURE 4** Genotype-to-phenotype correlation in 73 patients with homozygous mutation according to *ANTXR2* mutation classification.

Decreased foetal movement during pregnancy was reported in our case as well as another two cases with frameshift mutations (Vahidnezhad et al., 2015; Youssefian et al., 2017). ISH usually results in symptoms shortly after birth. The finding of decreased foetal movement, affected by a large number of factors, is expected. Further observations during pregnancy are required to clarify the age of onset of HFS.

Herein, we describe an ISH patient with a gross deletion in exons 7–17 and a missense mutation of the *ANTXR2* gene. We have thereby enriched the current understanding of the clinical features and genetic mutation spectrum of HFS. The prevalence of ISH is twice

that of JHF. Class I mutations are associated with joint symptoms and are systemically involved. Class III mutations may be associated with facial deformities and speech delays. Decreased foetal movement widens our knowledge of HFS.

#### AUTHOR CONTRIBUTIONS

YZ, XD, LS and DW collected the data. Yunqian Zhu drafted this manuscript. BW analysed the genetic data and confirmed phenotype genotype correlation. HW and BW reviewed the manuscript. All authors read and approved the final manuscript.

## ACKNOWLEDGEMENTS

The authors thank the patient and their families for their contribution to this study.

## CONFLICT OF INTERESTS

The authors have declared that no conflict of interest exists.

## ETHICAL COMPLIANCE

The study was in accordance with the Declaration of Helsinki and national guidelines. Informed consent was obtained from the parent of the patients.

## ORCID

Huijun Wang  <https://orcid.org/0000-0002-9992-6457>

Bingbing Wu  <https://orcid.org/0000-0001-9269-4414>

## REFERENCES

- Bell, S. E., Mavila, A., Salazar, R., Bayless, K. J., Kanagala, S., Maxwell, S. A., & Davis, G. E. (2001). Differential gene expression during capillary morphogenesis in 3D collagen matrices: Regulated expression of genes involved in basement membrane matrix assembly, cell cycle progression, cellular differentiation and G-protein signaling. *Journal of Cell Science*, *114*(Pt 15), 2755–2773.
- Çam, B., Kurkcu, M., Ozturan, S., Haytac, C., Uguz, A., & Ogden, G. (2015). Juvenile hyaline fibromatosis: A case report follow-up after 3 years and a review of the literature. *International Journal of Dermatology*, *54*(2), 217–221. <https://doi.org/10.1111/ijd.12033>
- Casas-Alba, D., Martínez-Monseny, A., Pino-Ramírez, R. M., Alsina, L., Castejón, E., Navarro-Vilarrubí, S., Pérez-Dueñas, B., Serrano, M., Palau, F., & García-Alix, A. (2018). Hyaline fibromatosis syndrome: Clinical update and phenotype-genotype correlations. *Human Mutation*, *39*(12), 1752–1763. <https://doi.org/10.1002/humu.23638>
- Chaudhry, C., Kaur, P., Srivastava, P., Panigrahi, I., & Kaur, A. (2021). Novel variation in ANTXR2 gene causing hyaline fibromatosis syndrome: A report from India. *Congenital Anomalies (Kyoto)*, *61*, 140–141. <https://doi.org/10.1111/cga.12414>
- Denadai, R., Raposo-Amaral, C. E., Bertola, D., Kim, C., Alonso, N., Hart, T., Han, S., Stelini, R. F., Buzzo, C. L., Raposo-Amaral, C. A., & Hart, P. S. (2012). Identification of 2 novel ANTXR2 mutations in patients with hyaline fibromatosis syndrome and proposal of a modified grading system. *American Journal of Medical Genetics. Part A*, *158a*(4), 732–742. <https://doi.org/10.1002/ajmg.a.35228>
- Deuquet, J., Lausch, E., Superti-Furga, A., & van der Goot, F. G. (2012). The dark sides of capillary morphogenesis gene 2. *The EMBO Journal*, *31*(1), 3–13. <https://doi.org/10.1038/emboj.2011.442>
- Dowling, O., Difeo, A., Ramirez, M. C., Tukel, T., Narla, G., Bonafe, L., Kayserili, H., Yuksel-Apak, M., Paller, A. S., Norton, K., Teebi, A. S., Grum-Tokars, V., Martin, G. S., Davis, G. E., Glucksman, M. J., & Martignetti, J. A. (2003). Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. *American Journal of Human Genetics*, *73*(4), 957–966. <https://doi.org/10.1086/378781>
- Hanks, S., Adams, S., Douglas, J., Arbour, L., Atherton, D. J., Balci, S., Bode, H., Campbell, M. E., Feingold, M., Keser, G., Kleijer, W., Mancini, G., McGrath, J., Muntoni, F., Nanda, A., Teare, M. D., Warman, M., Pope, F. M., Superti-Furga, A., ... Rahman, N. (2003). Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. *American Journal of Human Genetics*, *73*(4), 791–800. <https://doi.org/10.1086/378418>
- Koonuru, M. K., & Venugopal, S. P. (2015). Infantile systemic hyalinosis in identical twins. *Intractable & Rare Diseases Research*, *4*(4), 210–213. <https://doi.org/10.5582/irdr.2015.01027>
- Lu, J., Li, J., & Lin, F. Y. (2016). Infantile systemic hyalinosis: a case report and literature review. *Zhonghua Er Ke Za Zhi = Chinese Journal of Pediatrics*, *54*(12), 946–949. <https://doi.org/10.3760/cma.j.issn.0578-1310.2016.12.015>
- Murray, J. (1873). On three peculiar cases of Molluscum Fibrosum in Children in which one or more of the following conditions were observed: Hypertrophy of the gums, enlargement of the ends of the fingers and toes, numerous connective-tissue tumours on the scalp, &c. *Medico-Chirurgical Transactions*, *56*, 235–254.
- Qian, Q., Bo, L., Lin, Y., BingBing, W., Huijun, W., Xinran, D., Yulan, L. U., & Wenhao, Z. (2018). Application of copy number variation screening analysis process based on high-throughput sequencing technology. *Chinese Journal of Evidence-Based Pediatrics*, *13*(4), 275–279.
- Rahvar, M., Teng, J., & Kim, J. (2016). Systemic hyalinosis with heterozygous CMG2 mutations: A case report and review of literature. *The American Journal of Dermatopathology*, *38*(5), e60–e63. <https://doi.org/10.1097/dad.0000000000000467>
- Shieh, J. T., Swidler, P., Martignetti, J. A., Ramirez, M. C., Balboni, I., Kaplan, J., Kennedy, J., Abdul-Rahman, O., Enns, G. M., Sandborg, C., Slavotinek, A., & Hoyme, H. E. (2006). Systemic hyalinosis: A distinctive early childhood-onset disorder characterized by mutations in the anthrax toxin receptor 2 gene (ANTXR2). *Pediatrics*, *118*(5), e1485–e1492. <https://doi.org/10.1542/peds.2006-0824>
- Sun, J., & Collier, R. J. (2010). Disulfide bonds in the ectodomain of anthrax toxin receptor 2 are required for the receptor-bound protective-antigen pore to function. *PLoS One*, *5*(5), e10553. <https://doi.org/10.1371/journal.pone.0010553>
- Urbina, F., Sazunic, I., & Murray, G. (2004). Infantile systemic hyalinosis or juvenile hyaline fibromatosis? *Pediatric Dermatology*, *21*(2), 154–159. <https://doi.org/10.1111/j.0736-8046.2004.21214.x>
- Vahidnezhad, H., Ziaee, V., Youssefian, L., Li, Q., Sotoudeh, S., & Uitto, J. (2015). Infantile systemic hyalinosis in an Iranian family with a mutation in the CMG2/ANTXR2 gene. *Clinical and Experimental Dermatology*, *40*(6), 636–639. <https://doi.org/10.1111/ced.12616>
- Yang, J., Shang, X., Liu, F., Wang, Q., Liu, C., Sun, Y., & Li, G. (2021). Analysis of pathogenic variants in a Chinese pedigree affected with hyaline fibromatosis syndrome. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, *38*(3), 232–237. <https://doi.org/10.3760/cma.j.cn511374-20200625-00472>
- Yang, L., Kong, Y., Dong, X., Hu, L., Lin, Y., Chen, X., Ni, Q., Lu, Y., Wu, B., Wang, H., Lu, Q. R., & Zhou, W. (2019). Clinical and genetic spectrum of a large cohort of children with epilepsy in China. *Genetics in Medicine*, *21*(3), 564–571. <https://doi.org/10.1038/s41436-018-0091-8>

Youssefian, L., Vahidnezhad, H., Aghighi, Y., Ziaee, V., Zeinali, S., Abiri, M., & Uitto, J. (2017). Hyaline fibromatosis syndrome: A novel mutation and recurrent founder mutation in the CMG2/ANTXR2 gene. *Acta Dermato-Venereologica*, 97(1), 108–109. <https://doi.org/10.2340/00015555-2459>

### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Zhu, Y., Du, X., Sun, L., Wang, H., Wang, D., & Wu, B. (2022). Hyaline fibromatosis syndrome with a novel 4.41-kb deletion in ANTXR2 gene: A case report and literature review. *Molecular Genetics & Genomic Medicine*, 10, e1993. <https://doi.org/10.1002/mgg3.1993>