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Review

Molecular–Clinical Spectrum of the MRXHF1 Syndrome

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ABSTRACT

Intellectual disability-hypotonic facies syndrome X-linked, 1 (MRXHF1; OMIM #309580) is an X-linked recessive genetic disease caused by mutations in the ATRX gene, involving multiple organ and system abnormalities. The main manifestations include characteristic face, developmental and intellectual disability. In addition, it is also manifested as hypotonia, skeletal abnormalities, cardiac defects, abnormal vision, urogenital system disorders and gut dysmotility. Up to now, a clear diagnosis criterion for MRXHF1 is lacked, which is mainly based on the comprehensive analysis of clinical and genetic results. The main treatment of MRXHF1 is symptomatic and individualized treatment, while early intervention is helpful to improve the prognosis and the quality of life. This study aims to introduce the disease comprehensively, thus enhancing the recognition in MRXHF1.

Keywords: Intellectual disability-hypotonic facies syndrome X-linked; MRXHF1 syndrome; Intellectual disability; Characteristic face

INTRODUCTION

Wilkie et al [1] described for the first time that the significantly consistent clinical phenotype of children with developmental delay in 1990 who exhibited symptoms of severe intellectual disability, α-thalassemia and craniofacial deformity (ocular hypertelorism, epicanthus, low nasal bridge, short nose, carp-shaped mouth, midface hypoplasia, etc). This syndrome was designated as Alpha thalassemia-X-linked intellectual disability syndrome (ATR-X; OMIM#301040), a rare form of X-Linked Dominant inheritance (XLD). ATR-X is characterized by skeletal abnormalities, hypotonia, short stature, cardiac defects, renal/urinary abnormalities, genital abnormalities, in addition to the aforementioned symptoms [1]. Cloned a gene, called X-linked helicase-2(XH2/ATRX), and located on chromosome Xq13 in 1994 [2]. Identified ATRX gene mutationin in 13 patients diagnosed with ATR-X syndrome in 1995. Subsequent studies have found that some reported syndromes with similar clinical manifestations without α-thalassemia carying ATRX mutation, such as Smith-Fineman-Myers syndrome, Juberg-Marsidi syndrome, Chudley-Lowry syndrome, Holmes-Gang syndrome and Carpat-Waziri syndrome [3] with the development of Next G eneration Sequencing (NGS), ATRX-related diseases are divided into three categories according to the genetic patterns and the severity of α-thalassemia, XLD: ATR-X syndrome and Alpha-Thalassemia associated with Myelo Dysplastic Syndromes (ATMDS; OMIM#300448). X-Linked Recessive inheritance (XLR): MRXHF1 syndrome. Over the past year, studies have focused on ATR-X syndrome, MRXHF1 syndrome was very rare with a few cases reported in the literature [4] at present, there is no accurate statistics on the incidence and epidemiology of the disease, which is mainly identified by phenotype and further diagnosed by genetic testing.

LITERATURE REVIEW

Clinical description

Facial anomalies: Distinctive facial traits are to identify an important clinical manifestation of MRXHF1 syndrome, such as bushy eyebrows, epicanthic folds, depressed nasal bridge, flat nasal bridge, small triangular nose, anteverted nares, midface hypoplasia, triangular mouth, open mouths, widely spaced teeth,

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prominent lower lips, and there is prodigious dribbling. Evidence suggests that facial abnormalities do not become apparent in most patients until they are 4 years old [5,6].

Central nervous system and brain MRI: Patients usually have marked hypotonia in childhood. With age, some of them often develop a tendency toward hypertonia. However, some exceptions have also been reported in MRXHF1 phenotype, such as dystonia and spastic paraplegia.

Affected individuals usually have marked developmental milestones delay and an intelligence level lower than that of boys of a similar age. More severely patients do not walk until later in childhood and some never ambulate. Most have dysphasia and no speech. Generally, central nervous system involvement is non-progressive and most children go on to acquire new skills [7].

Seizures occur in 20% and slightly lower than ATR-X syndrome (30%). Most frequently are generalized tonic-clonic or myoclonic in nature and responds well to conventional antiepileptic drugs.

The brain CT scans/MRI of MRXHF1 syndrome showed some abnormal findings, such as white matter abnormalities, delayed myelination and nonspecific brain atrophy. The white matter abnormalities especially around the trigones, furthermore, widespread and scattered white matter abnormalities were seen in few patients.

Meanwhile, ATRX were categorized as syndromic Autism Spectrum Disorders (ASD) gene in AutismKB databases, suggesting that variants in ATRX could plausibly confer risk for ASD.

Skeletal abnormalities: Skeletal abnormalities are observed in 84% of these children and scoliosis is most common. Other abnormalities include fingers fixed flexion deformities, clinodactyly of the fifth fingers, foot deformity, pes equinovarus, pes-equinovalgus, high arch, kyphoscoliosis, spina bifida, abnormal vertebra.

Alpha-thalassemia: Hematological studies have shown that Hbh inclusion have been detected in about 32% of cases. An individual with alpha-thalassemia, which is usually mild, does not require any treatment.

Renal/urinary and genital abnormalities: Urinary system involvement was rare, with only 2 cases suffering from hypospadias. Most cases (70%) will have a genital abnormality, which may be very mild, ranging from cryptorchidism and micropenis to ambiguous female external genitalia.

Miscellaneous abnormalities: A minority of patients has abnormal vision, optic atrophy; optic hypoplasia, ocular albinism and strabismus are commonly noted.

NGS has been used in many studies to confirm ATRX genes were associated with neoplastic diseases. A recently published research reported on three patients with MRXHF1 syndrome were subsequently shown to diagnose with osteosarcoma. It is worth noting that all patients were diagnosed with osteosarcoma at a later age, and their symptoms and signs were not exactly the same.

Cardiac defects were seen in 7 cases and include aortic regurgitation, tetralogy of fallot, pulmonary stenosis, atrial septal defect, ventricular septal defect.

Recurrent vomiting or regurgitation, sometimes treated by fundoplication, is a common finding difficulty and seems likely to be a manifestation of a more generalised dysmotility of the gut.

Dysphagia, aspiration, or even the inability to swallow, is one of the phenotypic of dys-coordinated swallowing. Constipation is a very common presentation and may be a major nursing problem for children.

Absence of the spleen have been reported in two cases whose clinical presentation has involved recurrent pneumococcal infections. Prophylactic ampicillin and covered with pneumococcal and quadrivalent meningococcal vaccination can effectively treat and prevent invasive pneumococcal disease.

Table 1: Compared with the Frequency of Pathological Traits in MRXHF1 and Classic ATR-X Syndrome.

Clinical finding	Totala	Frequency of trait in MRXHF1 (%)	Frequency of b Trait in ATR-X (%)
Profound mental retardation	37/37	100	95
Characteristic face	35/36	97	94
Skeletal abnormalities	16/19	84	91
HbH inclusions	9/28	32	87
Neonatal hypotonia	5/13	38	85
Genital abnormalities	19/27	70	80
Microcephaly	20/28	71	76

Gut dysmotility	2/12	17	75
Short stature	13/18	72	66
Seizures	3/15	20	35
Cardiac defects	7/9	78	18
Renal/urinary abnormalities	3/13	23	14

A Total represents the number of patients on whom appropriate information is available and includes patients who do not have a thalassemia but in whom ATRX mutations have been identified.

B Data were obtained from references (4).

AETIOLOGY

Characterisation of the ATRX gene and protein product

The human ATRX gene is located on chromosome Xq13.1-q21.1, consists of 35 exons and the full-length cDNA contained a 11167 bp open reading frame that could be translated to a 2,492 amino acid polypeptide that is strongly expressed in brain, white blood cells and skeletal muscle. The gene encodes for transcriptional regulator ATRX protein, a chromatin-remodeler protein that is a member of the SNF2 family of chromatin remodeling factors. The N-terminus of the protein begins with the ATRX-dnmt3-dnmt3l (ADD) domain, which is encoded by exons 8-10 and predicted to promote interactions with H3K9me3/H3K4me0, consists of a GATA-like zinc finger (GATA), a plant homeodomain finger (PHD) and a long C-terminal α-helix.This combination of fused GATA-like and PHD fingers within a single domain is thus far unique5. The helicase/adenosine triphosphatase (ATPase) domain is located at the C-terminus, encoded by exon 17-31, containing seven highly conserved colinear helicase motifs, which are present in DNA-activated ATPase and DNA helicases that belongs to a group of the SNF2/SWI2 protein family.

Analysis of mutation characteristics of ATRX gene

Analysis of this larger comprehensive report found that compared with helicase region, mutations in the ADD domain produced more severe and permanent psychomotor impairment, usually preventing patients from walking and language acquisition, as well as, while C-terminal may play a special role in the genitourinary system.The N- and C-terminus mutations of ATRX proteins may cause a milder phenotype of alpha thalassemia. Recent studies reported that a large majority of mutations are concentrated in the ADD (50%) and helicase motifs (30%).

To date, the Human Gene Mutation Database (HGMD) counted only 23 ATRX gene variants associated with MRXHF1 syndrome (Figure 1), among them, missense mutation is more common than other types of mutations. In general, the protein encoded by the ATRX gene tend to cluster telomere, subtelomere and centromeric tandem repeatsand and is involved in chromatin remodeling epigenetic and epigenetic regulation of gene transcription7. Disruption of these activities may lead to developmental abnormalities associated with the disease.

The pathogenicity variation of ATRX gene has not been reported in normal males in the past, so the penetrance is assumed to be 100%. Female carriers showed no distinctive abnormalities in appearance or intelligence, because they show preferential inactivation of the mutated X-chromosome.

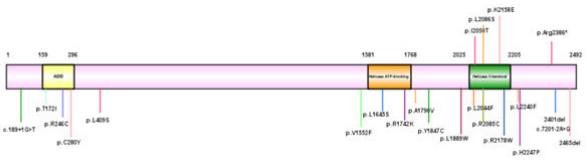

Figure 1: 2401del for c.7201-1_7203del; 2465 Del for c.7394 delG.

Diagnosis, clinical management and treatment

Diagnosis: Clinical phenotype that need to be considered are as follows: a) Delayed growth and development indicators, hypotonia, associated feeding difficulties, microcephaly and short statureand in infants and early childhood, furthermore, severe affected individuals presented with a cognitive deficit and absent speech. b) With aging, the face becomes rough and abnormal deformity gradually apparent. c) HbH inclusion is positive, although in most cases of MRXHF1 syndrome, HbH levels are too low to be detected by electrophoresis. d) Genital abnormalities, such as hypospadias, cryptorchidism, genital ambiguity.

Clinical management and treatment: Caregivers of patients with MRXHF1 syndrome often encounter behavioral, feeding, gastrointestinal, and salivation problems during parenting. Antipsychotic medications such as prochlorazine may be effective in children with severe behavioral problems. Recurrent vomiting, regurgitation reflux, or gastroesophageal reflux were probably secondary to pseudotorsion of the stomach, requiring surgical correction. Anticholinergic drugs can reduce saliva production, but these drugs can cause decreased gastrointestinal motion, causing constipation or intestinal obstruction. Other methods include Botulinum toxin TYPE A (Botox), salivary

gland injection, submandibular gland excision, and gland resection.

Alpha-thalassemia occurs in about 90% of cases and anemia is mild and does not require treatment. Skeletal deformity is common in patients and is generally secondary to hypotonia and movement disorder that should be closely monitored for changing in foot deformity, kyphosis and scoliosis. In addition, attention should be paid to the occurrence of tumors, epilepsy, spasticity and ASD. After diagnosis, sensorineural hearing loss, refractive error and genitourinary system screening should be carried out in time. Most of the children have poor prognosis and quality of life. Mortality was highest in children under 5 years of age, associated with gastroesophageal reflux and vomiting in infancy, followed by renal failure.

Differential diagnosis: At present, there is no consensus or guideline to systematically define the diagnostic criteria for MRXHF1, and the clinical manifestations are broad spectrum and non-specific, requiring differential diagnosis from other diseases (Table 2).

Table 2: The differentiated between MRXHF1 syndrome with other diseases.

No.	Diseases	Pathogenic genes	Genetic pattern	Clinical finding	
				The same	The different
1	Coffin-Lowry syndrome (OMIM#303600)	RPS6KA3	XLD	Intellectual disability; Developmental delay; Language defects or barriers; Sensorineural deafness ;Skeletal abnormalities(scoliosis /kyphosis, hypotonia)	Facial deformity (down-slanting palpebral fissures, broad nose, pudgy tapering digits, absence of genital abnormalities
2	Angelman syndrome (OMIM#105830)	UBE3A	AD	Intellectual disability; Developmental delay; Language barrier; Abnormal behavior; Microcephaly;epilepsyFeeding difficulty; hypotonia	Lack of facial deformities typical of MRXHF1 syndrome; Manifested by happy behavior, frequent loud laughter/smile; easy to get excited accompanied by clapping and hyperactivity; Abnormal EEG (high amplitude, slow spine wave)
3	Smith-Lemli-Opitz syndrome (OMIM#270400)	DHCR7	AR	Intellectual disability; Microcephaly; hypotonia;Abnormal facial features (drooping eyelids, varus nostril, short nose, micrognathus, low ear position); Polydactyly; Syndactyl;Genitourinary abnormalities (hypospadias, male genital dysplasia)	Syndactyl is more common in the second and third digits; Fat soluble vitamin deficiency and skin symptoms, allergy to sunlight, etc.; Biochemical tests showed that serum cholesterol decreased and its precursor 7-DHC increased
4	ATR-X syndrome (OMIM#301040)	ATRX	XLR	Intellectual disability;Facial abnormalities; Skeletal abnormalities;hypotoni	HbH inclusion positive (87%) was significantly higher

		a; Urogenital system abnormalities; Microcephaly; Gastrointestinal problems;Cardiac defects	than MRXHF1 syndrome (32%).

Note: AD:Autosoma Dominant; XLD: X-Linked Dominant; AR: Autosoma Recessive; XLR: X-Linked Recessive

CONCLUSION

MRXHF1 is a rare genetic disease with a large clinical phenotypic spectrum. Intellectual disability, facial anomalies and hypotonia are common in the disease and difficult to be distinguished at an early stage. As a result, a specific etiology cannot be determined, and many families have experienced a "long diagnostic process". The wide application of NGS will allow for us to make early diagnosis and precise treatment.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. Gecz J, Pollard H, Consalez G. Cloning and expression of the murine homologue of a putative human X-linked nuclear protein gene closely linked to PGK1 in Xq13.3. Hum Mol Genet. 1994;3:39-44.
2. Gibbons RJ, Picketts DJ, Villard L. Mutations in a putative global transcriptional regulator cause X-linked mental retardation with alpha-thalassemia (ATR-X syndrome). Cell. 1995;80:837-845.
3. Wilkie AO, Pembrey ME, Gibbons RJ. The non-deletion type of alpha thalassaemia/mental retardation: a recognisable dysmorphic syndrome with X linked inheritance. J Med Genet. 1991;28:724.
4. Gibbons RJ, Higgs DR. Molecular-clinical spectrum of the ATR-X syndrome. Am J Med Genet. 2000;97:204-212.
5. Argentaro A, Yang JC, Chapman L, Kowalczyk MS, Gibbons RJ, Higgs DR, et al. Structural consequences of disease-causing mutations in the ATRX-DNMT3-DNMT3L (ADD) domain of the chromatin-associated protein ATRX. Proc Natl Acad Sci USA. 2007;104:11939-11944.
6. Gibbons RJ, Wada T, Fisher CA, et al. Mutations in the chromatin-associated protein ATRX. Hum Mutat. 2008;29:796-802.
7. Law MJ, Lower KM, Voon HP, Hughes JR, Garrick D, Viprakasit V, et al. ATR-X syndrome protein targets tandem repeats and influences allele-specific expression in a size-dependent manner. Cell. 2010;143:367-378.