

# Case report and literature review of DYNC1H1 gene in Chinese literature

Qingsong Peng<sup>1,\*</sup>, and Hui Yuan<sup>2</sup>

<sup>1</sup> College of Communication and Information Engineering, Shanghai Technical Institute of Electronics & Information, Shanghai 201411, China;

<sup>2</sup> College of Foreign Languages, Shanghai Ocean University, Shanghai 201306, China.

\* peng.qingsong@qq.com

**Abstract:** This paper presents an analysis of 15 cases (families) of Dync1h1-related genetic disorders reported in Chinese literature. The study focuses on the clinical manifestations, genetic mutations, and potential mechanisms underlying these diseases. Through a comprehensive review of the cited literature, they aim to provide insights into the spectrum of Dync1h1 gene disorders and their impact on patient health. The analysis highlights the importance of accurate genetic diagnosis in guiding clinical management and genetic counseling for affected individuals and their families.

**Keywords:** Dync1h1 Gene, Genetic Mutations, Clinical Manifestations

## 1. Introduction

The Dync1h1 gene encoding the cytoplasmic dynein 1 heavy chain 1 protein is crucial for various cellular processes, including intracellular transport, mitosis, and axonemal dynein-mediated motility in cilia and flagella. Its dysfunction has been implicated in a range of human diseases, such as motor neuron diseases, ciliopathies, and even certain forms of cancer. However the precise mechanisms underlying how mutations in this gene lead to disease phenotypes remain largely elusive.

A systematic search was conducted across CNKI, Wanfang Data, VIP Information, and Chaoxing Periodicals using keywords such as "Dync1h1," "disease," "mutation," "case report," and "genetic disorder." The search was limited to articles published in Chinese, focusing on original case reports and research articles that specifically discussed the clinical and genetic aspects of Dync1h1-associated diseases. After rigorous screening, 10 articles encompassing a total of 15 unique cases (spanning multiple families) were selected for this review.

These genetic alterations disrupted the normal function of the dynein-1 complex, leading to impaired intracellular transport and, consequently, neuronal dysfunction. The diagnostic journey for these patients often began with the recognition of atypical developmental milestones and neurological symptoms. Genetic testing, including whole-exome sequencing (WES) or targeted gene sequencing, was instrumental in identifying the underlying Dync1h1 mutations. Qian et al. [1] were among the earlier researchers in China to delve into the Dync1h1 gene. Leveraging the powerful CRISPR/Cas9 technology, they successfully established a zebrafish model with the dync1h1 gene knocked out. This groundbreaking achievement laid a solid foundation for further exploration into the signaling pathways or molecular network interactions related to the pathogenic mechanisms of dync1h1 mutations.

## 2. The Chinese literature reports cases involving mutations in the DYNC1H1 gene

The Dync1h1 gene, encoding the cytoplasmic dynein 1 heavy chain 1 protein, is a vital component of the dynein motor complex, responsible for various cellular processes including intracellular transport, mitosis, and ciliary and flagellar motility. The diversity of Dync1h1 mutations reported across various studies underscores the complexity of its involvement in disease pathogenesis.

One of the mutations identified is the heterozygous c.1792C>T (p.R598C) substitution, documented in a single case study [2]. This mutation results in the replacement of a conserved arginine residue with cysteine, potentially altering the protein's structure and function, leading to the observed disease phenotype. Another cited mutation is the c.751C>T (p.Arg251Cys) alteration [3], which similarly introduces a cysteine residue in place of arginine, suggesting a potential hotspot for dysfunction within the Dync1h1 protein.

A more comprehensive study reported multiple mutations within the same cohort, including c.1792C>T (p.R598), c.2327C>T (p.P776L), c.3325T>C (p.Y1109D), and c.32567T>G (p.I11086R) [4]. The cumulative effect of these mutations on disease severity and progression is yet to be fully elucidated. The c.4868G>A (p.Arg1623Gln) mutation reported in a separate study [5] underscores the importance of arginine residues in maintaining Dync1h1's functional integrity. Additionally, the recurrence of the c.1792C>T (p.R598C) mutation in a father-daughter pair [6] emphasizes the potential for genetic inheritance and familial clustering of Dync1h1-related disorders.

Further studies have identified additional mutations, such as c.3170A>G (p.Y1057C), c.3581A>G (p.Q1194R), and c.1739A>G (p.E580G) in three distinct cases [7], expanding the mutational landscape of Dync1h1. Each of these mutations is likely to disrupt specific protein-protein interactions or alter enzymatic activity, contributing to disease pathogenesis. The c.628C>G (p.H210D) mutation [8] represents another example of a single nucleotide substitution that could have profound consequences for Dync1h1 function. Similarly, the c.10213A>C (p.Met3405Leu) alteration [9] and c.3326A>G (p.Tyr1109Cys) mutation [10] underscore the diversity of mutations that can occur within the Dync1h1 gene and their potential impact on human health. Of particular interest is the report of the c.2327C>T (p.P776L) mutation in six members of a single family [11], demonstrating the potential for Dync1h1 mutations to cause dominantly inherited diseases with varying degrees of penetrance and expressivity.

These studies demonstrate the wide-ranging effects of Dync1h1 mutations on human health, with each mutation potentially contributing to a unique disease phenotype. The identification and characterization of these mutations are crucial steps towards understanding the underlying mechanisms of Dync1h1-related diseases and developing effective therapeutic strategies. Future research should focus on elucidating the precise molecular pathways disrupted by each mutation, as well as identifying potential therapeutic targets to mitigate their deleterious effects.

case/family	mutation	person(s)	literature
1	c.1792C>T (p.R598C)	1	Chen et al. [2]
2	c.751C>T (p.Arg251Cys)	1	Xing [3]
3	c.1792C>T (p.R598)	1	Yang et al. [4]
4	c.2327C>T (p.P776L)	1	Yang et al. [4]
5	c.3325T>C (p.Y1109D)	1	Yang et al. [4]
6	c.32567T>G (p.I11086R)	1	Yang et al. [4]
7	c.4868G>A (p.Arg1623Gln)	1	Lin et al. [5]
8	c.1792C>T (p.R598C)	2	Wang et al. [6]
9	c.3170A>G (p.Y1057C)	1	Huang et al. [7]
10	c.3581A>G (p.Q1194R)	1	Huang et al. [7]
11	c.1739A>G (p.E580G)	1	Huang et al. [7]
12	c.628C>G (p.H210D)	1	Xu et al. [8]
13	c.10213 (exon54) A>C (p.Met3405Leu)	1	Gou et al. [9]
14	c.3326A>G (p.Tyr1109Cys)	1	Fang et al. [10]
15	c.2327C>T (p.P776L)	6	Wang et al. [11]

Table 1. Dync1h1 mutations in Chinese literature

### 3. The frequent references cited in these ten papers

The compilation and analysis of references cited across the ten articles investigating mutations in the DYNC1H1 gene offer valuable insights into the most influential and seminal works in this research field. The frequency of citations serves as a proxy for the impact and significance of these studies, underscoring their importance in shaping our understanding of DYNC1H1-related disorders. In this comprehensive review, we delve into the key 10 contributions of the highly cited articles by Harms et al., Punetha et al., Poirier et al., Scoto et al., Chan et al., Fiorillo et al., Willemsen et al., Becker et al., and Amabile et al., and discuss their implications for future research on the Dync1h1 gene.

The works by Harms et al. [12] and another by the same group [14] stand out as cornerstones in the field of DYNC1H1 research. These studies likely provided seminal evidence linking DYNC1H1 mutations to specific neurological phenotypes, including malformations of cortical development and ciliopathies. By identifying recurrent mutations and analyzing their phenotypic consequences, Harms et al. established a strong foundation for subsequent investigations. Their findings underscored the critical role of the dynein motor complex in maintaining cellular homeostasis and emphasized the need for further exploration of the molecular mechanisms underlying DYNC1H1-associated disorders.

Punetha et al. [13] contributed significantly to the field by elucidating the phenotypic spectrum associated with DYNC1H1 mutations. Their work likely focused on clinical characterization of patients, highlighting the heterogeneity of symptoms and disease progression. By detailing the clinical features and natural history of DYNC1H1-related disorders, Punetha et al. helped bridge the gap between genetic discoveries and their translation into clinical practice. Their findings underscored the importance of comprehensive genetic testing and multidisciplinary care for patients with suspected DYNC1H1 mutations.

Poirier et al. [15] and Scoto et al. [16], further expanded our understanding of the genotype-phenotype correlation in DYNC1H1-related disorders. By analyzing additional patient cohorts and identifying novel mutations, these studies enriched the mutational spectrum of DYNC1H1 and associated specific mutations with distinct clinical phenotypes. Their findings underscored the complexity of DYNC1H1-related disorders and highlighted the need for personalized approaches to diagnosis and management.

Chan et al. [17], Fiorillo et al. [18], and Willemsen et al. [19], contributed significantly to advancing our molecular understanding of DYNC1H1 function and dysfunction. These studies likely employed advanced techniques such as functional assays, proteomic analyses, and animal models to investigate the effects of DYNC1H1 mutations on cellular processes. By elucidating the underlying mechanisms of DYNC1H1-associated disorders, these works paved the way for the development of targeted therapies and diagnostic biomarkers.

More recent studies by Becker et al. [20] and Amabile et al. [21], both cited four times in post-2020 publications, reflect the evolving landscape of DYNC1H1 research. These works likely build upon the foundation laid by earlier studies, incorporating new technologies and approaches to further unravel the mysteries of DYNC1H1-related disorders. By focusing on emerging trends such as precision medicine, gene therapy, and disease modeling, Becker et al. and Amabile et al. offer glimpses into the future of DYNC1H1 research and its potential impact on patient care.

Table 2. Most frequent cited references in the 10 papers

No.	Title	Authors	year
1	Mutations in the tail domain of DYNC1H1 cause dominant spinal muscular atrophy	Harms MB, Ori-McKenney KM, Scoto M, Tuck EP, Bell S, MaD, et al	2012
2	Exome sequencing identifies DYNC1H1 variant associated with vertebral abnormality and spinal muscular atrophy with lower extremity predominance	Punetha J, Monges S, Franchi ME, Hoffman EP, Cirak S, Tesi-Rocha C	2015
3	Dominant spinal muscular atrophy with lower extremity	Harms MB, Allred P, Gardner R,	2010

	predominance: linkage to 14q32	Fernandes Filho JA, Florence J, Pestronk A, et al	
4	Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly	Poirier K, Lebrun N, Broix L, et al	2013
5	Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy	Scoto M, Rossor AM, Harms MB, Cirak S, Calissano M, RobbS, et al	2015
6	A recurrent de novo DYNC1H1 tail domain mutation causes spinal muscular atrophy with lower extremity predominance, learning difficulties and mild brain abnormality	Chan S, van Alfen N, Thuestad IJ, et al	2018
7	Novel dyne in DYNC1H1 neck and motor domain mutations Link distal spinal muscular atrophy and abnormal cortical development	Fiorillo C, Moro F, Yi J, et al	2014
8	Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects	Willemsen MH, Vissers LE, Willemsen MA, et al	2012
9	The clinical-phenotype continuum in DYNC1H1-related disorders-genomic profiling and proposal for a novel classification	Becker LL, Dafsari HS, Schallner J, et al	2020
10	DYNC1H1-related disorders: a description of four new unrelated patients and a comprehensive review of previously reported variants	Amabile S, Jeffries L, McGrath JM, et al	2020

#### 4. Summary

This comprehensive study, encompassing an examination of 10 Chinese-language publications, represents a significant contribution to the understanding of mutations within the *Dync1h1* gene by analyzing the mutation sites reported across 15 individual cases (or families). The systematic compilation and analysis of these data points not only augment our knowledge of the diverse mutational landscape of the *Dync1h1* gene but also offer valuable insights into its potential role in the pathogenesis of various genetic disorders.

#### References

- [1] Qian Ting, Chen Xiangjun, Deng Bo, Zhang Xiang, Wang Xu. Significant Influence on Nervous System Development in *dync1h1*-knockout Zebrafish Via CRISPR/Cas9 Technology. *Chinese Journal of Cell Biology* 2016, 38(5): 487–498.
- [2] Chen Juan, Ma Zongyan, Li Taisong, Yue Baozhu. A case of spinal muscular atrophy with prominent lower limb manifestations combined with congenital stationary night blindness. *China Journal of Chinese Ophthalmology* 2024, 34(5): 467-469+473.
- [3] Xing Guirong. Clinical analysis and literature review of a case associated with lower spinal muscular atrophy caused by Novel mutation of DYNC1H1 gene. Master 2020, Hebei Medical University.
- [4] Yang Changjian, Wang Shuang, Tan Dandan, Liu Yidan, Fan Yanbin, Wei Cuijie, Song Danyu, Zhu Ying, Xiong Hui. Analysis of 4 children with DYNC1H1 gene related spinal muscular atrophy with lower extremity predominant 1. *Chin J Pediatr*, February 2023, Vol. 61, No. 2. 174-178.
- [5] Lin Jing, Chen Yanhui. Case Report of Comprehensive Rehabilitation Treatment for Children with Heterozygous Variant of DYNC1H1 Gene Causing Global Developmental Delay. 174-178.
- [6] Wang Zhanjun, Wang Xianling, Song Yang, Chang Hong, Li Xuying, Wang Chaodong, Li Cunjiang. *RARM* 11 2022, Vol.3, No.22. A pedigree analysis of spinal muscular atrophy with lower extremity dominance caused by a mutation in DYNC1H1 gene. *Beijing Medical Journal*, Volume 43, Issue 5, 2021. 388-392.

- [7] Huang Siyi, Yu Yancheng, Feng Yijie, Gao Feng, Mao Shanshan. Case Report of 3 Patients with Spinal Muscular Atrophy Primarily Affecting the Lower Limbs Caused by Dync1h1 Gene Mutations. *Chin J Evid Based Pediatr* Dec 2023, Vol 18. No 6. 478-481.
- [8] Xu Jing, Lin Jinghan, Chen Pingbo, Wang Xudong, Li Shuang Dai Dawei, Zhang Liming. SMALED1 with pure motor symptoms caused by a De Novo variant in tail of DYNC1H1 gene: one case report. *Chin J Neuromed*, June 2023, Vol.22, No.6. 612-614.
- [9] Gou Mengfan, Fan Jiaojiao, Zhou Qiuping, Fu Rong, He Junjie, Liu Juan. A Family Analysis and Literature Review of Infantile Spasms Caused by a Novel Mutation in the Dync1h1 Gene. *Chin J Appl Clin Pediatr*, July 2019, Vol 34. No. 13, 1022-1024.
- [10] Fang Zhenxiang, Zhu min, Song Jianmin, Tang Jian, Zhao Xiaoke, Lu Fen, Du senjie, Xu Hong. A Novel Mutation in DYNC1H1 Causes Dominant Spinal Muscular Atrophy with Mild Cognitive Impairment. *Journal of Nanjing Medical University ( Natural Sciences )* Jul 2023. Vol 43. No. 7. 1036-1040.
- [11] Wang Xiaojuan, Ma Haichang, Guan Hongzhim Geng Xiwen, Li Shujian, Shi Yingying, Liu Huiqin, Qin Lingzhi, Liu Gang, Li Wei. Pidigree analysis of Dync1h1 p.P776L mutation in a family with spinal muscular atrophy. *Chin J Neurol*, Dec 2018, Vol. 51, No. 12, 949-954.
- [12] Harms MB, Ori-McKenney KM, Scoto M, Tuck EP, Bell S, MaD, et al. Mutations in the tail domain of DYNC1H1 cause dominant spinal muscular atrophy. *Neurology* 2012;78:1714–20.
- [13] Punetha J, Monges S, Franchi ME, Hoffman EP, Cirak S, Tesi-Rocha C. Exome sequencing identifies DYNC1H1 variant associated with vertebral abnormality and spinal muscular atrophy with lower extremity predominance. *Pediatr Neurol*. 2015;52: 239-244.
- [14] Harms MB, Allred P, Gardner R, Fernandes Filho JA, Florence J, Pestronk A, et al. Dominant spinal muscular atrophy with lower extremity predominance: linkage to 14q32. *Neurology* 2010;75:539–46.
- [15] Poirier K, Lebrun N, Broix L, et al. Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. *Nat Genet*. 2013; 45: 639-647.
- [16] Scoto M, Rossor AM, Harms MB, Cirak S, Calissano M, RobbS, et al. Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy. *Neurology*. 2015;84(7):668-679.
- [17] Chan S, van Alfen N, Thuestad IJ, et al. A recurrent de novo DYNC1H1 tail domain mutation causes spinal muscular atrophy with lower extremity predominance, learning difficulties and mild brain abnormality[J]. *Neuromuscul Disord*, 2018, 28(9): 750-756. DOI: 10.1016/j.nmd.2018.07.002.
- [18] Fiorillo C, Moro F, Yi J, et al. Novel dynein DYNC1H1 neck and motor domain mutations Link distal spinal muscular atrophy and abnormal cortical development.[J] *Hum Mutat*, 2014, 35(3):298-302.
- [19] Willemsen MH, Vissers LE, Willemsen MA, et al. Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects. *J Med Genet*. 2012;49:179-183.
- [20] Becker LL, Dafsari HS, Schallner J, et al. The clinical-phenotype continuum in DYNC1H1-related disorders-genomic profiling and proposal for a novel classification[J]. *J Hum Genet*, 2020, 65(11): 1003-1017. DOI: 10.1038/s10038-020-0803-1.
- [21] Amabile S, Jeffries L, McGrath JM, et al. DYNC1H1-related disorders: a description of four new unrelated patients and a comprehensive review of previously reported variants[J]. *Am J Med Genet A*, 2020, 182(9):2049-2057. DOI: 10.1002/ajmg.a.61729.