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Intellectual developmental disorder with hypertelorism and distinctive facies (IDDHDF) A case study with literature review

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Abstract

The research aims to investigate the clinical manifestations of neurodevelopmental problems in children with different facies and CCNK gene mutant characteristics. A literature study was carried out to identify the role of CCNK mutations in IDDHDF. Chinese and international search engines like PubMed, MEDLINE, Wanfang Data Knowledge, and Google Scholar were used to search. The search phrases "CCNK", "intellectual developmental disorder", "hypertelorism", and "distinctive facies" were used. A total of 5 studies were found, 11 cases were presented, 3 were thoroughly discussed, and 1 case was presented in this study. The clinical signs and genetic characteristics of children with intellectual developmental disorders with hypertelorism and unique facies were summarized. A male child was 1 year 4 months old. Last 1 year, he appeared of motor and cognitive lag, unable to crawl or stand. He had a large forehead head, wide eye spacing, and cognitive deficiencies, and he was clinically diagnosed with global developmental delay. C.437(exon5) T>C was not found in any of the child's parents and represents a de novo mutation. The main clinical signs were impairments in intellectual development, wide eye spacing, and facial feature features. The findings of the studies discussed here imply that mutations in the CCNK gene may cause IDDHDF. This is a very new kind of study in China to uncover the clinical aspects of a case of Intellectual developmental disorder with hypertelorism and distinctive facies (IDDF). It's discovered that wild-type mRNA coding CCNK partially repaired early defects but not the mRNA with the identified likely pathogenic variation c.331A>G. This shows that CCNK variations are involved in IDDF. The researchers also discovered that the likely pathogenic mutation c.331A>G may induce IDDF via a haploinsufficiency mechanism.

Keywords: Neurodevelopment deviations, Distinctive facial feature, CCNK gene mutation

Introduction

Neurodevelopment (Ruiz-Reig et al., 2024) is a complicated and detailed process involving the precise interaction of gene expression and coordinated cellular activity, from neurogenesis (Yu et al., 2024) to the construction of functional brain networks. Any disturbance in this delicate balance can result in neurodevelopmental disorders affecting about 1% of the world's population (Zamora‐moratalla et al., 2021). Genetic variables have been found in up to 42% of people with neurodevelopmental disorders, highlighting the importance of genetics in these problems. Neurodevelopmental disorders are problems marked by cognitive, motor, behavioral, or social functioning deficiencies. They are caused by abnormalities in neurodevelopment, which can happen at any stage of development, from infancy to adulthood (Sabariego-Navarro et al., 2022).

Cyclin-dependent kinases (CDKs) (Elmasry, 2023) and cyclins are essential proteins that regulate the cell cycle and transcription. Cyclin K (CCNK) is a cyclin protein containing 580 amino acids. CCNK (Dai et al., 2023), unlike certain other cyclins, does not oscillate with the cell cycle; instead, it largely controls transcription.CCNK regulates RNA polymerase II-mediated transcription in collaboration with its binding partners, CDK12 or CDK13. Its primary function is to regulate the elongation of gene transcripts. Despite its well-known actions, the precise physiological role of CCNK in humans is unknown. However, homozygous CCNK inactivation in mice causes embryonic mortality, showing its relevance in development (Malumbres, 2014).

Information and Methodology:

General Information:

The child, a male 1 year 4 months old, was taken to Nanjing Children's Hospital's Department of Rehabilitation in June 2023 owing to a "finding of 1 year of backwardness in cognitive and motor development." The baby was born healthy and on time. There was no history of hypoxia asphyxia or newborn jaundice at the time of birth. On early examination, the infant was born with wide eye spacing and typical facial features. At the time of admission to Nanjing Children's Hospital, the child's head was unstable. He had a crooked nose, a narrow chin, thin brows, a wide nasal tip, couldn't be elevated in the supine position, vision was normal, could follow hearing properly, and couldn't actively grip items. The Gesell Developmental Diagnostic Scale for children aged 0-6 years revealed that adaptive equivalence was 2 months, gross motor was 2 months, fine motor was 3 months, language was 3 months, and personal socialization was 3 months.

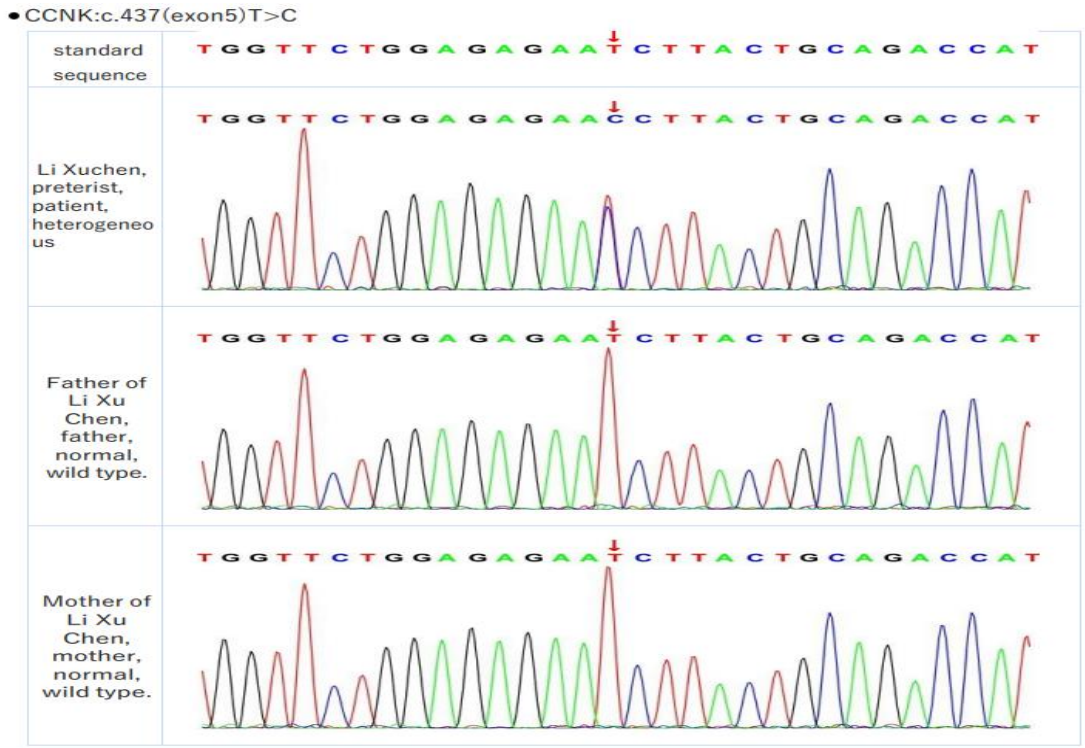
The parents are not consanguineous and have no family history of neurologic diseases. Physical examination revealed the following findings: 48 cm head circumference, normal cranial morphology, wide eye spacing, upturning of both eyes, powerful and regular heart sounds, and no evident murmur. The liver was normal, and the spleen was not swollen. Physiological reflexes: low muscular tone in all four limbs and inability to crawl. Liver and renal function, electrolytes, and thyroid function were all normal. The blood amino acid carnitine was normal during a test for hereditary metabolic disorders. A cardiac ultrasound

revealed that everything was fine. Initially diagnosed as a global developmental delay. The guardians of the children signed an informed consent form, and the hospital's Medical Ethics Committee authorized the study.

Genetic testing method:

2 ml of venous blood was drawn from the child and their parents, respectively, and placed in(EDTA) anti-coagulation in peripheral vein anti-coagulation tubes. Guangzhou Beijing Medical Laboratory performed whole-exome sequencing; protein functional domain where a pathogenic locus has been reported; a CCR (Constrained Coding Region) region where all missense variants are pathogenic and no benign missense variants; or a pathogenic hotspot (three or more pathogenic missense mutations within 10 bp of the variant and no benign missense variants). Protein functional domains that have been linked to disease-causing locations in normal population database frequency less than 0.0005 (AD/XL) or less than 0.001 (AR) is supporting evidence of pathogenicity.

A mild indication of pathogenicity PM6: in one or more phenotypically related but unrelated lineages, the mutation has been identified as de novo, leading to 1 ≤ PM6-Case_Score < 2 [current cases]. Missense variants on genes whose mis_Z score in the gnomAD database is more than or equal to 3.09, indicating that the variant damages the gene or gene product or interferes with splicing at the support threshold level. Computer simulations, including SIFT, PROVEAN, Mutation Taster, phyloP20way, and REVEL, predict that this variant significantly affects mRNA splicing. Therefore, this variant is considered to be a pathogenic variant.



Literature Review

A literature study was carried out to identify the role of CCNK mutations in IDDHDF. Chinese and international search engines like PubMed, MEDLINE, Wanfang Data Knowledge, and Google Scholar were used to search. The search phrases "CCNK", "intellectual developmental disorder", "hypertelorism", and "distinctive facies" were used. Literature from 2011 was searched and screened for clinical presentations described in the text. A total of 5 studies were found, 11 cases were presented, 3 were thoroughly discussed.

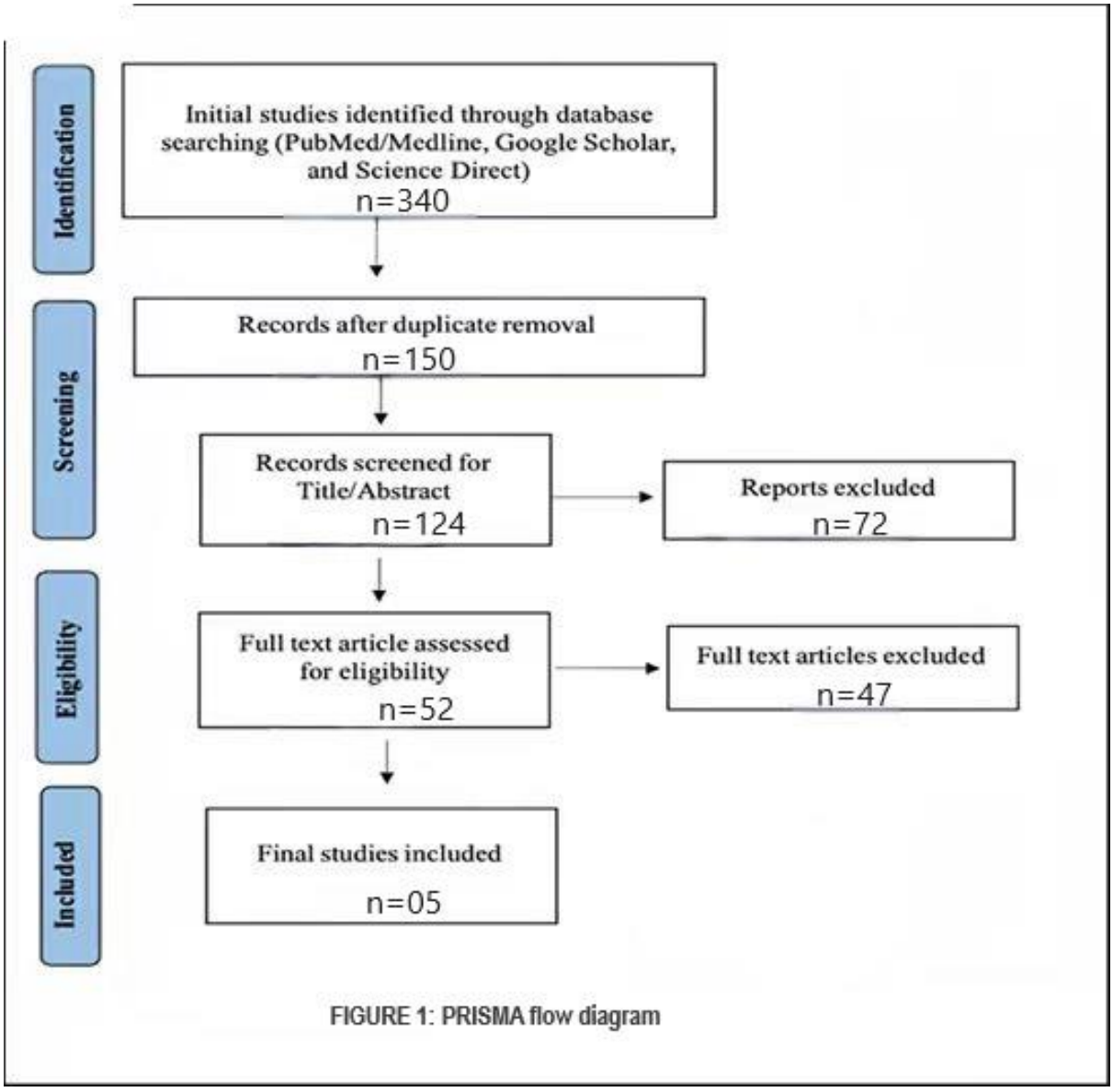


FIGURE 1: PRISMA flow diagram

Result

Fan et al. (2018) found that Chinese subjects 1, 2, and 3 come from separate families. They were all diagnosed with severe to extremely severe DD/ID and had significant linguistic impairments. The first candidate was identified as having severe ID. At four years old, he had

linguistic skills comparable to those of a six-month-old, with a major delay in speech and expression and a severe delay in auditory perception and comprehension. The 2nd candidate displayed a very serious ID. At nine years old, her verbal skills were comparable to those of an eighteen-month-old. She was unable to form phrases (J. Fan et al., 2018).

According to her parents' account, she missed several significant developmental milestones, and, at nine years old, her cognitive and social skills lag behind those of her two-year-old sibling, who does not have the deletion involving CCNK. Subject 3 also showed signs of acute ID and an exceptionally severe delay in language development; at age six, his linguistic skills were comparable to those of a 13-month-old. She also stereotypically flailed her hands. These four people shared some common facial dysmorphisms, such as a high hairline, hypertelorism, thin eyebrows, low-set ears with dysmorphic antihelix or scapha and enhanced posterior angulation, a broad nasal bridge and tip, a thin upper vermilion, and a narrow jaw. One had macrocephaly and overgrowth (weight and height above the 97th percentile). None provided any family history, and their birth histories were ordinary.

	Subject 1	Subject 2	Subject 3
Genes involved	BCL11B, SETD3, CCNK, CCDC85C	BCL11B, SETD3, CCNK, CCDC85C	c14orf177, BCL11B, SETD3, CCNK, CCDC85C, HHIPL1, CYP46A1, EML1
Gender	*male*	*female*	Female
Age	4*years*	9*years*	6years
DD/ID	severe	*extremely severe*	Severe
motor skills	*moderate effected*	*extremely severe effected*	Severe effected
Language	*Extremely severe*	*Extremely severe*	*Extremely severe*
Head circumference	*Large*	*large*	Large
Hypertelorism	*positive*	*positive*	Positive
thin eyebrows	*positive*	*positive*	Positive
Broad nasal bridge/tip	*positive*	*positive*	Positive
Narrow jaw	*positive*	*positive*	Positive
Wide eyes spacing	*positive*	*positive*	*positive*

Figure 02: Clinical and Genetic Findings in Three Subjects Harboring De Novo CCNK Variants

Fan et al. (2018) add to the confirmation supporting the link between CCNK alterations and intellectual disability (ID) with the discovery of a de novo heterozygous missense deletion in the CCNK gene (K111E) in a patient with IDDHDF. The suggested mechanism of haploinsufficiency, in which just one functioning copy of the CCNK gene is not enough for normal development, is a plausible justification for the observed findings (J. Fan et al., 2018). In humans, the CCNK gene is found on chromosome 14, more precisely in band 14q32. It covers base pairs 99,481,169 through 99,535,044. In mice, the CCNK gene is situated in band 12 F1|12 59.23 cM on chromosome 12, extending from base pair 108,145,838 to base

pair 108,169,618 (Y. Fan et al., 2018). Literature describes possible biological links between CCNK and the development of human intellect. Mutations in CCNK may interfere with early brain growth and impact RNA polymerase II-mediated transcription. Previous research has demonstrated that CCNK controls the phosphorylation of RNA polymerase II by forming a complex with CDK12/CDK13. The formation of mature, full-length mRNA and the productive elongation of transcripts are caused by this phosphorylation. Prior research on CCNK/CDK12 depletion also revealed changed RNA polymerase II-mediated expression of a subset of human genes, including a well-known downregulated set: the DNA damage response (DDR) genes.

Cellular death and genomic instability may arise from DDR downregulation. RNA polymerase II has a role in regulating the global gene expression pattern during neural precursor cell differentiation and its effect on DDR gene expression. Variations in CCNK may interfere with the temporal and spatial regulation of RNA polymerase II (Wang et al., 2023), thereby impairing the differentiation process. This theory aligns with the expression pattern of CCNK, which is highly expressed during the pluripotent embryonic stage and progressively reduced in differentiated tissues (Araki et al., 2023).

The phenotypic characteristics include a narrow jaw, hypertelorism, thin eyebrows, dysmorphic ears, broad nasal bridge and tip, and moderate-to-severe ID with specific language impairments. A recent study found that newly introduced missense mutations of CDK13, which codes for the binding site of CCNK, resulted in a correlated form of ID that largely overlaps with our cases and includes craniofacial deformities such as hypertelorism, posteriorly rotated ears, and thin upper lip vermilion. Thirteen Notably, Our patient with the CCNK missense variant had the wide spacing eyes with mental retardation and low motor nerves in all four limbs clinodactyly, a frequent digital defect seen in carriers of CDK13 mutations (Insco et al., 2023).

The relationship between recessive or dominant inheritance and the mental retardation phenotype has to be investigated further due to the small sample size. Patients with (IDDHDF) (Maity et al., 2023) may also have limb anomalies (conical fingers, flat feet), musculoskeletal system anomalies (macrocephaly, tapering fingers, narrow chin), and neurological abnormalities. Anomalies of the nervous system: widespread developmental delay abnormalities of the body wall, such as narrow eyebrows, a high anterior hairline, and other symptoms.

Upon physical inspection, we stated that the infant had prominent facial features large eye spaced at birth, and genetic testing indicated that the youngster carried a cc.437(exon5)T>C mutation in the CCKN gene (Coppine et al., 2020). The patient has very low motor functions in her four limbs and is unable to stand; her head size has grown, and there is no hereditary history. IDDHDF has no cure, but some therapies can help people manage their symptoms and improve their quality of life. Early intervention treatments, such as speech, occupational, and physical therapy, can assist children with IDDHDF in developing the abilities they need to learn, speak, and move. Children with IDDHDF may require special education programs to help them learn in school. Behavioral therapy can assist people with IDDHDF in learning how to manage their behavior and communicate with others. Medications can be used to address seizures, hyperactivity, and other issues that persons with IDDHDF may experience. Their

individual needs and symptoms will determine the particular therapy prescribed for someone with IDDHDF. A team of healthcare professionals, such as a developmental pediatrician, geneticist, and psychologist, can collaborate to design an appropriate treatment plan for the individual.

Conclusion

We present a new case of Intellectual developmental disorder with hypertelorism and unusual facies in China, and we hope that by describing this case, we will enhance doctors' knowledge of this disease. For children with wide eye spacing, weak motor limbs, and unusual faces, genetic testing should be undertaken early to understand the condition's etiology and obtain early diagnosis and management so that the disease can be treated as soon as possible.

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