Cardiofacioneurodevelopmental Syndrome: An Analysis Of Its Genotypic And Phenotypic Characteristics And The Role Of CCDC32

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Introduction

- Cardiofacioneurodevelopmental syndrome (CFNDS) is a rare genetic disorder recently recognized. This disorder results from homozygous recessive mutations in *CCDC32*, which encodes a chaperone protein essential for proper AP2 complex assembly (Wan,2024). CFNDS leads to a wide range of phenotypic impairments, with key clinical manifestations including bilateral cleft palate, cardiac defects, craniofacial abnormalities, and developmental delays. (Abdalla, 2022). However, additional manifestations exist, such as bicornuate uterus and abnormal organ positioning (Fernandes Da Rocha, 2024).
- The continuous appearance of new phenotypical characteristics complicates the creation of a cohesive and up-to-date source. Additionally, due to its novelty, genotypic information remains scattered greatly reducing the feasibility to establish genotypical patterns within the reported cases. Moreover, the relationship between the physical manifestations of CFNDS and CCDC32 mutations has only recently been explored. While several connections have been proposed, none have been fully established, and a comprehensive compilation of these findings has not been made.
- This lack of data integration reduces the ability to connect existing research on a syndrome that has been recently identified and previously misdiagnosed. The purpose of this research is to gather and organize reported phenotypic and genotypic characteristics of CFNDS and summarize CCDC32's role in its manifestations to streamline access to all relevant information and detect recurring patterns.

Methods

- To investigate the current knowledge of Cardiofacioneurodevelopmental Syndrome (CFNDS), a comprehensive literature review was conducted. Published case reports and research articles on CFNDS were reviewed to examine its phenotypic characteristics, genetic patterns, and underlying causes. Research on CCDC32 was also conducted as it has been linked to CFNDS, helping clarify its role in the disorder.
- Relevant findings were collected, focusing on CFNDS-related symptoms, genetic mutations, and their potential molecular mechanisms. Findings were categorized into phenotypic and genotypic tables to compare recurring manifestations and mutation types. Mutation nomenclature was reviewed using relevant articles to ensure the information was accurately represented. Additionally, the proposed connections between CFNDS manifestations and CCDC32 mutations were recorded to better understand their role in the disorder.

Results

Genotypic Characteristics Table

Case	Patient	Mutation Type	Nucleotide Change	Notes	Source
1	Arab Muslim Female	Frameshift	c.54dupT		Harel et al.
2	Arab Muslim Fetus	Frameshift	c.54dupT	Fetus pregnancy terminated. Sibling of Arab Muslim Female.	Harel et al.
3	Iranian Male	Frameshift	c.189_190dupGG		Harel et al.
4	Egyptian Female	Intragenic Deletion		9.7kb deletion involving exons 3 and 4	Abdalla et al.
5	Portuguese Female	Intragenic Deletion		32.6 kb deletion involving exons 3 and 4	Fernandes de la Rocha et al.

- Figure 2: Reported CCDC32 mutation characteristics of CFNDS patients.

Phenotypic Characteristics Table

	Simplified Description	Patient 1	Patient 2 (Fetus)	Patient 3	Patient 4	Patient 5
Sex		Female	Unknown	Male	Female	Female
Ethnicity		Arab Muslim	Arab Muslim	Iranian	Egyptian	Portuguese
Craniofacial Features						
Bilateral Cleft Lip and/or Palate		☑	☑	☑	☑	☑
Abnormal Interorbital Distance	Abnormal eye spacing	☑	☐	☑	☑	☐
Upslanting palpebral fissures	Upslanting eyes	☑	☐	☐	☑	☐
Nasal Anomalies	Abnormal nose shape	☑	☐	☑	☑	☑
Ear Anomalies	Including malformed or protruding ears	☑	☐	☑	☑	☑
Micrognathia	Small or receded jaw	☑	☐	☐	☐	☐
Microcephaly		☑	☐	☑	☑	☑
Cardiac Defects						
Atrioventricular canal defect		☑	☐	☐	☐	☐
Ventricular septal defect		☐	☐	☑	☐	☐
Pulmonary valve stenosis		☐	☐	☑	☐	☐
Atrial septal defect / Foramen Ovale		☐	☐	☐	☐	☑
Mitral valve prolapse		☐	☐	☐	☑	☐
Neurodevelopmental Issues						
Developmental delay/Intellectual Disability		☑	☐	☑	☑	☑
Feeding difficulties		☑	☐	☑	☑	☑
Brain Anomalies on Imaging		☑	☑	☐	☑	☐
Hyperactivity		☐	☐	☑	☐	☐
Skeletal Abnormalities						
Short Stature		☑	☐	☐	☑	☑
Clinodactyly	Curved fingers	☑	☐	☑	☐	☐
Camptodactyly	Bent fingers	☑	☐	☐	☐	☐
Kyphosis	Spinal curvature	☑	☐	☐	☐	☐
Syndactyly	Webbed fingers	☐	☐	☐	☑	☐
Brachydactyly	Short fingers/toes	☐	☐	☑	☐	☑
Foot Anomalies		☑	☐	☐	☐	☐
Delayed bone maturation		☑	☐	☐	☑	☐
Other Features						
Laterality Defects	Abnormal organ position	☑	☐	☐	☐	☐
Neck Anomalies	Short neck and/or webbing	☐	☐	☐	☑	☐
Thrombocytopenia		☑	☐	☐	☑	☐
Bicornuate Uterus	Double uterus	☐	☐	☐	☐	☑
Cryptorchidism	Undescended testicles	☐	☐	☑	☐	☐
Nail Clubbing		☑	☐	☐	☑	☐
Missing Teeth / Dental Anomalies		☑	☐	☐	☐	☐
Hypoplastic Cerebellar Tonsils	Underdeveloped cerebellar tonsils	☑	☐	☐	☐	☐
Nail Aplasia		☐	☐	☑	☐	☐
Hypoplastic Toenails	Underdeveloped toenails	☐	☐	☐	☐	☑

- Figure 1: Collection of reported phenotypic manifestations of CFNDS categorized per patient.

Results Continued

- According to Wan et al (2024), CCDC32 facilitates AP2 complex assembly by properly binding AP2 subunits. CCDC32 mutations in CFNDS therefore impair AP2 subunit binding and directly affect clathrin-mediated endocytosis, which is essential for cell signaling, regulation, and transport. Abdalla et al (2022), demonstrated that mice lacking certain AP2 subunits exhibited cleft palate and cardiac defects, similar to the core physical manifestations of CFNDS. Lastly, Harel et al (2020), demonstrated how zebrafish models with impairments in CCDC32 showed defects in ciliogenesis, linking cilia defects to the physical manifestations of CCDC32.

Conclusion

- This study aims to gather reported phenotypic and genotypic characteristics of CFNDS and analyze the role of CCDC32 in its manifestations as described by current research. The results support the core manifestations of CFNDS, including bilateral cleft lip, cardiac defects, and developmental delays. However, the results also emphasize the prevalence of skeletal abnormalities. Regarding genetic patterns, frameshift mutations were the most observed. Lastly, the results highlight the importance of CCDC32 in proper AP2 subunits assembly, which is essential for clathrin-mediated endocytosis and cilia formation, suggesting possible disrupted processes responsible for CFNDS manifestations.
- Although all current research provides strong evidence for the role of CCDC32 in CFNDS, none has been confirmed. While this research displays a comprehensive collection of CFNDS data to date, the limited number of reported cases restrains the strength of the observed patterns. Future research should examine whether CCDC32 impairments also alter other AP complexes, which could explain additional common manifestations of CFNDS.

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