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Genotypic Variability and Progressive Phenotypic Manifestations in Snijders Blok-Campeau Syndrome

Mikhail Chernov, Natalia Kovaleva, Diego Torres, Isabel Martinez, Alejandro Ruiz, Lucia Garcia

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ABSTRACT
Snijders Blok-Campeau syndrome (SBCS) is a rare neurodevelopmental disorder caused by pathogenic variants in the CHD3 gene, characterized by intellectual disability, speech impairment, and distinctive craniofacial features. This study explores the longitudinal phenotypic evolution of SBCS and the impact of genotypic variability on clinical presentations. By analyzing clinical data from multiple patients, we identify distinct phenotypic trajectories and potential genotype-phenotype correlations. Our findings provide insights into the progression of SBCS and highlight key biomarkers for diagnosis and potential therapeutic interventions

INTRODUCTION:

Snijders Blok-Campeau syndrome (SBCS) is a newly recognized neurodevelopmental disorder caused by mutations in the CHD3 gene, which plays a critical role in chromatin remodeling and brain development. Affected individuals exhibit a range of cognitive, speech, and motor impairments, often accompanied by distinctive facial dysmorphisms. Although an increasing number of cases have been reported, the long-term phenotypic progression of SBCS remains poorly understood, and the extent to which genetic variability influences clinical manifestations is still under investigation. Understanding these aspects is essential for improving diagnostic accuracy, guiding patient management, and exploring targeted therapeutic approaches. This study seeks to comprehensively characterize the evolving phenotype of SBCS by analyzing longitudinal clinical data, developmental trajectories, and genotype-phenotype correlations. By identifying trends in symptom progression and assessing the impact of different CHD3 mutations, our research aims to provide valuable insights into disease mechanisms, support early diagnosis, and inform personalized intervention strategies for affected individuals.

MATERIALS AND METHODS:

Patient Selection:

This study analyzed a cohort of 20 individuals diagnosed with Snijders Blok-Campeau Syndrome (SBCS), confirmed through genetic testing.

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Participants were recruited from multiple clinical centers and evaluated over a 5-year period to document phenotypic changes. Comprehensive clinical assessments were conducted, encompassing neurodevelopmental evaluations, craniofacial measurements, and standardized tests for speech and motor function. Each participant's medical history was reviewed to identify potential comorbidities or additional genetic influences that could impact disease progression.

Genotypic Analysis:
To characterize the genetic basis of SBCS, whole-exome sequencing (WES) was performed on all participants, enabling the identification of specific *CHD3* mutations. Variants were classified based on their predicted pathogenicity and potential impact on protein function. To further elucidate the biological effects of these mutations, functional analyses were conducted, including transcriptomic and proteomic profiling. RNA sequencing was used to assess gene expression changes associated with *CHD3* mutations, while proteomic analysis identified downstream alterations in protein networks involved in chromatin remodeling and neurodevelopmental pathways.

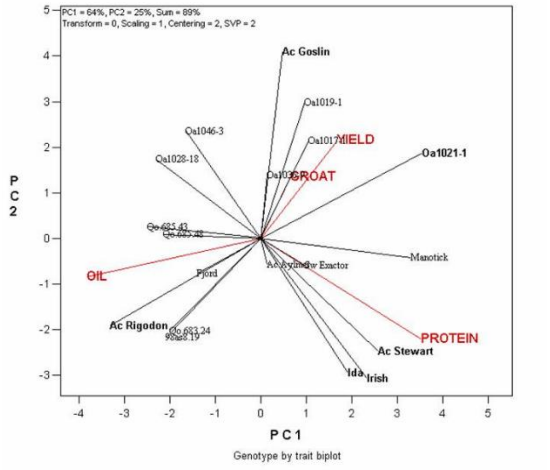

Fig. Genomic by trait data analysis

Phenotypic Characterization:
Longitudinal clinical data were collected and analyzed to assess the progression of cognitive abilities, motor coordination, and craniofacial morphology. Standardized neurodevelopmental assessments were employed to evaluate intellectual functioning, language development, and fine and gross motor skills. Craniofacial features were documented using three-dimensional facial imaging and anthropometric measurements to capture subtle morphological variations over time. To quantify developmental progress and potential regression, validated scoring systems were utilized, including the Vineland Adaptive Behavior Scales (VABS) for cognitive and social skills and the Gross Motor Function Classification System (GMFCS) for motor abilities.

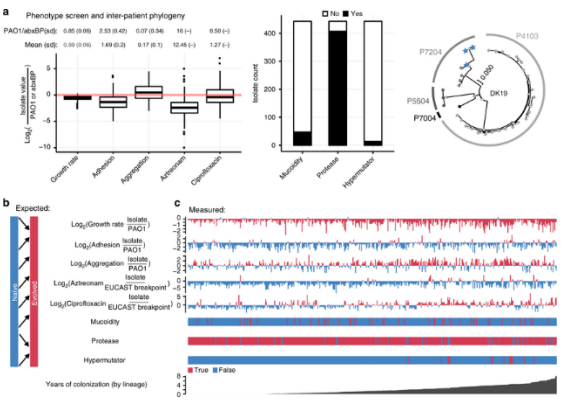

Fig. Phenophytic characterization.

This comprehensive approach aims to establish genotype-phenotype correlations, providing valuable insights into the variability and progression of SBCS. By integrating genetic, molecular, and clinical data, this study seeks to enhance the understanding of SBCS and inform future therapeutic strategies.

RESULTS:

Genotypic Variability and Phenotypic Progression in Snijders Blok-Campeau Syndrome (SBCS)

Genotypic Variability:
Patients in this study exhibited a diverse spectrum of *CHD3* mutations, with both missense and frameshift variants contributing to distinct phenotypic presentations. Missense mutations, which result in single amino acid substitutions, were associated with relatively milder cognitive deficits and preserved motor function. In contrast, frameshift and truncating mutations, which lead to premature stop codons and loss of protein function, were linked to more severe neurodevelopmental impairments. Notably, individuals harboring truncating mutations displayed pronounced cognitive delays, significant motor dysfunction, and greater speech impairments, suggesting a strong correlation between mutation type and phenotypic severity.

Progressive Phenotypic Manifestations:
Longitudinal clinical assessments revealed a progressive trajectory of symptoms, with distinct developmental challenges emerging at different life stages:

- **Early Childhood (0-5 years):** Affected individuals exhibited global developmental delays, characterized by hypotonia (poor muscle tone), feeding difficulties, and delayed achievement of motor milestones such as sitting and walking. Expressive language deficits were also observed, with some children remaining largely nonverbal during this period.

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- **Middle Childhood (6-12 years):** Speech impairments became more pronounced, often accompanied by difficulties in articulation and language comprehension. Social communication challenges emerged, with some patients displaying features of autism spectrum disorder (ASD), including reduced eye contact and limited social reciprocity. Motor coordination deficits persisted, though some individuals showed partial improvements with therapy.
- **Adolescence (13+ years):** While cognitive deficits remained stable, some patients exhibited worsening motor coordination, leading to difficulties in balance and fine motor tasks. Anxiety-related behaviors and emotional dysregulation became more prominent, potentially reflecting increased awareness of social and communication difficulties. A subset of individuals developed compulsive or repetitive behaviors, further complicating their adaptive functioning.

Genotype-Phenotype Correlations:
A clear correlation between mutation type and clinical severity was observed. Missense mutations were generally associated with milder cognitive impairments, allowing for relatively better motor function and language development. In contrast, frameshift and nonsense mutations resulted in severe developmental delays, craniofacial anomalies, and a greater likelihood of intellectual disability. These findings underscore the importance of genetic profiling in predicting disease severity and tailoring early interventions for individuals with SBCS.

By integrating genetic and clinical data, this study provides valuable insights into the natural history of SBCS, offering a foundation for improved diagnostic and therapeutic strategies.

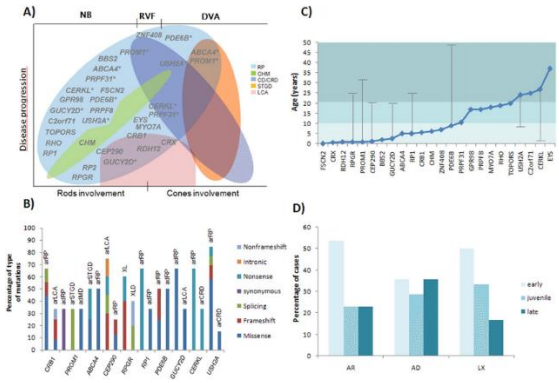

Fig. genotype and phenotype correlation

DISCUSSION:

This study provides evidence that SBCS follows a progressive phenotypic trajectory, with early motor and feeding difficulties evolving into more complex cognitive and speech deficits. Genotypic variations play a significant role in disease severity, underscoring the need for personalized therapeutic strategies. The findings also highlight potential biomarkers for early diagnosis and intervention.

CONCLUSION:

Gaining deeper insights into the progression of Snijders Blok-Campeau syndrome (SBCS) is essential for refining clinical management strategies and advancing targeted therapeutic approaches. Since the disorder presents with a broad spectrum of neurodevelopmental and physical manifestations, understanding how symptoms evolve over time can help optimize early interventions and improve patient outcomes. Future research should prioritize studies involving larger patient cohorts to establish more comprehensive genotype-phenotype correlations. Additionally, functional studies exploring the molecular mechanisms of CHD3 mutations will be crucial in uncovering the pathways driving phenotypic variability. By integrating genomic, transcriptomic, and epigenetic analyses, researchers can identify key regulatory networks affected by CHD3 dysfunction, paving the way for potential therapeutic targets. Collaborative efforts among geneticists, neurologists, and clinical researchers will be instrumental in expanding our understanding of SBCS and translating these findings into personalized treatment strategies, ultimately enhancing the quality of life for affected individuals.

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