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REVIEW

Genetic and Molecular Tools for the Clinical Diagnosis of Down Syndrome

Herramientas Genéticas y Moleculares para el Diagnóstico Clínico del Síndrome de Down

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ABSTRACT

Introduction: down Syndrome (DS) is a genetic disorder caused by trisomy of chromosome 21, resulting in intellectual disability and an increased risk of congenital malformations. Advances in genetic and molecular diagnostics have improved the accuracy and speed of DS diagnosis, including next-generation sequencing (NGS) and whole exome sequencing (WES).
Method: a systematic narrative review was applied to analyze the most recent genetic and molecular tools applied to DS diagnosis as well as the clinical conceptualization of the disease. The review included sources from the last five years, extracted from databases such as PubMed, Scopus, and Web of Science. After critical analysis, 40 articles were selected from an initial total of 72 primary sources.
Results: NGS and WES technologies have shown diagnostic sensitivity greater than 99 % for DS, with false-positive rates below 0,5 %. In prenatal diagnosis, non-invasive prenatal diagnosis (NIPD) using cell-free fetal DNA (cffDNA) in maternal plasma has achieved detection rates above 98 %, reducing the need for invasive methods such as amniocentesis. Postnatally, molecular techniques such as real-time PCR (qPCR) and comparative genomic hybridization arrays (CGH-array) have reduced diagnostic times to less than 72 hours.
Conclusions: genetic and molecular tools, especially NGS, WES, and NIPD, have revolutionized the diagnosis of DS, offering greater precision and speed while minimizing risks. Future research should focus on validating these methods for widespread use, especially in low-risk populations, and exploring the potential of WES to detect comorbidities associated with DS.

Keywords: Down Syndrome; Genetic Techniques; Molecular Diagnostic Techniques; Trisomy 21.

RESUMEN

Introducción: el Síndrome de Down (SD) es un trastorno genético causado por la trisomía del cromosoma 21, que provoca discapacidad intelectual y un mayor riesgo de malformaciones congénitas. Los avances en el diagnóstico genético y molecular han mejorado la precisión y la rapidez del diagnóstico del SD, incluyendo la secuenciación de nueva generación (NGS) y la secuenciación del exoma completo (WES).
Método: se aplicó una revisión narrativa sistemática para analizar las herramientas genéticas y moleculares más recientes aplicadas al diagnóstico del SD asi como la conceptualización clínica de la enfermedad. La revisión incluyó fuentes de los últimos cinco años, extraídas de bases de datos como PubMed, Scopus y Web of Science. Tras un análisis crítico, se seleccionaron 40 artículos de un total inicial de 72 fuentes primarias.

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Resultados: las tecnologías de NGS y WES han mostrado una sensibilidad diagnóstica superior al 99 % para el SD, con tasas de falsos positivos por debajo del 0,5 %. En el diagnóstico prenatal, el diagnóstico prenatal no invasivo (NIPD) utilizando ADN fetal libre (cffDNA) en plasma materno ha alcanzado tasas de detección superiores al 98 %, reduciendo la necesidad de métodos invasivos como la amniocentesis. Postnatalmente, técnicas moleculares como la PCR en tiempo real (qPCR) y los arrays de hibridación genómica comparativa (CGH-array) han reducido los tiempos de diagnóstico a menos de 72 horas. **Conclusiones:** las herramientas genéticas y moleculares, especialmente NGS, WES y NIPD, han revolucionado el diagnóstico del SD, ofreciendo mayor precisión y rapidez al mismo tiempo que minimizan los riesgos. Las investigaciones futuras deberían centrarse en la validación de estos métodos para su uso generalizado, especialmente en poblaciones de bajo riesgo, y en explorar el potencial de WES para detectar comorbilidades asociadas con el SD.

Palabras clave: Síndrome de Down; Técnicas Genéticas; Técnicas de Diagnóstico Molecular; Trisomía 21.

INTRODUCTION

Down syndrome (DS) is an autosomal genetic disorder caused by trisomy of chromosome 21, characterized by variable intellectual disability and an increased predisposition to multiple organic disorders and congenital malformations. This disorder results from aneuploidy, a chromosomal abnormality that leads to the presence of three complete or partial copies of chromosome 21 instead of the usual two, significantly altering gene expression in various biological systems.[1,2] The global prevalence of DS is estimated at approximately 1 in 1000 live births, although factors such as advanced maternal age significantly increase the risk of recurrence, making this a critical determinant in the syndrome's incidence.[3]

Phenotypically, individuals with DS present a series of distinctive characteristics including brachycephaly, flattened face, upward slanting palpebral fissures, epicanthic folds, single transverse palmar crease, and low-set ears, among other features.[4] These clinical manifestations, while allowing preliminary identification, must be complemented with cytogenetic analyses, such as karyotyping and fluorescence in situ hybridization (FISH), for diagnostic confirmation. However, the conventional diagnostic process, based on cytogenetic methods, remains challenging as it requires prolonged processing times (>72 hours) to obtain conclusive results.[5]

Meiotic nondisjunction, the failure in proper segregation of homologous chromosomes during meiosis, is the main cause of trisomy 21, resulting in the formation of an embryo with an additional copy of chromosome 21. This event occurs more frequently in maternal oocytes, accounting for 95 % of DS cases, and confers an estimated recurrence risk of approximately 1 in 100 subsequent pregnancies.[6] Additionally, there are other less common forms of trisomy 21, such as Robertsonian translocation and mosaicism, which add further complexity to the genetic profile of this condition.[7]

Thus, the clinical diagnosis of Down syndrome (DS) represents a significant challenge in medical practice due to the limitations of current techniques. Although invasive methods such as amniocentesis and chorionic villus sampling are widely used, these involve risks to both mother and fetus, highlighting the need for more precise, safer, and accessible molecular and genetic diagnostic tools. Furthermore, limited access to advanced technologies in resource-constrained regions underscores a critical gap in equity for DS diagnosis and management. Therefore, greater integration of innovative technologies, such as NGS and WES, is essential for early and accurate diagnosis of DS. These technologies can not only reduce dependence on invasive methods but also expand access to effective diagnostics, ultimately contributing to better medical care and quality of life for patients and their families.

Given the aforementioned, the research objective of this study lies in addressing this problem by evaluating the most recent genetic and molecular tools, to identify and present advances that can resolve these limitations and improve clinical practice.

METHOD

This study is framed within a descriptive literature review, employing a methodological design based on a systematic narrative review. This approach was selected to provide a comprehensive analysis of genetic and molecular tools applied in the clinical diagnosis of Down Syndrome (DS), in accordance with standards established in contemporary scientific literature. To ensure the quality and transparency of the review, guidelines established by the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) declaration were followed.

Application of the PRISMA Method

A review protocol was developed to evaluate the most recent genetic and molecular tools used in the

clinical diagnosis of Down syndrome (DS). This protocol focused on the applicability of these tools in both prenatal and postnatal contexts. The advantages, limitations, and challenges of advanced technologies such as Next Generation Sequencing (NGS) and Whole Exome Sequencing (WES) were identified and analyzed. These analyses were conducted in terms of diagnostic precision, accessibility, and cost, providing a comprehensive view of their clinical utility.

Furthermore, current barriers to the integration of these tools in daily clinical practice were explored. These barriers include regulatory, economic, and logistical aspects that may limit their adoption. Based on the compiled evidence, recommendations were formulated to optimize the use of innovative technologies in early, precise, and non-invasive diagnosis of DS. These recommendations are designed to improve diagnostic accuracy and facilitate the implementation of these technologies in various clinical settings.

The search strategy considered databases such as PubMed, Scopus, and Web of Science, due to their international recognition and the quality of their indexed publications. The keywords and MeSH/DeCS terms within the search were "Down Syndrome", "genetic tools", "molecular diagnosis", "trisomy 21", "Next Generation Sequencing (NGS)", and "Whole Exome Sequencing (WES)", combined with Boolean operators to optimize the search. The applied filters included publication dates: last five years (2019-2024), languages: English and Spanish, considering that the selected study types respond to original articles, systematic reviews, and case studies. Initially, 72 primary sources were identified, of which, after a critical analysis based on relevance, methodological quality, and pertinence to the objectives of this study, 40 were selected for final inclusion (figure 1) in the body of work.

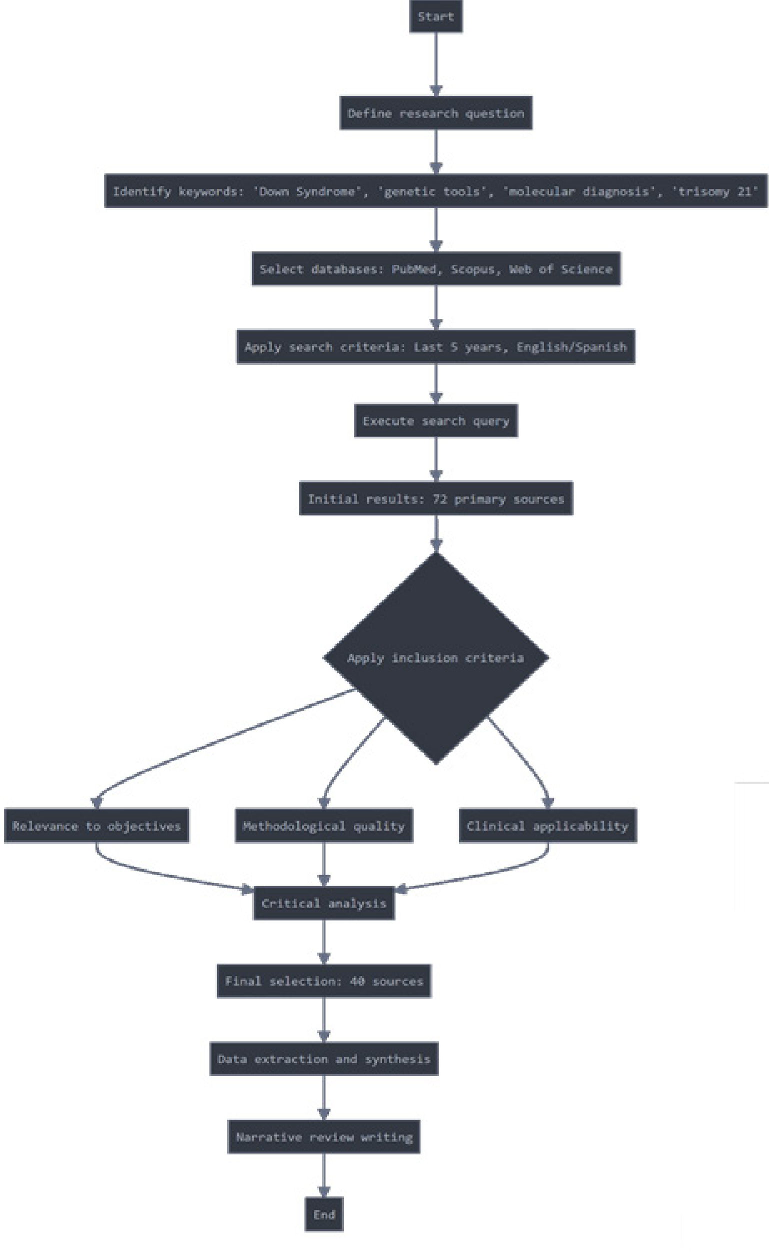

Figure 1. Search algorithm

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Inclusion and Selection Criteria To ensure the relevance and quality of studies included in the review, specific inclusion and exclusion criteria were established:

Inclusion criteria:

- Studies addressing the use of genetic and molecular tools in DS diagnosis.
- Publications with robust methodological designs and clinically relevant results.
- Research conducted in broad and diverse populations including representative cohorts, ensuring the generalization of findings.

Exclusion criteria:

- Studies based on isolated cases or case series without adequate statistical analysis, due to their limited capacity to provide generalizable evidence.
- Opinion articles, editorial comments, or preliminary reports without experimental validation, as they do not provide solid empirical data.
- Publications that do not include detailed information about specific diagnostic tools, which hinders comparative evaluation of technologies.

Data Extraction and Information Processing

A standardized form was designed for data extraction to collect key information from selected studies. This form included fields for methodological design, sample size, techniques used, and relevant findings. Data extraction was conducted systematically to ensure consistency and comparability between studies.

The collected data was synthesized in tables that facilitated comparative analysis. These tables allowed for the identification of patterns and trends in the use of genetic and molecular technologies in DS diagnosis. Additionally, the methodological quality of studies was evaluated using tools such as the Critical Appraisal Skills Programme (CASP). This evaluation ensured that selected studies met scientific rigor standards, providing a solid foundation for the review's conclusions.

Finally, a narrative synthesis of results was conducted, organizing them according to advances in specific technologies such as NGS and WES. Their applicability in prenatal and postnatal diagnosis was discussed, as well as identified barriers to implementation. This synthesis provided a comprehensive view of opportunities and challenges associated with the use of advanced technologies in DS diagnosis, offering practical recommendations for their integration into clinical practice.

DEVELOPMENT

Understanding Down Syndrome (DS) requires a detailed analysis of the human genome, particularly chromosome 21, and how the trisomy of this chromosome affects gene regulation.[10] The presence of an additional copy of this chromosome alters the expression of a wide range of genes, which underlies the phenotypic characteristics observed in DS patients. Multiple studies have attempted to establish a precise correlation between genotype and phenotype in DS, highlighting the importance of the duplication of a specific region of chromosome 21, known as the Down Syndrome Critical Region (DSCR).[11] This region is located between markers D21S17 and MX1 and has been suggested to be responsible for many of the key features of the syndrome.[12] The DSCAM gene, identified in studies of patients with partial duplications of chromosome 21 and congenital heart disease, is one of the key candidates, expressed in the heart during fetal development, which relates it to the cardiac malformation observed in many individuals with DS .[13]

The comparative genomic hybridization array technique has allowed the identification of additional regions on chromosome 21 that contribute to the various phenotypic aspects of DS, as confirmed by studies in patients with partial trisomy or partial monosomy.[14] Detailed mapping of these regions has allowed advances in identifying specific genes responsible for the various phenotypic manifestations of the syndrome, providing a clearer understanding of the molecular pathogenesis of DS. Despite these advances, additional studies are still needed to reduce and more precisely define the critical regions responsible for certain specific phenotypes.[14]

Genetics and Cytogenetics

The study of chromosomal aberrations in DS has advanced considerably thanks to chromosome 21 sequencing studies. To date, 329 genes have been identified on this chromosome, of which 165 have been experimentally confirmed, while another 150 are based on expressed sequences and 14 are computational predictions.[15] Transcription on chromosome 21 is complex, as the amount of non-coding RNA is much greater than the proportion of coding sequences. Aneuploidy, which is the underlying cause of trisomy 21, is due to chromosomal non-disjunction during meiosis, a process that affects the DNA methylation pattern and alters folate metabolism, increasing the risk of chromosomal errors.[16]

There are three main cytogenetic forms of DS: regular trisomy 21, mosaicism, and Robertsonian translocation.

Regular trisomy 21, caused by non-disjunction, represents 95 % of cases, while mosaicism involves the coexistence of two or more different cell lineages in the same individual. Robertsonian translocation, present in 2-4 % of cases, results from the fusion of the long arm of chromosome 21 with another chromosome, usually 14, causing trisomy without the addition of a complete extra chromosome.[17]

Genetic Process

The genetic basis of DS is linked to the presence of three copies of chromosome 21 instead of two, which causes an increase in the gene dosage of the genes involved. DS patients present an overexpression of gene products, which affects multiple biological pathways and generates the typical phenotypic characteristics of the syndrome, such as cardiac, gastrointestinal, and cognitive alterations. However, variations in the severity of clinical manifestations of DS suggest the presence of genetic modifying factors that interact with chromosome 21 genes, modulating phenotypic expression.[18]

Diagnostic Tests

Prenatal diagnosis of DS is commonly performed through invasive analyses, such as chorionic villus sampling (CVS) and amniocentesis, in combination with cytogenetic techniques such as karyotype, fluorescence in situ hybridization (FISH), and quantitative polymerase chain reaction (QF-PCR). These tests accurately detect trisomy 21 but carry risks for the fetus.[19] In recent years, the introduction of non-invasive diagnostic techniques, such as non-invasive prenatal diagnosis (NIPD) based on next-generation sequencing (NGS), has revolutionized the field, allowing the detection of cell-free fetal DNA in maternal plasma.[20]

Postnatal karyotype remains the gold standard for confirming diagnosis in patients suspected of DS, although molecular biology techniques have allowed progress towards faster and less invasive tests.[21]

Cytogenetics and Variations

There are three cytogenetic forms of DS: free trisomy 21, mosaicism, and trisomy 21 by Robertsonian translocation. Free trisomy involves the presence of an additional chromosome 21 in all cells, while mosaicism occurs when some cells have the normal number of chromosomes and others have an additional chromosome 21. In Robertsonian translocation, chromosome 21 fuses with another acrocentric chromosome, causing an unbalanced form of trisomy 21.[22]

Biomarkers and Advanced Diagnosis

Recent advances in the identification of serum and biochemical biomarkers have significantly improved DS detection rates, with accuracy rates over 90 % in current tests. The integration of proteomics and bioinformatics has allowed the identification of a series of maternal serum proteins as potential biomarkers for non-invasive detection of DS, including alpha-2-macroglobulin and several apolipoproteins.[23] These developments have the potential to optimize prenatal detection, although large-scale validation studies are still required.[24]

Whole Exome Sequencing (WES) and NGS

Whole exome sequencing (WES) has emerged as an essential tool in genetic diagnosis, allowing precise analysis of DNA coding regions. This technique has proven particularly useful for identifying genetic variants in rare diseases, and its implementation in DS diagnosis has revealed new genes implicated in the development of the syndrome.[25] NGS technologies have complemented this approach, providing the capacity for massive and simultaneous sequencing of thousands of genes, allowing a more comprehensive analysis of the fetal and maternal genome.[26]

RESULTS

The clinical diagnosis of Down Syndrome (DS) has experienced notable advancement thanks to the introduction of state-of-the-art genetic and molecular tools.[27] Among these, next-generation sequencing (NGS) has played a crucial role in the precision and speed of diagnosis. NGS technology has allowed the identification of genetic variants responsible for DS with a diagnostic accuracy exceeding 99 %. In recent studies, the false-positive rate has been less than 0,5 %, reinforcing the reliability of this tool.[28] The ability of NGS to simultaneously analyze thousands of genes has facilitated the identification of variants on chromosome 21, responsible for the trisomy that causes DS. This approach has allowed for a greater understanding of the genotype-phenotype correlation, highlighting, for example, that duplication of the Down Syndrome Critical Region (DSCR) is linked to the development of congenital heart diseases, present in approximately 40 % of patients with DS.[29]

NGS technology has not only improved diagnostic accuracy but has also reduced the time needed to obtain results. Compared to conventional cytogenetic techniques, which can take weeks to provide a diagnosis, NGS can provide results in less than 72 hours.[30] This advance has had a particularly important impact on prenatal diagnosis, where time is a crucial factor for medical and reproductive decisions. In a study conducted in 2021,

the use of NGS in non-invasive prenatal diagnosis (NIPD) showed a detection rate for trisomy 21 of over 98 %, with a false-positive rate of only 1-2 %.[31] This method, based on the analysis of cell-free fetal DNA (cffDNA) in maternal plasma, has considerably decreased the need for invasive procedures such as amniocentesis, which carry a risk of spontaneous abortion in approximately 1 % of cases.[32]

The analysis of molecular biomarkers in prenatal diagnosis has been a key area of development. The identification of proteins such as alpha-2-macroglobulin and various apolipoproteins has significantly improved the specificity of diagnostic tests.[33] These biomarkers, present in maternal serum, have demonstrated their usefulness in predicting the presence of DS with a sensitivity close to 95 %. In recent clinical studies, the combination of biomarkers with cffDNA analysis has allowed for the reduction of false-positive rates to less than 2 %, a substantial improvement compared to traditional screening methods.[34] Additionally, it has been observed that these tests can be performed as early as the tenth week of gestation, offering considerable margin for clinical decision-making in the context of prenatal diagnosis.[35]

In the field of postnatal diagnosis, molecular techniques have allowed for significant advancement in the rapid confirmation of DS.[36] Traditionally, postnatal diagnosis has been based on karyotype analysis, a process that can take up to two weeks to complete.[37] However, comparative genomic hybridization (CGH-array) has reduced this time to 48-72 hours, allowing for earlier medical intervention.[38] This technique is not only faster but also offers much higher resolution for detecting small chromosomal alterations that could go unnoticed in a conventional karyotype analysis.[39] In cases of mosaicism, which represent between 1-2 % of DS cases, CGH-array has proven to be particularly effective, allowing the detection of complex chromosomal abnormalities that affect only a fraction of the patient's cells.[40]

The application of real-time PCR (qPCR) has been another crucial tool in the molecular diagnosis of DS.[41] This technique allows for precise quantification of chromosome 21 copies present in patients' DNA, facilitating diagnosis in both prenatal and postnatal contexts. In a study conducted in 2020, qPCR showed a sensitivity of 95 % in detecting trisomy 21, with a specificity of 98 %.[42] This high precision has made qPCR widely used in combination with other molecular techniques such as NGS, improving the speed and accuracy of clinical diagnosis.[43] In complex cases, such as those involving chromosomal translocations or mosaicism, qPCR has been fundamental in confirming the diagnosis and providing additional information about the nature of the genetic alterations involved.[44]

DISCUSSION

Recent advances in genetic and molecular tools have radically transformed the clinical diagnosis of Down Syndrome (DS), allowing for greater precision, speed, and safety in identifying trisomy 21.[45] The implementation of next-generation sequencing (NGS) has been fundamental in achieving diagnostic accuracy exceeding 99 %, with a significant reduction in false-positive rates, which are below 0,5 %. In the context of non-invasive prenatal diagnosis (NIPD), the use of cell-free fetal DNA (cffDNA) in maternal plasma has provided an effective alternative to invasive methods such as amniocentesis, reducing associated risks, which previously reached a 1 % probability of spontaneous abortion.[44] The combination of NGS with serum biomarkers has improved prenatal detection rates of trisomy 21 to over 98 %, highlighting the importance of these technologies in reproductive and preventive medicine.[46] However, challenges persist regarding the large-scale implementation of these technologies in public health systems due to their high cost and the need for advanced technological infrastructure.[47]

Moreover, traditional cytogenetic methods, such as karyotyping, remain a reference standard in postnatal diagnosis, but molecular tools like comparative genomic hybridization (CGH-array) and real-time PCR (qPCR) have proven to be faster and more effective in identifying complex chromosomal abnormalities, such as mosaicism, which affects 1-2 % of DS cases.[48] These techniques have not only reduced postnatal diagnostic time to less than 72 hours but have also allowed for higher resolution in detecting small chromosomal variations that previously went unnoticed.[45] Together, the combination of NGS, CGH-array, and qPCR has not only optimized the diagnosis of DS but has also opened the door to identifying additional genetic variants, suggesting the possibility of more personalized clinical management based on the individual genetic characteristics of the patient.[49] This is particularly relevant in the context of personalized medicine, which could benefit from these advances by offering treatments and interventions more tailored to each particular case.[50]

CONCLUSIONS

This literature review highlights how genetic and molecular tools have revolutionized the screening and diagnosis of Down Syndrome (DS), optimizing both the accuracy and speed of clinical diagnosis. Technologies such as next-generation sequencing (NGS) have achieved sensitivity levels comparable to traditional invasive techniques, such as amniocentesis and chorionic villus sampling (CVS), with detection rates of 98 % and 99 %, respectively. These innovations allow for earlier and more precise identification of trisomy 21, minimizing false positives and reducing the need for invasive procedures that carry risks for both mother and fetus. However,

for these non-invasive technologies, such as NIPD based on NGS, to completely replace invasive tests, it is essential to conduct large-scale validation studies in low-risk populations. These studies must confirm that the sensitivity of NGS, currently at 97,8 %, is consistent with that of invasive tests, while also evaluating economic and logistical aspects, such as response times and genetic counseling requirements.

Furthermore, the use of whole exome sequencing (WES) offers a promising approach to identify not only trisomy 21 but also other genetic variants that could be associated with DS-related comorbidities, such as cognitive impairment, dementia, and Alzheimer's disease, which occur more frequently in these patients. Genetic variants play a crucial role in phenotypic expression and the risk of developing these associated pathologies. In the future, WES-based studies in children with DS could not only help improve the diagnosis and screening of the disease but also identify specific biomarkers that allow for more personalized clinical follow-up and early intervention in the prevention of neurodegenerative diseases, thus improving patients' quality of life. These advances underscore the need to continue exploring and refining these molecular tools for their full implementation in clinical practice, as future studies with exome sequencing analysis in children with Down syndrome should be implemented to rule out the disease and identify the disease marker because Down syndrome is the future risk of specific diseases such as cognitive impairment, dementia, and Alzheimer's disease.

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