Advances in Medicine and Engineering Interdisciplinary Research, 2025, Volume 3, Issue 1
DOI: 10.32629/ameir.v3i1.3656
ISSN Online: 2972-3825
ISSN Print: 2972-3833

New Deletion of Multiple Genes in the Pathogenic Subtelomeric Region Is Related to the Phenotypic Heterogeneity of Patients with Polymalformation Syndrome

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Abstract: Introduction: Genomic testing has advanced significantly, enabling the identification of changes ranging from specific locus modifications to genomic structural alterations. This has improved the diagnosis of diseases and the understanding of little-known genetic disorders. Objective: To describe the case of an adolescent with no consanguineous parents and no family history of genetic variants but with cognitive-behavioral impairment, epilepsy, hypothyroidism, tall stature, and minor facial dysmorphisms suggestive of an overgrowth syndrome. Due to the complexity of the patient's phenotype affecting multiple organs and systems, the patient underwent aCGH analysis to identify deletions or duplications. Methods: Genomic DNA was extracted from a peripheral blood sample of the patient. The DNA was labeled and hybridized using the Agilent® SurePrint G3 Human CGH array 4x180K. The data were scanned and analyzed with the Agilent CytoGenomics v5® software. Results: The aCGH analysis identified a sub-telomeric pathogenic heterozygous deletion in the chromosomal region 5q35.2-q35.3. A search was conducted in the Online Mendelian Inheritance in Man, Clinical Genome Resource, and GeneScout databases, where 12 out of 74 genes were associated with medical conditions. Of these, 9 had autosomal recessive inheritance mechanisms and the remaining 3 had autosomal dominant (AD) inheritance. For genes with AD and unclear inheritance mechanisms, and with a high risk of genotype/phenotype correlation (reversed phenotype, crucial for precise diagnosis), a Human Phenotype Ontology search was conducted. This search related the deletion to conditions such as hematological malignancy predisposition syndrome, hereditary angioedema, infantile hypercalcemia 2, Fanconi renotubular syndrome 2, nephrolithiasis/hypophosphatemic osteoporosis 1, Lewy body dementia, and Sotos syndrome. This deletion is associated with a complex phenotype, including autism spectrum disorder and several physical anomalies. Conclusions: Genetic tests such as aCGH are fundamental for diagnosing congenital anomalies and neurodevelopmental disorders. Identifying deletions in the 5q35 region enhances the understanding of polymalformative syndromes and facilitates genetic counseling, thereby improving prognosis and family planning for patients.

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Key words: neurodevelopment; conduct; autism; epilepsy; genomics; precision medicine

1. Introduction

Genomic diagnostic tests have evolved rapidly in recent decades, transitioning from low-resolution analyses to high-throughput and high-resolution genomic testing. They identify everything from modifications in specific loci, gains or losses of chromosomal regions or entire chromosomes, to changes in genomic structure or sequence, resulting in significant improvements in disease diagnosis. All of this has not only changed the way diseases are diagnosed but also increased clinical knowledge of lesser-known genetic disorders. [1, 2]

Currently, various techniques are employed for genetic analysis to identify chromosomal changes, aneuploidies, structural variants, or copy number variations (CNVs), and loss of heterozygosity; each with limitations and differences in their utility. [1, 3]

To locate CNVs, we primarily rely on chromosomal microarray analysis (CMA), which, according to different chip designs and detection principles, can be divided into single nucleotide polymorphism (SNP) and comparative genomic hybridization (aCGH), both with similar clinical utility. Their resolution is determined by the technology used and the density of the probes [2, 3].

aCGH is useful for detecting genetic CNVs with high performance in detecting unbalanced chromosomal alterations (deletions or duplications), with some platforms designed to identify alterations down to a single exon [1, 2].

Neurodevelopmental disorders in the pediatric population, with a combined prevalence close to 17%, are the most common chronic conditions in primary care. These conditions encompass a heterogeneous group of alterations in language, behavior, cognition, and motor skills that generate functional impairment not only at a personal level but also at a social, academic, and occupational level, imposing both a financial and emotional burden on both the patient and their family environment [4-6].

Being able to provide targeted genetic testing for understanding the various pathophysiological, molecular, and genetic mechanisms in patients suspected of genetic diseases shortens the diagnosis time and guides the initiation of precision and personalized therapies, leading to earlier care. It helps identify and prevent comorbidities, guide families and support groups for better understanding of the disease, share experiences that provide greater support, as well as inform prognosis and clarify the risk of recurrence, providing genetic counseling with a significant impact on family planning when making decisions about a new pregnancy, even considering in vitro fertilization in cases where it is possible [7-9]. Additionally, the lack of a clear diagnosis coupled with treatment expectations leads caregivers and patients, seeking to improve health, to a high risk of undergoing unnecessary and fruitless diagnostic studies or treatments [10, 11].

The aim of this article is to describe the case of a 17-year-old male adolescent with cognitive-behavioral impairment, epilepsy, hypothyroidism, tall stature, and minor facial dysmorphisms with clinical suspicion of overgrowth syndrome who underwent aCGH. The results revealed a pathogenic heterozygous subtelomeric deletion of the chromosomal region 5q35.2-q35.3, which includes 74 genes, some of them related to pathologies with various mechanisms of inheritance, gene penetrance, and variable expressivity.

2. Case Report

We present the case of a 17-year-old patient with no consanguineous parents and no family history of genetic variants but with cognitive-behavioral impairment associated with epilepsy, hypothyroidism, corrected strabismus, autism spectrum disorder, clinical suspicion of Sotos syndrome, overgrowth syndrome, based on a history of tall stature and a body mass index above normal standard deviations for age. Upon physical examination, the patient exhibited the following

phenotypic characteristics: macrocephaly, broad nasal bridge, almond-shaped eyes, epicanthal folds, corrected strabismus, and prognathism. Due to the complexity of the patient's phenotype affecting multiple organs and systems, the patient underwent aCGH analysis to identify deletions or duplications.

3. Methodology

An Array CGH with 180,000 probes (180K) was performed, where Comparative Genomic Hybridization array (aCGH) allows the simultaneous detection of copy number changes at the genomic level, including deletions (losses), duplications (gains), and unbalanced rearrangements.

The methodology for this test initially involved extracting genomic DNA from a peripheral blood sample of the patient and applying the corresponding quality controls. Subsequently, the patient's DNA and reference DNA (male control) were labeled and hybridized using the Agilent® SurePrint G3 Human CGH array 4x180K (array number: 252983082190_1_4-415041), following established protocols. Data scanning was then performed using SureScan®, and finally, data acquisition, quality analysis, and result analysis were completed using Agilent CytoGenomics v5® software.

4. Results

This analysis detected a pathogenic heterozygous subtelomeric deletion in the chromosomal region 5q35.2-q35.3 with genomic coordinates chr5:176517339-179570928, as represented in Figure 1 and Table 1.

Table 1. aCGH result

Copy number variant	Chromosomal location	Genomic coordinates (hg38)	Minimum size	Clinical significance
Deletion	5q35.2-q35.3	chr5:176517339-179570928	3.05 Mb	Pathogenic
Positive (abnormal). Array-CGH result (ISCN 2020): arr[GRCh38] 5q35.2-q35.3(176517339_179570928)x1 The submitted sample presents an XY genomic pattern.				

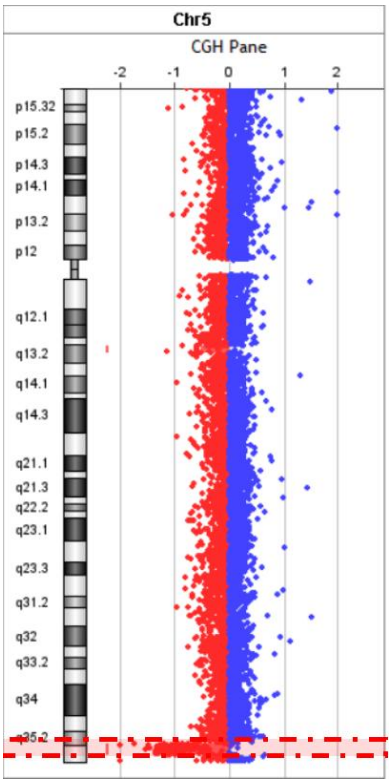

Figure 1. Schematic representation of the pathogenic deletion in the 5q35.2-q35.3 region of the patient.

The pathogenic heterozygous subtelomeric deletion of the chromosomal region 5q35.2-q35.3, with genomic coordinates chr5:176517339-179570928, is a CNV with a size of 3.05 megabases (Mb), involving 91 genes listed below: ADAMTS2, B4GALT7, CBY3, CDHR2, CLK4, COL23A1, C5orf60, DBN1, DDX41, DOK3, EIF4E1B, F12, FAM153A, FAM193B, FAM193B-DT, FGFR4, GMCL2, GPRIN1, GRK6, GRM6, HK3, HNRNPAB, HNRNPH1, LINC01574, LMAN2, LOC100128340, LOC100289470, LOC100502572, LOC105377753, LOC105377754, LOC105377757, LOC105377759, LOC105377762, LOC105377763, LOC107986489, LOC107986493, LOC107986494, LOC112267937, LOC124900195, LOC124901143, LOC124901144, LOC124901145, LOC124901146, LOC124901147, LOC124901148, LOC124901149, LOC124901224, LTC4S, MAML1, MGAT4B, MIR1229, MIR340, MIR4281, MRNIP, MRNIP-DT, MSANTD5, MXD3, N4BP3, NHP2, NSD1, PDLIM7, PFN3, PHYKPL, PRELID1, PROP1, PRR7, PRR7-AS1, RAB24, RASGEF1C, RGS14, RNF130, RMND5B, RNF44, RUFY1, RUFY1-AS1, SLC34A1, SQSTM1, SNCB, TBC1D9B, TMED9, TSPAN17, UIMC1, UNC5A, ZFP2, ZNF346, ZNF354A, ZNF354B, ZNF354C, ZNF454, ZNF454-DT, ZNF879. Of these genes, 12 are associated with diseases, which are depicted in Figure 2 [12, 13].

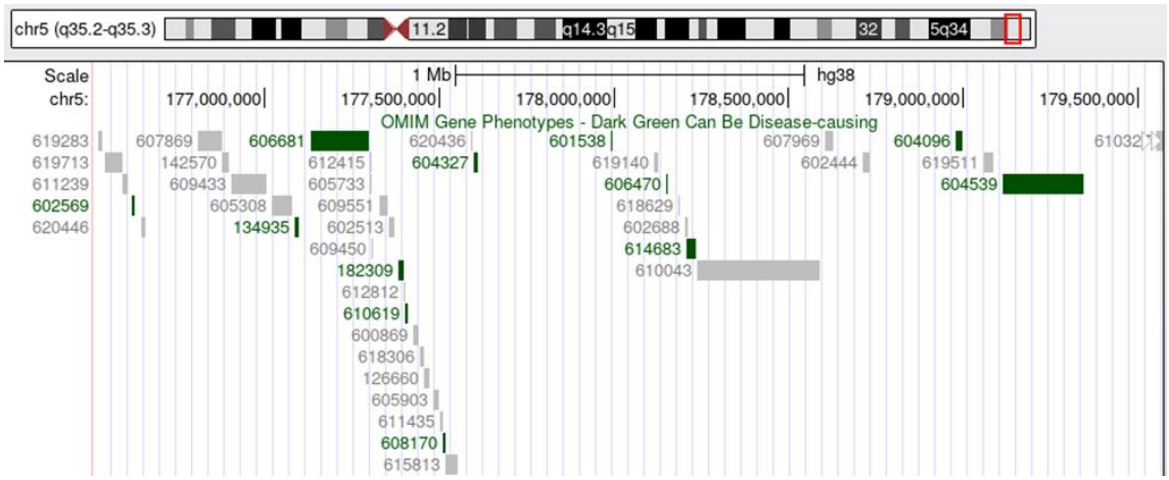

Figure 2. Graphic description of the 5q35.2-q35.3 deletion and possible related diseases by OMIM code.

To identify genes associated with pathologies included in the deleted region, a search was conducted in the OMIM (Online Mendelian Inheritance in Man) and ClinGen (Clinical Genome Resource) databases, as well as in GeneScout. It was documented that 12 out of the 74 genes are related to a condition, 9 of them with autosomal recessive inheritance mechanism and the remaining 3 with autosomal dominant inheritance (Table 2).

Table 2. Conditions related to the genes affected by the deletion of the chromosomal region 5q35.2-q35.3

Gene Gen MIM#	Gene name (in English)	Location (NCBI, GRCh38 (hg38))	Inheritance	Related disease
ADAMTS2 604539	ADAM metallopeptidase with thrombospondin type 1 element 2	chr5:179,110,853-179,345,461 (I)	A.R.	Ehlers-Danlos syndrome, dermatosparaxis type or Ehlers-Danlos syndrome type VIIC
B4GALT7 604327	β-1,4-galactosyltransferase 7	chr5:177,600,132-177,610,330	A.R.	Ehlers-Danlos syndrome, spondylodysplastic type 1
DDX41 608170	Helicase DEAD-box 41	chr5:177,511,577-177,516,961	A.D.	DDX41-related hematological malignancy predisposition syndrome
F12 610619	Coagulation factor XII	chr5:177,402,141-177,409,564	TO GIVE	Hereditary angioedema 3; Factor XII deficiency
FGFR4 134935	Fibroblast growth factor receptor 4	chr5:177,086,915-177,098,144	--	Cancer progression and tumor cell motility

Gene Gen MIM#	Gene name (in English)	Location (NCBI, GRCh38 (hg38))	Inheritance	Related disease
GRM6 604096	Metabotropic glutamate receptor 6	chr5:178,978,327-178,995,320	A.R.	Congenital stationary night blindness 1B
NHP2 606470	NHP2 ribonucleoprotein	chr5:178,149,463-178,153,885	A.R.	Autosomal recessive dyskeratosis congenita 2
NSD1 606681	Nuclear receptor binding SET domain protein 1	chr5:177,131,798-177,300,213	A.D.	Sotos syndrome
PHYKPL 614683	5-phosphohydroxy-L-lysine phospholiase	chr5:178,207,144-178,232,822	A.R.	Phosphohydroxylysinuria
PROP1 601538	PROP similar to paired homeobox 1	chr5:177,992,235-177,996,242	A.R.	Combined pituitary hormone deficiency 2
SLC34A1 182309	Solute Carrier Family 34 Member 1	chr5:177,384,434-177,398,848	AR;AD;AD	Infantile hypercalcemia 2; Fanconi renotubular syndrome 2; Nephrolithiasis/hypophosphatemic osteoporosis 1
SNCB 602569	beta synuclein	chr5:176,620,082-176,630,534	A.D.	Lewy body dementia

Taking into account the above, given that it is a heterozygous deletion for conditions with AR inheritance, the patient would be in a carrier state, which generally is asymptomatic and confers a risk of heritability.

For genes with AD inheritance mechanism, and in those where the inheritance mechanism is not clear and there is a high risk of genotype/phenotype correlation, an HPO (Human Phenotype Ontology) search is conducted, which reports (Table 3).

Table 3. HPO (Human Phenotype Ontology)

Gene	Location	Definition	NCBI Gene	Synonyms	Disease associations	
					ORPHA	OMIM
DDX41	5q35.3	DEAD box proteins, characterized by the conserved Asp-Glu-Ala-Asp (DEAD) motif, are putative RNA helicases. They are involved in a number of cellular processes involving alteration of RNA secondary structure, such as translation initiation, nuclear and mitochondrial splicing, and ribosome and spliceosome assembly.	51428	ABS, MPLPF	488647	616871
F12	5q35.3	This gene encodes coagulation factor XII which circulates in blood as a zymogen. This single chain zymogen is converted to a two-chain serine protease with a heavy chain (alpha-factor XIIa) and a light chain. The heavy chain contains two fibronectin-type domains, two epidermal growth factor (EGF)-like domains, a kringle domain and a proline-rich domain, whereas the light chain contains only a catalytic domain.	2161	HAE3, HAEX, HAF	528647, 100054, 330, 617919	610618, 234000, 330
FGFR4	5q35.2	The protein encoded by this gene is a tyrosine kinase and cell surface receptor for fibroblast growth factors. The encoded protein is involved in the regulation of several pathways, including cell proliferation, cell differentiation, cell migration, lipid metabolism, bile acid biosynthesis, vitamin D metabolism, glucose uptake, and phosphate homeostasis.	2264	CD334, JTK2, TKF	---	134935

Gene	Location	Definition	NCBI Gene	Synonyms	Disease associations	
					ORPHA	OMIM
NSD1	5q35.3	This gene encodes a protein containing a SET domain, 2 LXXLL motifs, 3 nuclear translocation signals (NLSs), 4 plant homeodomain (PHD) finger regions, and a proline-rich region. The encoded protein enhances androgen receptor (AR) transactivation, and this enhancement can be increased further in the presence of other androgen receptor associated coregulators. This protein may act as a nucleus-localized, basic transcriptional factor and also as a bifunctional transcriptional regulator.	64324	ARA267, KMT3B, SOTOS, SOTOS1, STO	1627, 116, 238613, 821, 3447, 228415	117550, 3447, 228415, 821
SLC34 A1	5q35.3	Enables sodium:phosphate symporter activity. Involved in several processes, including phosphate ion homeostasis; phosphate ion transport; and response to lead ion. Located in several cellular components, including apical plasma membrane; mitotic spindle; and nuclear speck.	6569	FRTS2, HCINF2, NAPI-3, NPHLOP1, NPT2, NPTIIa , SLC11, SLC17A2	300547, 244305, 157215, 3337	157215, 3337, 613388, 612286, 616963
SNCB	5q35.2	Encodes a member of a small family of proteins that inhibit phospholipase D2 and may function in neuronal plasticity.	6620	---	---	127750

5. Discussion

aCGH is a molecular cytogenetic technique capable of locating CNVs related to submicroscopic gains or losses at the chromosomal level, which has progressively escalated, becoming a valuable tool in the diagnosis of various conditions, displacing conventional methods as a first-line study for diagnosing patients with congenital anomalies, neurodevelopmental disorders, and even in the study of male infertility, providing faster detection of microdeletion and microduplication syndromes (Table 4) [6, 14, 15].

Table 4. Uses of comparative genomic hybridization [2-4]

Microarray chromosome	Type of alterations	Resolution	Examples of clinical indications
Comparative genomic hybridization (aCGH)	Aneuploidies, chromosomal rearrangements, copy number variants at the level of genes or exons associated with unbalanced structural changes	Based on design, usually single exon resolution for genes of interest	- As part of a phenotype-specific panel - As a complement to exome sequencing

Deletions of varying sizes that span a large genomic region often pose a challenge in understanding the precise role of specific loci among multiple genes in the onset of observed phenotypes [16]. The deletion of one gene may be compensated for or exacerbated by the deletion of another gene, resulting in unpredictable phenotypic effects. A microdeletion could confer a severe phenotype due to the involvement of causal mechanisms such as haploinsufficiency of more than one gene [16, 17].

The expression of nearby or related genes can be directly altered or through regulatory mechanisms, which can have a cascading effect on affected biological pathways. The positional effect on the regulation of gene expression flanking the microdeletion is an informative indicator of the positional effect of the studied deletions [17, 18]. The homozygosity of these regulatory genes can contribute to or modify the phenotypic characteristics [16].

Due to the complexity of genetic and molecular interactions, the deletion of multiple genes can manifest very variably in different individuals, even if they share the same deletion. [19, 20] The deletion of multiple genes can expose unexpected genetic interactions, due to the complex relationship between genes and regulatory elements within deletions. Individual genetic backgrounds may modulate the final clinical outcome of deletions in a specific region [16].

This pleiotropy could be due to the activity of proteins encoded by the remaining alleles or by compensatory mechanisms. Additionally, it is possible that the encoded genes do not equally contribute to the phenotypic characteristics or that the genes contained in the deletion lower the threshold for the expression of genetic variation in other parts of the genome [21].

According to the guidelines of the American College of Medical Genetics (ACMG) and the Clinical Genome Resource (ClinGen), alterations detected by CMA are classified as pathogenic if associated with diseases; likely pathogenic if evidence suggests an association with a disease, but additional evidence would clarify the variant's pathogenicity better; uncertain significance if there is insufficient information to consider it benign or pathogenic, in which case conducting parental studies to obtain additional information is useful to elucidate its pathogenicity; likely benign if current information does not suggest an association with a disease, but greater evidence would better explain such a condition; and benign if they are not related to any disease [4, 14, 22].

Regarding neurological disorders of unknown etiology, it has been reported that aCGH has an identification capacity between 15% and 20%, which varies depending on the symptoms, the cohort, and the type of test used [6, 23, 24]. Particularly for epilepsy with global developmental delay, intellectual disability, and Autism Spectrum Disorder (ASD), aCGH is increasingly useful for establishing diagnosis and detecting new susceptibility regions [4, 25]. These results have a strong association with associated comorbidities, where patients with syndromic conditions are more likely to present a CNV than those who do not have them, with cardiovascular and craniofacial defects being the ones that contribute most to the diagnostic possibility of CNV in patients with epilepsy or ASD [6].

In these neurological disorders, the interaction of genetic and environmental factors poses a significant challenge in etiological diagnosis, with the transcriptional component known as a key player in neurodevelopment and genetic etiology accounting for 25 to 50%. This includes single nucleotide variations, structural variants, and CNVs; the latter comprising deletions, insertions, and duplications due to errors in DNA replication or repair, which are the main causes of these disorders. They can generate different neurological development phenotypes depending on the size, number of affected genes, or compromised breakpoints, with an estimated quarter of neurological clinical manifestations being explained by CNVs of more than 400kb [5, 6, 26].

It has been found that variants and deletions in the 5q35 region trigger different polymalformative syndromes, which vary depending on the extent of involvement of the long arm of chromosome 5 in its terminal zone. These syndromes manifest with alterations in cognitive functioning, adaptive behavior, and behavior, as well as excessive growth, advanced bone maturation, and neurological involvement with hyperreflexia and hypotonia. [27, 28] Additional involvement at the level of the nervous system with agenesis of the corpus callosum, cardiovascular system with persistent ductus arteriosus and atrial septal communication, and urinary system with hydronephrosis and vesicoureteral reflux were only reported in those with deletions. [29]

The publication of Loeza et al. [30] reported on a 4-year-old patient with Sotos syndrome with a deletion 5q35.2-q35.3 [(175,571,962-177,422,761]x1) of 1.851 Mb containing 43 genes. González-Rodríguez et al. [31] reported a heterozygous deletion in 5q35.2-q35.3 (175580042-177386153) of 1.806 Mb in a patient with Sotos syndrome and nephrocalcinosis. Lin et al. [32] reported a case of a 5-year-old girl with macrocephaly, high and broad forehead,

developmental delay with a 1.86 Mb deletion in 5q35.2-q35.3 ([175559343_177422760]x1) associated with Sotos syndrome.

Deletions in chromosome 5q35.2-q35.3 result in a complete loss of the NSD1 gene (Nuclear Receptor-Binding Set Domain Protein 1), with haploinsufficiency of this gene being the main cause of Sotos syndrome (OMIM #117550), a disease with a prevalence of 1 in 15,000. It is characterized by prenatal and postnatal overgrowth with advanced bone age, gestalt facies (round face, hypertelorism, prominent forehead with frontotemporal alopecia, high-arched palate, downward slanting palpebral fissures, large ears, and pointed chin), macrodolichocephaly, and learning difficulties [30, 33, 34]. Other characteristics include neurodevelopmental delay, psychomotor difficulties, seizures, behavioral alterations, neonatal jaundice, cardiorenal malformations, and scoliosis [30].

While this syndrome presents with an autosomal dominant inheritance pattern, approximately 95% of patients have de novo variants [30]. On the other hand, these patients present an increased risk of neoplasms such as Wilms tumor, acute lymphoblastic leukemia, neuroblastoma, and sacrococcygeal teratoma, conditions that may be related to the alteration of NSD1, which is part of the NSD family, proteins that participate in chromatin integrity, whose variants at this level are associated with a variety of cancers, or due to the involvement of the FGFR4 gene (fibroblast growth factor receptor 4, OMIM #134935), which has been linked to cancer progression and the presence of metastasis [35, 36].

In the present case, it is found that the deleted region contains 12 genes with associated pathologies, where 5 of them (DDX41, F12, NSD1, SLC34A1, SNCB) have an autosomal dominant inheritance mechanism, and the FGFR4 gene without a defined mechanism but related to cancer progression/metastasis. Therefore, it is necessary to delve into the possible gene interactions contributing to the patient's phenotype.

Understanding reverse phenotyping as an approach that allows for an in-depth evaluation of unusual phenotypes, where genetic heterogeneity complicates the ability to conclude about genotypic conditions without having a substantial number of participants, avoids the inconvenience generated by inconsistent data collection. This allows for more specific and consistent phenotypic evaluations in a set of individuals with a variant. Such genotype-disease correlation expands the clinical spectrum of a known association and enables ex vivo analysis of a trait or disease, serving as a model for predictive genomic medicine [37].

Consequently, genomic determination can provide a more comprehensive picture of the pleiotropy of a genetic variant compared to phenotypic determination, without necessarily excluding one from the other. When a variant is predicted to be pathological through in silico models or when a genotype-disease association is postulated based on phenotypic determination research, reverse phenotyping can increase information about the pathogenicity of the variant in phenotypically unselected populations [37].

Interactions between proteins and small molecules are an integral part of biological processes in living organisms. Information on these interactions is dispersed over many databases, texts and prediction methods, which makes it difficult to get a comprehensive overview of the available evidence.

The NSD1 gene (Nuclear receptor SET domain-containing protein 1), UniProt A0A3G1LEI2(38), contains 541 amino acids (Figure 3) with family and domain databases: Gene3D: 3.30.40.10 Zinc/RING finger domain, C3HC4 (zinc finger) 1 hit; InterPro: IPR041306C5HCH IPR013083Znf_RING/FYVE/PHD; PANTHER: PTHR22884:SF312HISTONE-LYSINE N-METHYLTRANSFERASE, H3 LYSINE-36 SPECIFIC 1 hit PTHR22884SET DOMAIN PROTEINS 1 hit

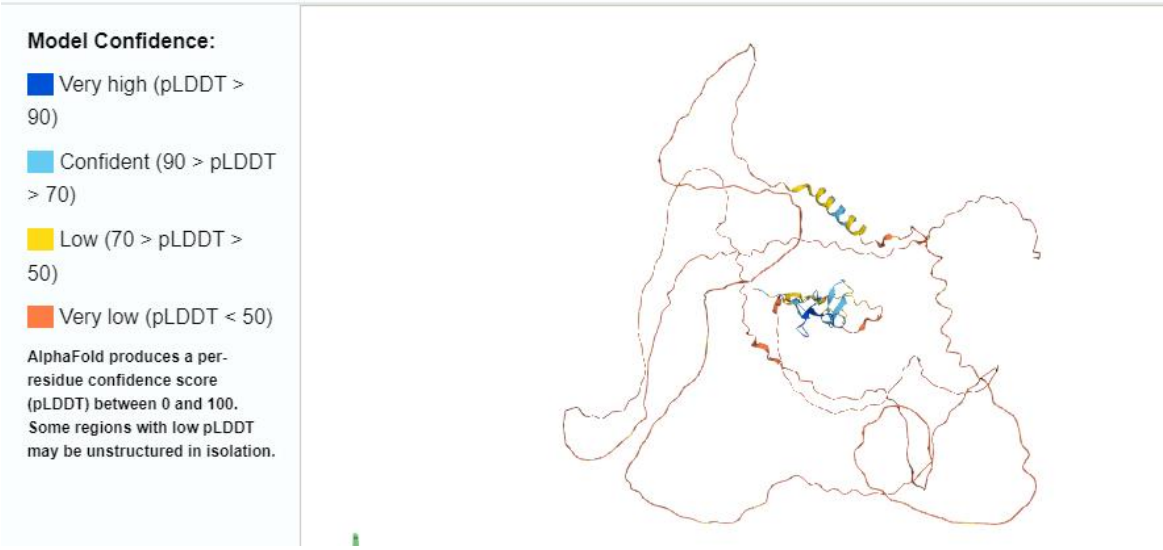

Figure 3. 3D Structure Protein (AlphaFoldDB) [38].

The concept of genetic interaction is simple, but the physiological repercussions can be profound. Genes don't usually act individually. They are part of a complex system, the genome, where genetic interactions occur, leading to the effects of one gene or genetic variant being modified by the action of another genetic element or influenced by a third [39].

Identifying interactions between genes is an essential step in understanding the functioning of cells and tissues, as well as in understanding how many human diseases occur. This knowledge could also contribute to determining why the presence of variants that should trigger a hereditary disease does not always result in pathology or why the same variant can manifest differently in two different individuals. Furthermore, since genome analysis is increasingly being used in medicine, both in diagnosis and in treatment decision-making, identifying gene interactions is especially important for providing the best patient care [39].

The basic principles emerged, allowing researchers to predict a gene's function and its relative importance for the cell's health based on its position in the network. Studies also revealed the identity of so-called "modifier genes" which can suppress the effect of damaging mutations and how genetic background influences trait inheritance.

According to STITCH (Search Tool for Interacting Chemicals), which integrates these disparate data sources for 430,000 chemicals into a single, easy-to-use resource. This gene-protein has various molecular interactions. STITCH V.5 is a database network view that gives the user the ability to view binding affinities of chemicals in the interaction network. This enables the user to get a quick overview of the potential effects of the chemical on its interaction partners. For each organism, STITCH provides a global network; however, not all proteins have the same pattern of spatial expression (Figure 4).

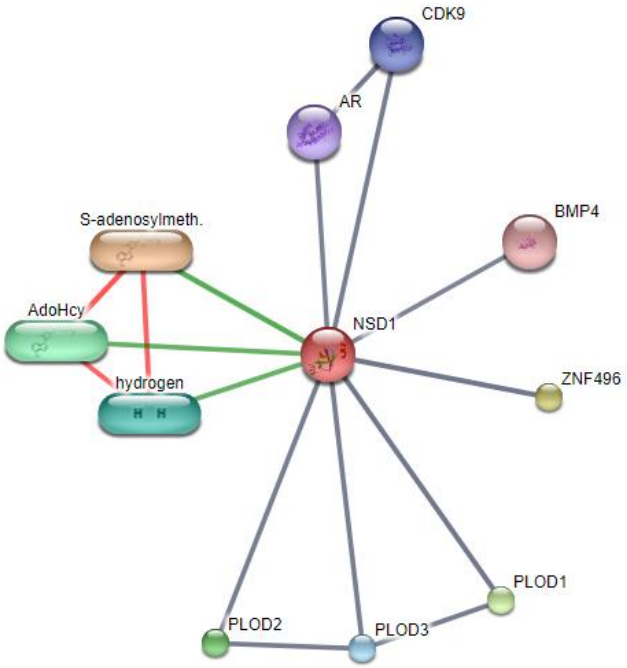

Figure 4. STITCH v.5.0 Representation of NSD1 Gene Interactions. [40]

In Figure 4, stronger associations are represented by thicker lines. Protein-protein interactions are shown in grey, chemical-protein interactions in green, and interactions between chemicals in red. Network nodes represent proteins: splice isoforms or post-translational modifications are collapsed, i.e., each node represents all the proteins produced by a single, protein-coding gene locus. Small nodes indicate proteins of unknown 3D structure, while large nodes indicate that some 3D structure is known or predicted. Edges represent protein-protein associations: associations are meant to be specific and meaningful, i.e., proteins jointly contribute to a shared function; this does not necessarily mean that they are physically binding each other. Edge confidence: low confidence edge (0.150); high confidence edge (0.700); medium confidence edge (0.400); highest confidence edge (0.900).

This gene-protein has Predicted Functional Partners:

- S-adenosylmeth: S-adenosylmethionine; Physiologic methyl radical donor involved in enzymatic transmethylation reactions and present in all living organisms. It possesses anti-inflammatory activity and has been used in the treatment of chronic liver disease. Score: 0.981

- ZNF496: zinc finger protein 496; DNA-binding transcription factor that can act as both an activator and a repressor (587 aa). Score: 0.951

- PLOD1: procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1; Forms hydroxylysine residues in -Xaa-Lys-Gly- sequences in collagens, essential for the stability of intermolecular collagen cross-links (727 aa). Score: 0.947

- PLOD2: procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2; Forms hydroxylysine residues in -Xaa-Lys-Gly- sequences in collagens, essential for the stability of intermolecular collagen cross-links (758 aa). Score: 0.902

- AdoHcy: 5'-S-(3-Amino-3-carboxypropyl)-5'-thioadenosine. Formed from S-adenosylmethionine after transmethylation reactions. Score: 0.900

- Hydrogen: In chemistry, a hydron is the general name for a cationic form of atomic hydrogen, represented with the symbol H^+ . The term "proton" refers to the cation of protium, the most common isotope of hydrogen. The term "hydron" includes cations of hydrogen regardless of their isotopic composition: thus it refers collectively to protons (1H+) for the

protium isotope, deuterons (2H+ or D+) for the deuterium isotope, and tritons (3H+ or T+) for the tritium isotope. Unlike other ions, the hydron consists only of a bare atomic nucleus. Score: 0.900

- PLOD3: procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3; Forms hydroxylysine residues in -Xaa-Lys-Gly- sequences in collagens, essential for the stability of intermolecular collagen cross-links (738 aa). Score: 0.900

- CDK9: cyclin-dependent kinase 9; Protein kinase involved in the regulation of transcription. Member of the cyclin-dependent kinase pair (CDK9/cyclin-T) complex, also called positive transcription elongation factor b (P-TEFb), which facilitates the transition from abortive to productive elongation by phosphorylating the C-terminal domain of RNA polymerase II. Score: 0.898

- AR: androgen receptor; Steroid hormone receptors are ligand-activated transcription factors that regulate eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Transcription factor activity is modulated by bound coactivator and corepressor proteins. Transcription activation is down-regulated by NR0B2. Activated, but not phosphorylated, by HIPK3 and ZIPK/DAPK3. Score: 0.874

- BMP4: bone morphogenetic protein 4; Induces cartilage and bone formation. Also acts in mesoderm induction, tooth development, limb formation, and fracture repair. Acts in concert with PTHLH/PTHRP to stimulate ductal outgrowth during embryonic mammary development and to inhibit hair follicle induction. Score: 0.859

Understanding gene interactions holds the key to personalized medicine.

GeneMANIA is a program that identifies the most related genes to a query gene set using a guilt-by-association approach. The plugin uses a large database of functional interaction networks from multiple organisms, and each related gene is traceable to the source network used to make the prediction.

A search for interactions of the 6 actionable genes by GeneMANIA was conducted, which reported Networks: Co-expression: 100%: Showing 20 related genes, with 26 total genes, 0 attributes, and 33 total links (figure 5).

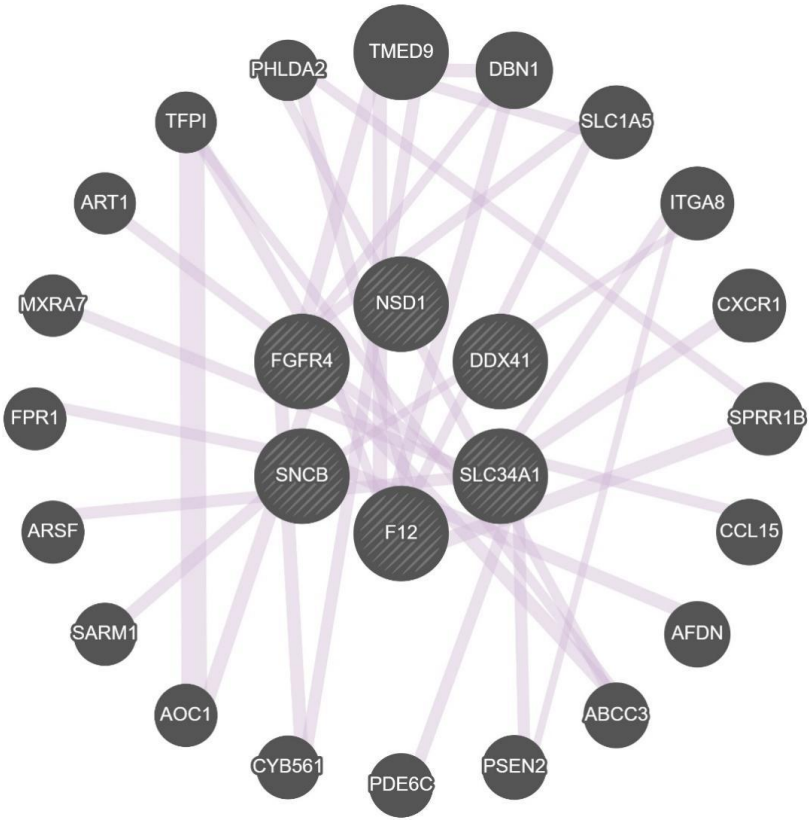

Figure 5. GeneMANIA: Interaction genes DDX41, F12, NSD1, SLC34A1, SNCB, FGFR4 [41].

Taking the above into account, it is important to evaluate the patient's clinical condition, conduct reverse phenotyping, and search for other elements of multimodal diagnosis in pursuit of personalized, preventive, predictive, and precision medicine.

6. Conclusion

Neurological disorders of unknown etiology pose a significant etiological challenge due to multiple genetic and environmental interactions, where aCGH has become a valuable tool in diagnosing various congenital anomalies, neurodevelopmental alterations, and behavioral disorders.

The presence of deletions in the 5q35 region triggers different syndromes with varied manifestations depending on the extension, highlighting neurological alterations and bone maturation abnormalities, leading to excessive growth and cognitive-behavioral impairment.

The current case presents a series of clinical manifestations consistent with reported alterations in deletions at the 5q35.2-q35.3 region. The presence of multiple genes involved in the deleted zone should prompt a deeper investigation of each one and its possible expressivity, conducting reverse phenotyping and using other complementary diagnostic strategies (multimodal management) to establish a genotype-phenotype correlation when interpreting genomic study results.

Furthermore, the subtelomeric deletion reported in this case, with an extension of 3.05 Mb, has not been previously reported according to the reviewed literature, thereby contributing to new knowledge. A holistic approach to the patient is emphasized to establish a specific diagnosis, initiate targeted therapeutic options, determine prognosis, establish follow-up guidelines, provide genetic counseling, and search for possible carriers, all in pursuit of personalized, preventive, predictive, and precision medicine.

Bioinformatics

The chromosomal regions were evaluated using information provided by the Online Mendelian Inheritance in Man (OMIM, http://omim.org/), Genescout (https://genescout.omim.org/), DECIPHER (http://decipher.sanger.ac.uk), UCSC (http://genome.ucsc.edu), ClinGen (http://dosage.clinicalgenome.org/), Human Phenotype Ontology (HPO, https://hpo.jax.org/), UniProt (https://www.uniprot.org/), InterPro (https://www.ebi.ac.uk/interpro/), AlphaFold (https://alphafold.ebi.ac.uk/), STITCH v.5.0 (http://stitch.embl.de/), GeneMania (https://genemania.org/) databases

Declarations

Ethics approval and consent to participate: Not applicable to this case report.

Consent for publication: Written and oral informed consent was obtained from patient and/or their legally authorized representative (LAR).

Availability of data and materials: The dataset supporting the conclusions of this article is included within the article.

Competing interests: The authors declare that they have no competing interests. This manuscript is not being considered by any other journal.

Authors' Contributions

Each author contributed to the redaction, proofreading, and correction of the manuscript. DPB and NYM contributed to the research, writing, and proofreading, while LJNM contributed in corrected and adding relevant medical changes to the case. All authors read and approved the final manuscript. All authors participated in the acquisition, analysis, and interpretation of the data. Each author has agreed both to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, (even ones in which the author was not personally involved), are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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