

PSEUDOTRISOMY 18

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Introduction and Definition of Pseudotrismy 18

Pseudotrismy 18 describes a rare and severe congenital disorder characterized by a constellation of complex clinical features that are virtually indistinguishable from those observed in true Trisomy 18 (Edwards Syndrome). The designation 'pseudo' is critical, as it signifies that the affected individuals exhibit the full phenotypic spectrum of Trisomy 18—including severe growth restriction, multiple major congenital anomalies, and distinctive dysmorphic features—yet possess a normal karyotype with respect to chromosome 18. This fundamental cytogenetic distinction means that the condition is not caused by the presence of a third copy of chromosome 18, but rather by an underlying, non-aneuploidic genetic mechanism that results in a profound disruption of early embryonic development, mimicking the widespread effects of the chromosomal imbalance. The clinical recognition of this phenocopy is vital, necessitating specialized diagnostic pathways to identify the specific molecular etiology rather than assuming the standard recurrence risks and underlying pathology associated with classic aneuploidy.

The disorder is classified as a phenocopy, meaning it shares the physical appearance and severe systemic impact of a well-known genetic condition, but originates from a different genetic cause. While true Trisomy 18 is a large-scale genomic disorder typically arising sporadically from non-disjunction, **Pseudotrismy 18** is often caused by specific gene mutations, possibly following Mendelian inheritance patterns, such as autosomal recessive inheritance. This distinction carries immense weight for genetic counseling and future family planning. The condition's severity is evidenced by the consistent presence of profound developmental compromise across all affected subjects, confirming the intrinsic, destructive nature of the underlying genetic lesion. The symptoms converge upon the Trisomy 18 phenotype because the causative gene mutation, regardless of its chromosomal location, interferes with the same critical developmental pathways that are disrupted by the dosage imbalance of chromosome 18 genes.

Etiology and Genetic Differentiation

The etiology of **Pseudotrismy 18** is inherently heterogeneous, reflecting the fact that multiple, distinct molecular errors can lead to the converging phenotype. The primary task of genetic differentiation is the definitive exclusion of chromosome 18 trisomy through high-resolution cytogenetic testing, such as karyotyping, Fluorescence In Situ Hybridization (FISH), or chromosomal microarray analysis (CMA). Once this major aneuploidy is ruled out, investigation focuses on identifying pathogenic variants in specific genes that govern organogenesis and central nervous system development. Research suggests that mutations in genes responsible for regulating crucial embryonic processes, such as cellular proliferation, migration, and differentiation, are the most likely candidates. The wide variation in specific underlying genetic faults means that **Pseudotrismy 18** is not a single molecular entity but rather a descriptive classification encompassing several rare, severe monogenic syndromes.

In many instances, the specific molecular cause remains elusive, though advancements in whole-exome sequencing (WES) are increasingly linking cases to specific gene mutations. The identified pathogenic variants often appear in genes that, when mutated, cause syndromes known to overlap phenotypically with Trisomy 18, such as forms of lethal multiple pterygium syndrome or specific types of primary microcephaly syndromes. Furthermore, some cases may involve complex, subtle genomic rearrangements, like microdeletions or microduplications in non-chromosome 18 regions, that disrupt dosage-sensitive genes critical for the developmental profile. The necessity of this detailed molecular analysis highlights the transition in genetic diagnostics from broad chromosomal screening to precise, sequence-level investigation, especially when dealing with phenocopies of major aneuploidies.

Understanding the specific genetic mechanism is paramount for accurate counseling. If the underlying condition is autosomal recessive, parents who are unaffected carriers face a 25% risk of recurrence in subsequent pregnancies, a stark difference from the typically low recurrence risk associated with the sporadic nature of full Trisomy 18. This genetic differentiation impacts reproductive choices and allows families access to technologies such as preimplantation genetic diagnosis (PGD). Therefore, the diagnostic process requires a systematic, multi-step approach: clinical recognition of the phenotype, cytogenetic confirmation of a normal karyotype, followed by advanced molecular sequencing to pinpoint the responsible locus. This meticulous methodology ensures that patients are provided with the most accurate prognostic and risk information possible.

Clinical Manifestations and Phenotype

The clinical manifestations of **Pseudotrismy 18** are characterized by their profound severity and multi-systemic involvement, faithfully replicating the features of Edwards Syndrome. Typically observed features include severe intrauterine and postnatal growth restriction, resulting in low birth weight and microcephaly. Characteristic craniofacial dysmorphism often includes micrognathia (small jaw), cleft lip and/or palate, and low-set, abnormally shaped ears. Distinguishing limb anomalies are also consistently present, notably the characteristic overlapping or "clenched" finger position (clenched hands with the index finger overlapping the third finger), hypoplastic nails, and various forms of foot deformities, such as rocker-bottom feet or talipes equinovarus (clubfoot). These external stigmata raise the initial clinical suspicion, demanding immediate and rigorous investigation to differentiate the condition from true Trisomy 18.

Internally, the structural anomalies are often life-threatening and involve the major organ systems. Congenital heart defects (CHDs) are nearly universal and represent the primary cause of early morbidity and mortality. Common cardiac findings include large ventricular septal defects (VSDs), atrial septal defects (ASDs), and complex valvular anomalies or outflow tract obstructions. Furthermore, renal malformations are highly prevalent, including horseshoe kidneys, hydronephrosis, or polycystic kidneys, leading to compromised renal function. Gastrointestinal

abnormalities, such as Meckel's diverticulum, malrotation, or omphalocele, may also contribute to the complex clinical picture. The combination of these severe structural defects necessitates highly specialized neonatal intensive care and often dictates therapeutic decisions regarding the feasibility and ethics of aggressive surgical intervention.

A defining and non-negotiable component of the **Pseudotrisomy 18** phenotype is the presence of **severe intellectual disability**. This universal finding confirms that the underlying genetic error profoundly impacts the development and function of the central nervous system. The severity of the cognitive impairment dictates that affected individuals require comprehensive, lifelong supportive care, being unable to achieve independent developmental milestones. While the specific physical malformations may exhibit slight variation depending on the precise genetic mutation, the consistently devastating neurological outcome serves as a critical diagnostic and prognostic marker, underscoring the classification of this syndrome as one of profound developmental impairment.

Neurological Implications and Intellectual Disability

The neurological consequences of **Pseudotrisomy 18** are among the most debilitating aspects of the syndrome, characterized by extensive structural brain abnormalities and resultant severe global developmental delay. Structural defects visualized on neuroimaging can include anomalies of the cerebral cortex, corpus callosum agenesis, or cerebellar hypoplasia, reflecting fundamental errors in neurogenesis that occur during the critical periods of embryonic development. These structural lesions directly correlate with the severity of the intellectual disability, which is uniformly classified within the severe to profound range. The faulty genetic programming responsible for the peripheral anomalies is equally damaging to the central nervous system, ensuring that cognitive development is severely restricted regardless of the specific underlying molecular mechanism.

Developmental milestones, including sitting, walking, and meaningful language acquisition, are significantly delayed or entirely absent. Motor development is typically compromised by generalized hypotonia (low muscle tone) and central motor dysfunction, often leading to limited mobility. Moreover, associated neurological complications, such as intractable epilepsy (seizure disorders), are frequently observed, requiring complex pharmacological management. Feeding difficulties, stemming from poor oral motor coordination and underlying neurological deficits, are constant challenges, often necessitating the placement of a gastrostomy tube to ensure adequate hydration and nutrition, crucial for managing the child's fragile health status.

The historical observation that **all affected subjects have evidence of mental retardation** remains a cornerstone of the diagnosis. This requirement ensures that the disorder is fundamentally linked to a global developmental failure rather than being a syndrome of isolated structural defects. The consistent severity of the intellectual impairment dictates that management

focuses heavily on supportive, palliative, and rehabilitative strategies, utilizing physical therapy, occupational therapy, and communication specialists to optimize the quality of interaction and comfort, accepting the non-reversible nature of the cognitive deficit. The pervasive neurological involvement confirms the high level of genetic disruption inherent in conditions mimicking major aneuploidies.

Diagnostic Criteria and Differential Diagnosis

The diagnostic pathway for **Pseudotrismy 18** mandates a dual approach: clinical recognition followed by rigorous genetic exclusion. The initial suspicion is raised by the presence of multiple, severe congenital anomalies characteristic of Edwards Syndrome. However, the definitive diagnostic step is the confirmation of a normal, euploid karyotype regarding chromosome 18. This is typically achieved through high-resolution cytogenetic analysis. Once true Trisomy 18 is ruled out, the diagnosis shifts to **Pseudotrismy 18**, which then necessitates a comprehensive differential diagnosis to pinpoint the specific molecular etiology. This systematic process is essential for providing accurate prognostic information and genetic counseling.

Differential diagnoses include ruling out other phenotypically similar, yet distinct, congenital syndromes. These include specific microdeletion syndromes, such as 22q11.2 deletion syndrome (DiGeorge syndrome) which shares some cardiac features, or rare monogenic disorders known to cause severe fetal growth restriction and multiple malformations, such as certain types of restrictive dermopathy or severe forms of syndromic arthrogryposis. The breadth of the differential reflects the fact that numerous genetic pathways, when disrupted, can lead to developmental convergence. The current gold standard for resolving the differential diagnosis is often whole-exome sequencing, which attempts to identify a specific, causative gene mutation that explains the pattern of defects.

The diagnostic necessity of distinguishing **Pseudotrismy 18** from true Trisomy 18 is crucial for genetic counseling. A misdiagnosis could lead to significantly incorrect assessment of recurrence risk for future pregnancies. True Trisomy 18 is generally associated with a low recurrence risk (excluding cases related to rare parental translocations), whereas many underlying causes of **Pseudotrismy 18** carry substantial recurrence risks (e.g., 25% for autosomal recessive disorders). Therefore, the process mandates precision, moving beyond mere phenotypic observation to confirm the absence of aneuploidy and, ideally, identifying the precise monogenic cause.

Management and Therapeutic Approaches

Management of an individual diagnosed with **Pseudotrismy 18** is highly complex, focusing primarily on supportive care, symptom management, and addressing the severe, multi-systemic

congenital defects. Given the uniformly poor prognosis and the severity of the neurological impairment, therapeutic decisions often involve delicate ethical considerations regarding the extent of aggressive medical intervention versus a focus on palliative care and maximizing comfort. Immediate postnatal care requires the coordination of a specialized multidisciplinary team, including neonatologists, pediatric cardiologists, surgeons, and geneticists.

Key areas of ongoing management include:

Cardiovascular and Respiratory Support: Addressing severe congenital heart defects (CHDs) through medication or, selectively, surgical repair, balanced against the overall prognosis. Managing chronic respiratory insufficiency and recurrent infections.

Nutritional Intervention: Overcoming severe feeding difficulties and failure to thrive, almost always requiring specialized methods like nasogastric or gastrostomy tube feeding to ensure adequate caloric intake.

Neurological Management: Pharmacological treatment of seizures and providing intensive physical, occupational, and developmental therapies tailored to the patient's profound delays.

Symptom Palliation: Ensuring comfort, managing pain associated with skeletal and muscular anomalies, and preventing secondary complications such as aspiration pneumonia.

The goal of these therapeutic strategies is to mitigate suffering and manage acute crises, rather than achieving a cure, as the underlying developmental errors are irreversible.

Genetic counseling is integral to the therapeutic approach, particularly once the specific etiology of the **Pseudotrismy 18** is confirmed. Families require detailed explanations of the disorder, its natural history, and, critically, the mechanism of inheritance. If an autosomal recessive pattern is identified, genetic counselors provide support regarding reproductive options, including the availability of prenatal diagnosis or preimplantation genetic diagnosis for future pregnancies. Furthermore, counseling provides crucial psychological and emotional support, assisting families in navigating the profound challenges and complex, difficult decisions related to the care of a child with a severe, life-limiting congenital syndrome.