

Escobar Syndrome: A Case Report of a Neonate with a Homozygous CHRNG Pathogenic Variant (c.459dup, p.Val154Serfs*24) Diagnosed Prenatally via Whole Exome Sequencing

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Abstract:

*Escobar syndrome (OMIM #265000) is a rare autosomal recessive disorder caused by CHRNG (OMIM #100730) mutations affecting the fetal acetylcholine receptor, leading to joint contractures, pterygia, and variable multisystem involvement. We report a 9-day-old male neonate prenatally diagnosed via whole exome sequencing, who presented with characteristic joint contractures, neck webbing, and a narrow chest, along with scoliosis, a tethered cord, cardiac anomalies (PFO, PDA), and a duplicated right collecting system. Genetic analysis revealed a homozygous c.459dup mutation in CHRNG (p.Val154Serfs*24), confirming the diagnosis. A multidisciplinary approach was promptly initiated, including respiratory support, orthopedic management, cardiac monitoring, and genetic counseling. This case broadens the clinical spectrum of Escobar syndrome and underscores the importance of early molecular diagnosis in guiding management and family counseling.*

Introduction:

“Escobar syndrome (OMIM #265000) is a rare autosomal recessive disorder caused by CHRNG (OMIM #100730) mutations affecting the fetal acetylcholine receptor, leading to joint contractures, pterygia, and variable multisystem involvement.”

Escobar syndrome, also known as multiple pterygium syndrome (non-lethal type), is a rare congenital disorder characterized by joint contractures, skin webbing (pterygia), and multisystem involvement. The syndrome arises from pathogenic variants in the CHRNG gene, which encodes the gamma subunit of the fetal acetylcholine receptor—a critical component for neuromuscular development during gestation. Inheritance is autosomal recessive, necessitating that affected individuals inherit a pathogenic variant from both carrier parents (1, 2).

Diagnosing Escobar syndrome poses significant challenges due to its phenotypic overlap with other arthrogryposis syndromes and neuromuscular disorders. The variability in clinical presentation—even among patients with identical mutations—complicates early diagnosis and may delay appropriate intervention. As a result, molecular genetic testing, such as whole exome sequencing (WES), has become an invaluable tool in distinguishing Escobar syndrome from other congenital contracture disorders (3, 4).

According to available medical literature, only a limited number of Escobar syndrome cases have been reported, with estimates ranging from around 50 cases (OMIM#265000). Reporting this

case is significant as it contributes to the growing literature on the variable expressivity of Escobar syndrome and highlights the critical role of prenatal and postnatal genetic evaluations in guiding management.

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Case Description:

JM is a 9-day-old male neonate who was prenatally diagnosed with Escobar syndrome after whole exome sequencing (WES) was performed on amniotic fluid. His prenatal evaluation revealed several congenital anomalies, including right hydronephrosis, rocker bottom feet, a ventricular septal defect (VSD), cystic hygroma, and increased nuchal translucency. Born at 39 weeks and 1 day via Cesarean section, he weighed 3205 g and presented with a constellation of findings that underscored the severity of his condition.

Immediately after birth, JM exhibited several characteristic features associated with Escobar syndrome. Notably, he had scoliosis, which was evident in imaging studies, a tethered cord at the level of L3, and undescended testes. On physical examination, distinct findings included low-set ears, a webbed neck (pterygium), redundant skin around the neck and joints, and a relatively narrow chest. Joint contractures were apparent in multiple regions, particularly affecting the elbows, knees, and fingers. Family history showed that the father has a bicuspid aortic valve, and there are reports of arthrogryposis and joint contractures in extended family members, although no consanguinity was reported.

Neuroimaging revealed prominent left frontal and anterior temporal extra-axial spaces, mild mandibular hypoplasia with retrognathia, low-set ears, and right posterior scalp edema, suggesting a possible syndromic etiology. Spinal imaging

demonstrated a right convex thoracic scoliosis with a rotatory component and a low-lying, tethered spinal cord at L3, raising concerns for potential neurological complications. The cardiac evaluation identified a patent foramen ovale (PFO) with a small shunt and a trivial patent ductus arteriosus (PDA) with left-to-right shunting, though ventricular function remained normal. Abdominal ultrasound revealed a duplicated right collecting system with two ureters, calyceal dilatation in the right lower pole moiety (UTD P2), and echogenic debris, possibly indicating urinary stasis or early infection. Genitourinary imaging confirmed bilateral undescended testes but otherwise normal testicular and epididymal structures. These findings suggest a complex congenital disorder, necessitating further genetic evaluation and a multidisciplinary approach for long-term management.

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Genetic Testing and Findings:

Prenatal genetic evaluation was initiated following the detection of multiple congenital anomalies on ultrasound. Whole exome sequencing (WES) was performed on amniotic fluid using next-generation sequencing (NGS) technology. The WES analysis identified a homozygous duplication in the *CHRNA3* gene, specifically c.459dup, which is predicted to cause a frameshift and premature protein termination (p.Val154Serfs*24). This variant disrupts the normal function of the fetal acetylcholine receptor and has been previously reported in association with Escobar syndrome, thereby supporting its classification as pathogenic (1, 2). Population frequency data from databases such as gnomAD further corroborate its rarity, consistent with a disorder inherited in an autosomal recessive manner (3, 4). Both parents are heterozygous carriers of the pathogenic *CHRNA3* allele.

Management and Outcome:

Following the confirmation of the diagnosis, a comprehensive multidisciplinary management plan was promptly instituted to address JM's complex clinical needs. He was maintained on continuous positive airway pressure (CPAP) therapy to ensure adequate respiratory function with vigilant oxygen saturation monitoring. Once the impact of his musculoskeletal abnormalities, particularly scoliosis and joint contractures, were recognized, the orthopedic team and physical and occupational therapy were

involved. These therapies aim to improve joint flexibility, enhance motor function, and prevent the progression of contractures, which are key concerns in patients with Escobar syndrome. The Cardiac team managed cardiac anomalies. Integral to the overall management was genetic counseling. The family received detailed education regarding the autosomal recessive inheritance pattern of Escobar syndrome, emphasizing the 25% recurrence risk for future pregnancies.

The patient was transferred to another hospital for continuing care. Overall, this tailored, multidisciplinary approach has been fundamental in addressing the diverse clinical challenges posed by Escobar syndrome, thereby optimizing his immediate care and establishing a framework for long-term management.

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Discussion:

Disease Features:

Escobar syndrome, also known as non-lethal multiple pterygium syndrome, is characterized by a distinct constellation of clinical features. Patients typically present with joint contractures and skin webbing (pterygia), particularly around the neck and major joints, which form the hallmarks of the condition. Common features include scoliosis, short stature, and facial dysmorphisms, such as low-set ears and micrognathia. Cardiac anomalies (for example, a patent foramen ovale or patent ductus arteriosus) and urogenital abnormalities (such as undescended testes or duplicated collecting systems) are also documented, albeit less frequently. These clinical findings, when observed in conjunction with prenatal or postnatal imaging and physical examination, contribute significantly to the diagnostic criteria of the syndrome. Given the overlap in features with other arthrogryposis syndromes and congenital contracture disorders, differential considerations include arthrogryposis multiplex congenita and the lethal forms of multiple pterygium syndrome, among others (1, 2).

A literature review reveals a broad phenotypic spectrum associated with Escobar syndrome. While many affected individuals display classic musculoskeletal abnormalities, several studies have reported significant variability in systemic involvement. For instance, Carrera et al. and Dahan-Oliel et al. (3, 4) have described cases where, in addition to joint contractures and pterygia, patients exhibit cardiac defects, urogenital anomalies, and even neurological abnormalities such as a tethered cord. This phenotypic heterogeneity underscores the challenges of making a definitive diagnosis based solely on clinical findings and

emphasizes the indispensable role of molecular genetic testing in establishing the diagnosis.

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The case presented here not only manifests the classic features of Escobar syndrome—such as joint contractures and neck webbing—but also includes additional less frequently reported anomalies.

Disease Pathophysiology:

Escobar syndrome is fundamentally a neuromuscular development disorder resulting from *CHRNA3* gene mutations, which encode the gamma subunit of the fetal acetylcholine receptor (AChR) (5). During fetal development, the gamma subunit plays an essential role in the formation and function of the AChR at the neuromuscular junction. In normal physiology, this receptor facilitates the transmission of nerve impulses to muscle fibers, thereby promoting fetal movement. As development progresses, the gamma subunit is typically replaced by the epsilon subunit after birth, allowing for the maturation of neuromuscular transmission (6).

The *CHRNA3* mutation identified in our patient—c.459dup, which causes a frameshift and premature protein termination (p.Val154Serfs*24)—leads to the production of a truncated, non-functional protein (7). This molecular defect disrupts the assembly and clustering of the fetal AChR, leading to impaired neuromuscular transmission. The resulting reduction in fetal movement, known as fetal akinesia, is thought to be the initiating event in the cascade that leads to the multiple joint contractures and pterygia characteristic of Escobar syndrome (8).

At the cellular level, the absence of a functional gamma subunit hinders the proper formation of the receptor complex, thereby compromising synaptic stability and signaling at the neuromuscular junction. This disruption affects muscle development and function and contributes to secondary structural anomalies

such as scoliosis and other skeletal deformities observed in affected individuals (9). Animal studies and in vitro models have corroborated the critical role of the gamma subunit in maintaining synaptic integrity, highlighting its importance in ensuring normal neuromuscular development (10).

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Genetics and Genotype-Phenotype Correlations:

The *CHRNA3* gene, located on chromosome 2q37.1, encodes the gamma subunit of the fetal acetylcholine receptor (AChR), which is critical for neuromuscular junction formation during fetal development. Escobar syndrome follows an autosomal recessive inheritance pattern. This transmission mode means that affected individuals inherit pathogenic variants from both parents, typically asymptomatic carriers. Over the years, several mutations in *CHRNA3* have been reported to be associated with Escobar syndrome. The spectrum of mutations includes frameshift, nonsense, and splice-site variants. Among these, frameshift mutations, such as the c.459dup identified in our patient, are most commonly encountered and lead to premature protein termination and a loss of function of the gamma subunit. These truncating mutations are consistent with the disorder's pathogenic mechanism (1, 2).

Genotype-phenotype correlations in Escobar syndrome remain complex and only partially defined (11). Although truncating mutations typically suggest a severe loss-of-function scenario, the clinical manifestations among affected individuals vary considerably. Some studies have noted that while many patients exhibit the classic features of joint contractures and pterygia, there is significant variability in the degree of cardiac, skeletal, and urogenital involvement, and interfamilial variability of severity is also reported (7). This heterogeneity implies that additional genetic or environmental modifiers may influence the final phenotype.

Current Management and Future Directions:

Currently, the management of Escobar syndrome is predominantly

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supportive, as no curative treatments exist for this condition. A multidisciplinary approach is essential to address the diverse and multisystemic manifestations of the disorder. Respiratory support remains a cornerstone of management. In neonates with chest wall deformities that compromise lung function, continuous positive airway pressure (CPAP) and other supportive measures are utilized to maintain adequate oxygenation and prevent respiratory complications (2). Orthopedic management is equally critical; physical and occupational therapy is initiated early to improve joint mobility and mitigate the progression of joint contractures. Surgical interventions may be warranted in patients with severe skeletal deformities, such as pronounced scoliosis, to correct deformities and improve overall function (3). Cardiac monitoring is also integral, given the frequent association of congenital heart defects—such as a patent foramen ovale (PFO) and a patent ductus arteriosus (PDA)—with Escobar syndrome. Regular follow-up with pediatric cardiology allows timely intervention should these anomalies evolve or lead to complications (1). Genetic counseling is provided to affected families to explain the autosomal recessive inheritance pattern, the resultant 25% recurrence risk for future pregnancies, and the importance of parental carrier testing. This counseling is crucial for informed reproductive planning and the early diagnosis of subsequent cases.

Regarding emerging therapies, while gene therapy has shown promise in several neuromuscular disorders, its application in Escobar syndrome remains experimental. Preclinical studies targeting neuromuscular junction defects have yielded encouraging results in related conditions (12); however, these approaches have not yet progressed to clinical trials for Escobar syndrome (4). Similarly, other molecular therapies, such as cholinesterase inhibitors, have been investigated in disorders with neuromuscular transmission defects (13, 14), but their utility in correcting the specific pathogenesis of Escobar syndrome is limited due to the irreversible nature of the CHRNG defect.

Thus, while current supportive measures can significantly improve quality of life and mitigate complications, their effectiveness is inherently constrained by the underlying genetic defect. Continued

research into targeted molecular and gene therapies is essential to develop interventions that address the root cause of the disorder, potentially altering its natural course in the future.

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Literature review:

A literature review reveals that the core clinical features of Escobar syndrome—namely joint contractures and pterygia—are consistently observed across reported cases. However, our patient's presentation is distinguished by additional anomalies, such as a tethered cord, pronounced scoliosis, and combined cardiac and urogenital malformations. While similar multisystem involvement has been noted in studies by (3, 4), the extent and combination of these features in our case broaden the recognized phenotypic spectrum of Escobar syndrome.

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This case contributes to the existing knowledge base by underscoring the heterogeneity of clinical presentations associated with CHRNG mutations. It reinforces the importance of a thorough, multidisciplinary diagnostic approach integrating advanced

prenatal genetic testing—such as whole exome sequencing—with detailed postnatal clinical, imaging, and family evaluations. The early identification of the homozygous c.459dup mutation confirmed the diagnosis and facilitated the implementation of targeted supportive care, which is crucial for optimizing outcomes.

Challenges in this case primarily stemmed from the variability in clinical presentation, which necessitated comprehensive evaluation and coordination among multiple specialties. This case, therefore, not only corroborates current beliefs regarding the role of CHRNG mutations in Escobar syndrome but also extends our understanding by demonstrating that the clinical spectrum can be broader than previously recognized. Such evidence supports the ongoing evolution of clinical practice, where individualized and comprehensive management plans are imperative for patients with rare genetic disorders.

Conclusion:

This case report of a neonate with Escobar syndrome—confirmed by a homozygous CHRNG pathogenic variant (c.459dup, p.Val154Serfs*24)—highlights the clinical heterogeneity of the condition, multisystem nature and the diagnostic challenges posed by its variable expression. The main findings include the presence of characteristic joint contractures, neck webbing, and additional anomalies such as scoliosis, a tethered cord, and cardiac and urogenital malformations. These findings confirm the diagnosis and expand the known clinical spectrum of Escobar syndrome, emphasizing the need for comprehensive diagnostic evaluations that integrate advanced prenatal genetic testing with detailed postnatal assessments.

The implications of this case are significant for both clinical practice and future research. Clinically, it reinforces the importance of a multidisciplinary approach that includes respiratory, orthopedic, cardiac, and genetic expertise in managing patients with complex congenital disorders. Moreover, early and precise genetic diagnosis using methods such as whole-exome sequencing can facilitate timely interventions and better-informed genetic counseling, ultimately improving patient outcomes. From a research perspective, the variability observed in this case highlights the necessity of further studies into genotype-phenotype correlations and the exploration of potential targeted therapies, including emerging gene-based interventions.

Take-Home Messages:

- **Early Diagnosis is Critical:** Utilizing advanced genetic testing such as whole exome sequencing enables early and accurate diagnosis, which is crucial for timely intervention and management in neonates with rare congenital disorders like Escobar syndrome.
- **Phenotypic Variability:** Escobar syndrome exhibits a broad spectrum of clinical features—from classic joint contractures and pterygia to atypical findings such as scoliosis, tethered cord, and combined cardiac and urogenital anomalies—highlighting the complexity of genotype-phenotype correlations.
- **Multidisciplinary Management is Essential:** Effective care requires the collaboration of respiratory, orthopedic, cardiac, and genetic specialists. A coordinated approach improves overall patient outcomes by addressing the multisystem nature of the disorder.
- **Importance of Genetic Counseling:** Due to its autosomal recessive inheritance pattern, families should receive detailed genetic counseling regarding a 25% recurrence risk for future pregnancies, and parental carrier testing is recommended.

- **Ongoing Research and Future Therapies:** While current management is supportive, the case underscores the need for further research into targeted molecular therapies and gene-based interventions that could address the root genetic defect.
- **Contribution to Clinical Knowledge:** Reporting and analyzing cases with atypical and multisystem involvement expand our understanding of the disorder, inform clinical practice, and guide future research in rare congenital syndromes.

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