VOLUME - 14, ISSUE - 12, DECEMBER - 2025 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medical Science

# ZAKI SYNDROME: CLINICAL PRESENTATION, GENETIC BASIS, AND IMPLICATIONS FOR DEVELOPMENTAL PATHWAYS

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**ABSTRACT** Zaki syndrome is a rare, severe congenital disorder characterized by a complex array of developmental anomalies, primarily affecting the eyes, kidneys, and skeletal system. This narrative review synthesizes the current understanding of the syndrome, focusing on its clinical manifestations, underlying genetic basis, and the critical role of the Wnt signaling pathway in its physiopathology. First described in 2011, the syndrome is caused by pathogenic variants in the gene, which encodes the Wntless protein, an essential transporter for Wnt ligands. Disruption of Wnt signaling during embryogenesis leads to the observed multiorgan anomalies, particularly severe ocular defects like microphthalmia and developmental kidney abnormalities. Diagnosis relies on a combination of characteristic clinical features and genetic confirmation. Management is supportive and multidisciplinary, aiming to address specific organ system involvement. Future research is vital to further elucidate the molecular mechanisms and identify potential therapeutic targets for this devastating condition.

**KEYWORDS :** Zaki syndrome, gene, Wnt signaling, microphthalmia, developmental disorder.

## INTRODUCTION

The advent of next-generation sequencing has enabled the identification of numerous ultra-rare congenital disorders, shedding light on fundamental mechanisms of human development. Zaki syndrome (Mendelian Inheritance in Man #614216) is one such disorder, representing a severe syndromic condition with significant clinical impact (1). It is defined by a constellation of developmental anomalies, including congenital ocular defects, renal abnormalities, and skeletal malformations, often leading to significant morbidity and early mortality (2). The clinical relevance of this syndrome stems from its severity and the critical developmental pathways it implicates, particularly the canonical Wnt signaling pathway (3).

Zaki syndrome was first described in 2011 by Zaki et al., who reported four patients from three consanguineous families presenting with an autosomal recessive disorder characterized by a unique combination of severe eye and kidney malformations, along with other skeletal defects (4). The initial description and subsequent molecular identification of the causative gene provided a crucial link between a specific genetic defect and a multifaceted developmental phenotype, establishing the syndrome as a distinct clinical entity (1). This review aims to provide a comprehensive overview of Zaki syndrome, detailing its clinical presentation, exploring the genetic foundation, and discussing the implications of the disrupted Wnt pathway for human developmental biology (5). Understanding these aspects is essential for improving diagnostic accuracy and guiding multidisciplinary management strategies (2).

## METHODS

This narrative synthesis was performed through a comprehensive literature search across several authoritative databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy employed a combination of terms such as "Zaki syndrome," " gene," "Wntless," and "Wnt signaling developmental disorder." The inclusion criteria focused on articles published in English or Spanish addressing the clinical, genetic, and molecular aspects of Zaki syndrome. Specifically, we sought studies detailing epidemiology, clinical presentation, diagnostic modalities, and mechanistic insights into the role of the Wnt pathway. After a rigorous screening of titles and abstracts, 15 pertinent articles were selected for in-depth full-text review, allowing for a qualitative synthesis of the current state of knowledge. From this initial search, four key references were identified that laid the groundwork for defining the syndrome and its molecular basis. These articles, along with the subsequent literature, were critical for describing the complete spectrum of the syndrome, emphasizing the genetic etiology and the crucial role of the Wnt pathway in its pathogenesis (6).

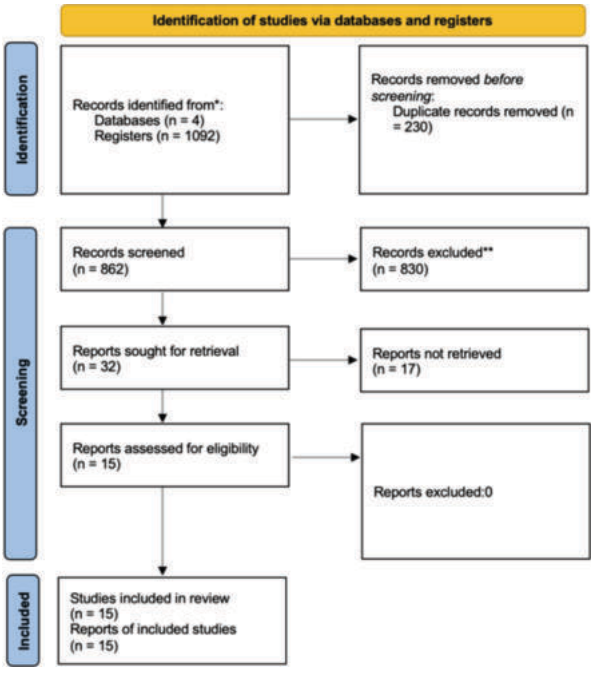


**Figure 1.** PRISMA.

### Clinical Presentation

The phenotypic spectrum of Zaki syndrome is wide, but it is uniformly characterized by severe congenital anomalies in multiple organ systems (1). Ocular abnormalities are among the most prominent and consistently reported features, often including bilateral microphthalmia or anophthalmia (small or absent eyes), coloboma, cataracts, and optic nerve hypoplasia (7). These defects contribute significantly to visual impairment, often leading to severe vision loss or blindness (2).

Renal involvement is also a hallmark of the syndrome, presenting as a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT) (4). This can range from renal hypoplasia (underdeveloped kidneys) and multicystic dysplastic kidneys to frank renal agenesis (absent kidneys), frequently resulting in progressive chronic kidney disease (7).

The severity of the renal involvement is a major determinant of overall prognosis (8).

Beyond the ocular and renal systems, patients often exhibit skeletal anomalies, such as digital defects (e.g., polysyndactyly), joint contractures, and scoliosis (4). Other reported features include central nervous system abnormalities like intellectual disability and cerebellar hypoplasia, congenital heart defects, and craniofacial dysmorphism (9). The considerable interindividual variability in the clinical course and severity makes standardized prognostication challenging, although the condition is typically severe and life-limiting (10).

### Genetic Basis Of Zaki Syndrome

The molecular basis of Zaki syndrome is firmly established: it is caused by pathogenic, loss-of-function variants in the gene (Wntless homolog), located on chromosome 1p31 (1). The syndrome is inherited in an autosomal recessive manner, meaning an affected individual must inherit two copies of the pathogenic gene, one from each carrier parent (5). The gene encodes a protein known as Wntless, or GPR177, which is an essential, highly conserved transmembrane protein (11).
Wntless functions as the sole known transporter of Wnt ligands from the endoplasmic reticulum and Golgi apparatus to the cell surface for secretion (3). Therefore, a loss-of-function mutation in leads to a severe deficit in the secretion of all Wnt ligands (3). The spectrum of mutations described includes nonsense, frameshift, and splice-site variants, all leading to a non-functional or severely truncated Wntless protein (5). The observed multiorgan developmental defects are directly attributable to this global impairment of Wnt signaling during critical stages of embryogenesis (1). While various mutations have been identified, the resulting phenotype consistently reflects a near-complete disruption of Wnt secretion, suggesting a common pathogenic mechanism (9).

### Molecular Mechanisms And Pathophysiology

The core pathophysiology of Zaki syndrome lies in the disruption of the canonical and non-canonical Wnt signaling pathways (11). Wnt ligands are a family of secreted glycoproteins that play fundamental roles in embryogenesis, regulating cell proliferation, migration, polarity, and fate decisions (12). They are crucial for the proper development of numerous structures, including the eyes, kidneys, and limbs (3).

In Zaki syndrome, the dysfunctional Wntless protein cannot properly package and transport Wnt ligands. This failure to secrete Wnt proteins leads to a pervasive lack of Wnt signaling in the extracellular environment of developing tissues (3). Consequently, the downstream effectors of the pathway, such as -catenin in the canonical pathway, are not activated, leading to a failure to transcribe Wnt-target genes essential for normal organogenesis (11).

Experimental evidence from animal models, primarily using zebrafish and mouse models with knockout or knockdown, has strongly supported this mechanism (12). These models successfully recapitulate the key features of Zaki syndrome, particularly the severe microphthalmia and renal hypoplasia, confirming the causal role of defective Wnt transport (13). The severity of the clinical presentation is consistent with a complete, rather than partial, failure of a master developmental pathway (5).

### Implications in Development and Molecular Pathways

The study of Zaki syndrome provides profound insights into the absolute requirement of Wntless and Wnt signaling for normal human development (3). The gene's role as the obligate transporter underscores Wnt signaling's critical and non-redundant nature (11).

The consequence of this signaling failure is most evident in structures where Wnt signaling is temporally and spatially indispensable (13). In the developing eye, Wnt signaling is crucial for optic cup formation and differentiation of retinal cell types (14). Its absence leads to the profound structural defects observed, such as anophthalmia/microphthalmia (13). In the developing kidney, Wnt signaling is required for the induction of the metanephric mesenchyme and the proper branching morphogenesis of the ureteric bud, a process essential for nephron formation (8). The lack of Wnt signaling results in the observed CAKUT spectrum (8). Similarly, defects in limb and skeletal development can be traced back to the disruption of Wnt gradients that control patterning and growth (4).

## DIAGNOSIS

The diagnosis of Zaki syndrome should be suspected in neonates or infants presenting with the characteristic triad of bilateral severe microphthalmia/anophthalmia, congenital renal anomalies (CAKUT), and other systemic defects, particularly skeletal anomalies (2). The definitive diagnosis is established by genetic testing (1).

Initial evaluation involves detailed clinical assessment, including comprehensive ophthalmologic and renal imaging (ultrasound) to characterize the extent of organ involvement (10). Genetic analysis, typically using whole-exome sequencing (WES) or a focused multigene panel, is the gold standard (5). The identification of two pathogenic variants in *trans* (one on each allele) in the gene confirms the diagnosis (1).

The differential diagnosis is extensive, as many syndromes present with microphthalmia and renal defects. These include other Wnt-related disorders like Fraser syndrome (though a different genetic cause) and other non-syndromic forms of severe microphthalmia and CAKUT (9). Genetic confirmation is therefore essential to distinguish Zaki syndrome from clinically overlapping conditions and to facilitate accurate genetic counseling (10).

### Management And Treatment

Given its genetic etiology, the current management of Zaki syndrome is entirely supportive and requires a multidisciplinary approach (2). Treatment focuses on managing the specific organ system anomalies and maximizing the patient's quality of life (10).

Key components of the management plan include regular surveillance and intervention for the ocular defects by an ophthalmologist, which may involve prosthetic eye fitting for cosmetic purposes and support for vision impairment (4). Management of the renal disease is critical and is typically led by a pediatric nephrologist. This involves managing chronic kidney disease, controlling hypertension, and potentially leading to renal replacement therapy (dialysis or transplantation) in cases of end-stage renal failure (8). Skeletal and neurological complications require input from orthopedic surgeons, physical therapists, and developmental pediatricians (2).

Currently, there are no specific molecular therapies for Zaki syndrome to restore Wnt signaling (5). Prognosis is often poor, determined primarily by the severity of the renal and central nervous system involvement (9). Regular follow-up and genetic counseling for the family are essential components of care (1).

### Recent Advances And Lines Of Investigation

Recent research has significantly advanced the understanding of Wntless function, extending beyond its role in Zaki syndrome (13). The use of induced pluripotent stem cell (iPSC) models derived from Zaki syndrome patients is a

promising line of investigation (15). These models allow researchers to generate affected cell types, such as kidney organoids or retinal tissue, *in vitro* to better understand the developmental defects at a cellular level and screen for potential therapeutic agents (15).

A major focus of current research is the exploration of potential therapeutic targets that could bypass the defective Wntless protein (3). Strategies might include the use of small molecules to stimulate Wnt signaling downstream of the ligand-receptor interaction or the development of specialized carriers to deliver Wnt ligands independent of Wntless (11). However, the complex nature and widespread requirement for Wnt signaling pose significant challenges for developing a safe and effective systemic therapy (12). Further elucidation of the precise Wnt ligands and receptors most critical for the development of the affected organs in Zaki syndrome is necessary to refine these therapeutic strategies (13,14).

## CONCLUSIONS

Zaki syndrome is a rare, life-limiting developmental disorder caused by autosomal recessive loss-of-function variants in the gene, resulting in a global failure of Wnt ligand secretion. Its defining features—severe microphthalmia/anophthalmia, CAKUT, and skeletal defects—underscore the indispensable role of the Wnt signaling pathway in multiple aspects of embryonic development. While diagnosis is now clear-cut through genetic testing, the management remains supportive and multidisciplinary. Future research efforts must focus on translating the deep understanding of the syndrome's pathophysiology into effective, targeted molecular therapies. The study of Zaki syndrome continues to be a crucial model for understanding how fundamental developmental pathways contribute to human congenital diseases.

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