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Original Research

SYNDACTYLY SYNDROME IN ASIAN POPULATIONS: GENETIC IDENTIFICATION AND PROGNOSTIC PERSPECTIVES

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ABSTRACT: Syndactyly is among the most common congenital limb malformations and is characterized by substantial genetic and clinical heterogeneity. Although its global incidence is well recognized, accumulating evidence indicates that Asian populations exhibit distinct mutational spectra and variable prognostic profiles. This review systematically summarizes recent molecular and clinical findings from Asian cohorts, with emphasis on pathogenic variants, modifier effects, surgical outcomes, and advances in prenatal diagnostics. Literature published between 2008 and 2023 was retrieved from major biomedical databases following PRISMA-guided principles. Studies from Chinese, Mongolian, and Vietnamese families have repeatedly identified pathogenic variants in key developmental genes, including HOXD13, GLI3, GJA1, and FGFR2, highlighting the central role of convergent signaling pathways such as Hedgehog, WNT/BMP, and FGF in digit morphogenesis and interdigital apoptosis. Asian cohort data further demonstrate incomplete penetrance and intrafamilial variability, suggesting contributions from modifier gene networks and epigenetic influences. Clinically, the integration of next-generation sequencing into surgical planning and prenatal counseling has improved diagnostic precision and prognostic stratification, although molecular evidence remains uneven across Southeast Asia. Asian-specific syndactyly research provides critical insights into population-adapted genetic counseling and emerging precision medicine strategies. Future multi-center genomic studies with standardized clinical reporting will be essential to refine genotype–phenotype correlations and advance individualized management across diverse Asian populations.

Keywords: Syndactyly; Asian populations; HOXD13; GLI3; GJA1; FGFR2; genotype–phenotype correlation; prenatal diagnosis; precision medicine.

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1. INTRODUCTION

Syndactyly refers to the congenital fusion of two or more digits of the hands or feet, resulting from incomplete apoptosis of the interdigital mesenchyme during embryogenesis (Ngoc et al., 2020). It represents one of the most prevalent congenital limb malformations, with a global prevalence of approximately 1 in 2,000–3,000 live births (Jordan et al., 2012) (Figure 1). The condition can manifest in various forms, ranging from simple soft tissue fusion to complex osseous unions, and may be unilateral or bilateral, symmetrical or asymmetrical. Syndactyly is also classified into syndromic and non-syndromic forms, with over 300 syndromic associations described, including Apert, Poland, and Timothy syndromes (Zaib et al., 2022).

Ethnic and geographic differences in the incidence and phenotype of syndactyly have been documented. Epidemiological studies in Chinese populations indicate distinct patterns when compared with Western cohorts, including a higher prevalence of specific subtypes and a possible male predominance (Chen et al., 2023). Mongolian and Vietnamese studies further demonstrate unique genetic mutations and inheritance patterns, emphasizing the importance of region-specific investigations (Husile et al., 2022; Ngoc et al., 2020).

Genetic factors are critical in syndactyly pathogenesis. More than a dozen genes have been implicated, including HOXD13, FGFR2, GLI3, LRP4, LMBR1, and GJA1, many of which are central to embryonic limb patterning and apoptosis signaling pathways (Umair et al., 2018). For example, HOXD13 mutations have been linked to both isolated syndactyly and synpolydactyly, while GLI3 variants contribute to a spectrum of digital anomalies, including polydactyly and overlapping syndromes (Ngoc et al., 2020). Moreover, GJA1 mutations, associated with gap junction function, highlight the role of intercellular communication in limb morphogenesis.

Prognostic outcomes vary considerably according to the underlying mutation, inheritance pattern, and syndromic involvement. In syndromic cases such as Timothy syndrome, prognosis is driven by systemic complications (e.g., cardiac arrhythmias) rather than limb anomalies

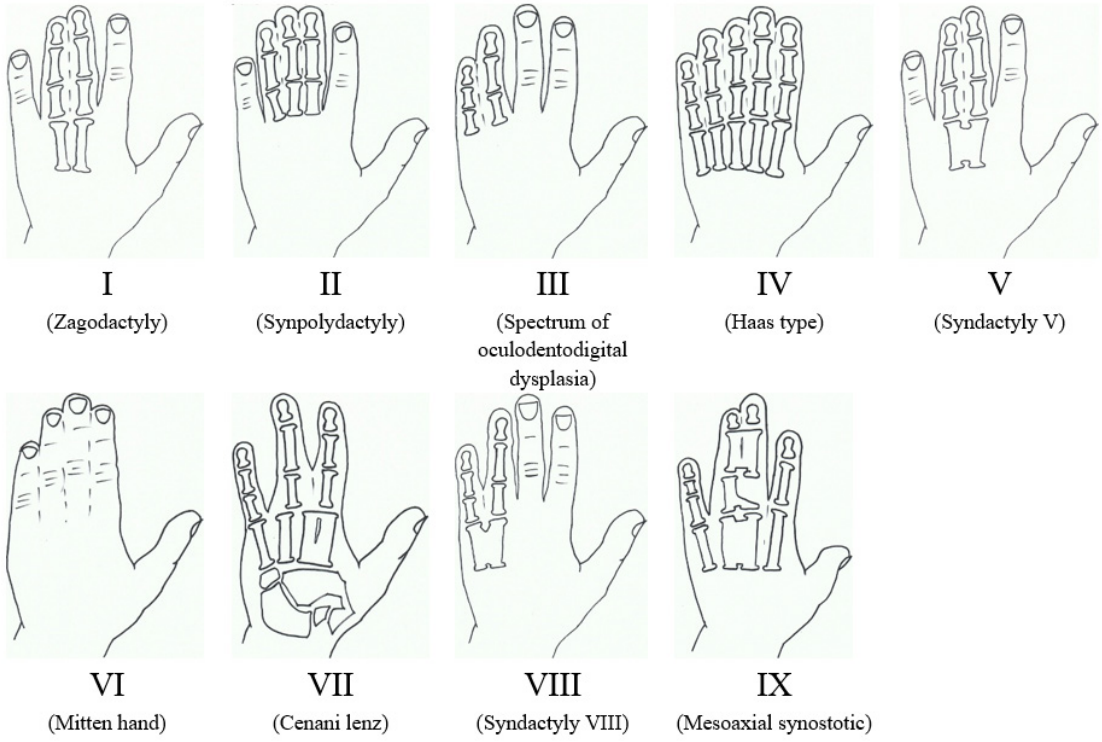

Figure 1. The non-syndromic forms of syndactyly (I-IX) (Jordan et al., 2012)

alone (Gao et al., 2013). Meanwhile, in isolated cases, prognosis may depend on the extent of fusion, functional impairment, and timing of surgical correction.

Advances in molecular genetics, including next-generation sequencing, have revolutionized the identification of pathogenic variants and enabled precise classification of syndactyly subtypes. These techniques are particularly relevant in Asian cohorts, where novel mutations continue to be identified (Qin et al., 2018). Such findings have implications not only for clinical management but also for genetic counseling, prenatal diagnostics, and public health surveillance.

In summary, syndactyly in Asian populations provides a unique lens through which to study the interplay of genetics, epidemiology, and prognosis. This manuscript integrates recent discoveries and clinical advances, with a particular emphasis on molecular pathways, surgical outcomes, and prenatal diagnostics, to provide a comprehensive overview of current knowledge and future directions.

2. METHODS

2.1. Literature search strategy

This study was conducted as a systematic literature review in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles. A comprehensive search of peer-reviewed articles was performed using PubMed, Springer, Nature, Elsevier, and MDPI databases. The search covered publications from January 2008 to December 2023.

Search terms included combinations of: "syndactyly", "genetic mutation", "HOXD13", "GLI3", "GJA1", "FGFR2", "prenatal diagnosis", "surgical outcome", and "Asian population". Boolean operators ("AND", "OR") were applied to optimize sensitivity and specificity.

2.2. Eligibility criteria

Studies were included if they met the following criteria: (1) original research articles or systematic reviews; (2) investigation of syndactyly in Asian populations; (3) reporting genetic, molecular, prognostic, surgical, prenatal diagnostic data; (4) published in English.

Exclusion criteria were: (1) studies focusing exclusively on non-Asian populations; (2) case reports without genetic or prognostic relevance; (3) conference abstracts, editorials, or letters without original data; (4) articles lacking full-text availability.

2.3. Study selection process

All retrieved records were imported into a reference management system, and duplicate articles were removed. Titles and abstracts were independently screened for relevance. Full-text articles of potentially eligible studies were then assessed against the predefined inclusion and exclusion criteria. Discrepancies were resolved through discussion and consensus among the authors.

2.4. Data extraction and synthesis

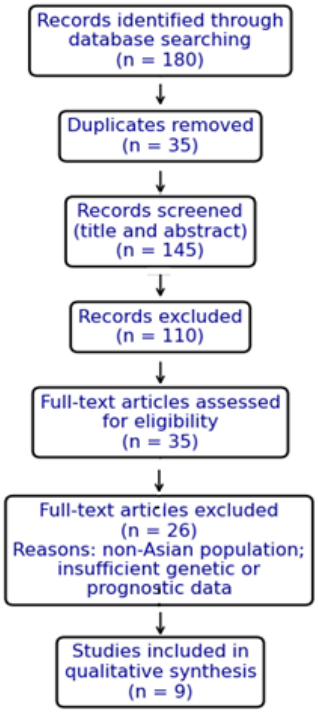

Figure 2. PRISMA flow diagram of study selection

The literature search identified 180 records, of which 145 remained after duplicate removal. Following title and abstract screening, 35 full-text articles were assessed for eligibility. Ultimately, nine studies met the inclusion criteria and were included in the qualitative synthesis (Figure 2).

3. RESULTS

3.1. Epidemiology in Asian cohorts

A nationwide surveillance-based study in China reported evolving epidemiological patterns of syndactyly in newborns, suggesting that incidence and phenotype distribution may be shifting with changing population demographics and environmental factors (Chen et al., 2023). Vietnamese studies revealed novel mutations linked to syndactyly, contributing to the genetic epidemiology of Southeast Asia (Ngoc et al., 2020). Population-based comparisons have highlighted that while the overall incidence of syndactyly in Asia is comparable to Western countries, the genetic variants involved may be distinct, indicating the need for ethnic-specific genetic screening.

3.2. Genetic identification

Recent genetic investigations in Asian populations have underscored the heterogeneity of syndactyly and the importance of precise molecular characterization. In Mongolian families, mutations in HOXD13 have been associated with incomplete penetrance and striking variability in clinical presentation, complicating predictive assessments (Husile et al., 2022). Whole-exome sequencing in Vietnamese trios has revealed novel missense variants in GLI3 (c.G1622A:p.T541M) and GJA1 (c.T274C:p.Y92H), genes that play central roles in Hedgehog signaling and gap junction communication, respectively, thereby linking these pathways to abnormal digit development (Ngoc et al., 2020). In addition, Chinese cohorts investigated through next-generation sequencing have identified pathogenic variants in FGFR2, often correlated with syndromic manifestations such as craniofacial anomalies (Qin et al., 2018).

In addition to these population-specific findings, broader reviews have highlighted the contribution of genes such as LRP4 and LMBR1 in regulating WNT/BMP signaling and interdigital apoptosis, expanding the catalog of genes implicated in digit separation (Umair et al., 2018). These findings not only demonstrate ethnic-specific mutational spectra but also underscore the clinical value of incorporating comprehensive sequencing strategies into diagnostic and counseling practices (Table 1).

3.3. Modifier genes and phenotypic variability

Although pathogenic variants in core developmental genes such as HOXD13, GLI3, GJA1, and FGFR2 constitute the primary genetic drivers of syndactyly, increasing evidence indicates that additional modifier genes contribute substantially to the observed phenotypic heterogeneity of the disease. This phenomenon is particularly evident in familial cases showing incomplete

Table 1. Key genetic variants associated with syndactyly in Asian populations

Gene	Mutation	Population studied	Clinical relevance	Reference
HOXD13	c.917G>A (p.R306Q)	Mongolian family	Incomplete penetrance, variable expression	Husile et al., 2022
GLI3	c.G1622A:p.T541M	Vietnamese trios	Disrupted Hedgehog signaling, digital anomalies	Ngoc et al., 2020
GJA1	c.T274C:p.Y92H	Vietnamese trios	Gap junction dysfunction, impaired apoptosis	Ngoc et al., 2020
FGFR2	Multiple	Chinese cohorts	Syndromic associations, craniofacial anomalies	Qin et al., 2018
LRP4	Variant in limb bud domain	Literature (Asian)	WNT/BMP regulation, interdigital apoptosis	Umair et al., 2018

penetrance and marked intrafamilial variability, as demonstrated in Mongolian families carrying identical HOXD13 variants yet exhibiting clinical presentations ranging from mild cutaneous syndactyly to complex synpolydactyly (Husile et al., 2022) .

Modifier genes are thought to influence digit separation by modulating key signaling pathways involved in limb patterning and interdigital apoptosis, including Hedgehog, WNT, BMP, and FGF pathways (Umair et al., 2018; Zaib et al., 2022). Genes such as LRP4 and LMBR1, which regulate WNT/BMP signaling, may alter the spatial or temporal threshold of interdigital apoptosis, thereby modifying the severity, symmetry, and anatomical extent of syndactyly (Umair et al., 2018) .

Similarly, GJA1, beyond its established role as a causative gene in oculodentodigital dysplasia, may act as a modifier by affecting gap junction–mediated intercellular communication, a process essential for coordinated tissue remodeling during limb morphogenesis. Evidence from Vietnamese trios harboring GLI3 or GJA1 variants further supports this concept, as phenotypic variability could not be fully explained by the primary mutation alone, suggesting interactions with additional genetic or epigenetic factors (Ngoc et al., 2020) .

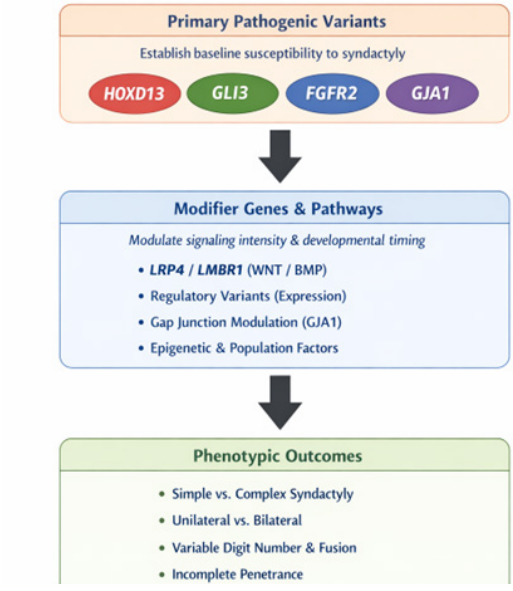

Figure 3. Conceptual model illustrating the role of modifier genes in phenotypic variability of syndactyly

Collectively, these findings indicate that syndactyly represents a genetically complex condition in which primary pathogenic variants establish susceptibility, while modifier genes fine-tune phenotypic outcomes, contributing to variable expressivity and incomplete penetrance across individuals and populations (Husile et al., 2022; Zaib et al., 2022). (Figure 3)

3.4. Molecular pathways

Digit separation during embryonic limb development is governed by the coordinated interaction of Hedgehog, WNT/BMP, and FGF signaling pathways. Sonic Hedgehog (SHH) signaling regulates the processing of GLI3 into its activator (GLI3A) and repressor (GLI3R) forms, thereby controlling transcriptional programs essential for digit patterning. Concurrently, WNT and BMP signaling, modulated by LRP4 and LMBR1, influences β-catenin–dependent transcription and SMAD-mediated pathways that regulate interdigital apoptosis. FGFR2-mediated FGF signaling further integrates proliferative and survival cues through downstream RAS/MAPK and PI3K/AKT pathways. Disruption of these tightly regulated networks alters apoptotic thresholds within the interdigital mesenchyme, leading to incomplete digit separation and the development of syndactyly.

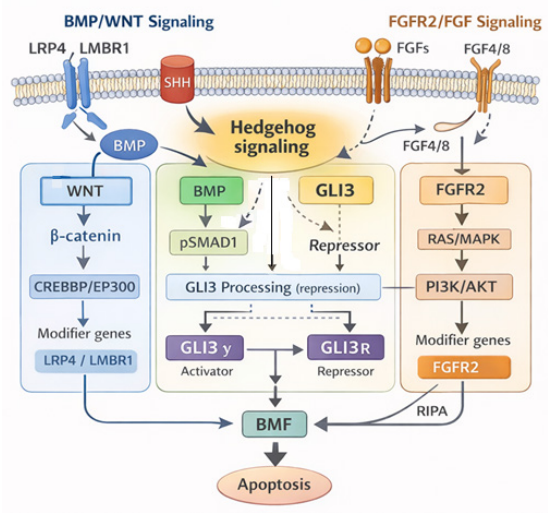

Figure 4. Summary of molecular pathways contributing to syndactyly development, highlighting apoptosis regulation and Hedgehog signaling.

As illustrated in Figure 4, syndactyly arises from dysregulation of a convergent

network of developmental signaling pathways rather than from disruption of a single gene. Hedgehog signaling occupies a central position by controlling the balance between GLI3 activator and repressor forms, a mechanism critical for digit identity and separation. Modifier genes acting within the WNT/BMP axis, such as LRP4 and LMBR1, can shift apoptotic signaling thresholds in the interdigital mesenchyme, thereby modulating phenotypic severity. In parallel, FGFR2-dependent FGF signaling provides proliferative and survival inputs that further influence tissue remodeling. This integrated pathway model explains how identical primary pathogenic variants may give rise to variable phenotypes through pathway-level modulation of apoptosis and developmental timing.

3.5. Surgical outcomes and prenatal diagnostics

Surgical correction remains the primary treatment for syndactyly. Asian surgical studies report that outcomes depend on timing, surgical technique, and extent of fusion. Early surgery (before school age) prevents functional impairment, though complex bony fusions present challenges. Advances in microsurgery, local flaps, and skin grafting have improved both aesthetic and functional results. Genetic profiling now assists in predicting surgical complexity, particularly for HOXD13- and GLI3-associated cases, allowing surgeons to anticipate complications and refine techniques.

Table 2. Prognostic considerations for syndactyly in Asian populations

Prognostic factor	Impact on outcome	Reference
Genetic penetrance	Variable expressivity complicates prediction	Husile et al., 2022
Syndromic involvement	Systemic complications drive prognosis	Gao et al., 2013; Kwok et al., 2018
Epidemiological shifts	Changing incidence affects screening needs	Chen et al., 2023
Prenatal detection	Enables preparation for postnatal interventions	Ngoc et al., 2020

Prenatal detection of syndactyly in Asia is advancing with high-resolution ultrasonography, three-dimensional imaging, and non-invasive prenatal testing (NIPT). Molecular confirmation via exome sequencing is increasingly feasible. Identification of high-risk families, particularly with HOXD13, GJA1, or GLI3 mutations, enables targeted prenatal testing, improving counseling and pregnancy management. In some cases, prenatal detection has allowed preparation for early surgical intervention and multidisciplinary care immediately after birth (Table 2).

The integration of molecular diagnostics has improved accuracy in predicting recurrence risk and guiding surgical interventions. Reviews emphasize the importance of genetic counseling tailored to ethnic background, given variations in mutation frequency and penetrance across Asian populations (Zaib et al., 2022).

4. DISCUSSION

The expanding body of evidence from Asian populations has provided valuable contributions to the understanding of syndactyly, particularly by uncovering population-specific mutational spectra and diverse clinical outcomes. Compared with Western cohorts, studies in Chinese, Mongolian, and Vietnamese families have identified recurrent pathogenic variants in genes such as HOXD13, GLI3, GJA1, and FGFR2, reinforcing the importance of embryonic signaling pathways including Hedgehog, WNT/BMP, and FGF in digit separation and interdigital apoptosis.

Beyond primary causative mutations, Asian cohorts have highlighted the complexity of phenotypic variability, particularly through incomplete penetrance and intrafamilial heterogeneity observed in HOXD13-associated syndactyly. Such findings suggest that modifier gene networks and epigenetic influences may substantially shape clinical severity, complicating prognostic prediction despite advances in molecular diagnostics.

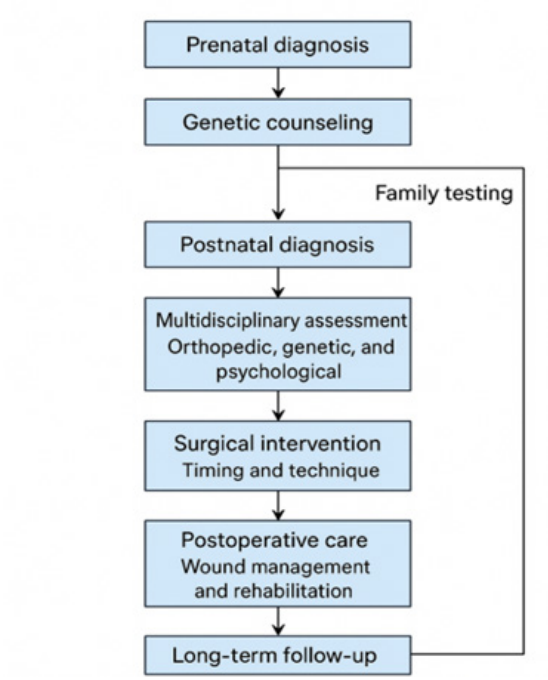

Figure 5. Clinical Management of Syndactyly Syndrome in Asian population

From a clinical perspective, surgical correction remains the cornerstone of management, with outcomes dependent on fusion complexity, timing of intervention, and reconstructive technique. The increasing integration of genetic profiling into surgical planning represents an emerging translational approach, potentially enabling clinicians to better anticipate anatomical challenges and optimize functional outcomes.

Prenatal diagnostics also constitute a growing frontier in Asia, supported by advances in high-resolution ultrasonography, non-invasive prenatal testing, and exome sequencing. Early molecular confirmation in high-risk families provides opportunities for improved counseling and multidisciplinary care planning, particularly in syndromic conditions where prognosis extends beyond limb anomalies.

Overall, Asian-specific investigations offer essential insights for refining syndactyly classification frameworks, expanding mutation databases, and strengthening population-adapted clinical strategies (Figure 5).

5. LIMITATIONS

Despite the advances summarized in this review, several limitations should be acknowledged. First, the majority of genetic studies on syndactyly in Asian populations remain constrained by small sample sizes, frequently limited to single-family reports or narrow regional cohorts. This restricts the ability to establish robust genotype–phenotype correlations and reduces the generalizability of prognostic interpretations.

Second, selection bias is likely, as published data predominantly originate from referral centers and clinically severe or syndromic presentations, whereas mild or isolated forms may be underrepresented.

Finally, substantial geographic gaps persist, particularly across Southeast Asia, where large-scale molecular epidemiological studies remain scarce. This imbalance may obscure population-specific mutational spectra and limits the development of comprehensive ethnicity-adapted screening and counseling strategies.

Addressing these limitations will require broader multi-center cohort studies with standardized genomic and clinical reporting across diverse Asian populations.

6. CONCLUSION

Research in Asian populations has significantly enriched the global understanding of syndactyly by revealing distinct mutational spectra, variable penetrance patterns, and diverse prognostic profiles. Recurrent pathogenic variants in developmental genes such as HOXD13, GLI3, GJA1, and FGFR2 underscore the central role of convergent signaling pathways in digit morphogenesis and interdigital apoptosis.

Importantly, Asian cohort evidence demonstrates that clinical outcomes are shaped not only by primary mutations but also by modifier effects and syndromic involvement, reinforcing the need for integrated molecular diagnostics alongside surgical and prenatal management strategies.

Although current evidence remains uneven across Asia, particularly in Southeast Asian regions, continued expansion of multi-ethnic genomic studies will be essential for strengthening

genotype–phenotype correlations and supporting the transition toward precision medicine frameworks.

Collectively, Asian syndactyly research provides a critical foundation for advancing early diagnosis, ethnicity-informed counseling, and genetically guided therapeutic planning across diverse populations.

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