

BORJESON-FORSSMAN-LEHMANN SYNDROME

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BORJESON-FORSSMAN-LEHMANN SYNDROME (BFLS)

Primary Disciplinary Field(s): Medical Genetics, Pediatric Neurology, Endocrinology

1. Core Definition

The Borjeson-Forssman-Lehmann Syndrome (BFLS) is a rare, inherited X-linked intellectual disability syndrome characterized by a complex constellation of physical and neurological abnormalities. Classified primarily as a concept within medical genetics, BFLS represents a severe clinical phenotype resulting from a mutation in the *PHF6* gene. This disorder predominantly affects males due to its X-linked recessive inheritance pattern, although female carriers may occasionally exhibit milder symptoms related to skewed X-chromosome inactivation. The cardinal features defining BFLS include severe to profound intellectual disability, significant growth failure leading to short stature, microcephaly, and pronounced endocrine deficiencies, particularly hypogonadism.

The syndrome is defined by the combination of neurodevelopmental delay and distinctive dysmorphic features. The severity of the intellectual impairment often necessitates lifelong assisted living and comprehensive special education services, placing BFLS among the more impactful X-linked syndromes in terms of necessary patient care. While the specific manifestations can vary slightly, the consistent presentation of central nervous system anomalies alongside pituitary and gonadal dysfunction provides a definitive diagnostic profile for clinicians specializing in rare genetic disorders. Understanding BFLS requires an appreciation of how a single genetic mutation can cascade into multi-systemic dysfunction, affecting brain development, skeletal growth, and reproductive maturity.

Crucially, BFLS is classified as a genetically determined developmental disorder, contrasting sharply with acquired intellectual disabilities. The underlying pathology involves defective gene expression crucial for transcription and cellular differentiation, particularly in neural and endocrine tissues. The early recognition of the syndrome is vital, as timely intervention, especially hormonal replacement therapy for hypogonadism, can mitigate some long-term complications and improve the quality of life for affected individuals. The clinical profile tends to become more pronounced as the affected male reaches adolescence, coinciding with the expected onset of puberty which fails to materialize due to the underlying endocrine deficits.

2. Etymology and Historical Development

Borjeson-Forssman-Lehmann Syndrome derives its name from the three Swedish physicians who first described the condition in the mid-20th century. Mats Gunnar Borjeson, Hans Axel Forssman, and J.O. Orla Lehmann published their initial findings detailing a familial syndrome affecting several males across multiple generations, noting the peculiar combination of intellectual disability, obesity, and arrested sexual development. Their seminal work established the clinical boundaries

of the syndrome, distinguishing it from other forms of X-linked intellectual disability based on the specific endocrinological components and facial features observed within the affected pedigrees.

For several decades following its initial description, BFLS remained a purely clinical diagnosis based on the recognition of the characteristic phenotype. The understanding of its genetic basis only solidified with the advent of advanced molecular biology techniques in the late 20th and early 21st centuries. In 1999, researchers successfully mapped the locus for BFLS to the long arm of the X chromosome, specifically Xq26-q27. This localization was a pivotal step, enabling focused gene hunting efforts that culminated in the identification of the causative gene, *PHF6* (P-H-F-six), shortly thereafter.

The identification of the *PHF6* gene revolutionized the diagnosis and classification of BFLS. Located at Xq26.3, *PHF6* encodes a protein known as PHF6 (Plant Homeodomain Finger Protein 6), which functions as a transcriptional regulator. The majority of mutations identified are loss-of-function mutations, including nonsense, frameshift, and splicing errors, leading to a truncated or absent protein product. This genetic confirmation transitioned BFLS from a purely phenotypic concept to a defined molecular entity, allowing for precise carrier detection, prenatal diagnosis, and a deeper understanding of the pathophysiological mechanisms underlying the multi-systemic manifestations observed in patients.

3. Key Characteristics and Clinical Presentation

The clinical presentation of BFLS is highly characteristic, spanning neurological, physical, and endocrine domains. Neurologically, the most consistent feature is the presence of severe to profound intellectual disability, impacting adaptive functioning, communication skills, and cognitive development from early childhood. Behaviorally, affected individuals often exhibit mood instability, anxiety, and occasionally autistic features, though these are secondary to the primary neurological impairment. Hypotonia (low muscle tone) is also commonly noted in infancy, contributing to motor skill delays.

Endocrine dysfunction forms the second critical pillar of the syndrome. Affected males invariably present with hypogonadotropic hypogonadism, meaning the failure of sexual maturation due to deficient secretion of gonadotropin-releasing hormone (GnRH) or gonadotropins (LH and FSH) from the pituitary gland. This results in small testes (microorchidism), lack of secondary sexual characteristics, and a notable absence or paucity of pubic and axillary hair in adulthood--a feature explicitly mentioned in the original description. Furthermore, growth hormone deficiency leading to proportional short stature is frequent, often accompanied by truncal obesity developing later in childhood or adolescence, compounding the physical challenges faced by patients.

Dysmorphic features, though subtle in infancy, become more apparent with age. These include microcephaly (small head circumference), prominent supraorbital ridges, large fleshy ears, and

small palpebral fissures (eye opening). Skeletal anomalies are also common, such as short, broad fingers and toes (brachydactyly), specific vertebral abnormalities, and occasionally kyphoscoliosis. Ophthalmic issues, particularly progressive deterioration of vision due to underlying retinal or optic nerve issues, may also contribute significantly to disability over time.

4. Genetic Basis and Molecular Mechanism

BFLS is caused by pathogenic variants in the *PHF6* gene, located on the X chromosome. The PHF6 protein, which contains two Plant Homeodomain (PHD) finger motifs, is understood to act as a critical transcriptional regulator, participating in chromatin remodeling complexes. These complexes are essential for regulating gene expression during development, particularly in the brain, pituitary gland, and gonads--precisely the tissues most affected in BFLS.

The mechanism of disease is typically haploinsufficiency or a dominant negative effect, whereby the mutated *PHF6* protein fails to integrate correctly into its regulatory complexes, leading to the misregulation of downstream target genes. This failure of transcriptional regulation during critical developmental windows is thought to underpin the severe neurological deficits and the failure of normal hypothalamic-pituitary-gonadal (HPG) axis function. The diverse spectrum of clinical features--from intellectual impairment to skeletal anomalies and endocrine failure--is reflective of the widespread regulatory role of PHF6 in various cell lineages.

Because BFLS is X-linked recessive, males (XY) possessing the mutation are fully symptomatic. Females (XX) who inherit one mutated copy are generally carriers and phenotypically normal, as the healthy X chromosome compensates. However, a small percentage of female carriers may present with mild intellectual disability, behavioral issues, or subtler facial features. This variability in female expression is attributed to non-random or "skewed" X-chromosome inactivation, where the healthy X chromosome is preferentially silenced, leading to a functional deficit of the PHF6 protein even in heterozygous females. The identification of the specific mutation allows genetic counselors to accurately assess recurrence risk and provide informed reproductive options to affected families.

5. Diagnosis and Differential Diagnosis

Diagnosis of BFLS is typically initiated following clinical suspicion based on the triad of intellectual disability, specific facial dysmorphism, and hypogonadism in a male child. Historically, diagnosis relied entirely on clinical criteria. Today, confirmation requires molecular genetic testing focusing on the *PHF6* gene. Standard genetic sequencing can detect point mutations, deletions, or duplications within the coding sequence. If sequencing is negative, techniques such as multiplex ligation-dependent probe amplification (MLPA) may be employed to detect larger deletions involving the entire gene or flanking regions.

The differential diagnosis for BFLS is extensive, encompassing several other syndromes characterized by X-linked intellectual disability combined with short stature and hypogonadism. Key syndromes to rule out include Prader-Willi syndrome (which shares obesity and hypogonadism but has a distinct genetic etiology on chromosome 15), Coffin-Lowry syndrome, and certain forms of Kallmann syndrome (which typically lacks the severe intellectual disability seen in BFLS). Accurate differentiation is crucial because the genetic counseling and management strategies, especially pharmacological interventions, vary significantly among these conditions.

Clinical scoring systems, which assign points based on the presence of key features like microcephaly, hypogonadism, and intellectual disability severity, can aid in guiding the initial diagnostic workup. However, the definitive diagnosis rests solely on identifying a pathogenic variant in *PHF6*. The availability of reliable genetic testing has streamlined the diagnostic pathway, ensuring families receive a precise label, which is essential for accessing targeted medical and educational resources. Furthermore, early genetic confirmation can prevent unnecessary, invasive diagnostic procedures aimed at investigating the growth or endocrine deficiencies in isolation.

6. Management and Prognosis

Management of BFLS is primarily supportive and multidisciplinary, addressing the profound neurological and endocrine deficits systematically. Due to the severe intellectual disability, individuals require lifelong educational support tailored to their cognitive capacity, often focusing on adaptive skills and basic communication. Physical therapy, occupational therapy, and speech therapy are integral components of early intervention to maximize functional independence and address hypotonia. Behavioral interventions may also be necessary to manage potential mood and anxiety disorders associated with the condition.

Endocrine management is perhaps the most critical medical intervention. Treatment for hypogonadism typically involves hormonal replacement therapy (HRT) initiated at the expected time of puberty. Testosterone replacement in males is necessary to induce secondary sexual characteristics, improve bone density, and potentially enhance psychosocial well-being, though it does not address the underlying intellectual deficits. Growth hormone deficiency, if present, is treated with exogenous growth hormone administration to mitigate short stature, often resulting in significant improvements in final adult height.

The prognosis for individuals with BFLS is variable but generally involves a life of dependence due to the severity of the intellectual disability. While medical interventions can successfully manage the endocrine and growth aspects of the syndrome, the core neurological deficits remain refractory to current treatments. Long-term care planning is essential, including considerations for managing potential complications such as seizures, ophthalmological issues, and cardiac anomalies that may occasionally accompany *PHF6* mutations. Ongoing research aims to explore therapies targeting

the gene regulatory pathways disrupted by the PHF6 deficiency, offering potential avenues for future treatments that might impact cognitive outcomes.

7. Further Reading

[Online Mendelian Inheritance in Man \(OMIM\): Borjeson-Forssman-Lehmann Syndrome \(BFLS\)](#)

[Genetics Home Reference \(NIH\): PHF6 gene](#)

[Wikipedia: Borjeson-Forssman-Lehmann syndrome](#)

[NCBI PubMed: PHF6-related syndromes: Borjeson-Forssman-Lehmann syndrome and mental retardation with short stature, microcephaly, and hypogonadism](#)

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