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Case Report

Ochoa Syndrome Associated with a Novel HPSE2 Deletion: A Case Report

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ABSTRACT

Ochoa syndrome is a rare disorder characterized by abnormal facial expression and severe lower urinary tract dysfunction. We report a two-year-old girl with recurrent urinary tract infections and a novel homozygous *HPSE2* exon 5-11 deletion. Early recognition and timely intervention are essential in order to prevent renal damage and improve clinical outcomes.

Keywords: Ochoa syndrome, urofacial syndrome, *HPSE2*, recurrent urinary tract infection, vesicostomy

Introduction

Ochoa syndrome, also referred to as urofacial syndrome (UFS), is a rare disorder characterized by the coexistence of abnormal facial expression and lower urinary tract dysfunction in the absence of an identifiable neurological or anatomical obstruction. Affected individuals typically demonstrate an inverted facial expression during smiling or laughing (1). UFS follows an autosomal recessive inheritance pattern, and pathogenic variants involving the *inactive heparanase-2* (*HPSE2*) gene have been identified in the majority of reported cases (2). As the characteristic facial findings may be subtle during early childhood, recognition of this syndrome can be delayed, leading to recurrent urinary tract infections (UTIs) and progressive upper urinary tract damage. We present this case in order to emphasize the importance of early recognition of Ochoa syndrome as a rare but significant cause of severe lower urinary tract dysfunction, recurrent UTI, and chronic kidney disease.

Case Report

A two-year-old girl was referred with recurrent febrile UTIs. Physical examination demonstrated poor weight gain and failure to thrive associated with repeated infectious episodes. Perineal and lumbosacral examinations were unremarkable. However, an abnormal inverted facial expression while smiling was noticed during clinical evaluation (Figure 1). Antibiotic prophylaxis was initiated.

There was no known family history of Ochoa syndrome or other hereditary urinary tract disorders, and no known parental consanguinity. Urinary ultrasonography demonstrated bilateral grade 3 hydroureteronephrosis, severe bladder wall thickening, and thinning of the left

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renal parenchyma. Dimercaptosuccinic acid scintigraphy revealed cortical irregularities, upper pole parenchymal thinning, and mild dilatation of the left collecting system. Voiding cystourethrography demonstrated vesicoureteral reflux together with trabeculation and diverticular changes of the bladder wall.

Based on the coexistence of characteristic facial findings and severe lower urinary tract dysfunction, Ochoa syndrome was suspected. Molecular confirmation was obtained through whole exome sequencing analysis. Sequence evaluation did not reveal any pathogenic or likely pathogenic single nucleotide variants associated with the phenotype. However, copy number variation (CNV) analysis identified a homozygous deletion within the 10q26.3 region (Hg19: chr10:100242132-100481844), involving exons 5-11 of the *HPSE2* (*NM_021828.4*) gene. No additional morbid OMIM genes were identified within the deleted region.

Figure 1. An abnormal inverted facial expression while smiling

This deletion had not previously been reported in databases including DGV or gnomAD. According to American College of Medical Genetics and Genomics criteria, the CNV was classified as likely pathogenic. Integrative Genomics Viewer analysis demonstrated a complete absence of read depth across exons 5-11 of the *HPSE2* gene, whereas adequate read depth was present in the control samples processed in the same sequencing run (Figure 2). Confirmation analysis was planned; however, multiplex ligation-dependent probe amplification (MLPA) confirmation could not be performed because no specific probe for *HPSE2* was available. In addition, the parents declined segregation analysis.

Despite continuous antibiotic prophylaxis, the patient experienced two episodes of urosepsis requiring hospitalization during follow-up. Considering the severity of the lower urinary tract dysfunction and the patient's clinical condition, vesicostomy was performed. During the first postoperative year, she remained infection-free and demonstrated improvement in growth parameters appropriate for her age. Follow-up radiological evaluation showed improvement of the upper urinary tract. Based on her favorable clinical course, radiological improvement, and satisfactory cystoscopic bladder mucosal appearance, vesicostomy closure with anti-reflux surgery was performed in the 14th postoperative month.

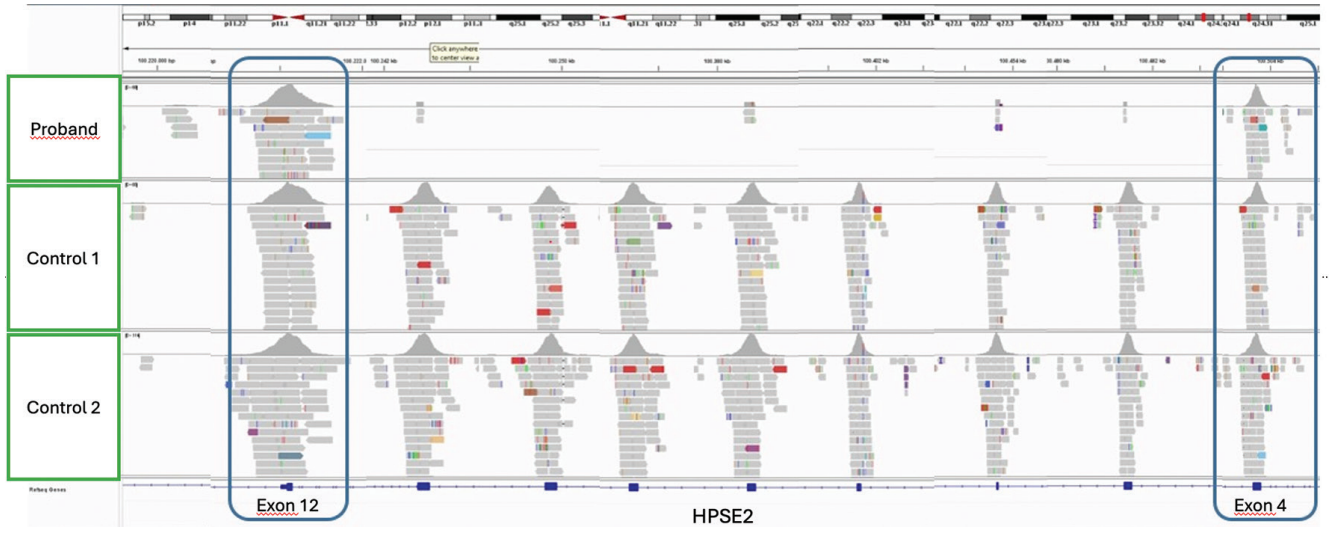

Figure 2. Integrative Genomics Viewer analysis demonstrating the homozygous *HPSE2* exon 5-11 deletion in the patient.

Discussion

Ochoa syndrome, also known as UFS, was initially described clinically in the early 1960s. In 1979, the term 'Ochoa syndrome' was introduced by Elejalde (4) following genetic investigations of the affected families (3). The diagnosis of Ochoa syndrome is established in the presence of one or both of the following findings: 1) inverted facial expression accompanied by clinical and radiological evidence of lower urinary tract dysfunction, and 2) identification of a homozygous pathogenic variant involving the *HPSE2* or *leucine-rich repeats and immunoglobulin-like domains protein 2* (*LRIG2*) gene.

Lower urinary tract dysfunction in these patients may manifest with recurrent UTIs, dysuria, urinary incontinence, frequency, urgency, or enuresis, and may eventually progress to end-stage renal disease if left untreated (5). Although the characteristic paradoxical facial expression during smiling is considered highly suggestive of the syndrome, it may remain unrecognized as bladder-related symptoms usually dominate the clinical presentation.

From a genetic perspective, UFS is an autosomal recessive disorder caused by pathogenic variants affecting both alleles of either the *HPSE2* or *LRIG2* gene (6). Advances in next-generation sequencing (NGS) technologies over the last decade have significantly improved the identification of inherited Mendelian disorders. NGS allows for the simultaneous evaluation of multiple genomic regions in a single analysis and has become a practical and cost-effective diagnostic approach for those patients with suspected genetic diseases (7). Nevertheless, conventional NGS analysis may be insufficient for the detection of CNVs, including exon-level deletions, which represent an important mechanism underlying many genetic disorders. The incorporation of CNV detection algorithms into NGS-based diagnostic workflows has therefore substantially increased diagnostic accuracy in genetically heterogeneous conditions (8,9).

In the present case, whole exome sequencing combined with CNV analysis identified a homozygous deletion involving exons 5-11 of the *HPSE2* gene in the 10q26.3 region, which was classified as likely pathogenic. Previous studies have highlighted the functional importance of exon deletions affecting *HPSE2*. Beaman et al. (10) demonstrated four possible heparanase-2 isoforms generated through differential splicing of exons 3 and 4. In addition, Daly et al. (2) described a family with UFS carrying a whole exon 3 deletion in *HPSE2*. Unlike previously reported variants, our patient demonstrated a homozygous deletion spanning exons 5-11, a finding that has not previously been described in association with UFS. This observation further expands the known mutational spectrum of *HPSE2*. The absence of isoforms involving exons 5-11 may interfere with the pathways required for normal bladder innervation and facial muscle function, thereby contributing to the typical clinical phenotype observed in UFS.

Although the molecular findings strongly supported the diagnosis, several limitations should be acknowledged. Confirmatory MLPA analysis could not be performed because a specific probe for *HPSE2* was unavailable, and the family declined segregation analysis. Despite these limitations, our findings support the growing evidence regarding the central role of *HPSE2* in the pathogenesis of Ochoa syndrome and underline the importance of comprehensive genomic analysis in rare inherited disorders. However, extensive genetic confirmation should not delay the initiation of treatment, since timely management remains essential for the preservation of renal function and the improvement of long-term outcomes, particularly considering that approximately 16% of patients may not harbor currently recognized mutations (1).

Conclusion

In children presenting with severe lower urinary tract dysfunction, recognition of the characteristic inverted facial expression may facilitate an earlier diagnosis of Ochoa syndrome. Timely intervention is essential in order to reduce the risk of progressive renal impairment.

Ethics

Informed Consent: Written informed consent was obtained from the patient's legal guardian for publication of this case report and the accompanying clinical images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.E., Design: S.T., Analysis or Interpretation: S.T., Literature Search: E.I., Writing: G.E., T.T.T.

Conflict of Interest: The authors declare no conflict of interest.

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