



Case Report

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Preconception and Prenatal Carrier Screening of GJB2 in 87736 Patients Revealed its High Carrier Prevalence in the US

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Abstract

Hearing loss is one of the most common congenital conditions, with a higher incidence in the general population than that of cystic fibrosis (CF), spinal muscular atrophy (SMA), hemoglobinopathies, critical congenital heart defects, or common metabolic diseases. Mutations in the *GJB2* gene are the most common cause for genetic hearing loss. The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) provide foundational guidelines for genetic carrier screening in prenatal and preconception care. While screening for autosomal recessive CF and SMA has been recommended for over a decade, recent ACMG practice resources now recommend Tier 3 expanded carrier screening, which includes hearing loss genes such as *GJB2*. In this study, we analyzed the results of the GxVISION® Carrier Screening in 87,736 patients to evaluate the prevalence of *GJB2* mutations in the US population. Our data revealed 3,736 *GJB2* carriers, establishing a carrier rate of 1 in 23.5. Notably, this prevalence exceeds that of CF (1 in 26) and SMA (1 in 66) in the same screened cohort. Furthermore, screening identified numerous novel null variants in *GJB2* gene, including nonsense, frameshift and start loss mutations. We further present a clinical case where the identification of maternal *GJB2* carrier status and subsequent biological father reflex testing resolved a diagnostic odyssey for a child with previously unexplained hearing loss and enabled immediate clinical management for a second affected sibling. These findings support the inclusion of *GJB2* in routine carrier panels to bridge existing gaps in newborn hearing loss screening and improve clinical outcomes.

Keywords: *GJB2*, Prenatal Carrier Screening, Cystic Fibrosis, *CFTR*, SMA, *SMN1*, Autosomal Recessive, Hearing Loss

Abbreviations: CF: Cystic fibrosis; *GJB2*: Gap Junction Protein Beta 2; *CFTR*: Cystic Fibrosis Transmembrane Conductance Regulator; SMA: Spinal Muscular Atrophy; *SMN1*: Survival Motor Neuron 1; ACOG: The American College of Obstetricians and Gynecologists; ACMG: The American College of Medical Genetics and Genomics; MLPA: Multiplex-ligation dependent probe amplification; PCR: Polymerase Chain Reaction; NGS: Next generation sequencing

Introduction

Carrier screening serves as a critical tool in prenatal and preconception care, allowing individuals to identify their risk of passing genetic conditions to their offspring. The American

College of Obstetricians and Gynecologists (ACOG) established foundational guidelines through Committee Opinions #690 and #691 [1, 2], which recommend that screening for cystic fibrosis

(CF) and spinal muscular atrophy (SMA) be offered to all women who are pregnant or considering pregnancy. These guidelines also encourage obstetrician-gynecologists to establish a standard carrier screening approach including offering an extended option for patients seeking more comprehensive genetic information and/or based on medical necessity.

Building upon these standards, the American College of Medical Genetics and Genomics (ACMG) released a 2021 practice resource recommending Tier 3 expanded carrier screening for all pregnant and preconception patients [3]. This tiered approach explicitly includes prevalent hearing loss genes, and other autosomal and X-linked recessive genes. Furthermore, both ACOG and ACMG emphasize the importance of testing the biological father to determine the carrier status of the couple if the mother is identified as a carrier, thus providing a complete reproductive risk assessment.

Hearing loss is one of the most common congenital conditions in the general population, more frequent than critical congenital heart defects, CF, SMA, hemoglobinopathies (sickle cell disease, α -thalassemia, β -thalassemia), or common congenital metabolic diseases [4-6]. Two to three of every 1000 children born in the US are deaf or hard-to-hear. Prelingual intervention significantly facilitates speech and language development [7], and early diagnosis is critical for effective prelingual intervention. About 50% of the congenital hearing loss is genetic. Mutations in the *GJB2* gene, which encodes the Gap Junction Protein Beta 2, also known as connexin 26, are the most frequent cause of autosomal recessive non-syndromic genetic hearing loss in all ethnicities examined [8]. Despite mandatory newborn hearing loss screening at the state level, significant clinical gaps remain. Follow up of failed hearing loss screening is impeded with complex etiology, varying management by pediatricians and specialists, limited access to molecular and genetic diagnosis, and practical challenges to patients' families [9]. In addition, conventional screening sometimes has varying results and often misses infants with mild or late-onset hearing impairment. Crucially, 95% of newborns with hearing loss identified by the newborn hearing loss screening are born to hearing parents [10], which obscures the fact that ~50% of the congenital hearing loss is genetic and makes the need for genetic diagnosis unexpected.

We developed GxVISION® Carrier Screening for prenatal and preconception clinical management. The test applies next generation sequencing (NGS), in combination with multiplex-ligation dependent probe amplification (MLPA), PCRs, and Sanger sequencing. In our analysis of 87,736 patients in the United States, we identified a high prevalence of *GJB2* carriers, further supporting the need for its inclusion in standard prenatal and preconception carrier screening panels. This report details the implementation of *GJB2* in a basic carrier screening option, the resulting carrier rates, and a case illustrating how the inclusion of *GJB2*, with reflex testing of the biological father, bridged gaps in newborn hearing loss screening and led to a positive clinical management outcome.

Case Presentation

The GxVISION® Carrier Screening targets coding sequences, splicing sites, and known intronic pathogenic sequence changes. In addition to single nucleotide variants and small indels, exon-based and known noncoding region-based large deletions and duplications are included for analysis. *GJB2* is included in a basic carrier screening option, together with *CFTR* and *SMN1* and a few other genes.

Our large-scale screening of 87,736 patients revealed 3,736 *GJB2* carriers, representing a carrier rate of 1 in 23.5. Remarkably, this prevalence exceeds that of traditionally mandated conditions: the *GJB2* carrier rate of 1 in 23.5 is more frequent than that of CF (1 in 26) and significantly higher than SMA (1 in 66) in the same patient population.

The prevalence of the *GJB2* carrier positive rate is often initially surprising to the providers followed by an epiphany of how the results provide valuable insight for some common clinical encounters. There are multiple case examples of such realizations. In particular, a pregnant patient underwent the GxVISION® carrier screening, and learned that she was positive for a pathogenic *GJB2* variant. This result provided insight regarding the patient's first child, who had failed the mandatory newborn auditory screening at birth. Despite numerous evaluations by pediatricians and specialists, the first child had not yet received a conclusive origin for the hearing loss.

Following the maternal carrier identification, the biological father's sample was submitted for reflex testing. Results confirmed that the father was also a carrier of a *GJB2* pathogenic variant. Upon patients' consent, the genetic carrier screening results were shared with first child's providers, given them the information needed for confirmatory testing of parental *GJB2* variants in the first child, thus establishing a diagnosis of autosomal recessive hearing loss.

When the second child was born, the child had varying newborn auditory screening results, with assessment ultimately deemed as inconclusive. Genetic testing performed via GxVISION® testing shortly after birth confirmed that the second child had also inherited both *GJB2* pathogenic variants from the parents. Because the genetic risk had been identified during the prenatal period, the family and clinical team were able to finalize the diagnosis, initiate an immediate and focused management plan, overcoming the diagnostic inconsistency and delays experienced with the first child.

Discussion

This report highlights a critical discrepancy between traditional routine screening recommendations and the actual genetic landscape of the US population. Our large-scale screening of 87,736 patients revealed 3,736 *GJB2* carriers, representing a carrier rate of 1 in 23.5, more frequent than that of Cystic Fibrosis (1 in 26) and significantly higher than Spinal Muscular Atrophy (1 in 66), even

when considering the increased risk for SMA silent carriers at 1 in 28. These statistics underscore the clinical significance of *GJB2* as a high-prevalence condition that meets and exceeds the frequency criteria typically used to justify universal screening.

Beyond the high carrier frequency, our screening identified numerous novel null variants within the *GJB2* gene, including nonsense mutations, frameshift mutations, canonical splicing site alterations, and start-loss variants. In addition, there are novel variants of uncertain significance that lack clinical and research evidence for their definitive classification and can be selected for functional studies. The identification of these previously uncharacterized null variants emphasizes the importance of using comprehensive sequencing approaches—such as the GxVISION® platform—rather than limited genotyping mutation panels, which may miss rare or population-specific pathogenic alleles.

The clinical impact of these findings is exemplified by the presented case. Without the inclusion of *GJB2* in the mother's prenatal panel, the etiology and recurrence chance of their first child's hearing loss remained an undiagnosed "mystery," leading to a protracted diagnostic odyssey involving multiple specialists and appointments. The identification of maternal and paternal *GJB2* variants provided a retrospective diagnosis for the first child that overcame inconsistent auditory screening results and allowed for an immediate, targeted intervention plan for the second child, who also inherited both pathogenic variants.

Furthermore, this case addresses the inherent limitations of current newborn hearing loss screening. Because the majority of infants with hereditary hearing loss are born to asymptomatic parents with no family history, the diagnosis is rarely anticipated. Adding *GJB2* to standard carrier screening bridges a gap for newborns who fail auditory screening, providing immediate etiological clarity and enabling earlier access to speech-language pathology and audiological interventions, and family education. Our findings is aligned with ACMG recommendation for autosomal and X-linked recessive conditions and supports the inclusion of *GJB2* in the basic carrier screening options as a standard of care to ensure that high-prevalence conditions like *GJB2*-related hearing loss are no longer overlooked in routine prenatal care.

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the GxVISION® carrier screening program, whose data contributed to our understanding of *GJB2* prevalence in the US population.

Conflict of Interest

Allie Norse, Angela Alexander, Dong Qian, John Spainhour, Alexander Lin, Wenxiao Jiang, and Ping Chen are employees of Otogenetics Corporation. Otogenetics Corporation provides the GxVISION® carrier screening mentioned in this report. The authors declare that this financial relationship did not influence the objectivity of the clinical data or the interpretation of the results presented.

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