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## OtoChip™ Test For Hearing Loss and Usher Syndrome

### Background:

Hearing loss is the most common sensory impairment with an incidence of 1 in 250 births. Over half of these children have a genetic cause for their hearing loss with approximately 100 genes implicated in isolated hearing loss and several hundred in syndromic hearing loss. Of the many genes associated with hearing loss, clinical testing has only been available for a subset. The comprehensive approach of the OtoChip now makes it possible to sequence ~70,000 bases of DNA across 19 genes in parallel, which tests for the following clinical presentations.

- **Nonsyndromic autosomal recessive/sporadic hearing loss:** *CDH23*, *DFNB31 (WHRN)*, *GJB6*, *MYO6*, *MYO7A*, *OTOF*, *PCDH15*, *SLC26A4 (PDS)*, *TMC1*, *TMIE*, *TMPRSS3*, *USH1C*
- **Nonsyndromic autosomal dominant hearing loss:** *GJB6*, *MYO6*, *MYO7A*, *TMC1*
- **Maternally-inherited/Aminoglycoside-induced:** *MTTS* (*tRNA<sup>Ser</sup>(UCN)*) and 6 mutations in *MTRNR1* (*12S rRNA*)
- **Auditory neuropathy/dys-synchrony:** *OTOF*
- **Pendred syndrome/Hearing loss with EVA or Mondini dysplasia:** *SLC26A4 (PDS)*
- **Usher syndrome (Hearing loss and retinitis pigmentosa):** *CDH23*, *CLRN1*, *DFNB31*, *GPR98* (exons 8, 20, 31-41 & 89), *MYO7A*, *PCDH15*, *USH1C*, *USH1G*, *USH2A*

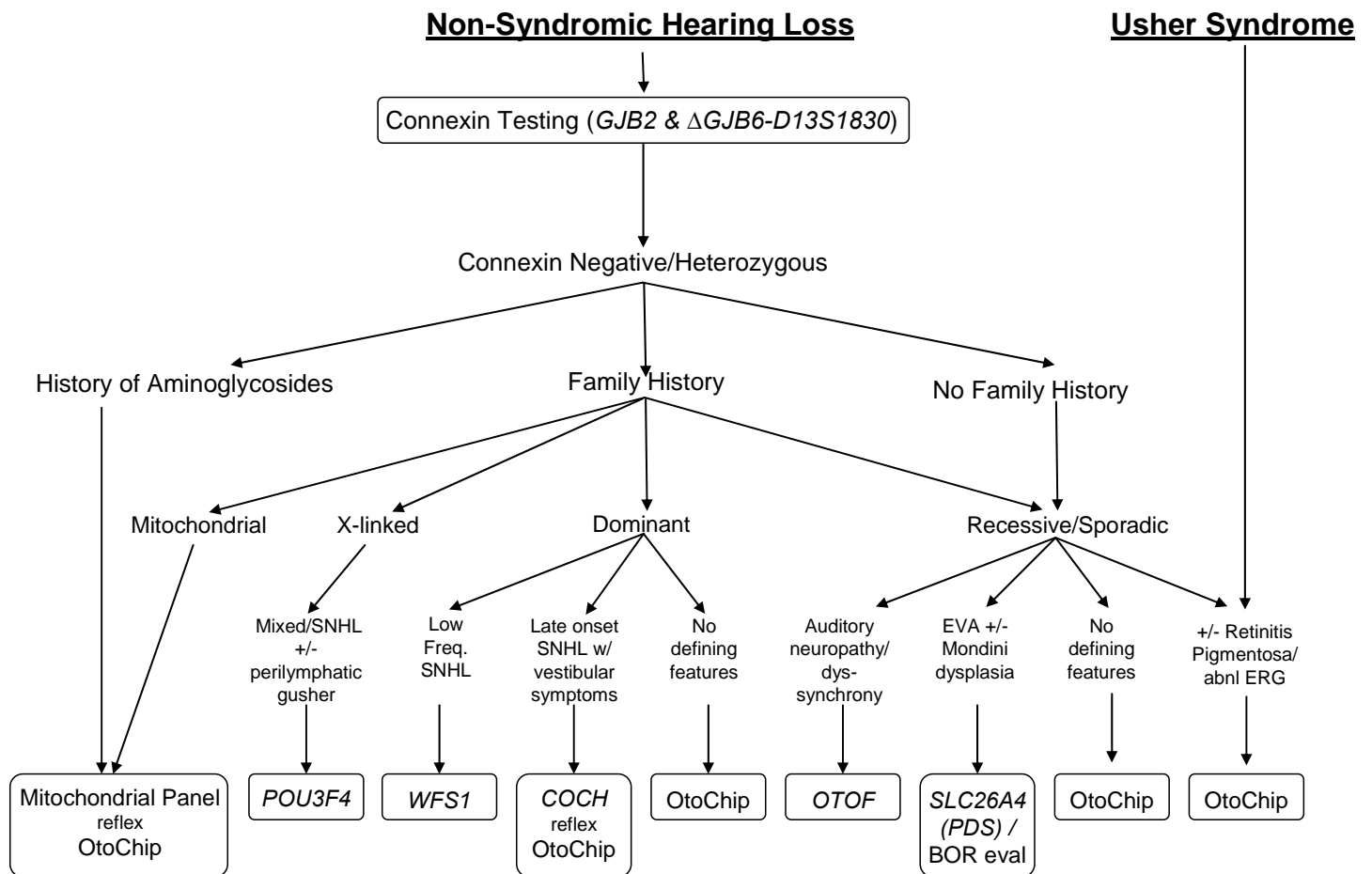


Determining the etiology of hearing loss is important for management. Such a discovery aids in determining prognosis (i.e. whether the loss will worsen), the best intervention (e.g. hearing aids, cochlear implant, sign language) and recurrence risks to future children and other family members. Furthermore, it can either eliminate the possibility that a syndrome might be present, with other clinical problems that have not yet manifested (e.g. adolescent-onset retinitis pigmentosa in Usher syndrome), or predict the onset of such features if a test for a syndromic cause is positive. Of individuals with sensorineural hearing loss up to 5% have hearing loss associated with Pendred syndrome and up to 10% have Usher syndrome.

**Testing Strategy:** The approach to genetic testing for individuals with hearing loss or Usher syndrome is outlined in the following flow chart. Pathogenic variants in the *GJB2* (Connexin 26) gene and the  $\Delta$ *GJB6-D13S1830* (Connexin 30) deletion are the most common cause of nonsyndromic hearing loss and testing is positive in 15-20% of children with hearing loss. The OtoChip does not detect the common 35delG & 167delT variants in *GJB2* or the  $\Delta$ *GJB6-D13S1830* deletion. Therefore, individuals with nonsyndromic hearing loss should have *GJB2*/ $\Delta$ *GJB6-D13S1830* testing before the OtoChip. In addition, if an individual has hearing loss with EVA or Mondini dysplasia we recommend *SLC26A4* gene sequencing before the OtoChip. If an individual has auditory neuropathy/dys-synchrony, we recommend OTOF gene sequencing before the OtoChip. This is because these tests have a higher analytical sensitivity than chip-based sequencing. Individuals with hearing loss and retinitis pigmentosa should go directly to the OtoChip.

The OtoChip is a sequencing based array that has a similar detection rate for substitution mutations as compared to traditional dideoxy sequencing. However, the OtoChip has a lower detection rate for small deletions/insertions. If an individual is found to have one pathogenic mutation in a particular gene on the OtoChip it is recommended that they have follow-up testing of that gene by dideoxy sequencing to determine if there is a second mutation in the gene that was not detected by the OtoChip.

## GENETIC TESTING STRATEGY



If you have any questions, please call the Laboratory for Molecular Medicine at 617-768-8500 or email us at [LMM@partners.org](mailto:LMM@partners.org)

For more information about the OtoChip, or how to order this test through your physician, please contact:

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