

Review

Temperature-Sensitive Auditory Neuropathy: A Scoping Review of Clinical, Genetic, and Neurobiological Evidence

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Abstract

Temperature-sensitive auditory neuropathy (TSAN) is a rare and clinically distinct subtype of auditory neuropathy. TSAN is characterized by reversible deterioration of auditory neural function during hyperthermic states despite well-preserved cochlear outer hair cell activity. Although several case reports, familial studies, and experimental investigations have described this disorder, the available evidence remains inconclusive. This scoping review integrates clinical, genetic, and neurobiological evidence on TSAN, sheds light on its underlying mechanisms, and explores genotype-phenotype correlations. A comprehensive search of PubMed, PMC, Scopus, Web of Science, and Google Scholar was conducted up to December 2025. Studies reporting temperature-dependent auditory dysfunction consistent with TSAN were included regardless of their study design. Eligible publications comprised case reports, case series, familial cohorts, genetic studies, and mechanistic investigations. We



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narratively synthesized the extracted study data because of their methodological heterogeneity. Thirteen studies met the inclusion criteria and were grouped into clinical, genetic, and mechanistic studies. Clinically, TSAN is characterized by preserved otoacoustic emissions and/or cochlear microphonics with absent or severely abnormal auditory brainstem responses during hyperthermia. Hearing thresholds and speech perception typically deteriorate during febrile episodes and often improve following temperature normalization. Genetic evidence supports an autosomal recessive *OTOF*-related basis in reported TSAN cases, with temperature-sensitive phenotypes more frequently reported in genotypes containing certain non-truncating variants. Mechanistic evidence across molecular, synaptic, cortical, and translational levels supports a model of temperature-dependent presynaptic dysfunction, including impaired otoferlin-mediated synaptic vesicle release and altered neural synchrony. TSAN represents a temperature-dependent presynaptic synaptopathy in which thermal vulnerability of synaptic proteins, particularly otoferlin, may contribute to reversible neural dysfunction. Integration of clinical, genetic, and experimental data supports a coherent neurobiological framework with important consequences for diagnosis, genetic counseling, and translational auditory neuroscience.

Keywords

Temperature-sensitive auditory neuropathy; auditory neuropathy; *OTOF*; synaptopathy; hyperthermia

1. Introduction

Auditory neuropathy (AN) is a heterogeneous condition differentiated by impaired neural synchrony within the auditory pathway despite normal cochlear outer hair cell (OHC) function. Individuals with AN typically exhibit normal otoacoustic emissions (OAEs) and/or cochlear microphonics (CM) alongside absent or severely abnormal auditory brainstem responses (ABRs). This condition results in disproportionate difficulties in temporal processing and speech perception, particularly in noisy environments [1, 2]. Advances in electrophysiology and genetic analyses show that AN encompasses diverse underlying mechanisms, including presynaptic inner hair cell (IHC) synaptopathy, auditory nerve dysfunction, and central auditory processing abnormalities [3, 4].

Within this spectrum, temperature-sensitive auditory neuropathy (TSAN) is a rare and distinct subtype, manifesting as reversible hearing loss triggered by elevated body temperature (e.g., during fever, physical exertion, or environmental heat exposure). Despite its biological relevance, researchers have not systematically synthesized TSAN within a unified neurobiological framework. Notably, most studies do not identify standardized thresholds for hearing deterioration, suggesting the limited quantitative characterization of this temperature-dependent phenotype [5-9]. This condition provides a unique model for studying the temperature-dependent vulnerability of auditory synapses and neural conduction, indicating the dynamic nature of synaptic transmission in response to thermal stress [10-12].

Genetic research has implicated biallelic *OTOF* variants as an important genetic basis of reported TSAN cases. *OTOF* encodes otoferlin—a critical protein mediating synaptic vesicle release at IHC

ribbon synapses [6, 8, 11]. Certain *OTOF* variants can cause temperature-dependent deficits in synaptic transmission, resulting in episodic hearing loss during hyperthermic states [7, 8]. The *OTOF* I515T mouse model demonstrates similar synaptic dysfunction, auditory fatigue, and temperature sensitivity, further supporting human clinical observations [3]. Together, these studies underline how molecular defects in synaptic proteins explain clinically observable TSAN. Despite these insights, the literature on TSAN remains inconclusive, encompassing individual case reports, small familial cohorts, genetic analyses, and mechanistic studies, often with heterogeneous audiological protocols and small sample sizes [1, 5-9, 12, 13]. Therefore, a comprehensive synthesis integrating clinical, genetic, and neurobiological evidence is lacking. Such a review should outline the clinical and audiological phenotype of TSAN, integrate genotype-phenotype correlations, elucidate underlying neurobiological mechanisms, and recognize gaps for future research. Accordingly, this scoping review aims to chart the current landscape of TSAN research, bridging human clinical observations with mechanistic and genetic insights to inform both basic neuroscience and translational applications in diagnosis and management.

2. Materials and Methods

This scoping review study was conducted in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [14].

2.1 Literature Search Strategy

A comprehensive literature search was conducted to identify studies on TSAN. Multiple electronic databases were searched: PubMed, PMC, Scopus, Web of Science, and Google Scholar. The search combined keywords related to temperature sensitivity and auditory disorders, using Boolean operators to ensure completeness. Examples of temperature-related keywords included “temperature sensitive,” “temperature-induced,” “heat-sensitive,” “cold-sensitive,” “thermal sensitivity,” “temperature-related,” “thermally sensitive,” “temperature-dependent,” “temperature-responsive,” “temperature-triggered,” and “thermal fluctuation.” Auditory-related keywords included “auditory neuropathy,” “hearing disorder,” “hearing loss,” “auditory dysfunction,” “auditory neuropathy spectrum disorder,” “auditory nerve dysfunction,” “auditory neuropathy/dyssynchrony,” “neural hearing loss,” “cochlear nerve disorder,” “hearing nerve damage,” “neural hearing impairment,” “sensorineural hearing disorder,” and “auditory processing disorder.” The search also included specific TSAN phrases, such as “temperature-sensitive auditory neuropathy” and “temperature-induced auditory neuropathy.” Boolean operators (AND/OR) were applied to combine terms (e.g., temperature-related AND auditory neuropathy) and maximize sensitivity.

2.2 Screening and Eligibility Criteria

We searched for relevant articles up to December 2025; articles written in English were eligible for evaluation. Given the scoping review design, studies were included if they reported temperature-dependent auditory dysfunction, particularly TSAN, regardless of study design. Eligible study types comprised case reports, case series, familial cohorts, cross-sectional studies, and other observational designs that provided explicit clinical, audiological, genetic, or mechanistic data

related to TSAN. The exclusion criteria comprised editorials, commentaries, letters to the editor, and conference abstracts without full-text data. We also excluded studies that lacked explicit information on temperature-dependent auditory changes.

2.3 Study Selection

We imported all identified accounts into EndNote and removed duplicates. Two authors (M.A. and Z.I.M.) independently screened titles and abstracts, then assessed full texts. Subsequently, they checked the full text of eligible studies against the predetermined inclusion criteria. Discrepancies were resolved through discussion or by consulting a third author. The extracted data were organized in an Excel spreadsheet.

2.4 Data Extraction and Quality Assessment

Two authors (M.A. and P.H.) independently extracted data using a standardized data extraction form. Extracted information included study characteristics (author, year, country, and study design), participant characteristics (age, sex, familial or sporadic presentation), audiological findings (ABRs, OAEs, cochlear microphonics, pure-tone audiometry [PTA], speech perception, and febrile versus afebrile thresholds), genetic findings (gene, variant, and inheritance pattern), and mechanistic findings (animal models, electrophysiological measures, and synaptic studies). Given the scoping review design, substantial heterogeneity in included study designs, and the predominance of case reports and case series, formal critical appraisal or risk-of-bias assessment was not performed. Instead, methodological limitations and the nature of the available evidence were considered descriptively during data synthesis.

2.5 Data Synthesis

Due to the heterogeneity of study designs, populations, and audiological protocols, we used narrative synthesis. Descriptive tables were generated to summarize clinical, genetic, and mechanistic findings. Although formal quality appraisal is not mandatory in scoping reviews, methodological limitations and the nature of the available evidence were considered descriptively to enhance transparency.

3. Results

3.1 Study Selection

The database search yielded 554 records. After removing 63 duplicate records, 491 records remained for title and abstract screening. Of these, 470 were excluded because they did not meet the predefined eligibility criteria. The remaining 22 articles underwent full-text assessment, of which 13 met the inclusion criteria. We excluded eight articles after full-text assessment for the following reasons: review articles, articles in other languages, and theses and conference abstracts. Figure 1 summarizes the study selection process. We categorized the included studies into 3 main groups: human clinical studies, genetic studies, and mechanistic/experimental studies. Table 1 summarizes each included study.

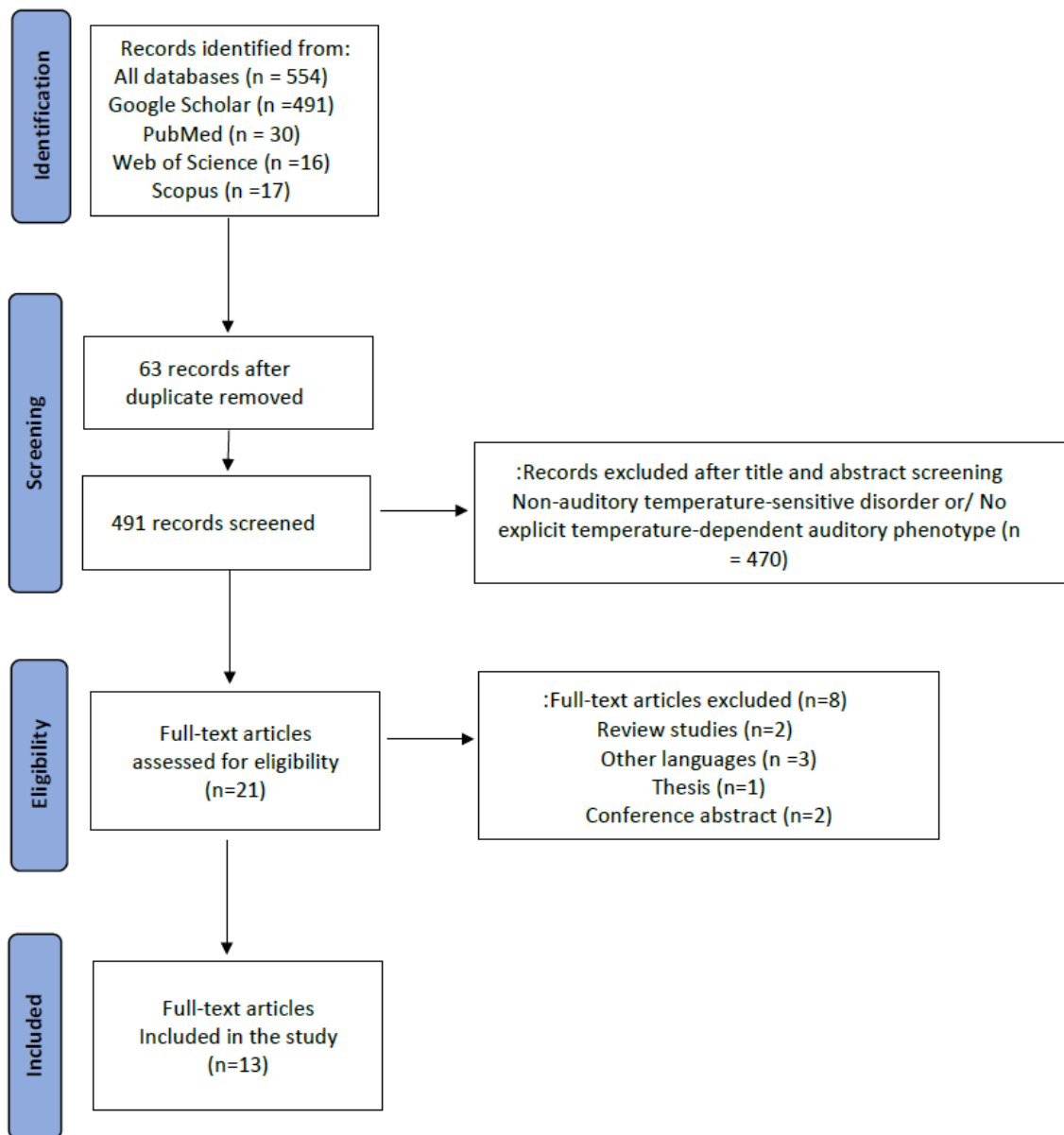


Figure 1 PRISMA flowsheet showing the decision-making process for the articles included in the study. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Three categories of all included articles.

Categories	Studies	Key Findings
Human clinical studies	Starr et al., 1998 [1], Cianfrone et al., 2006 [2], Madanoglu et al., 2007 [13], Varga et al., 2006 [5], Wang et al., 2010 [6], Marlin et al., 2010 [7], Zhang et al., 2016 [8], Zhu et al., 2021 [12], Forli et al., 2023 [9], Yazdani 2021 [11]	Fever-induced reversible hearing loss; preserved OAEs/CM; ABR absent; variable PTA; speech perception impaired during febrile states
Genetic studies	Varga et al., 2006 [5], Wang et al., 2010 [6], Marlin et al., 2010 [7], Matsunaga et al., 2012 [10], Zhang et al., 2016 [8], Zhu et al., 2021 [12], Forli et al., 2023 [9]	Mutations: I515T, Glu1804del, etc.; autosomal recessive; genotype-phenotype correlation; population-specific variants
Mechanistic/ Experimental studies	Strenzke et al., 2016 [3], Dimitrijevic et al., 2011 [4], Zhu et al., 2021 [12]	<i>OTOF</i> mutant mice: ABR wave I reduction, auditory fatigue, synaptic vesicle release impairment; temperature-dependent neural dysfunction

3.2 Human Clinical Studies

A total of 10 human clinical studies were included, comprising case reports, case series, and familial cohort investigations. The TSAN phenotype was generally characterized by preserved OAEs and/or cochlear microphonics, with absent or severely abnormal ABRs during hyperthermic episodes [2, 5-9, 11-13]. PTA thresholds varied across studies, ranging from normal or mild loss in afebrile states to moderate or severe loss during febrile episodes [1, 2, 5-9, 11-13]. Speech perception was commonly reduced during hyperthermia and showed partial or full recovery after temperature normalization [1, 2, 5-9, 11, 13]. The most frequently reported triggers were febrile illness and physical exertion, with hearing deterioration reported during febrile or elevated-temperature states. However, the temperature at which hearing deterioration occurs varies across individuals and studies [1, 2, 5-9, 11-13]. Auditory function often recovers within hours to days after fever resolves, although some cases report incomplete recovery or persistent deficits [1, 2, 5-9, 11, 13] (Table 2).

Table 2 Clinical Studies of TSAN.

Author (Year)	Study design	Participants with TSAN	Audiological profile	Speech/ temporal findings	Hearing recovery after defervescence
Starr et al., 1998 [1]	Case series	3 children	Preserved OAEs/CM; absent ABR; variable PTA; absence of middle-ear muscle reflexes	Impaired speech perception during fever	Hearing recovery
Cianfrone et al., 2006 [2]	Case report	1 adult	Preserved OAEs; absent ABR; abnormal PTA	-----	Hearing recovery
Varga et al., 2006 [5]	Familial cohort	8 families (12 children & adults)	Preserved OAEs; absent ABR; fluctuating PTA	Impaired speech perception during fever	Partial hearing recovery
Madanoglu et al., 2007 [13]	Case report	1 family (2 children & 3 adults)	Preserved OAEs/CM/MLR; absent ABR; fluctuating PTA, absence of middle-ear muscle reflexes, Normal MRI and neurologic examination	Impaired speech perception during fever	Hearing recovery
Wang et al., 2010 [6]	Familial cohort	1 child	Preserved OAEs; absent ABR	Impaired speech perception during fever	Hearing recovery
Marlin et al., 2010 [7]	Familial cohort	3 children (siblings)	Preserved cochlear responses; absent ABR	Temporal processing deficits during fever	Hearing recovery
Zhang et al., 2016 [8]	Familial cohort	3 children	Preserved OAEs/CM; absent ABR; moderate to severe PTA; absence of middle-ear muscle reflexes	Impaired speech perception during fever	Hearing recovery in 2 patients
Zhu et al., 2021 [12]	Familial cohort	4 children (siblings)	Preserved CM; absent ABR	Impaired speech perception during fever	Hearing recovery
Yazdani 2021 [11]	Case report	2 children (siblings)	Preserved OAEs/CM; absent ABR; fluctuating PTA; absence of middle-ear muscle reflexes	Impaired speech perception during fever	Hearing recovery
Forli et al., 2023 [9]	Case report	1 child	Preserved OAEs; absent ABR; moderate to severe PTA	Impaired speech perception during fever	Hearing recovery

3.3 Genetic Studies

The genetic studies in this review primarily focus on variants in the *OTOF* gene [5-10, 12]. These studies report variants and genotypes, including missense, truncating, and compound heterozygous variants, with predicted or reported effects on otoferlin function [5-10, 12]. Reported genotype–phenotype correlations indicate that temperature-sensitive phenotypes are more frequently associated with biallelic *OTOF* genotypes containing certain non-truncating variants. In contrast, biallelic truncating genotypes are more commonly associated with severe and persistent auditory dysfunction. However, this relationship is not absolute, and phenotypic variability has been reported across *OTOF* genotypes [5-10, 12]. Several studies also described population-specific variants and founder mutations, emphasizing the importance of targeted genetic screening in different ethnic groups [6, 7, 9, 10, 12] (Table 3).

Table 3 Genetic Studies of TSAN.

Author (Year)	Country	Sample	Methods	Gene	Variant(s)	Inheritance	<i>OTOF</i> Genotypes
Varga et al., 2006 [5]	USA	8 families (12 children & adults)	PCR	<i>DFNB9/OTOF</i>	Multiple missense & truncating variants	Autosomal recessive	missense allele I515T
Wang et al., 2010 [6]	China	1 child	PCR	<i>OTOF</i>	Missense variants	Autosomal recessive	two novel mutant alleles (c.2975_2978delAG + c.4819C>T)
Marlin et al., 2010 [7]	France	3 children (siblings) from a consanguineous family	PCR	<i>DFNB9/OTOF</i>	Missense mutation	Autosomal recessive	a novel mutation p.Glu1804del in exon 44 of <i>OTOF</i>
Matsunaga et al., 2012 [10]	Japan	1 adult	PCR	<i>OTOF</i>	Founder and recurrent variants	Autosomal recessive	Non-truncating/non-truncatingp.G541S/p.G541S
Zhang et al., 2016 [8]	China	3 children	NGS/PCR	<i>OTOF</i>	Compound heterozygous variants	Autosomal recessive	c.2975_2978delAG/c.4819C>T, c.4819C>T/c.4819C>T, or c.2382_2383delC/c.1621G>A
Zhu et al., 2021 [12]	China	4 children (siblings)	NGS/PCR	<i>OTOF</i>	Novel and known variants	Autosomal recessive	one novel variant, c.4882C>A (p.Pro1628Thr)
Forli et al., 2023 [9]	Italy	1 child	NGS	<i>OTOF</i>	Novel variants	Autosomal recessive	a missense variant (c.2521G>A) in exon 21, classified as pathogenic; and a loss-of-function deletion of 7.4 Kb

PCR: Polymerase chain reaction; NGS: Next-generation sequencing.

3.4 Mechanistic and Experimental Studies

Three studies provided mechanistic or neurobiological evidence relevant to TSAN, across presynaptic synaptic models, cortical electrophysiology, molecular protein studies, and translational genetic analyses [3, 4, 12] (Table 4). Strenzke et al. [3] described direct experimental evidence from the *OTOF* I515T mutant mouse model. Controlled temperature elevation reduced ABR wave I amplitudes, impaired synaptic vesicle release at IHC ribbon synapses, and caused auditory fatigue. These findings provide evidence of temperature-dependent impairment of presynaptic auditory function and Ca^{2+} -dependent exocytosis. Dimitrijevic et al. [4] reported abnormal cortical N100 responses in patients with presynaptic auditory neuropathy. Although they did not assess temperature manipulation, these findings are consistent with altered neural synchrony and afferent transmission, providing indirect neurophysiological support for a neural component of TSAN. Finally, Zhu et al. [12] integrated human genetic findings with functional interpretation, demonstrating variant-dependent temperature-sensitive phenotypes in *OTOF*-related auditory neuropathy. Their findings link clinical genetics to synaptic dysfunction, supporting thermal vulnerability of otoferlin-mediated exocytosis. Together, mechanistic evidence spans molecular, synaptic, cortical, and translational levels, supporting a presynaptic temperature-dependent synaptopathy model for TSAN.

Table 4 Mechanistic and Experimental Studies of TSAN.

Author (Year)	Model Type	Biological model	Temperature Manipulation	Main Neurophysiological Finding	Mechanistic Interpretation	Strength of Evidence for TSAN
Dimitrijevic et al., 2011 [4]	Human cortical AN	Central auditory cortex	Not temperature-specific	Abnormal N100 responses; neural dys-synchrony	Impaired neural synchrony	Indirect supportive evidence
Strenzke et al., 2016 [3]	<i>OTOF</i> I515T mouse model	Presynaptic synapse (IHC ribbon)	Controlled elevation	Reduced ABR wave I amplitude; impaired synaptic vesicle release; auditory fatigue	Ca ²⁺ -dependent exocytosis failure	Direct mechanistic evidence
Zhu et al., 2021 [12]	Human genetic cohort	Translational synaptopathy	Febrile episodes (clinical)	Variant-dependent temperature-sensitive phenotype	Otoferlin thermal vulnerability	Translational genetic evidence

4. Discussion

4.1 Human Clinical Studies

Clinical evidence consistently shows that TSAN is a distinct phenotype within AN. TSAN is characterized by reversible hearing loss prompted by high body temperature, with preserved OAEs and/or cochlear microphonics and absent or severely abnormal ABRs during hyperthermia. This pattern shows that the primary pathology is neural (synaptic or neural conduction) rather than cochlear hair cell dysfunction. Additionally, speech perception may deteriorate during fever or heat exposure and may partially or completely recover after return to normothermia. These clinical features distinguish TSAN from other forms of AN that are usually stable and non-reversible. Early clinical reports by Starr et al. and Cianfrone et al. provided the first evidence of TSAN [1, 2]. Subsequent familial and pediatric cohort studies expanded the phenotype across different populations and confirmed the recurrent clinical pattern [5-9, 11, 13]. The recurrent observation of this phenotype in familial cases supports a genetic etiology and underlines the need to evaluate fever/heat history in patients with inconsistent audiological findings.

4.2 Genetic Studies (*OTOF* and Genotype-Phenotype Correlations)

The available genetic evidence implicates biallelic recessive *OTOF* variants in reported cases of TSAN. Across reported studies, individuals with biallelic *OTOF* genotypes that include certain non-truncating variants, particularly missense variants, have shown temperature-sensitive phenotypes. In contrast, biallelic truncating genotypes are more commonly associated with severe and persistent auditory dysfunction [5-9, 12]. This genotype-phenotype association suggests that some non-truncating otoferlin variants retain residual function at normothermia but become functionally impaired under thermal stress, resulting in reversible auditory dysfunction. However, the available evidence is insufficient to establish that all non-truncating variants confer temperature sensitivity or that all truncating variants result in a stable phenotype [5-9, 12].

Population-specific *OTOF* variant spectra reported in the USA, China, Japan, Iran, and Italy demonstrate genetic heterogeneity and support the value of targeted genetic testing [5-9, 12]. However, differences between populations may also reflect founder effects, referral patterns, genetic testing strategies, and limited sample sizes rather than established population-specific differences in temperature sensitivity [6, 7, 9-12]. Consistent with the broader genetic architecture of AN, *OTOF* is an important disease-associated gene, but the genetic spectrum varies across clinical and population subgroups [6].

Overall, the genetic evidence supports an *OTOF*-related autosomal recessive basis for reported TSAN cases, with certain biallelic genotypes containing non-truncating variants that may preserve residual otoferlin function at normothermia but become dysfunctional under hyperthermic conditions. This interpretation aligns with a temperature-dependent presynaptic mechanism; however, variant-specific functional studies and larger cohorts are required to determine whether this mechanism is shared across TSAN-associated *OTOF* variants [3, 5-9, 12].

4.3 Mechanistic and Experimental Studies (Neurobiological Evidence)

The mechanistic evidence found in this review supports a multi-level neurobiological model of TSAN involving temperature-sensitive presynaptic dysfunction. The strongest direct experimental support comes from the *OTOF* I515T mouse model [3], where controlled temperature elevation resulted in reduced ABR wave I amplitudes and impaired synaptic vesicle release at IHC ribbon synapses. These findings provide direct experimental evidence that otoferlin dysfunction can compromise Ca^{2+} -dependent exocytosis under thermal stress, providing a physiological explanation for the reversible ABR abnormalities observed during febrile episodes in humans. Translational genetic evidence further strengthens this model. Zhu et al. [12] verified that specific *OTOF* variants are associated with temperature-dependent phenotypes, suggesting that certain missense mutations retain partial functionality at normothermia but become unstable during hyperthermia. This aligns with genotype-phenotype correlations observed in clinical cohorts. At a broader molecular level, Berson et al. [15] describe temperature-sensitive protein misfolding, providing a conceptual basis for thermal protein instability. Although this evidence is not specific to otoferlin or TSAN, it supports the biological plausibility that elevated temperature may alter protein conformation, stability, trafficking, or membrane localization and thereby contribute to transient functional impairment. Cortical electrophysiological findings by Dimitrijevic et al. [4] further indicate that damaged neural synchrony portrays presynaptic auditory neuropathy. Although these data were not directly temperature-controlled, they are consistent with disrupted afferent signaling secondary to synaptic failure. Taken together, these studies support a neurobiological model in which temperature-dependent presynaptic dysfunction contributes to the TSAN phenotype, with thermal vulnerability of otoferlin potentially impairing synaptic vesicle release at IHC ribbon synapses. This model plausibly explains the reversible and episodic nature of hearing loss, but its applicability across different *OTOF* variants remains to be established.

4.4 Clinical and Translational Implications

TSAN diagnosis carries significant clinical implications. Awareness of temperature-dependent hearing fluctuations can prevent misdiagnosis and unnecessary interventions. Clinicians should suspect TSAN when patients present with recurrent hearing loss during fever or heat exposure, especially when OAEs/CM are preserved, and ABR is abnormal during hyperthermia [1, 2, 5-9]. Genetic testing for biallelic *OTOF* variants helps confirm an *OTOF*-related phenotype, guide family counseling, and provide anticipatory guidance. Identification of certain non-truncating *OTOF* variants may support consideration of a temperature-sensitive phenotype, whereas biallelic truncating variants are more commonly associated with severe, persistent impairment [5-9, 12]. Audiological monitoring during febrile episodes and after recovery is recommended to document the dynamic course of the disorder. In cases with persistent or severe deficits, cochlear implantation may be considered, particularly when recovery is incomplete, or speech perception remains poor [8].

4.5 Methodological Considerations and Future Directions

The available evidence supports TSAN as a temperature-dependent auditory phenotype; however, the current evidence base remains limited. Thirteen studies met the inclusion criteria. The

evidence base consisted predominantly of small clinical and familial studies, supplemented by genetic and mechanistic investigations. No large multicenter clinical cohort was identified. These small samples limit the generalizability of the findings and reduce the reliability of genotype–phenotype and temperature-response estimates [1, 2, 5-9, 11-13].

Small sample sizes also introduce substantial uncertainty into genotype–phenotype correlations. Reported TSAN cases are predominantly associated with biallelic *OTOF* genotypes that include certain non-truncating variants, whereas biallelic truncating variants are more commonly associated with severe and persistent auditory dysfunction [5-9, 12]. However, the small number of patients carrying individual variants does not allow reliable estimation of variant-specific penetrance or prediction of temperature sensitivity, severity, or reversibility. Therefore, interpret this relationship as an association rather than a definitive genotype-based rule. Consistent with the broader genetic architecture of AN, *OTOF* is an important disease-associated gene, but the genetic spectrum varies across clinical and population subgroups [6]. Differences in reported mutation spectra may also reflect founder effects, referral patterns, testing strategies, and sampling variation rather than true population-specific biological differences [6, 7, 9-12].

Temperature sensitivity is likewise difficult to quantify across studies. Differences in body-temperature measurement, timing of audiological testing relative to fever or heat exposure, ABR methodology, and criteria for defining hearing deterioration and recovery may contribute to variability in reported temperature thresholds and recovery duration [1, 2, 5, 6]. Therefore, the reported temperature ranges and recovery times are not standardized biological thresholds.

Evidence is limited for the clinical phenotype, low to very low for specific genotype–phenotype correlations, and particularly limited for precise temperature thresholds. Mechanistic evidence supports temperature-dependent presynaptic dysfunction, but direct experimental evidence is concentrated in the *OTOF* Ile515Thr model [3]. Findings from this model, together with human genetic observations, support the proposed mechanism but cannot be assumed to apply uniformly to all *OTOF* variants associated with TSAN [3, 7, 12].

Future studies should use larger multicenter cohorts and standardized temperature-monitored protocols, with predefined measurements of body temperature, pure-tone thresholds, speech perception, ABR, and cochlear microphonic responses. Functional studies of additional *OTOF* variants under controlled temperature conditions are also needed to determine whether temperature sensitivity represents a shared mechanism or a variant-specific effect.

5. Conclusion

TSAN represents a rare but biologically informative subtype of auditory neuropathy. It is characterized by reversible, hyperthermia-induced disruption of auditory neural function despite preserved cochlear outer hair cell activity. Clinical evidence exhibits episodic worsening of auditory brainstem responses and speech perception during raised body temperature, often followed by partial or complete recovery. Available genetic evidence supports an autosomal recessive *OTOF*-related basis in reported TSAN cases, with temperature-sensitive phenotypes more frequently reported in genotypes containing certain non-truncating variants. Converging mechanistic evidence from molecular, synaptic, cortical, and translational studies supports a presynaptic synaptopathy model in which thermal vulnerability of otoferlin may impair Ca^{2+} -dependent synaptic vesicle release at inner hair cell ribbon synapses. This temperature-dependent synaptic vulnerability

mechanistically explains the episodic and reversible nature of the disorder. Beyond its clinical relevance, TSAN offers a unique human model for studying activity-dependent synaptic resilience and thermal modulation of neurotransmission. Accurate diagnosis and management require improved recognition, temperature-monitored audiological assessment, and targeted genetic testing. Future multicenter, longitudinal investigations, integrating functional genomics and electrophysiological biomarkers are needed to refine the neurobiological framework and clarify the translational implications of this condition. TSAN provides a rare opportunity to study reversible synaptic failure in humans under physiologically relevant thermal stress.

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Author Contributions

Study concept: M.A. and Z.I.M.; Study design: M.A.; Supervision: M.A.; Materials: M.A., Z.I.M., and P.H.; Data collection and processing: M.A. and Z.I.M.; Analysis and interpretation: M.A. and P.H.; Literature search: M.A. and Z.I.M.; Writing the original draft: M.A., Z.I.M., and P.H.; Critical reviews: M.A. and P.H.

Competing Interests

The authors have no conflict of interest to declare. This research project was supported by the Research Deputy of AJUMS, Ahvaz, Iran (Contract No: PHT-0415).

AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of this manuscript. Specifically, OpenAI's ChatGPT was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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