Is *CABP2*-Associated Hearing Loss (DFNB93) a Gene Therapy Target? Preclinical Progress and Patient Registry

What if we could connect patients across the world, while contributing to preclinical development of future gene therapies? Patient registries make this a reality by simultaneously providing a scientific resource and a community for individuals living with rare forms of hearing loss.

Hearing impairment is one of the most common sensory conditions worldwide and has an extraordinarily diverse genetic basis. While advances in sequencing now make rapid genetic diagnoses possible, translation via gene therapies face two major challenges: identifying the right patients at the right time and ensuring there is sufficient longitudinal and phenotypic data to design and execute appropriate clinical trials. Patient registries directly address these challenges by centralizing clinical and genetic information, creating a structured framework for natural history studies, and building the patient cohorts necessary for trial readiness. In parallel, they foster patient communities, especially for families who may otherwise be isolated by the rarity of their diagnosis. Registries are thus essential tools for advancing precision medicine.

Among the many hearing loss genes, *CABP2* (Calcium Binding Protein 2) stands out as an ideal target for therapy design. Promising pre-clinical studies in Göttingen have signaled feasibility to move towards translation (Oestreicher et al., 2021, 2024). *CABP2* plays a critical role in regulating $Ca_V1.3$ Ca^{2+} channels at the ribbon synapse of inner hair cells, structures that are responsible for transmitting sound signals with remarkable speed and precision. Biallelic variants in *CABP2* cause recessive, non-syndromic hearing impairment (DFNB93). *CABP2* is an attractive therapeutic candidate because its coding sequence is small enough to fit within a single adeno-associated viral (AAV) vector, a widely used vehicle for inner ear gene delivery; it is expressed in hair cells already well targeted by existing AAV serotypes; and preclinical studies in mouse models have shown that gene replacement restores inner hair cell calcium currents and significantly improves hearing function. Together, these features place *CABP2* among the most attractive next targets for clinical translation following current trials for *OTOF*-associated hearing loss.

Recognizing the rarity of *CABP2*-associated hearing loss and its therapeutic potential, we developed the *CABP2* Registry (ClinicalTrials.gov: NCT06680934) as a dedicated platform for patients, clinicians, and researchers (Vona et al., 2025). Registry design involved an interdisciplinary team of clinicians, human geneticists, and basic researchers with three goals: to collect robust, longitudinal clinical and genetic data to support natural history studies; to identify and engage patients for future clinical studies, ensuring recruitment feasibility even for a rare form of hearing loss; and to empower families by connecting them to a broader network and involvement in trial design. The registry uses a secure, GDPR-compliant REDCap platform with strict separation of patient-identifiable and clinical/genetic data; an electronic consent process available for adults, adolescents, and children (with parental co-consent) to enable broad participation; structured electronic case report forms that collect genetic test results, family history, disease course, and hearing rehabilitation data; and the ability for participants to update their records and upload new audiograms, ensuring the registry remains dynamic and clinically current.

The *CABP2* Registry builds directly on earlier experience in establishing the Otoferlin (*OTOF*) Registry (ClinicalTrials.gov: NCT05946057) (Vona et al., 2024). Otoferlin-associated hearing loss (DFNB9) is now the subject of multiple ongoing clinical trials, and the registry is already serving as a critical recruitment and natural history resource. Together, these resources form a framework for registry-driven precision medicine for hereditary hearing loss. They demonstrate the strong

possibility of mobilizing families with rare diagnoses to work with research communities by providing real-world data and facilitating patient stratification for clinical trials. This serves as a model that can be expanded to other hearing loss genes as the therapeutic field evolves. Of note, these are the first innovative registries worldwide to support patients with isolated hearing loss and are distinctly different from those for patients with various syndromic forms of hearing loss. These have already contributed valuable experiences towards larger longer-term goals that include building a national patient registry for stratifying genetic forms of hearing loss to support further clinical trials. These are highly relevant goals for the field and such frameworks are crucial for keeping Germany as an attractive location for running clinical trials.

The *CABP2* Registry forms a bridge for patients, clinicians, and researchers. It enables detailed phenotyping, longitudinal tracking, and translational readiness, while providing a mechanism to ensure that patients with hereditary hearing loss are not left behind as gene therapies advance. Equally important, registries foster a sense of belonging. Families who once faced their diagnosis in isolation can now connect, share experiences, and learn about therapeutic progress.

The *CABP2* Registry represents a pioneering effort to proactively build infrastructure required for next generation therapies in rare hearing loss in Germany. Specifically, the registry translates basic discoveries in calcium-binding proteins and auditory synaptopathies into a clinical research platform, provides a ready cohort for upcoming trials, significantly accelerates the path from bench to bedside, demonstrates how academic initiatives can fill the gaps left by limited commercial interest in ultra-rare conditions, and serves as a model for precision medicine that can be replicated across other rare auditory disorders. Receiving the Research Prize Tinnitus & Hearing 2025 would not only recognize the work that has gone into developing this registry but also highlight and communicate the vital role of patient registries in hearing research and therapy development. Such recognition would amplify the message that registries are indispensable tools for bridging discovery and care, especially in a field where timely patient identification and engagement can make the difference between treatment success and missed opportunity.

References

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