

LS25-014 - Decoding GNB1E: Advanced Drug Repurposing for Personalized Treatment

Zusammenfassung

We aim to discover novel treatment options for GNB1 Encephalopathy (GNB1E), a severe neurologic disorder caused by germline mutations in the G β 1 subunit of G-proteins, for which no cure exists. Over 30 disease-causing GNB1 variants have been identified, causing developmental delay, motor disorders, epilepsy, and more. Some GNB1 germline mutations overlap with somatic mutations, highlighting the broader relevance of G β 1 dysfunction.

GNB1E exemplifies the complexity of ultra-rare diseases, where single-gene mutations cause pleiotropic effects across pathways. The G β subunit forms a heterotrimer with G-alpha and Gy and plays a pivotal role in GPCR signaling, a fundamental cellular process. G β regulates neuronal excitability and metabolism by modulating Ca $^{2+}$ and inwardly rectifying K $^{+}$ channels, adenylyl cyclases, and other effectors. Mutations disrupt these interactions, causing severe, variant-specific symptoms.

Our approach uniquely addresses the challenges of ultra-rare diseases, where data scarcity and mutational heterogeneity limit traditional AI and omics methods. By integrating a unique combination of physics-based simulations, novel AI-enhanced drug screening, and docking studies with patient-derived models and RNA-sequencing, we decode molecular consequences, classify mutations, and identify FDA-approved drugs for repurposing. Unlike phenotype-driven methods, our strategy targets the root causes, enabling highly targeted, cost-effective personalized therapies.

Supported by the patient group, we leverage patient registries, natural history data, and clinical expertise to enable future N=1 or small cohort trials. Scalable and adaptable, our approach bridges molecular mechanisms with real-world therapeutic use, offering a roadmap for precision medicine that ensures no patient is left behind.

Wissenschaftliche Disziplinen:

Pharmacology (35%) | Computational chemistry (35%) | Neuropathology (30%)

Keywords:

ion channel electrophysiology molecular dynamics simulations drug repurposing neuronal development organoids

Principal Investigator: Anna Weinzinger
Institution: University of Vienna
Co-Principal Investigator(s): Nicole Amberg (Medical University of Vienna)
Nathan Dascal (Tel Aviv University)

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Weiterführende Links zu den beteiligten Personen und zum Projekt finden Sie unter <https://wwtf.at/funding/programmes/ls/LS25-014/>