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 Gß1 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 Gß1 dysfunction.

GNB1E exemplifies the complexity of ultra-rare diseases, where single-gene mutations cause pleiotropic effects across pathways. The Gß subunit forms a heterotrimer with G-alpha and Gy and plays a pivotal role in GPCR signaling, a fundamental cellular process. Gß regulates neuronal excitability and metabolism by modulating Ca2+ 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 electrophysiologymolecular dynamics simulationsdrug repurposingneuronal developmentorganoids

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