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Comprehensive Database for Ryanodine Receptor Type-1 Related Disorders: Concept and Progress Update

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Background:

RYR1 gene encodes the largest ion channel in humans, the skeletal muscle ryanodine receptor (RyR1). RyR1 gates calcium in the sarcoplasmic reticulum and is critical to excitation-contraction coupling. Pathogenic *RYR1* variations cause a diverse spectrum of rare neuromuscular disorders including congenital and late-onset myopathies, rhabdomyolysis-myalgia syndrome, and are linked to malignant hyperthermia (MH) susceptibility. There is no approved treatment for *RYR1*-related disorders. >1000 *RYR1* variations have been reported. A majority are classified as variants of uncertain significance (VUS) for which interpretation remains challenging for researchers, clinicians, and affected individuals. We therefore developed two datasets as the foundation for a dedicated database for *RYR1*-related disorders:

(1) Clinical dataset: genotype-phenotype data on >2500 patients

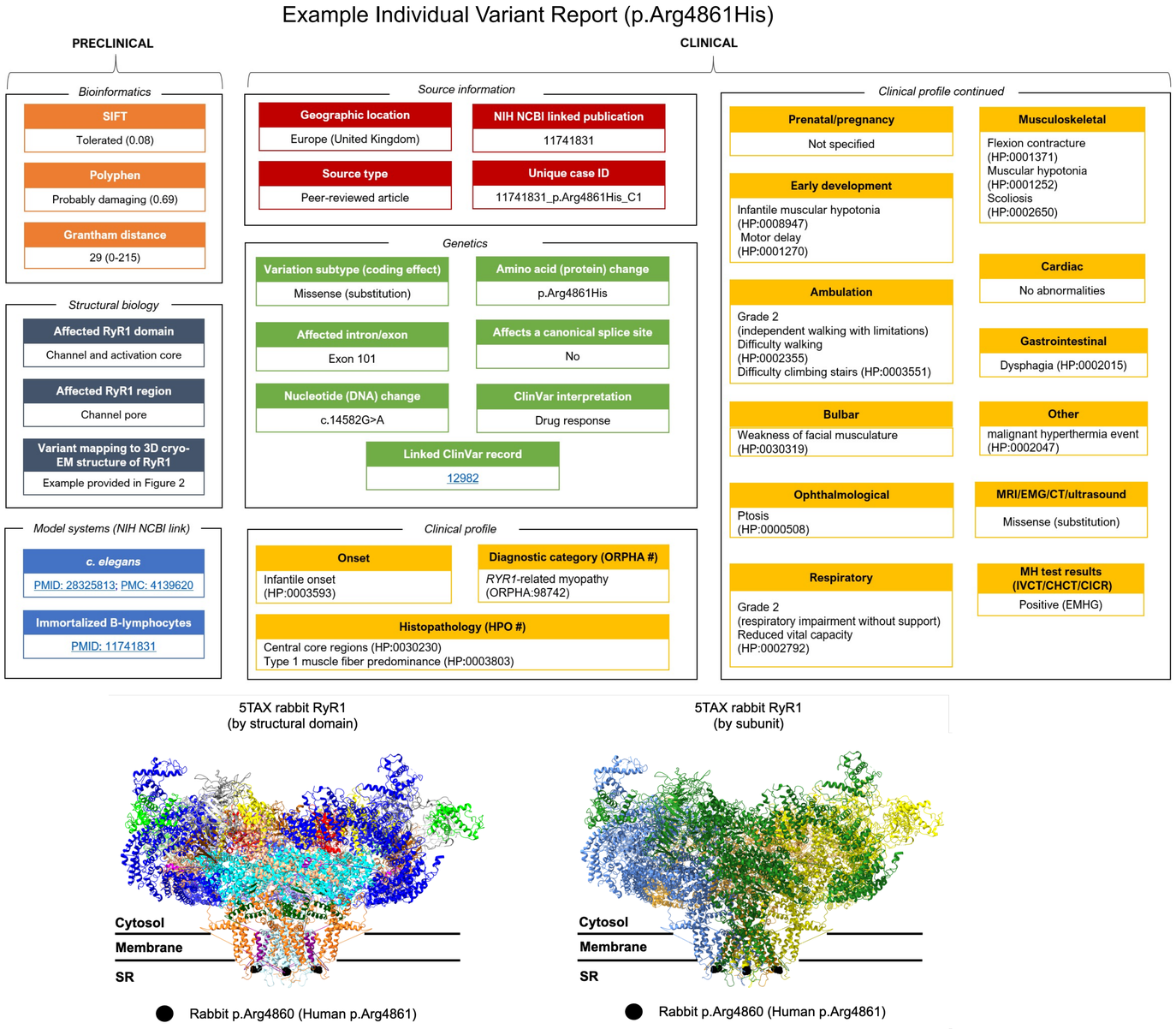
(2) Preclinical dataset: analyses on >200 published *RYR1* variations

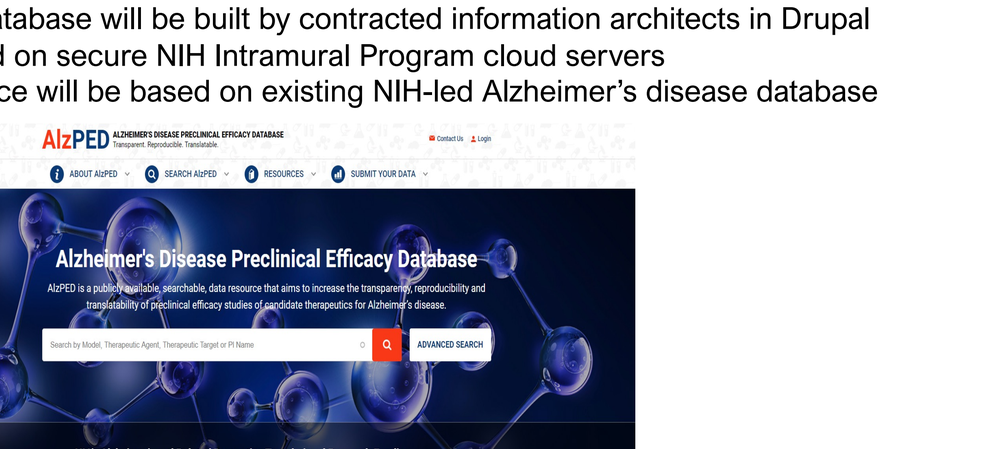
Aims:

1. Combine existing preclinical and clinical *RYR1* datasets to establish the database taxonomy
2. Engage the patient community, research scientists, and medical professionals to refine and optimize database interface
3. Launch database for *RYR1*-related disorders
4. Establish a mechanism for long-term curation and funding of the database

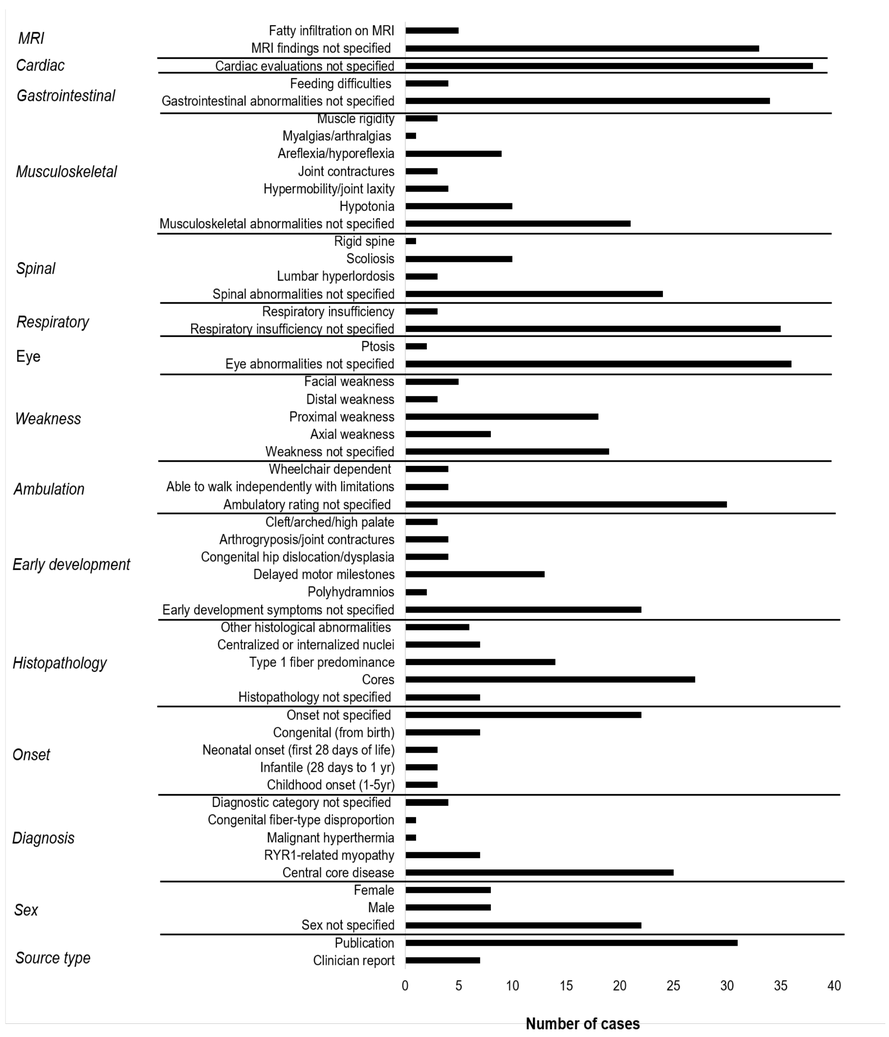
Aim 1: Database Taxonomy

Example Individual Variant Report (p.Arg4861His)





Example Aggregate Clinical Report (p.Arg4861His)



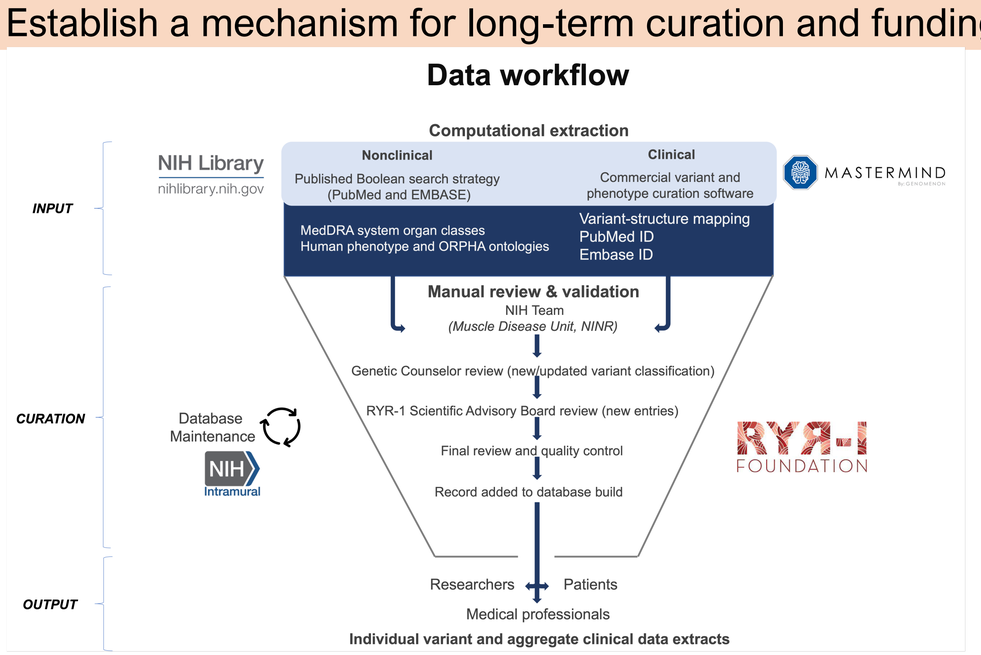
Aim 2: Engage the patient community, research scientists, and medical professionals to refine and optimize database interface

- Semi-structured survey of stakeholders (minimal risk IRB approved protocol)
- Recruitment strategies: existing patient registries (RYR-1 Foundation, Congenital Muscle Disease International Registry), patient advocacy groups and research consortia (Muscular Dystrophy Association, Treat-NMD, European Neuromuscular Centre, EMHG), and medical/research institutions

Aim 3: Launch database for *RYR1*-related disorders

- The database will be built by contracted information architects in Drupal
- Hosted on secure NIH Intramural Program cloud servers
- Interface will be based on existing NIH-led Alzheimer's disease database

Aim 4: Establish a mechanism for long-term curation and funding



Progress Update

- On-going manual review & validation by NIH team
- Structural biology team identified
- Submission of minimal risk protocol for IRB approval in 2023
- Submission of Infrastructure Grant application to the Muscular Dystrophy Association (MDA) in 2023

References:
- **Kushnir A, Todd JJ, Witherspoon JW et al: Intracellular calcium leak as a therapeutic target for RYR1-related myopathies. Acta Neuropathologica 2020, 139(6):1089-1104**
- **Lawal TA, Wires ES, Terry NL, Dowling JJ, Todd JJ: Preclinical model systems of ryanodine receptor 1-related myopathies and malignant hyperthermia: a comprehensive scoping review of works published 1990-2019. Orphanet J Rare Dis 2020, 15(1):113.**
- **Global Rare Disease Commission, (2019). Ending the Diagnostic Odyssey for Children with a Rare Disease: Global Commission Year One Report. https://globalraresiseasecommission.com/Report/assets/static/documents/GlobalCommissionprint-021919-a68c8ce2a5.pdf**

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