### **P.09** Comprehensive Database for Ryanodine Receptor Type-1 Related Disorders: Concept and Progress Update

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National Institute of **Neurological Disorders** and Stroke





## **Background**:

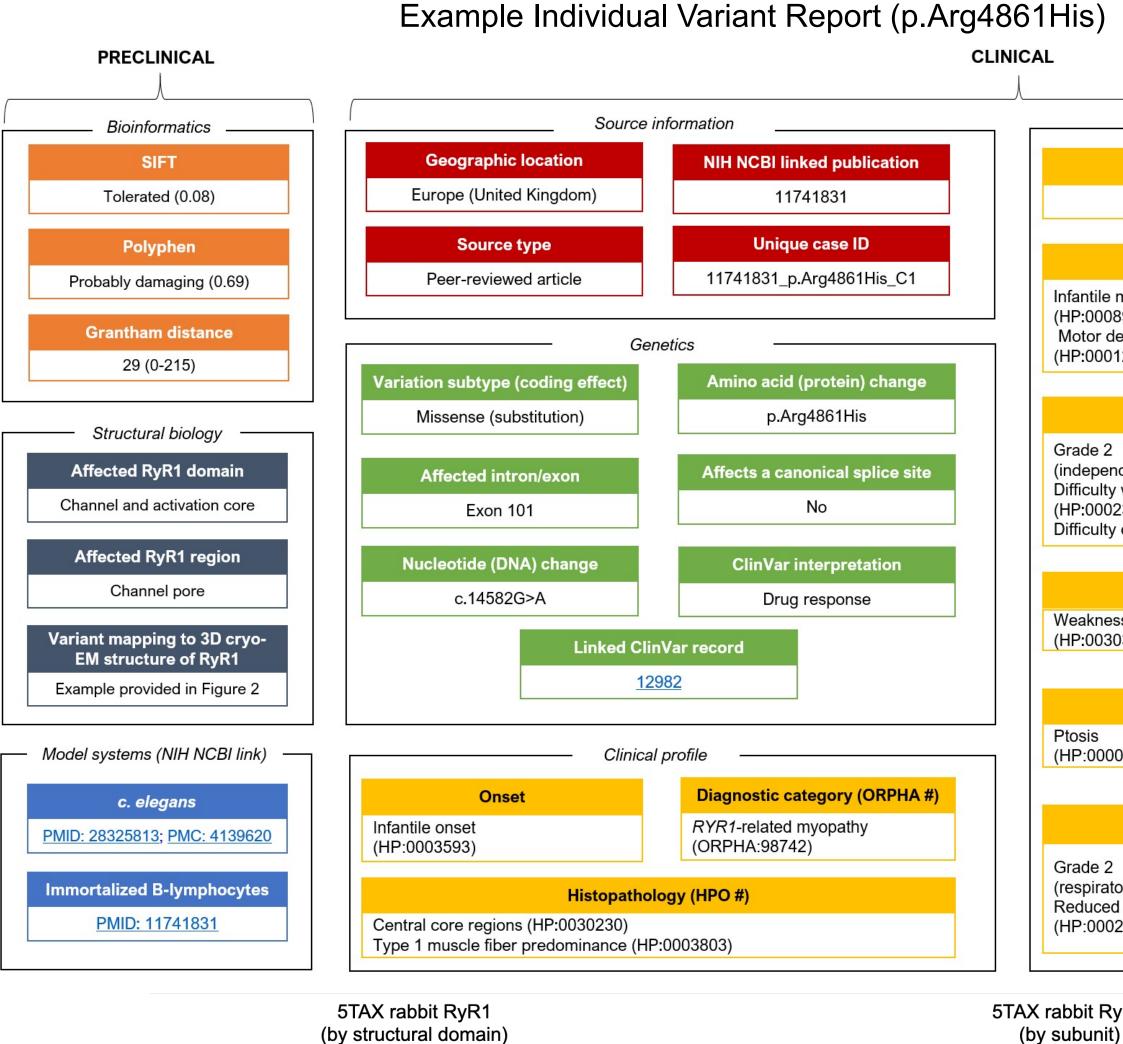
*RYR1* gene encodes the largest ion channel in humans, the skeletal muscle ryanodine receptor (RyR1). RyR1 gates calcium in the sarcoplasmic reticulum and is critical to excitation-contraction coupling. Pathogenic RYR1 variations cause a diverse spectrum of neuromuscular disorders including congenital and late-onset myopathies, rare 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

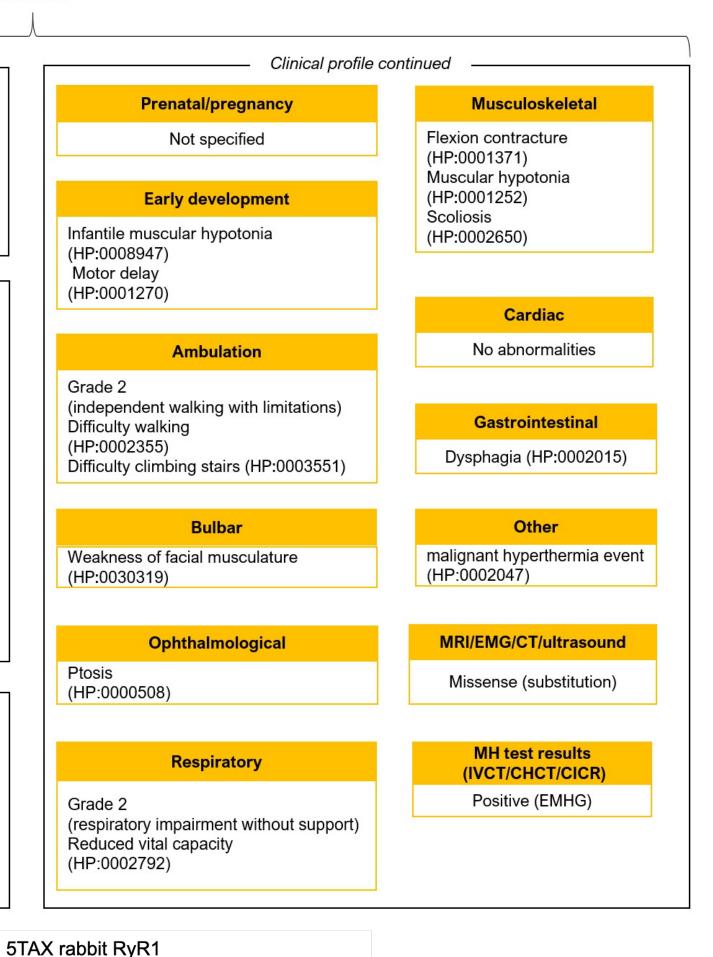
**Aim 1:** Database Taxonomy

#### Aims:

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



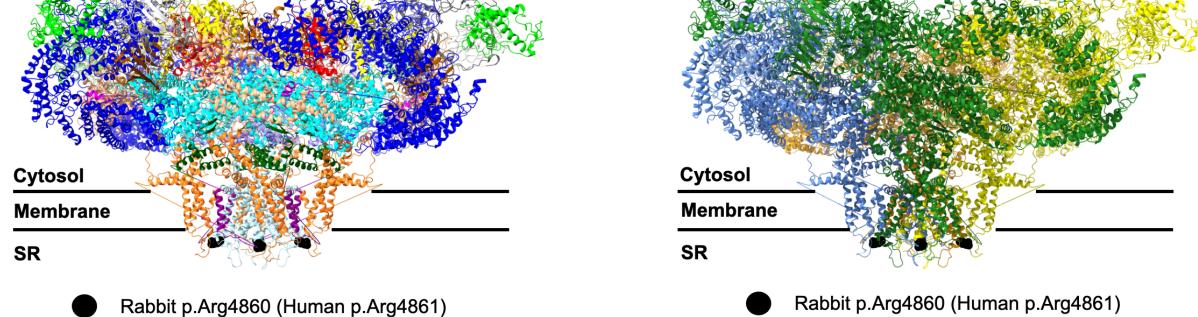
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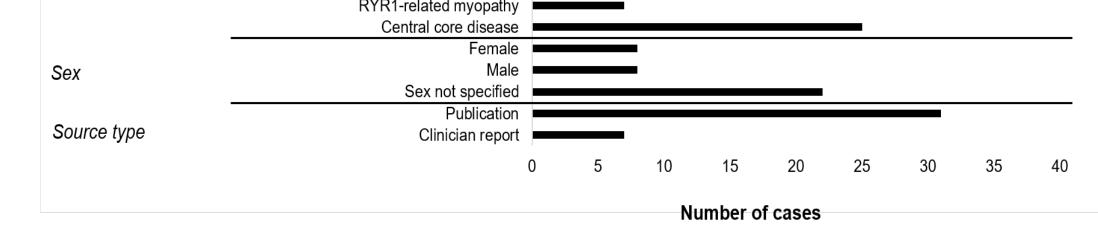


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Example Aggregate Clinical Report (p.Arg4861His)

MRI	Fatty infiltration on MRI	
Cardiaa	MRI findings not specified	
Cardiac	Cardiac evaluations not specified Feeding difficulties	
Gastrointestinal	Gastrointestinal abnormalities not specified	
	Muscle rigidity	
Musculoskeletal	Myalgias/arthralgias	
	Areflexia/hyporeflexia	
	Joint contractures	
	Hypermobility/joint laxity	
	Hypotonia	
	Musculoskeletal abnormalities not specified	
Spinal	Rigid spine	
	Scoliosis	
	Lumbar hyperlordosis	
	Spinal abnormalities not specified	
	Respiratory insufficiency	
Respiratory	Respiratory insufficiency not specified	
_	Ptosis	
Eye	Eye abnormalities not specified	
	Facial weakness	
	Distal weakness	
Weakness	Proximal weakness	
	Axial weakness	
	Weakness not specified	
	Wheelchair dependent	
Ambulation	Able to walk independently with limitations	
	Ambulatory rating not specified	
	Cleft/arched/high palate	
	Arthrogryposis/joint contractures	
Early development	Congenital hip dislocation/dysplasia	
	Delayed motor milestones	
	Polyhydramnios	
	Early development symptoms not specified	
Histopathology	Other histological abnormalities	
	Centralized or internalized nuclei	
	Type 1 fiber predominance	
	Cores Histopathology not specified	
	Onset not specified	
Onset	Congenital (from birth)	
	Neonatal onset (first 28 days of life)	
	Infantile (28 days to 1 yr)	
	Childhood onset (1-5yr)	
	Diagnostic category not specified	
Diagnosis	Congenital fiber-type disproportion	
	Malignant hyperthermia	
	RYR1-related myopathy	





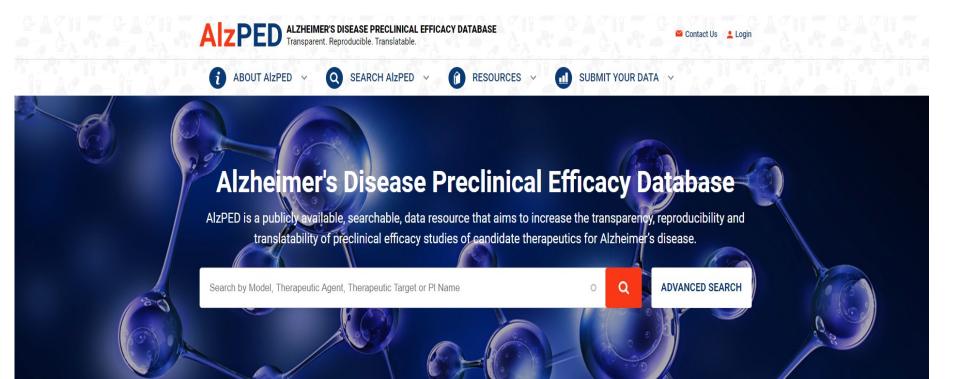
#### **Aim 2:** Engage the patient community, research scientists, and medical professionals to refine and optimize database interface

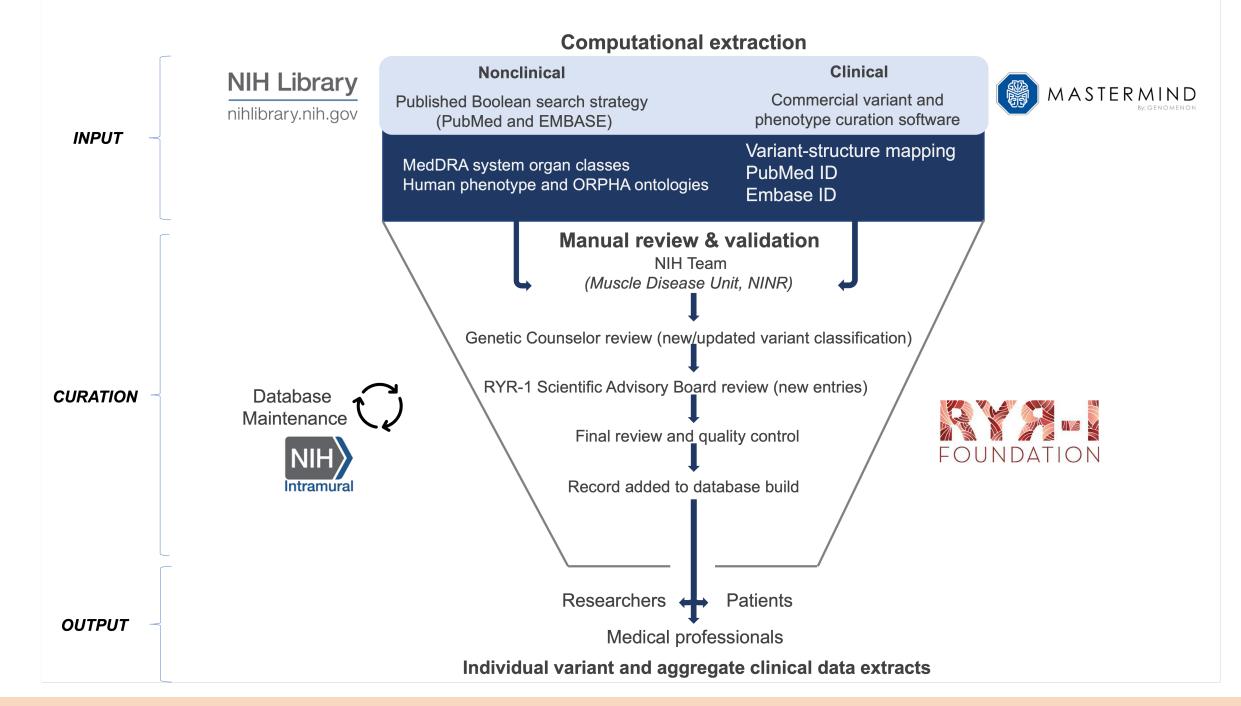
- Semi-structured survey of stakeholders (minimal risk IRB approved protocol)
- Recruitment strategies: existing patient registries (RYR-1 Foundation, Congenital Muscle Disease International Registry), patient advocacy groups and research consortia (Muscular Dystrophy Association, Treat-NMD, European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

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

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

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





#### **Data workflow**



### **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



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- 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

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