A **MONTHLY** PERSONALIZED MEDICAL MAGAZINE

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ATGC life

THE PIONEER IN GENETIC TESTING & REPORTING

Malignant Hyperthermia in the Genomic Era:

From Risk Detection to Personalized Care

GenepoweRx®
Genetic Science powered by K&H

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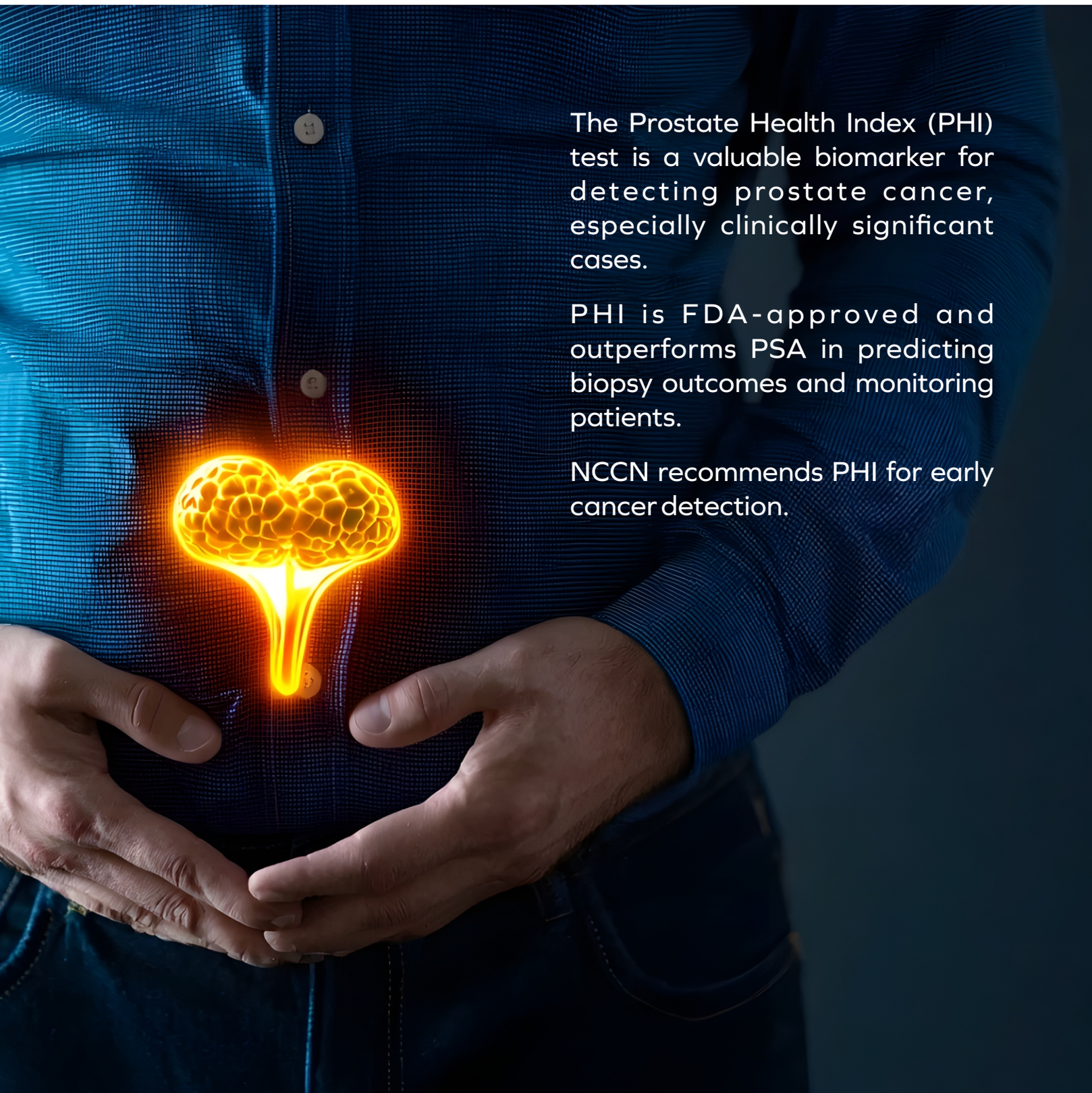
Prostate Health Index phi

Ideal for men:
50 years or older
PSA range: 2-10 ng/mL



The Prostate Health Index (PHI) test is a valuable biomarker for detecting prostate cancer, especially clinically significant cases.

PHI is FDA-approved and outperforms PSA in predicting biopsy outcomes and monitoring patients.

NCCN recommends PHI for early cancer detection.

Editorial Note

Dear Readers,

This edition of ATGC Life explores Malignant Hyperthermia (MH) through a genomic and personalized medicine perspective. MH is a rare but life-threatening pharmacogenetic disorder triggered by certain anesthetics, primarily linked to mutations in the RYR1 and CACNA1S genes. The articles in this issue examine the genetic mechanisms, clinical variability, and the challenges posed by variants of uncertain significance (VUS).

We also highlight cutting-edge developments including iPSC-based functional studies, CRISPR gene-editing prospects, and the integration of AI in pharmacogenomic registries. These advances are transforming MH management—from early risk identification to precision anesthetic planning.

For clinicians, genetic counselors, and genomics professionals, this issue emphasizes the growing role of next-generation sequencing, variant interpretation, and multi-omic profiling in improving patient outcomes. As a genomics-driven publication, ATGC Life remains committed to translating research into actionable insights that support personalized, preventive, and proactive care in clinical practice.

Warm Regards,

Dr. Hima J. Challa
Director, GenepoweRx

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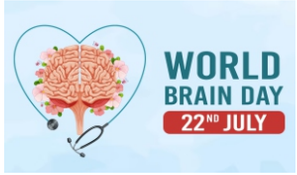


Decoding Malignant Hyperthermia: A Genomic Perspective

Malignant Hyperthermia (MH) is a life-threatening pharmacogenetic disorder triggered by certain anesthetic agents and muscle relaxants. At the heart of this condition lies a genetic defect in the calcium regulation pathway within skeletal muscle, particularly involving the *RYR1* (ryanodine receptor type 1) and *CACNA1S* (calcium channel, voltage-dependent, L type, alpha 1S subunit) genes. These genes play a critical role in excitation-contraction coupling—a tightly controlled mechanism that governs skeletal muscle contraction.

The RYR1 gene, located on chromosome 19q13.2, encodes the ryanodine receptor, a large intracellular calcium channel found in the sarcoplasmic reticulum. Upon exposure to volatile anesthetics or the depolarizing muscle relaxant succinylcholine, individuals with pathogenic variants in RYR1 experience uncontrolled calcium release, leading to sustained muscle contraction, hypermetabolism, rhabdomyolysis, and hyperthermia. Over 300 RYR1 variants have been identified, though only a subset are currently classified as causative according to the European Malignant Hyperthermia Group (EMHG) and the North American MH Group (NAMHG).

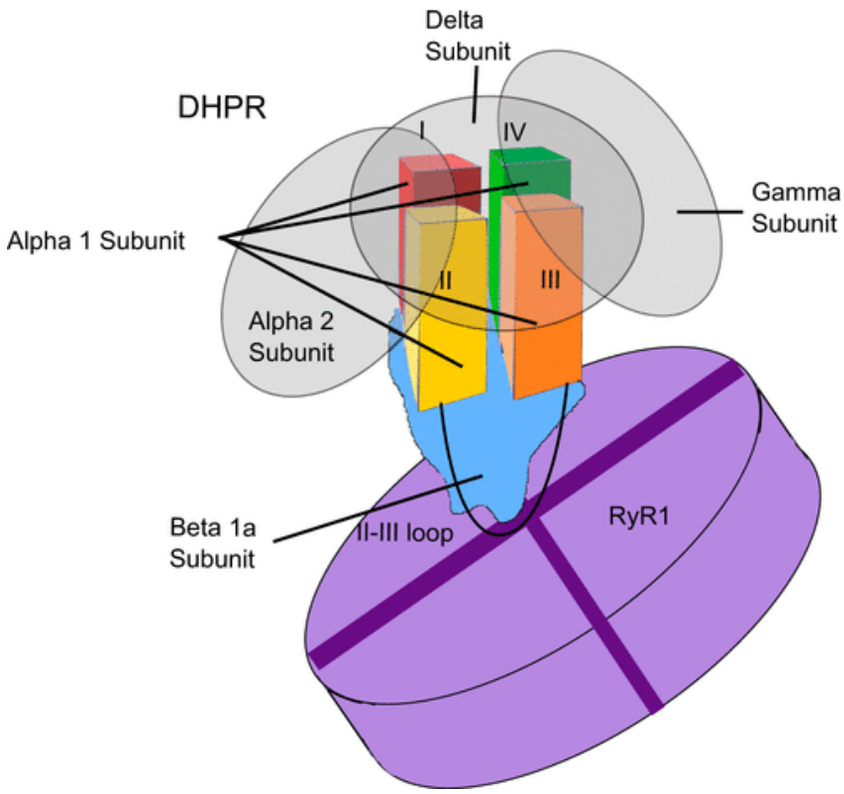
The CACNA1S gene, located on chromosome 1q32.1, encodes the alpha-1S subunit of the dihydropyridine receptor (DHPR), which serves as a voltage sensor in the transverse tubule system of skeletal muscle. Though less frequently mutated in MH (around 1% of cases), CACNA1S variants can alter calcium release indirectly by affecting *DHPR-RYR1* interactions.

These genes are inherited in an autosomal dominant fashion, meaning only one copy of a pathogenic variant is sufficient to predispose an individual to MH. However, incomplete penetrance—where not all mutation carriers show symptoms—poses a challenge in clinical risk prediction.

Thanks to advancements in next-generation sequencing (NGS), especially targeted gene panels and whole exome sequencing (WES), identifying MH susceptibility has become more accessible. For genomics-driven companies, offering *RYR1/CACNA1S* screening as part of a pharmacogenetic panel allows for personalized perioperative risk management.

Additionally, certain RYR1 mutations are associated with congenital myopathies such as central core disease, multiminicore disease, and centronuclear myopathy, highlighting the pleiotropic effects of these genetic alterations. This dual relevance underscores the need for comprehensive variant interpretation, especially in symptomatic patients with unclear anesthetic history.

The growing field of personalized medicine positions genomic testing as a powerful tool—not just for diagnosis, but for proactive planning, family screening, and integration into anesthetic safety protocols.



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The Genetic Basis of Malignant Hyperthermia: Spotlight on *RYR1* and *CACNA1S*

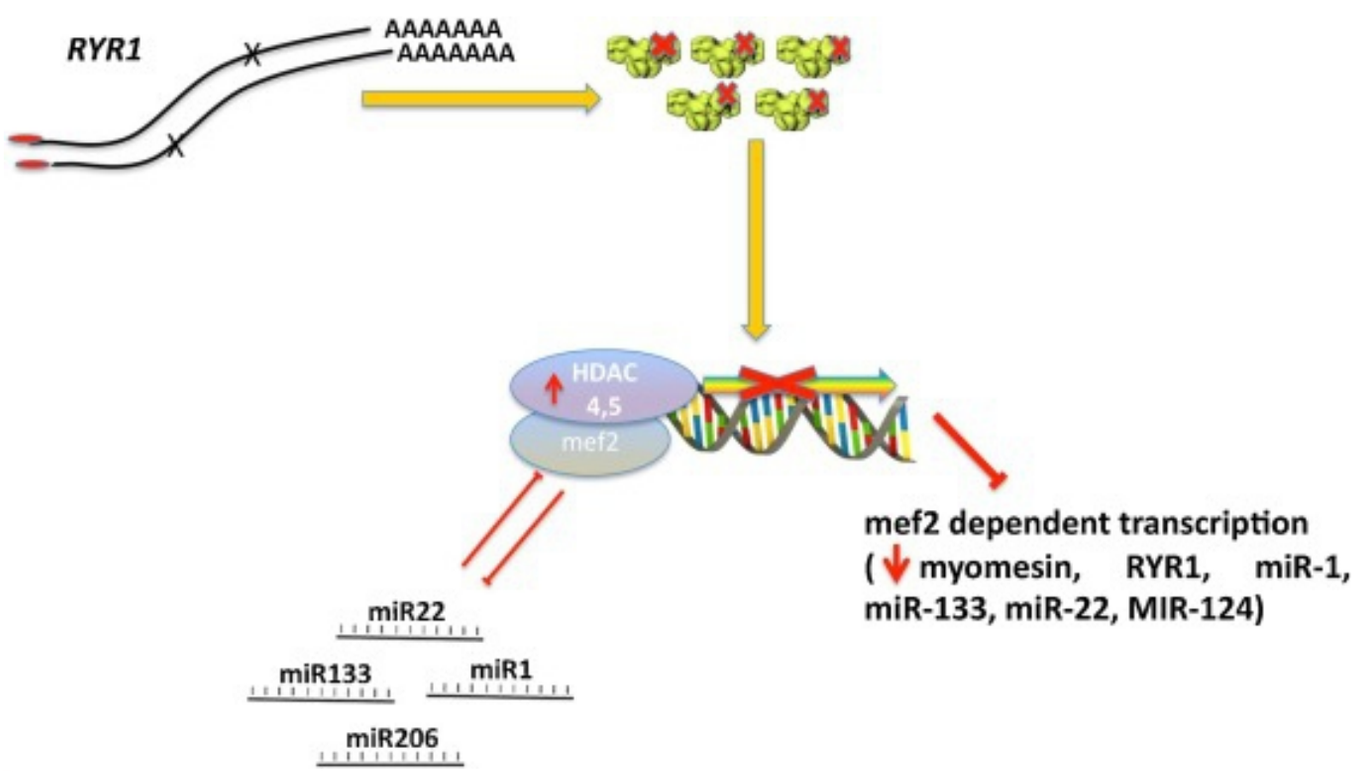
Malignant Hyperthermia (MH) is a rare, pharmacogenetic disorder of skeletal muscle calcium regulation triggered by specific anesthetic agents. It is predominantly associated with mutations in the **RYR1** (ryanodine receptor type 1) and **CACNA1S** (calcium voltage-gated channel subunit alpha1 S) genes. These genes encode critical proteins involved in excitation-contraction coupling in skeletal muscle cells.

The RYR1 gene, located on chromosome 19q13.2, encodes a calcium-release channel in the sarcoplasmic reticulum. Pathogenic variants in this gene lead to dysregulated calcium release upon exposure to triggering agents, such as volatile anesthetics (e.g., sevoflurane, desflurane) or depolarizing neuromuscular blockers like succinylcholine. More than 300 **RYR1** variants have been identified, although only a subset (~50) is considered causative by the European Malignant Hyperthermia Group (EMHG) and the North American MH Group (NAMHG).

CACNA1S, on chromosome 1q32.1, encodes the alpha-1 subunit of the dihydropyridine receptor (DHPR), a voltage-sensitive calcium channel. Mutations here disrupt voltage sensing, affecting RYR1-mediated calcium release indirectly. Although **CACNA1S** mutations are less common (~1% of cases), they are important in differential diagnosis and may contribute to overlapping syndromes like hypokalemic periodic paralysis.

MH is inherited in an autosomal dominant pattern with variable penetrance. Thus, a single copy of the pathogenic allele is sufficient to increase susceptibility, but not all carriers exhibit clinical symptoms. This underscores the significance of genetic counseling and cascade testing in affected families.

Notably, certain **RYR1** mutations are associated not only with MH but also with congenital myopathies, including central core disease, multiminicore disease, and centronuclear myopathy. This overlap illustrates the pleiotropic nature of these mutations and highlights the value of a comprehensive clinical-genetic correlation.



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Interpreting Variants of Uncertain Significance (VUS): Challenges in MH Genomics

In the era of precision medicine, genomic testing has revolutionized how we detect susceptibility to rare conditions like Malignant Hyperthermia (MH). However, with increased sequencing comes a growing challenge: the frequent identification of Variants of Uncertain Significance (VUS). Nowhere is this more critical than in *RYR1* and *CACNA1S*, the two primary genes implicated in MH.

What is a VUS?

A VUS is a genetic alteration for which the association with disease risk is unclear. In MH, over 300 variants have been reported in *RYR1*, yet only a fraction have strong functional evidence and clinical validation to be classified as "pathogenic" or "likely pathogenic." The rest fall into the gray zone, lacking sufficient evidence for decisive clinical interpretation.

This uncertainty creates a dilemma for clinicians, patients, and genomics companies alike—how should a variant be reported and managed when its impact is ambiguous?

Why Do VUS Arise in MH Testing?

- **Complex gene structure:** *RYR1* spans 106 exons and encodes a massive 5,038-amino acid protein. Mutations can occur throughout the gene, and missense mutations dominate, often with subtle effects on protein function.
- **Incomplete functional data:** Unlike *BRCA* or *CFTR* genes, MH-associated genes lack widespread, high-throughput functional validation pipelines, making it hard to determine the pathogenicity of newly discovered variants.
- **Population variation:** Some variants may be rare but benign polymorphisms, especially in under represented ethnic populations where allele frequency data is limited.

Approaches to Interpreting VUS in MH

- **ACMG-AMP Guidelines:** These provide a structured framework for classifying variants based on criteria such as population frequency, computational prediction, segregation, and functional assays.
- **In silico tools:** Algorithms like PolyPhen-2, SIFT, and CADD help predict the impact of amino acid substitutions on protein structure and function, though these are only supportive evidence.
- **Functional testing:** The Caffeine-Halothane Contracture Test (CHCT) and in vitro contracture test (IVCT) remain gold standards to assess MH susceptibility, especially when VUS is detected. However, these are invasive and not widely accessible.
- **Patient-derived models:** Emerging tools such as induced pluripotent stem cells (iPSCs) and CRISPR-Cas9 gene editing may soon allow for real-time functional characterization of uncertain variants in patient-specific models.

The Role of Genomics Companies

Genomics service providers play a vital role in:

- Annotating and flagging VUS transparently
- Offering periodic variant reclassification as new evidence arises
- Collaborating with clinicians to determine when additional family or functional studies are warranted

Until VUS can be definitively reclassified, conservative clinical management is advised—especially in MH where a single misjudgment in anesthesia can be fatal.

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Beyond Diagnosis: Genomic Innovations and Future Therapies for Malignant Hyperthermia

The genomic era has dramatically improved our ability to identify individuals susceptible to Malignant Hyperthermia (MH) through *RYR1* and *CACNA1S* screening. But the promise of personalized medicine extends well beyond diagnosis. As genomics intersects with functional biology, pharmacology, and digital health, new frontiers are opening in prevention, therapeutic development, and patient-specific care for MH.

1. Whole Genome and Transcriptome Profiling

While targeted gene panels have helped identify known pathogenic variants, whole genome sequencing (WGS) and transcriptomic profiling now allow a broader understanding of MH's molecular architecture. These tools can:

- Detect deep intronic variants or regulatory mutations not covered by exome panels
- Assess modifier genes that may influence penetrance or severity
- Identify transcriptomic signatures of calcium channel dysregulation during stress responses

For genomics companies, integrating multi-omics approaches into MH panels may offer a more complete risk profile.

2. iPSC Models and Functional Genomics

One of the most promising tools in MH research is the use of induced pluripotent stem cells (iPSCs) derived from patients carrying *RYR1* or *CACNA1S* variants. These iPSCs can be differentiated into skeletal muscle cells that recapitulate the patient's muscle physiology in vitro.

Such "disease-in-a-dish" models enable:

- Functional testing of Variants of Uncertain Significance (VUS)
- Screening of protective compounds or anesthetic alternatives
- Precision drug discovery for those with severe or atypical MH phenotypes

3. CRISPR and Gene Editing Prospects

Though not yet in clinical use for MH, CRISPR-Cas9 and base editing technologies are being explored for correcting pathogenic mutations in *RYR1*. Preliminary animal studies suggest that targeted gene correction may prevent abnormal calcium release under triggering conditions.

While ethical and technical hurdles remain, the future possibility of gene-editing therapies offers hope, especially for patients with RYR1-related congenital myopathies who face chronic symptoms beyond acute MH risk.

4. Pharmacogenomic Registries and AI

Global MH registries are starting to integrate AI and machine learning to analyze genotype-phenotype correlations, predict risk scores, and improve variant classification. Genomics companies contributing to open-access MH databases can accelerate reclassification of VUS and promote collaborative therapy development.

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- Wong CH, et al. iPSC models of MH for therapeutic testing. Stem Cell Res. 2019;41:101597.
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Meet the Doctors

Dr Kalyan Uppaluri is the co-founder and the owner of GenepoweRx Personalized medicine clinic and research institute, He did his medical training at the prestigious Gandhi Medical College. He then moved to the United States, where he specialized in Internal Medicine at the McLaren Hospital, Michigan. He also got a degree in Medical Genomics from Ivy league Institute, Stanford University and pursued Cancer research at Wayne State University.

Dr Hima Challa graduated from Gandhi Medical college and was among top few in her batch. She specialized in Internal Medicine at St. Joseph Mercy Oakland, Michigan in United States. She graduated in Medical genomics from the Ivy league Institution of Harvard Medical School. She also holds a master's in nutrition science from the Texas Women University and in integrative medicine from Arizona University.

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