American Heart Association.

GPM Journal Bytes

A quarterly online publication of journal summaries brought to you by the American Heart Association's **Council on Genomic and Precision Medicine**.

The opinions of the summary authors in this publication are their own and not necessarily those of the American Heart Association.

Dear Colleagues,

I think you will find that this issue of Journal Bytes highlights several important and provocative papers from the past several months. As you know, GPM Journal Bytes is intended to summarize important and relevant papers from multiple journal sources in the realm of genomic and precision medicine from the past quarter and provide concise summaries with a goal of helping you save time while staying well informed.

We welcome any suggestions you may have to help us make Journal Bytes serve you better. If you have any suggestions, or questions, please do not hesitate to contact us. Don't forget to follow the GPM Council on twitter @GenPrecisionMed.

Best wishes,
Sharon Cresci MD, FAHA, FACC, FASE
Chair, GPM Professional/Public Education & Publications Committee

Assessing Diverse Populations Yields a Novel Variant with a Novel Mechanism of Pathogenicity in Hypertrophic Cardiomyopathy

Sharon Cresci, MD, FAHA, FACC, FASE
@SharonCresciMD
Washington University School of Medicine

Aguib Y, Allouba M, Walsh R, Ibrahim AM, Halawa S, Afify A, Hosny M, Theotokis PI, Galal A, Elshorbagy S, Roshdy M, Kassem HS, Ellithy A, Buchan R, Whiffin N, Anwer S, Cook SA, Moustafa A, ElGuindy A, Ware JS, Barton PJR, Yacoub M. New Variant with a Previously Unrecognized Mechanism of Pathogenicity in Hypertrophic Cardiomyopathy. Circulation. 2021 Aug 31;144(9):754-757. doi: 10.1161/CIRCULATIONAHA.120.048295. Epub 2021 Aug 30. PMID: 34460321; PMCID: PMC8389346.

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disease and is caused by more than 1,500 pathogenic variants in the genes encoding cardiomyocyte sarcomeric proteins; almost 80% of identifiable pathogenic or likely pathogenic variants occur in the genes encoding β-myosin heavy-chain (*MYH7*) and myosin-binding protein C (*MYBPC3*). In comparison to HCM-causing *MYBPC3* variants, which are thought to cause HCM by resulting in truncated proteins and haplo-insufficiency, previously reported HCM-causing *MYH7* variants have resulted in gain-of-function "poison peptides." Aguib et al. describe a novel variant in *MYH7* in a large cohort of unrelated Egyptian patients with HCM. The variant, c.5769delG, a frameshift variant that results in a premature stop codon in the distal portion of *MYH7*, is the first variant in *MYH7* thought to cause HCM by haplo-insufficiency. This novel variant was not observed to be present in more than 6,000 White individuals with HCM, supporting the premise that assessment of diverse populations has great potential for identifying novel variants and pathways important for understanding this disease.

In Vivo Gene Editing for Transthyretin Amyloidosis in Humans

Ferhaan Ahmad, MD, PhD, FAHA, FACC
@FerhaanAhmad
University of Iowa Carver College of Medicine

Gillmore JD, Gane E, Taubel J, Kao J, Fontana M, Maitland ML, Seitzer J, O'Connell D, Walsh KR, Wood K, Phillips J, Xu Y, Amaral A, Boyd AP, Cehelsky JE, McKee MD, Schiermeier A, Harari O, Murphy A, Kyratsous CA, Zambrowicz B, Soltys R, Gutstein DE, Leonard J, Sepp-Lorenzino L, Lebwohl D. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. N Engl J Med. 2021 Aug 5;385(6):493-502. doi: 10.1056/NEJMoa2107454. Epub 2021 Jun 26. PMID: 34215024.

Transthyretin (ATTR) amyloidosis is a progressive and ultimately fatal disorder characterized cardiomyopathy and/or polyneuropathy secondary to tissue deposition of amyloid fibrils consisting of misfolded transthyretin (TTR) protein. ATTR amyloidosis may be acquired (wildtype ATTR) or may be heritable as an autosomal dominant trait (hATTR) caused by pathogenic variants in the gene encoding TTR. The recent introduction of agents that stabilize the tetrameric form of TTR or inhibit TTR synthesis represent great therapeutic advances that lead to functional improvement and prolonged survival. However, they require long-term administration, do not always arrest progression of disease, and can be associated with serious side effects. The investigators developed a lipid nanoparticle targeting the liver that delivered a CRISPR-Cas9 gene editing system to knock out the gene encoding TTR (NTLA-2001). After safety and pharmacodynamic preclinical studies in mice and monkeys, the investigators conducted a phase 1 clinical study in 6 human subjects with hATTR. Mild adverse events were observed in 3 subjects. Reductions of up to 96% in serum TTR concentrations were observed by 28 days following infusion of NTLA-2001. This strategy may potentially be used to effect cures in a wide range of disorders with a single administration of an agent to knock out expression of other mutant genes or even to correct the mutations.

Valsartan in early-stage hypertrophic cardiomyopathy: a randomized phase 2 trial

Anjali Tiku Owens, MD
@tikuowens
University of Pennsylvania Perelman School of Medicine

Ho CY, Day SM, Axelsson A, Russell MW, Zahka K, Lever HM, Pereira AC, Colan SD, Margossian R, Murphy AM, Canter C, Bach RG, Wheeler MT, Rossano JW, Owens AT, Bundgaard H, Benson L, Mestroni L, Taylor MRG, Patel AR, Wilmot I, Thrush P, Vargas JD, Soslow JH, Becker JR, Seidman CE, Lakdawala NK, Cirino AL; VANISH Investigators, Burns KM, McMurray JJV, MacRae CA, Solomon SD, Orav EJ, Braunwald E. Valsartan in early-stage hypertrophic cardiomyopathy: a randomized phase 2 trial. Nat Med. 2021 Oct;27(10):1818-1824. doi: 10.1038/s41591-021-01505-4. Epub 2021 Sep 23. PMID: 34556856.

Sarcomeric hypertrophic cardiomyopathy (HCM) leads to left ventricular hypertrophy, diminished myocardial compliance and increased risk of arrhythmias and heart failure. VANISH was an international, double-blind, placebo-controlled phase 2 clinical trial to assess the safety and efficacy of valsartan in attenuating disease progression in patients with genotype positive, mild phenotype HCM. 178 participants were randomized to receive valsartan or placebo for 2 years. Changes in LV wall thickness/mass/volume, left atrial volume, diastolic function, levels of high-sensitivity troponin T and N-terminal pro-B-type natriuretic protein were integrated into a composite z-score as the primary outcome. Valsartan improved cardiac structure and function compared to placebo with an increase in the composite z-score (between-group difference +0.231, 95% confidence interval (+0.098, +0.364); P = 0.001). Valsartan was well tolerated amongst the study population and emerges as a safe and available medication to mitigate disease progression in early HCM.

Gene therapy to treat heart failure with reduced ejection fraction

Naveen L Pereira, MD
@nl_pereira
Mayo Clinic

Liu S, Li K, Wagner Florencio L, Tang L, Heallen TR, Leach JP, Wang Y, Grisanti F, Willerson JT, Perin EC, Zhang S, Martin JF. Gene therapy knockdown of Hippo signaling induces cardiomyocyte renewal in pigs after myocardial infarction. Sci Transl Med. 2021 Jun 30;13(600):eabd6892. doi: 10.1126/scitranslmed.abd6892. PMID: 34193613.

The Hippo pathway serves as an organ size and growth regulator and plays an important role in cardiac regeneration. This pathway is upregulated in heart failure resulting in inhibition of cardiomyocyte proliferation and regeneration. Martin et al have previously shown (Nature 2017) that deletion of Salvador which is a component of the Hippo pathway in mice post infarct hearts resulted in improved ejection fraction, less fibrosis and increased cardiomyocyte numbers. In this study, they demonstrate in a larger animal (pig) model that administration of adeno-associated virus 9 (AAV9)-based gene therapy to knock down Salvador after ischemia/ reperfusion induced myocardial infarction using catheter based subendocardial injection delivery resulted in a 14.3% improvement in left ventricular ejection fraction and increased cardiomyocyte proliferation with reduced infarct scar size. There appear to be in no other off target effects, especially resultant malignancies. Gene based therapy and CRISPR-Cas9 technology is increasingly being evaluated in early phase clinical trials in the treatment of cardiomyopathy and heart failure.

Anjali Tiku Owens
@tikuowens

Ferhaan Ahmad
@FerhaanAhmad

Naveen Pereira
@nl_pereira

Sharon Cresci
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