# Regeneron Genetics Center Discovers Rare Mutations In The CIDEB Gene That Protect Against Liver Disease

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*New research published in* The New England Journal of Medicine *reveals that people with certain genetic loss-of-function mutations have more than 50% lower risk of nonalcoholic liver disease and nonalcoholic cirrhosis*

*Regeneron and Alnylam have developed an siRNA therapeutic candidate targeting CIDEB that could enter clinical stages of development in the next year*

*Unprecedented size of Regeneron Genetics Center human sequence database – representing approximately two million individuals and growing – enables discovery of protective gene variants too rare to be previously identified*

TARRYTOWN, N.Y., July 27, 2022 /PRNewswire/ -- Regeneron Pharmaceuticals, Inc. (NASDAQ: **REGN**) announced today that scientists from the Regeneron Genetics Center® (RGC) have uncovered rare genetic loss-of-function mutations in the *CIDEB* gene that are associated with substantial protection from liver disease, including serious diseases such as nonalcoholic steatohepatitis (NASH) and cirrhosis. The new discovery has been published today in *The New England Journal of Medicine*.

"The unprecedented protective effect that these *CIDEB* genetic variants have against liver disease provides us with one of our most exciting targets and potential therapeutic approaches for a notoriously hard-to-treat disease where there are currently no approved treatments," said Aris Baras, M.D., Senior Vice President and Head of the Regeneron Genetics Center at Regeneron. "RGC has repeatedly demonstrated the value of large-scale genetic sequencing in identifying novel and important targets for many serious diseases and this is yet another example of how we are fueling our pipeline through genetics discovery. Our growing dataset enables us to discover more rare and more powerful protective variants with the ultimate goal of improving human health."

In the largest sequencing study to date on the genetic basis of liver health, RGC sequenced the exomes of more than 540,000 individuals across five ancestry groups and multiple cohorts, including the UK Biobank and the Geisinger Health System MyCode cohort. By analyzing this genetic data in conjunction with deidentified health records, RGC researchers found that individuals who carry loss-of-function mutations in one of two copies of the *CIDEB* gene had an approximately 53% reduction in the risk of nonalcoholic liver disease and approximately 54% reduction in the risk of nonalcoholic cirrhosis. The study also found that *CIDEB* mutations had greater protective associations in individuals with obesity or type 2 diabetes, who are traditionally at higher risk for NASH, compared to individuals without these conditions.

Therapeutics that effectively mimic these protective mutations by blocking *CIDEB* expression or function could, therefore, potentially help prevent or treat NASH and other forms of liver disease. Based on these findings, Regeneron has already initiated a new therapeutic program to target *CIDEB* utilizing collaborator Alnylam Pharmaceuticals, Inc.'s RNA interference technology which can effectively silence genes in the liver. Regeneron and Alnylam already have two other investigational gene silencing treatments for NASH identified via human genetics, targeting the *PNPLA3* and the *HSD17B13* genes. The HSD17B13 program, which is in early-phase human clinical trials, was initiated based on a previous RGC discovery of protective associations for mutations in the *HSD17B13* gene.

"RGC's discovery of *CIDEB* mutations, with one of the most powerful protections from liver disease seen to date, is a milestone in our understanding of the genetic basis of this disease," said Luca A. Lotta, M.D., Ph.D., Vice President and Head of Cardiometabolic and Musculoskeletal Disease Genetics at Regeneron. "By catalyzing multiple therapeutic development programs targeting distinct genetic mechanisms of liver disease, the RGC's insights are helping Regeneron develop a diversified slate of genetically-validated targets for NASH, including *HSD17B13, PNPLA3* and now *CIDEB*."

The *CIDEB* discovery represents the latest example of rare protective gene variants that were identified through the unprecedented size of the RGC large-scale database, that includes genomic data from approximately two million volunteers. Other recently published examples include the discovery of rare gene variants in the *GPR75 gene* that provide protection against obesity. The *CIDEB* and *GPR75* protective genetics findings suggest that the rarer the genetic discovery, the stronger the effect on disease protection – providing promise for novel therapeutic applications.

**About NASH and *CIDEB***
Nonalcoholic steatohepatitis (NASH) is a severe type of nonalcoholic fatty liver disease (NAFLD), which can lead to cirrhosis, a condition in which liver tissue is replaced by scar tissue, and liver failure. NASH is rapidly becoming the leading cause of liver transplant and poses a substantial unmet medical need; dozens of drug development programs have failed leaving a large treatment gap with no currently approved therapies. In the United States, it is estimated that nearly 25% of adults have NAFLD, and more than 6% have NASH.[1]

The *CIDEB* gene is most highly expressed in human liver cells, where it has been hypothesized to enable fat buildup by helping enlarge fat-storage structures called "lipid droplets" within cells. After discovering the protective association through exome sequencing and health record comparisons, scientists studied the mechanism of the protective *CIDEB* mutations by silencing the *CIDEB* gene in human cells to mimic loss of function mutations. They found that this prevented fat buildup in liver cells and resulted in smaller lipid droplets.[2,3,4]

**About the Regeneron Genetics Center**
The Regeneron Genetics Center LLC (RGC) is a wholly owned subsidiary of Regeneron Pharmaceuticals, Inc. that focuses on early gene discovery and functional genomics. The primary goal of RGC is to improve patient outcomes by identifying novel drug targets, clinical indications for development programs, and genomic biomarkers for pharmacogenomic applications. RGC is tackling large-scale sequencing and analytical approaches and has established numerous collaborations with leading human genetics researchers. To enable this large-scale sequencing and

analysis program, RGC utilizes fully automated sample preparation and data processing, as well as cutting-edge cloud-based informatics.

At RGC, scientists around the globe with diverse skills and backgrounds work together to uncover the genetic basis of human disease. Their efforts have culminated in landmark discoveries like *CIDEB* in NASH and have led to multiple new therapeutic development programs at Regeneron across a range of therapeutic modalities. Since its inception in 2014 and through a network of over 120 collaborators globally, RGC has developed one of the largest and richest human genetics datasets in the world by sequencing around 2 million exomes.

**About Regeneron**
Regeneron (NASDAQ: REGN) is a leading biotechnology company that invents, develops and commercializes life-transforming medicines for people with serious diseases. Founded and led for nearly 35 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to nine FDA-approved treatments and product candidates in development, almost all of which were homegrown in our laboratories. Our medicines and pipeline are designed to help patients with eye diseases, allergic and inflammatory diseases, cancer, cardiovascular and metabolic diseases, pain, hematologic conditions, infectious diseases and rare diseases.

Regeneron is accelerating and improving the traditional drug development process through our proprietary *VelociSuite*® technologies, such as *VelocImmune*®, which uses unique genetically humanized mice to produce optimized fully human antibodies and bispecific antibodies, and through ambitious research initiatives such as the Regeneron Genetics Center, which is conducting one of the largest genetics sequencing efforts in the world.

For additional information about the company, please visit [www.regeneron.com](www.regeneron.com) or follow @Regeneron on Twitter.

**Forward Looking Statements and Use of Digital Media**
*This press release includes forward-looking statements that involve risks and uncertainties relating to future events and the future performance of Regeneron Pharmaceuticals, Inc. ("Regeneron" or the "Company"), and actual events or results may differ materially from these forward-looking statements. Words such as "anticipate," "expect," "intend," "plan," "believe," "seek," "estimate," variations of such words, and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements concern, and these risks and uncertainties include, among others, the impact of SARS-CoV-2 (the virus that has caused the COVID-19 pandemic) on Regeneron's business and its employees, collaborators, and suppliers and other third parties on which Regeneron relies, Regeneron's and its collaborators' ability to continue to conduct research and clinical programs, Regeneron's ability to manage its supply chain, net product sales of products marketed or otherwise commercialized by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Products"), and the global economy; the nature, timing, and possible success and therapeutic applications of Regeneron's Products and product candidates being developed by Regeneron and/or its collaborators or licensees (collectively, "Regeneron's Product Candidates") and research and clinical programs now underway or planned, including without limitation the use of human genetics in Regeneron's research and any potential therapeutics targeting the CIDEB gene mutations discussed in this press release for protection from nonalcoholic steatohepatitis ("NASH") and cirrhosis; the extent to which the results from the research and development programs conducted by Regeneron and/or its collaborators or licensees (including those discussed in this press release) may be replicated in other studies and/or lead to advancement of product candidates to clinical trials, therapeutic applications, or regulatory approval; uncertainty of the utilization, market acceptance, and commercial success of Regeneron's Products and Regeneron's Product Candidates and the impact of studies (whether conducted by Regeneron or others and whether mandated or voluntary), including the studies investigating gene silencing treatments for NASH targeting the PNPLA3 and the HSD17B13 genes referenced in this press release, on any of the foregoing or any potential regulatory approval of Regeneron's Products and Regeneron's Product Candidates; the likelihood, timing, and scope of possible regulatory approval and commercial launch of Regeneron's Product Candidates and new indications for Regeneron's Products; the ability of Regeneron's collaborators, licensees, suppliers, or other third parties (as applicable) to perform manufacturing, filling, finishing, packaging, labeling, distribution, and other steps related to Regeneron's Products and Regeneron's Product Candidates; the ability of Regeneron to manufacture and manage supply chains for multiple products and product candidates; safety issues resulting from the administration of Regeneron's Products and Regeneron's Product Candidates in patients, including serious complications or side effects in connection with the use of Regeneron's Products and Regeneron's Product Candidates in clinical trials; determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize Regeneron's Products and Regeneron's Product Candidates; ongoing regulatory obligations and oversight impacting Regeneron's Products, research and clinical programs, and business, including those relating to patient privacy; the availability and extent of reimbursement of Regeneron's Products from third-party payers, including private payer healthcare and insurance programs, health maintenance organizations, pharmacy benefit management companies, and government programs such as Medicare and Medicaid; coverage and reimbursement determinations by such payers and new policies and procedures adopted by such payers; competing drugs and product candidates that may be superior to, or more cost effective than, Regeneron's Products and Regeneron's Product Candidates; unanticipated expenses; the costs of developing, producing, and selling products; the ability of Regeneron to meet any of its financial projections or guidance and changes to the assumptions underlying those projections or guidance; the potential for any license, collaboration, or supply agreement, including Regeneron's agreements with Sanofi, Bayer, and Teva Pharmaceutical Industries Ltd. (or their respective affiliated companies, as applicable), as well as Regeneron's collaboration with Alnylam Pharmaceuticals, Inc. referenced in this press release, to be cancelled or terminated; and risks associated with intellectual property of other parties and pending or future litigation relating thereto (including without limitation the patent litigation and other related proceedings relating to EYLEA® (aflibercept) Injection, Dupixent® (dupilumab), Praluent® (alirocumab), and REGEN-COV® (casirivimab and imdevimab)), other litigation and other proceedings and government investigations relating to the Company and/or its operations, the ultimate outcome of any such proceedings and investigations, and the impact any of the foregoing may have on Regeneron's business, prospects, operating results, and financial condition. A more complete description of these and other material risks can be found in Regeneron's filings with the U.S. Securities and Exchange Commission, including its Form 10-K for the year ended December 31, 2021 and its Form 10-Q for the quarterly period ended March 31, 2022. Any forward-looking statements are made based on management's current beliefs and judgment, and the reader is cautioned not to rely on any forward-looking statements made by Regeneron. Regeneron does not undertake any obligation to update (publicly or otherwise) any forward-looking statement, including without limitation any financial projection or guidance, whether as a result of new information, future events, or otherwise.*

*Regeneron uses its media and investor relations website and social media outlets to publish important information about the Company, including information that may be deemed material to investors. Financial and other information about Regeneron is routinely posted and is accessible on Regeneron's media and investor relations website ([http://newsroom.regeneron.com](http://newsroom.regeneron.com)) and its Twitter feed ([http://twitter.com/regeneron](http://twitter.com/regeneron)).*

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