Sanguine

Translational Genetics

What's Inside?

Chicken-or-egg paradox sheds light on genetic variants **4**

Evolution and genetic variation 4

Forms of genetic variation 5

Classifying genetic variants and their role in disease 5

Why disease-causing genetic variants persist 6

Rare Disease Research Opens Many Doors **7**

Rare diseases, burdens and types 7

The potential of rare diseases 8

Therapies for rare diseases 8

CRISPR Craze **10**

Biography 11

The CRISPR Craze Webinar 11

How CRISPR is Changing the Medical Landscape **12**

Existing and emerging therapies 12

What the future holds 13

Summary

Translational genetics aims to harness discoveries that are made in genetic research towards clinical applications to be able to improve patient health and disease outcomes. Technological advances in genetics and genomics are enabling researchers to develop better prognostic biomarkers for disease, tailored therapeutic interventions and improved prophylactic preventative modalities. The path to being able to translate bench discoveries to applications at the bedside is complex and still in its infancy but is showing promise for novel therapeutics during drug development and tailoring existing therapeutics to the right patient subpopulations.

In this eBook, we explore some of the hottest topics being pursued in translational genetics – from untangling the complexity of genetic variants, to research and therapies for rare diseases and how CRISPR is revolutionizing the medical landscape. First, we'll look at the influence and importance of genetic variants in health and disease, particularly for diseases with complex etiology. Understanding how some of these variants can influence the efficacy of long-standing treatments and novel therapeutics under development has the potential to improve patient care substantially. Next we cover how rare disease research is particularly challenging due to small patient populations per disease, limited research funding and high degree of failure during drug development. Lastly, a look at how the applications of CRISPR technology have been transforming the potential for gene editing, with promising therapeutics emerging for both inherited and non-inherited diseases. As the CRISPR field continues to rapidly evolve, this new era brings great excitement as well as ethical challenges that require careful considerations.

About Sanguine

At Sanguine, our mission is to accelerate translational biomedical research by removing the barriers to patient participation.

Through transparent communications, respectful patient support, and appropriate compensation, we keep patients engaged in the research process for a better patient experience and more impactful research biospecimens.

Chicken-or-Egg Paradox Sheds Light on Genetic Variants

The dilemma of untangling cause and effect is perhaps best encapsulated by the chicken-or-egg paradox. It may provide cocktail party banter, but to an evolutionary biologist, it's pretty simple: eggs are much older than chickens. At some point, an almost-complete chicken creature produced an egg from which a full-fledged chick pecked its way out.[1]

Genetic variation is at the heart of this yolky evolutionary tale—just like it's at heart of genetic disease research.[2]

Evolution and genetic variation

When the physical characteristics and genetic makeup of species change over time, we call it evolution. But evolution as we know it depends upon the intrinsic genetic variation within a population.[3] Genetic variation refers to the variable and permanent changes that occur within the DNA sequence coding for a gene. One or more nucleotides may encompass a genetic variant.[4]

Genetic variants generally arise in 1 of 3 ways: through heredity, non-heredity, or spontaneously in children. Heritable variants are passed from parent to child, are present for the affected person's lifetime, and can be found in virtually every bodily cell.[4]

Non-heritable variants arise at some time in a person's life—possibly as a result of an error during cell division, or from environmental or occupational exposure to factors like ultraviolet radiation. Non-inherited variants may be found in bodily cells other than sperm or eggs and are and often called somatic variants. But sometimes variants simply appear in children, without being in either parent—though in some cases the variant may also occur only in a parent's sex cells (eggs or sperm).[4]

Forms of genetic variation

Genetic variants occur in many different forms. Some arise due to nucleotide substitutions, where base pairs are swapped. Others arise from the insertion or deletion of a nucleotide — or sometimes simultaneously in what's referred to as an indel variant. When spans of 1 or more nucleotides are copied by mistake, it's called a duplication variant, and when they are copied multiple times it is known as a repeat expansion. Sometimes multiple nucleotide sequences are even copied backward, in what is called an inversion variant. All of these variants can result in muddling coding instructions that produce proteins that do not work properly.[5]

When someone carries a genetic variant that is linked to a disease or health condition, the variant affects how their cells make proteins. Every cell in our bodies relies on the careful orchestration of proteins that must be in certain places at certain times to do certain things. When a variant alters the instructions for how to make a protein—maybe it makes too much, too little, or none at all—the cascading effects may interfere with normal development or produce a health condition or disease. Some variants can be severe enough to be incompatible with life, while others produce mild or severe disease.[6]

Classifying genetic variants and their role in disease

A small proportion of variants provide positive benefits and many have no impact on health or development at all. But some are associated with, or cause, disease. Researchers have a system for classifying variants to describe their role in disease. People who receive genetic testing, for example, may be told that a variant they carry is:[7]

- ***Pathogenic:*** there is lots of evidence it causes disease
- ***Likely pathogenic:*** the evidence is weaker, but it probably causes disease
- ***Variant of uncertain significance:*** there is not enough evidence for scientists to say what role it plays, the evidence neither confirms nor rejects that it causes disease
- ***Likely benign:*** the evidence shows the variant likely does not cause disease
- ***Benign:*** lots of evidence shows the variant does not cause disease

But genes are not destiny. Recent research shows there is actually a low risk, roughly 7%, of developing disease when someone carries a known pathogenic variant.[8]

Why disease-causing genetic variants persist

We tend to think of evolution as a self correcting process that finds and amplifies advantageous genetic variations. For example, some genetic variants may provide an advantage to survival that can be inherited.3 But then how to explain why deleterious, harmful, genetic variants persist in populations and produce disease and disability?[9]

This can happen for a couple of reasons. First, some genetic variants may not show up until later in someone's life, after they've already passed on their genetic contribution to their children. Second, some people who carry a variant may not show signs or symptoms of the disease it is associated with and they may pass it on without ever knowing they have it. This is known as reduced penetrance. Third, there are also cases where having 1 copy of a variant provides an advantage, such as disease resistance, whereas having both copies produces disease.[9]

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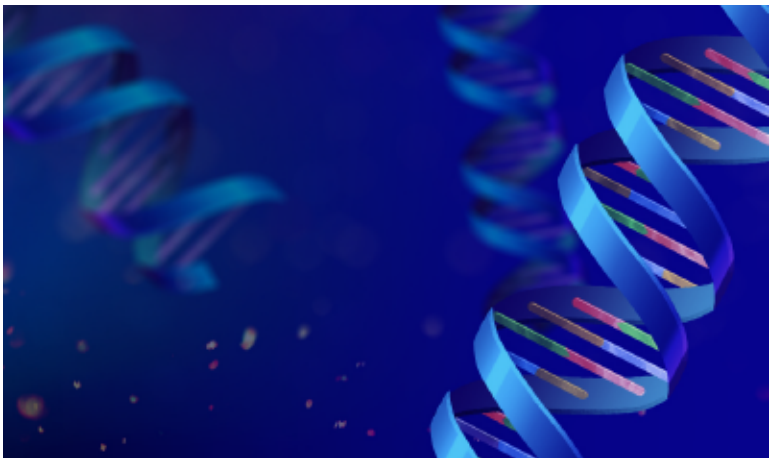
Rare Disease Research Opens Many Doors



Rare diseases are a paradoxic — they are both uncommon and common. And understanding them may help us to gain insights into more ordinary diseases.

If a disease affects fewer than 200,000 people in the United States, it is considered a rare disease. But there are an estimated 5,000 to 8,000 rare diseases. In a country with 329.5 million people, this means roughly 1 in 10 Americans likely has a rare disease.[1] And more than 300 million people globally are estimated to live with a rare disease.[2]

While each rare disease may be an individual rarity, having a rare disease is more common than one may think.1 As genomic techniques advance, it is expected that the actual number of known rare diseases may expand to more than 10,000.[3]

Rare diseases, burdens and types

Of the thousands of known rare diseases, only about 300 have an approved treatment.1 This unmet need presents a rich opportunity for research. But because rare diseases affect few people by definition, they tend to get short shrift in research funding.

This ripples into a lack of clinical trials, a dearth of novel treatment options, plus increased health care costs and resource use for those who are living with a rare disease.[4] The economic burden of rare diseases is estimated to range between $400 — $768 billion in direct medical costs.[5] Developing new treatments would help relieve individual financial strains, but also the strain on our health care systems.

Most rare diseases are caused by specific genetic variants, but they can take other forms. For example, some rare diseases are cancers, autoimmune diseases, or infectious diseases.[6] No matter their origin, they pose similar clinical challenges because most physicians are unfamiliar with diagnosing or managing rare diseases.[3]

The potential of rare diseases

Research into rare diseases may yield expansive benefits beyond those who live with them. This is because sometimes the same genetic pathways are involved in multiple rare diseases, or between a rare and a common disease. Investigating the underlying genetic features of a rare disease may also uncover previously unknown gene functions, which could benefit common diseases and health conditions.[4]

Take Rett syndrome, for example. This is a condition caused by a mutation of the MECP2 gene. Proteins made by this gene are abundant in the brain where it promotes neural activity and is thought to assist in maintaining connections between neurons via synapses.[7] People with Rett syndrome experience a damaging overproduction of MeCP2 proteins.

This condition mostly affects girls and first appears in childhood. Children with Rett syndrome who learn to walk and talk soon lose these abilities. They experience neurodegenerative symptoms such as loss of purpose-driven use of their hands, seizures, and delays and declines in conscious mental activity.[8]

But the MECP2 gene is also involved with several other conditions, some of which are more dominant in one sex or the other. Genetic changes in this gene have been found in some females with autism9 and in PPM-X syndrome, which affects males more than females.[9] But MECP2-related severe neonatal encephalopathy10 and MECP2 duplication syndrome only affect males.[11] Better understanding the MECP2 gene could benefit people who live with all of these conditions.

Therapies for rare diseases

Economics are often cited as a primary obstacle for developing new therapies for rare diseases. High costs of developing drugs or biological products and bringing them to market can prevent pharmaceutical companies from moving forward when they anticipate a small market for sales, and limits on their return on investment.[12]

Another challenge is the high cost of gene therapies, which are a potential platform for many rare diseases with underlying genetic causes. Additional barriers include long development times due to the need to expand existing knowledge and build natural history databases, and extending recruitment timelines for clinical trials given the limited pool of people who may meet inclusion criteria.[12]

Despite these challenges, there is much room for optimism. Gene therapies are gaining traction and success in many diseases. These include gene transfers using viral vectors, disruptive gene therapies such as antisense oligonucleotides, RNA interference and micro-RNA modulators to change or obstruct a protein involved in the disease. Gene-modified cell therapies and gene editing techniques are also showing promise.[12]

The national government is also supporting rare disease research through several different programs. The National Center for Advancing Translational Sciences, a part of the National Institutes for Health (NIH), operates a program to catalyze research on rare diseases called the Therapeutics for Rare and Neglected Diseases.[13]

A separate partnership between the NIH and the Food

and Drug Administration plus several private groups, the Bespoke Gene Therapy Consortium (BGTC), also seeks to speed the development of therapies for those with rare diseases. By developing a therapeutic platform for treating rare diseases, the BGTC aims to support development of therapies for many different diseases all at once.[14]

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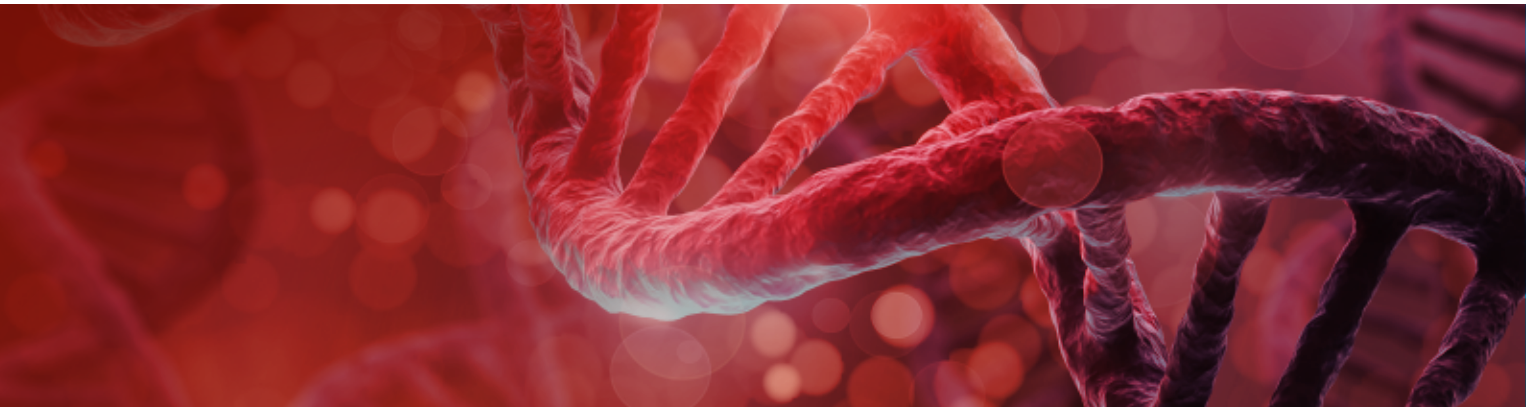
CRISPR Craze



2022 marks the 10th anniversary of a remarkable paper in Science that paved the way for the CRISPR gene editing revolution. The senior authors of that study – Jennifer Doudna and Emmanuelle Charpentier – shared the Nobel Prize in Chemistry in 2020. The "genetic scissors" have already been deployed in the clinic, essentially curing a handful of patients with sickle-cell disease and a growing number of other genetic disorders.

But like many new technologies, CRISPR also has a dark side. In 2018, following experiments editing a single gene in human embryos, gene-edited twin girls were born in China. This triggered an international firestorm that culminated in the lead researcher, He Jiankui, being imprisoned for three years. The health of "Lulu" and "Nana" is unknown.

I admit I was a bit late to the CRISPR party: most of my publishing endeavors (launching journals, writing books, giving talks) focused on advances in our ability to read or sequence DNA. The idea of editing the genetic code had seemed fanciful and far off. But CRISPR changed all that. In 2017, I'd heard enough: I decided not only to launch the first journal dedicated to CRISPR (cleverly titled The CRISPR Journal) but to write a book on the subject.

With impeccable timing, Editing Humanity: The CRISPR Revolution and the New Era of Genome Editing, was published one day before the 2020 Nobel Prize was announced. It's my attempt to tell the grand story of this amazing technology – the heroes who discovered it (and in some cases are feuding over it); the early successes in precision gene therapy; the ethical scandals and fallout surrounding the #CRISPRbabies scandal; and the future applications, from resurrecting woolly mammoths to feeding a hungry planet.

Biography

Kevin Davies, PhD

British science writer Kevin Davies, Ph.D., is the author of EDITING HUMANITY: The CRISPR Revolution and the New Era of Genome Editing (Pegasus Books, 2020). Kevin's latest book is the riveting story of the development of the Nobel Prize-winning technology for editing genes, driving breakthroughs in science, medicine, and agriculture, while igniting ethical controversies about designer babies and the future of humanity.

Kevin has 30 years' experience in science publishing and public speaking. He is the founding editor of Nature Genetics and the founding Executive Editor of The CRISPR Journal. He is currently spearheading the launch of a new marquee science journal called GEN Biotechnology in 2022.

Kevin's previous books include Breakthrough: The Race for the Breast Cancer Gene; Cracking the Genome (translated into 15 languages), an inside account of the race for the Human Genome Project; and The $1,000 Genome, which details the revolution in personalized medicine and consumer genetics. He also collaborated with Nobel laureate Jim Watson and Andrew Berry on an updated edition of DNA: The Story of the Genetic Revolution.

Kevin graduated with a degree in Biochemistry from Oxford University and took his PhD in molecular genetics from the University of London. He hung up his lab coat after two fairly inconsequential postdocs at MIT and Harvard Medical School. Kevin won a Guggenheim Fellowship for science writing in 2017 to support his research on Editing Humanity.

How CRISPR is Changing the Medical Landscape

CRISPR-Cas is a defense system that evolved in single-celled organisms to target and destroy viruses. Researchers have harnessed the precision-targeting nature of this exquisitely sensitive system to edit specific sections of DNA and RNA, from any organism, in a wide range of applications.[1] From eradicating malaria through gene drives in wild mosquitoes,[2] to engineering food crops resistant to disease and climate change,[3] the possibilities seem endless—especially in therapeutic medical applications to cure diseases.

It took decades of discoveries by may different scientists from across the globe to develop the CRISPR-Cas techniques that are applied today in biomedical research and that are FDA-approved as precision medicine therapies. It's been a long but promising journey that began when CRISPR was first discovered in 1993 by Francisco Mojica.[4] By 2012, two separate research teams had reported how to harness its power with Cas9-mediated cleavage to precisely edit mouse and human genomes.[4] Many other teams contributed additional nuggets of understanding for how the CRISPR-Cas system works—and can be manipulated.[4]

CRISPR-Cas techniques have fundamentally changed how researchers envision cures tied to gene therapy. The genetic editing process is so precise, it's been widely compared to using a pair of scissors. Its cost-effectiveness and speed also make it highly attractive. Medical therapies based on CRISPR-Cas techniques have already successfully cured people of certain kinds of diseases, with the promise of more on the horizon.

Existing and emerging therapies

Today, CRISPR-Cas-therapies are being developed for both inherited and non-inherited diseases.[5] These techniques are being tested in clinical trials to cure specific blood diseases (sickle cell anemia and beta thalassemia)[6] and eye diseases (Leber congenital amaurosis, retinitis pigmentosa) in some patients.[5] A gene therapy that used CRISPR to cure retinal dystrophy that is specifically due to a biallelic mutation in gene RPE65 was approved by the Food and Drug Administration in 2017. Its longterm effects are still being evaluated.[5]

Current investigational applications include:[5]

Cancer treatments

- B-cell acute lymphoblastic leukemia
- Lung and esophageal cancers
- Multiple myeloma
- Cervical cancer

Neurodegenerative disorders

- Alzheimer's disease
- Huntington's disease
- Duchenne muscular dystrophy

Cures for non-genetic diseases

- HIV
- Diabetes
- Autism spectrum disorder

CRISPR has deep potential in medical applications. But there are a few limitations that researchers are tackling to unleash its full power to the broadest number of people.

Of particular interest is how a person's immune system responds to aspects of this therapy. Some people's immune system reacts to the viral capsid that functions as a cargo-delivery shell to usher the editing tools into a cell (eg, adeno-associated virus therapies).[1] An immune limiting response is more common if a person needs to undergo the therapy more than once;[1] but it can exclude some patients from being able to receive the treatment.[7]

An innovative approach that is underway to side step this problem is to engineer a different delivery system, such as biodegradable synthetic lipid nanoparticles.[1,7] But sometimes a person's immunity is also triggered by the Cas9 proteins themselves. This is spurring an innovative search for synthetic variants.[7]

Most CRISPR gene editing approaches to curing diseases have so far focused on conditions caused by single genes, which makes sense as the technique is being developed. But many diseases involve multiple genes and their interactions. In the future, it's very likely that existing limitations will be engineered into the rear review mirror, and that tomorrow's CRISPR therapies will target multiple genes and the epigenome.

Current research is already paving the way for this to become reality.

What the future holds

Diversification of the distinct classes of CRISPR-targeting systems is expanding.[8] Researchers at ETH Zurich are working on an update to the CRISPR system that substitutes the Cas12a enzyme for the more commonly used Cas9 enzyme. This switch allows researchers to edit genes in 25 targeted sites simultaneously, delivered on a single plasmid. In the future, dozens or even hundreds of sites could be edited simultaneously using this approach. This would allow "a powerful platform to investigate and orchestrate the sophisticated genetic programs underlying complex cell behaviors," the researchers report.[9]

Future CRISPR-based therapies may shift emphasis not just from single to multiple genes, but also to editing applied to the epigenome.[7] Researchers at Duke University are experimenting with an approach that uses multiple proteins and is centered on a process

called CRISPR-associated complex for antiviral defense (CASCADE). This approach allows for the activation and repression of targeted gene expression, and it offers a way around undesirable issues with a patient's immunogenic response.[1]

But the potential of CRISPR-based therapies in precision medicine are hampered somewhat by the regulatory process. "Current regulatory models that require large numbers of patients to establish safety and efficacy are not applicable to curative technologies that address a mutation that is found in a single patient or very few patients," according to Karen Bulaklak and Charles Gerbach, who recently wrote a commentary in Nature Communications on the future of gene therapy.[8] For CRISPR-based therapies to become widely available, and for personalized gene-based therapies to become a reality, regulatory changes may be needed.

Demonstrating safety and efficacy is still important, even if a trial consists of 1 patient. But the approval process could be simplified by green-lighting "drugs that have an established platform . . . but with different underlying nucleic acid targets," according to a team of researchers who recently summarized the approaches and challenges in translating CRISPR-Cas therapies.[10]

Several CRISPR-based drugs are working their way through the drug development pipeline, and we will likely be hearing news of their achievements and new applications for quite some time.

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