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CCR5: The Perfect Mutation?

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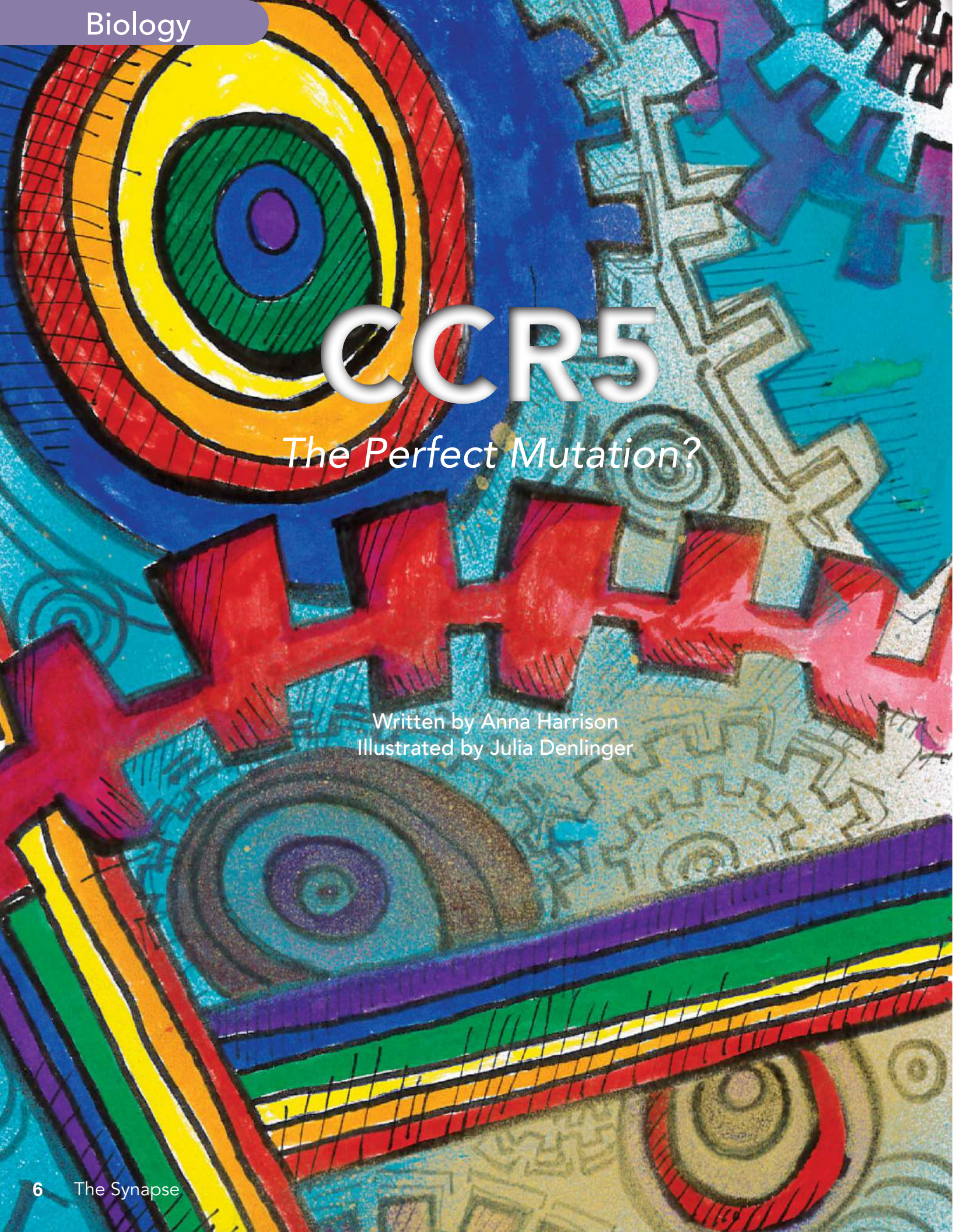

CCR5

The Perfect Mutation?

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Scientists have had the ability to edit genes for years, yet in 2012 a new development made gene editing much easier, cheaper, and more precise. Since then this tool, known as CRISPR-Cas9, has been integral to many advancements in fields across all disciplines of science. Of particular interest are the applications of this tool to the genes of germline cells.

Last year, Chinese geneticist He Jiankui was the first to implant CRISPR-Cas9 edited human twin embryos, which were carried to full term and apparently healthy upon birth in 2018. Since the father of the twins was infected with HIV, Jiankui attempted to reduce the twins' chances of contracting the virus during pregnancy by targeting the well known CCR5 delta 32 mutation. This mutant variant, which is associated with resistance to the bubonic plague, prevents most strains of HIV from infecting host T-cells—major players of the immune system—and is naturally prevalent in the human population. The resulting phenotype is resistance to contracting HIV.

But what exactly is this mutation? The CCR5 gene codes for a membrane protein that is present on many cells in the immune system. It is thought to play a role in guiding our immune cells to their foreign targets in order to initiate immune responses. Like most immune mechanisms, CCR5 activity can have positive and

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negative effects, depending on the context. HIV has exploited the membrane protein to anchor down onto T-cells, allowing the virus to inject its virion or infectious genome. Due to the structural changes in the mutant variant, CCR5 delta 32, it cannot be expressed on the T-cell membrane. These differences prevent most strains of HIV from injecting its noxious genome and proliferating infection.

Since this mutation resulted in resistance to the plague, it is naturally prevalent in the population, making it relatively easy to study. Various health outcomes have been the topic of interest related to CCR5 delta 32. The shocking part of these outcomes is that most of the effects are positive. CCR5 delta 32 has been shown to prevent or slow the progression of several chronic inflammatory diseases, such as West Nile virus and Hepatitis B. The mutation also reduces the risk and recovery time of stroke, traumatic brain injury, dementia, and Alzheimer's disease.

The mechanism by which the mutation improves neuroinflammatory conditions is not entirely understood. The absence of active CCR5 dampens the host's immune response to neuroinflammatory diseases, thus reducing symptoms and damage, and allowing the brain to heal itself. In healthy people, the CCR5 gene is thought to promote learning and memory by regulating the excitability of neurons. The dampening of this excitatory effect is thought to limit damage in the context of stroke or traumatic brain injury. Conflicting studies have shown that individuals with the CCR5 delta 32 variant have enhanced memory and reduced risk for dementia.

While individuals with the CCR5 delta 32 variant may have a slightly greater susceptibility to certain viral infections, they tend to live normal, healthy lives. It is possible that the body responds to the absence of CCR5 gene expression by expressing other genes that allow "mutant" individuals to lead healthy lives. This is why isolating the CCR5 mutation could be dangerous: The body may not have the same negative feedback responses. The greatest concern, however, is for the off-target effects that gene manipulation may have. Additionally, certain strains of HIV remain able to infect mutant T-cells that do not express CCR5 through a different T-cell membrane protein, CXCR4. The broad distribution of CCR5 delta 32 T-cells through gene therapy may simply select for the strain of HIV that does not require CCR5 to get into the T-cell, just as certain antiretroviral therapies have selected for certain strains.

In theory, it is feasible that in order to eliminate the possibility of HIV infecting human T-cells on a population level, a combination gene-therapy would be necessary to eliminate risks of resistant strains developing. However, the odds of off-stream effects developing in such cells skyrocket. Most scientists would agree that we are still many years away from editing the genome of an embryo that will be carried to full term, and that He Jiankui's use of CRISPR on an implanted embryo was irresponsible at best.

In fact, the geneticist did not create the well studied and widely present CCR5 delta 32 mutation in the genetically modified twins. It is believed that this "delta 32" mutation is characterized by a deletion of 32 base pairs in the DNA sequence that normally codes for the membrane protein. Jiankui performed different deleterious mutations in each twin: a deletion of two base pairs and a deletion of fourteen. While it is possible that the mutations which he created will result in the same phenotype as the well-known delta 32 mutation, this manipulation comes across as poor science. Results of his ethically concerning "experiment" will be confounded because the mutations that he introduced aren't well studied in the population or the lab.

Ultimately, the negative effects of having an inactive CCR5 gene are not well understood. Neither are the negative effects of mutating this gene. By extension, the effects of two relatively new mutations that were introduced in these two twins are unpredictable. Dr. Jiankui may have set back the progress in this incredibly important field dramatically by performing this procedure without proper testing or approval. Restrictions have tightened globally since Jiankui's announcement. A global moratorium was written to ban the use of human germline modification around the world, and 30 countries have already implemented laws prohibiting such use.

Whether or not this mutation is the "best," it may very well be the one we know the most about, having the most diverse and possibly therapeutic effects. Yet as we reflect on the incredible work that has been done to reveal the roles of CCR5, this is but one of a million stories that our genes have to tell about the potential that they hold. • • •