Homozygous Familial Hypercholesterolemia (HoFH) is a rare genetic disease that causes a buildup of bad cholesterol (LDL-C) in the blood. Genetic mutations lower the activity of the LDL-receptor (LDLR), which prevents the liver from capturing and breaking down LDL molecules, causing them to accumulate in the blood.

Gene therapy has proven relatively safe and effective in animal models of HoFH. Gene therapy has the potential to last for many years.

MIGHT GENE THERAPY HELP HoFH PATIENTS?

This promising new experimental therapy strives to overcome the patient’s genetic mutation by delivering a healthy copy of the LDLR gene to the liver.

1. A normal healthy copy of the LDLR gene is produced.
2. Gene is inserted into a harmless Adeno-Associated Virus (AAV) to create a viral vector.
3. AAV vector is delivered to the patient’s vein, sending it to the liver.
4. Liver cells (hepatocytes) take up vector and begin to express functional LDLR.
5. Functional LDLR can help remove excess LDL from the blood, lowering levels of bad cholesterol (LDL-C).

Current treatments have limitations:

- **Medications:** Limited efficacy and/or major side effects
- **Lipoprotein apheresis:** Must be repeated every 1-2 weeks
- **Liver transplant:** Limited availability, high risk

One-time treatment:
- Gene therapy has the potential to last for many years.

Safety first:
- Gene therapy has proven relatively safe and effective in animal models of HoFH.

What’s next?
- The same vector has shown promise in patients with hemophilia.
- Early clinical trials will begin to test the safety of this promising new therapy in patients with HoFH.

Penn Medicine Orphan Disease Center