The researchers started with two key assumptions: The mutation must disrupt an important process and must not have been identified before. They also began by searching the medical literature for any genes associated with any of Nicholas’ key symptoms. This gave them a preliminary list of more than 2,000 suspects.

**Sequencing process**

**A. Getting DNA from Nicholas’ blood**
- A research technician used detergents and a centrifuge to break apart Nicholas’ blood sample and isolate the white blood cells, the portion that contains DNA.
- The technician broke open the white blood cells and removed proteins, fats and sugars until all that remained was DNA.

**B. Zooming in on the exons**
- Scientists decided to examine Nicholas’ exons, the part of each gene that contains the recipe for making proteins.
- Scientists loaded Nicholas’ DNA onto a special chip that attracts only his exons.

**C. Putting machine to work**
- The exons were attached to tiny beads and spread over a sequencing plate the size of a Post-it note. The plate was then loaded into the sequencing machine.
- One by one the machine sent the four chemical bases over the plate containing Nicholas’ exons.
- A light flashed whenever a base encountered its match in Nicholas’ exons.

**D. Finding the answer**
- Nicholas’ sequence contained 16,124 variations – sections in which his pattern of bases differed from the norm.
- Medical College researchers used a new software tool they created to weed out variations that could not have triggered Nicholas’ disease.
- They homed in on eight suspects and examined them in detail by searching medical literature and gene functions.
- They discovered a newly published paper linking the XIAP gene to inflammatory bowel disease, which shares some symptoms with Nicholas’ illness.
- An immune system specialist conducted two tests to confirm that Nicholas’ mutation had disrupted the function of an important protein.

*Photos: GARY PORTER/*
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What researchers found deep within Nicholas’ DNA

The blueprint: How the body stores its protein plans

Each cell’s nucleus contains 46 chromosomes. Twenty-three are inherited from the mother, 23 from the father. Together, they hold the body’s DNA blueprint.

Pairs of DNA strands are intertwined into shapes called a double helix. They are then coiled into the well-known “X” shapes associated with chromosomes.

In the course of a lifetime, the body’s DNA continually produces proteins. These proteins initiate nearly every process each cell needs to carry out its purpose.

On Nicholas’ X chromosome, the gene XIAP contains a single mistake in the sequence. Nicholas’ has thymine-adenine-thymine in a part of the sequence that should read thymine-guanine-thymine.

Copy and deliver: How the blueprint is made into molds

Inside the nucleus, RNA polymerase and transcription factors form a transcription molecule. Racing along the DNA strands, the molecule unzips the DNA template (the gene it needs to copy).

Chemical bases are assembled in complementary order to the strand being read. The resulting ribbon called mRNA ventures outside the nucleus and into the cytoplasm.

For Nicholas, that slight change in sequence (TAT instead of TGT) means that his blueprint will call for the amino acid tyrosine instead of cysteine in a key position of the genome.

The factory: How the molds produce proteins

When the mRNA reaches the cytoplasm, ribosomes will form around it. As the mRNA ratchets through the ribosome, its chemical bases are read in codons, or sets of three.

1. The ribosome receives protein-building amino acids in sets of three from transfer molecules.

2. If a match is made, the amino acids are released.

3. A protein chain is formed.

If a mutation exists, it gets translated as well. Some mutations don’t produce noticeable effects. But if a key gene has even one base out of place, ribosomes will generate the wrong protein.

In Nicholas’ case, the single misplaced amino acid is now one of 497 that make up a key protein that is supposed to keep his immune system from attacking his intestine in response to bacteria. His immune system is at war with his intestine.

Coming Sunday: Armed with an answer, doctors must decide how to treat Nicholas’ condition.

Source: Children’s Hospital of Wisconsin; Medical College of Wisconsin; DNA: The Secret of Life

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