IT ALL BEGINS WITH THE AHC PATIENT And The Scientific Process

AHC RESEARCH

- AHC Patients Need Help!
- Genetic discovery
- Researchers hypothesize and predict potential outcomes
- Researchers collect DNA samples from patients
- Researchers screen samples
- Researchers analyze data
- Researchers interpret and evaluate data
- Researchers collect data on AHC patients (observation)
AHC FAMILIES NEED HELP UNDERSTANDING GENETICS

Are you a little confused by all this talk about “The Gene Discovery”?

Do you wish you had a simple means of understanding why DNA and genes are so important to understanding AHC?

Do you know how to get tested for the gene mutation?

The Alternating Hemiplegia of Childhood Foundation is here to help. We are pleased to provide you with this guide on understanding several basic points on AHC and genetic research.

We hope this guide will help you feel comfortable asking questions of your physicians and talking about the latest scientific discoveries around AHC.
UNDERSTANDING BASIC GENETIC DEFINITIONS

PROTEINS
Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body’s tissues and organs.

CELLS
Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions.

DNA
DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person’s body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria.

GENES
A gene is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes.

CHROMOSOMES
In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

# Understanding Genetic Research and Alternating Hemiplegia of Childhood

## The Basics of Genetic Testing and the AHC Patient

<table>
<thead>
<tr>
<th>What is Genetic Testing?</th>
<th>What methods of genetic testing can be used to help identify variations or mutations that lead to a genetic disorder?</th>
<th>How does Genetic Testing Help AHC Patients?</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results can confirm the existence of a genetic disorder.</td>
<td><strong>Molecular Method</strong> tests single genes or short lengths of DNA</td>
<td>Once a mutation is identified, it can be used to confirm the diagnosis of AHC</td>
</tr>
<tr>
<td><strong>Chromosomal Method</strong> analyzes whole chromosomes or long lengths of DNA</td>
<td><strong>Biochemical Method</strong> studies the amount or activity level of proteins</td>
<td>Once a mutation is identified, researchers can begin the process of searching for a treatment</td>
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HOW DOES GENETIC TESTING WORK?

AHC patent blood sample is collected.

DNA from cells is extracted.

DNA is sequenced.

Compare patient DNA sequence to reference sequence.

Search database to determine if patient mutation is associated with disease.

Genetic counselors or physicians work with patients and their families to understand the test process.

Lab technicians work with patient samples in the lab, purifying and sequencing the DNA.

Computer programs help researchers analyze data.

Researchers perform experiments with patient samples to find variation in the genes that might cause AHC.

Doctors use the knowledge gained from genetic testing to care for their AHC patients and researchers can begin looking for AHC treatments.

Based on the Genetic Research Slide #9 http://www.nwabr.org/sites/default/files/learn/bioinformatics/AdvL1.pdf

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UNDERSTANDING GENE MUTATIONS & AHC

What is a Gene Mutation?
A mutation is a change in a gene that prevents it from making its usual (working) protein.

What are Genetic Disorders?
It is a disease that is caused by an abnormality in an individual’s DNA. Abnormalities can range from a small mutation in a single gene to the addition or subtraction of an entire chromosome or set of chromosomes.

Why is this Gene Discovery so Important?
This discovery assists new patients in the diagnosis of the disorder. It also provides direction for determining possible drug treatments.

Are Gene Mutations Hereditary?
When there is a dominantly inherited gene, there is a 1 in 2 chance that a child will inherit the genetic mutation instead of a working copy of the gene.
THE PROCESS OF AHC GENETIC RESEARCH

AHC FOUNDATIONAL RESEARCH
Identify all genes responsible for causing AHC in patients

AHC TRANSLATIONAL RESEARCH
Investigate known and novel disease causing genes to determine pathogenic mechanisms

DRUG DISCOVERY
Screen for drugs based on pathogenic mechanisms

DRUG DEVELOPMENT
Conduct clinical trials for AHC therapies

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THE PATH TO THE BIGGEST AHC GENETIC DISCOVERY

AHC IS IDENTIFIED AS A DISORDER IN 1972
Physicians credited with identifying AHC
Patients begin to be diagnosed

THE AHC FOUNDATION BEGINS IN 1993
Patient families come together and create foundations to raise money & awareness
AHCF funds research to find cause of AHC

THE AHCF WON THE PEPSI CHALLENGE IN 2010
$250,000 is awarded to The University of Utah and they screen for causal genes. The AHCF invites Univ. of Utah research team to collaborate with Duke Univ. research team. International collaboration begins as researchers share DNA samples from around the world.

THE ATP1A3 Gene Mutation is identified to be the major cause of AHC in 74% of patients

For more history on the AHCF, go to http://ahckids.org/about-ahcf/history/
WHAT IS THE ATP1A3 GENE MUTATION?

ATP1A3 is a protein responsible for establishing and maintaining the electrochemical gradients of potassium and sodium ions across the cell membrane affecting nerves and muscles.

ATP1A3 is located on chromosome 19

BREAKING DOWN THE DEFINITION

Proteins are large biological molecules consisting of amino acids. They perform a variety of functions including: metabolic reactions, replicating DNA, responding to stimuli, and transporting molecules from one location to another.

An electrochemical gradient is a measurement of energy stored in the form of potential, usually for an ion that can move across the membrane.

The gradient consists of two parts, the electrical potential and a difference in the chemical concentration across a membrane.

The difference of electrochemical potentials can be interpreted as a type of potential energy available for work in a cell.
WHAT DOES ATP1A3 ACTUALLY DO?

The ATP1A3 gene provides instructions for making one part of a protein known as the sodium pump.

ATP1A3 pumps sodium ions out of cells and potassium ions into cells.

The movement of sodium and potassium ions helps regulate the activity of these cells and plays an important role in the signaling process that controls muscle movement.

http://faculty.southwest.tn.edu/rburkett/GB1-osmosis.htm
WHAT DOES THE ATP1A3 MUTATION MEAN TO AHC PATIENTS?

ATP1A3 mutations are likely to be responsible for at least 74% of all AHC cases.

The first step begins with getting tested for the ATP1A3 mutation. The AHCF can assist you in this process. Please contact our Medical Liaison, Sharon Ciccodicola, at Sharon@ahckids.org for assistance.

Is there a drug treatment for this mutation and AHC? Not yet, this is the next major step in AHC research.

Is there a cure for this mutation in AHC patients? No. Research into gene therapy would need significant funding to begin.

ATP1A3 and Epilepsy
Of those with this mutation 54% have a history of seizures.

What causes AHC for the remaining 26%? More research is needed to find the remaining causes for ALL AHC patients.
### WHAT ARE THE NEXT STEPS IN RESEARCH?

#### A Vision for the Future

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>ATP1A3</th>
<th>TREATMENT</th>
<th>CURE</th>
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</thead>
</table>
| • Continue to screen DNA to identify disease causing gene mutations in remaining 26% of AHC patients | • Conduct biochemical studies of gene mechanism to understand how the mutation affects AHC patients  
• Conduct functional studies of how the gene mutation causes problems | • Testing of existing drug therapies  
• Testing of novel drug therapies  
• Conduct clinical trials | • Conduct gene therapy research as soon as practical |

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## WHAT WILL THE RESEARCH COST?

All contributions big and small are vital. Here are some important ways everyone can contribute.

<table>
<thead>
<tr>
<th>ANNUAL COSTS</th>
<th>GENERALIZED PROJECT DESCRIPTIONS</th>
<th>(not currently funded by AHCF)</th>
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</thead>
<tbody>
<tr>
<td>$0</td>
<td>Volunteer with the AHCF or volunteer for a research study</td>
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<tr>
<td>$0</td>
<td>Tell others about our foundation and the need for donations</td>
<td></td>
</tr>
<tr>
<td>$150</td>
<td>Pay for one patient’s DNA test kit</td>
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<tr>
<td>$400</td>
<td>Pay for 500 educational brochures about AHC &amp; the ATP1A3 mutation</td>
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<tr>
<td>$10,000</td>
<td>Sponsor the next international research symposium on AHC</td>
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<tr>
<td>$20,000</td>
<td>Sponsor a white paper on AHC &amp; behavior</td>
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<tr>
<td>$25,000</td>
<td>Sponsor the creation of a handbook on AHC</td>
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<tr>
<td>$30,000</td>
<td>Sponsor the 2014 Family Meeting for AHCF families in Minneapolis, MN</td>
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<tr>
<td>$38,000</td>
<td>Fund a grant to screen a drug library for new therapeutic treatments (19,000 drugs)</td>
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<tr>
<td>$50,000</td>
<td>Sponsor a genetic research fellow for one year</td>
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<tr>
<td>$75,000</td>
<td>Study long-term effects of Flunarizine on patients with AHC</td>
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<tr>
<td>$100,000</td>
<td>Screen for new mutations in patients without ATP1A3</td>
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<tr>
<td>$200,000</td>
<td>Screen cell lines to see impact of electrical activity of the cell</td>
<td></td>
</tr>
<tr>
<td>$200,000</td>
<td>Screen cell lines for drug treatment protocols</td>
<td></td>
</tr>
<tr>
<td>$252,000</td>
<td>Create international patient repository of ips cells and disease models for study</td>
<td></td>
</tr>
<tr>
<td>$500,000</td>
<td>Fund drug trials for pharmaceutical treatments</td>
<td></td>
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<tr>
<td>$1,000,000</td>
<td>Fund gene therapy research to find a cure for AHC</td>
<td></td>
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</tbody>
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HOW CAN YOU HELP?

- Be active with AHCF
- Raise money for a treatment
- Share information with family & friends
- Participate in research
- Visit our website
- Read & share our newsletter

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The AHCF Board of Directors offer our sincerest appreciation to all the families who have raised money to advance genetic research into the causes of AHC. We are also grateful to all of the researchers and physicians who have contributed to the science behind AHC.

TO LEARN MORE ABOUT THE AHC FOUNDATION

The foundation website is located at: www.ahckids.org

The foundation president is Lynn Egan, Lynn@ahckids.org
The foundation medical liaison is Sharon Ciccodicola, Sharon@ahckids.org
The foundation fundraising chair is Mollie Erpenbeck, Mollie@ahckids.org

For questions about this presentation, contact Vicky Platt at Vicky@ahckids.org

TO LEARN MORE ABOUT THE SCIENCE OF GENETICS

Please Visit
National Human Genome Research Institute at www.genome.gov
Scitable by Nature Education at http://www.nature.com/scitable/topic/genes-and-disease-17
The University of Utah Genetic Science Learning Center at http://learn.genetics.utah.edu/