

# ACDA NOTES

From The Alveolar Capillary Dysplasia Association

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Dear Friends and Family,

We would like to thank the [redacted] family of South Carolina and the [redacted] family of Washington for recently offering to help the ACDA with some of its efforts. We really cannot run the ACDA without the help of our members so we truly appreciate any assistance, fundraising or support that any of you can offer. For those of you that have helped us in the past, we are grateful. As we have seen with the NORD grant to Baylor last year, we may be a small group of families but we can make a difference.

[redacted] and [redacted] and his father, [redacted], are helping us evaluate the tradeoffs of the ACDA becoming a legal non-profit organization (501(c)3). This has been a goal of the ACDA for some time so we are grateful that the [redacted]'s can assist us in this decision. The [redacted]s, who just lost their son to ACD this summer, have a printing business and have offered to assist us in that area. That could be the perfect compliment for the letter writing campaign we'd like someone to spearhead. We have ideas but lack the time to follow through with many of them so we are so appreciative of everyone's help.

Keep up posted on new arrivals, stories you would like to share, fundraisers you conduct, change of addresses and the like.

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## Update on ACD Study at Baylor College of Medicine

Parth Sen, Ph.D. and Dr. Claire Langston are continuing to conduct the research on ACD at Baylor, Houston. Their current research involves reviewing the slides for the immunohistochemical studies on seven different proteins known to be involved in vasculogenesis and angiogenesis, particularly in lungs (see end of this article for definitions).

Slides made from lung tissues of ACD patients are being compared to that of normal newborn lung tissue. (See the Fall 05/Winter 06 ACDA Newsletter for an overview of the Baylor research and also the Learning Series article in that same newsletter for a detailed overview of their research approach and techniques). The results of this work should be available in the next newsletter. This study is supported from the grant that Baylor received last fall from NORD. The NORD funding for the Baylor grant came from the generous contributions of ACDA members and their families and friends – we are making a difference.

Dr. Sen also reported that three new families have contacted Baylor recently about participating in the ACD study. Thank you to those families and all the other families that have supported this much needed

Continued on Page 2

INSIDE

- |   |                                 |
|---|---------------------------------|
| 1 | <i>Update on ACD Study</i>      |
| 2 | <i>Announcements</i>            |
| 3 | <i>Meet New Families</i>        |
| 4 | <i>Learning Series – Part 3</i> |

research. We hope to award another study grant through NORD next year. Please help us on our goal to reach the \$35,000 contribution level that is required for NORD to award another research grant. We currently have just over \$11,000 in the ACD research account at NORD.

Some of you may know that two of the researchers at Baylor College of Medicine in Houston, Dr. Bassem Bejjani and Dr. David Stockton, have left to pursue opportunities at other research facilities. We want to thank them for their contributions to ACD research and wish them the best of luck in their future pursuits. To inquire about participation in the Baylor ACD research or for specific questions, please contact Dr. Sen:

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Definitions courtesy of Wikipedia:

Immunohistochemical staining is a common immunological technique used in the biological sciences for the detection of proteins within the context of the tissue in which the protein is found. It takes its name from the roots "immuno," in reference to antibodies used in the procedure, and "histo," meaning tissue.

The term angiogenesis denotes the formation of new blood vessels from pre-existing ones, while vasculogenesis is the term used for the formation of new blood vessels when there are no pre-existing ones.

## \*\*\*\*\*ANNOUNCEMENTS\*\*\*\*\*

- As of September 8, 2006, the balance of the ACD Restricted Research Account at NORD was \$11,455. Thank you to everyone that has contributed!
- We are still looking for someone to lead our ACDA letter writing campaign. If you are interested, please contact us at [sdesj@verizon.net](mailto:sdesj@verizon.net).
- The loving efforts of the [REDACTED] family and numerous friends have resulted in the publication of "Recipes from the Heart," a tribute to [REDACTED] [REDACTED], who died of ACD in 2002. This cookbook contains over 400 recipes from around the world, including some from our ACDA families. It is being sold for \$8.00 (US) plus shipping. When all the cookbooks are sold, at least \$4,000 will be donated to NORD for ACD research. To receive a copy of the cookbook or to obtain copies to sell, e-mail [REDACTED] [REDACTED] [REDACTED]. Credit cards and checks are accepted.



## **LEARNING SERIES – Part 3**

This is Part 3 in a series of articles about the technical aspects of genetics, research methods and associated topics to provide a broader understanding of ACD- related information. This Newsletter's focus is to provide an overview of the hereditary transmission modes (ways that ACD could be passed from parents to child) to try to answer the question that is most commonly asked of the ACDA:

### ***What are the chances of having another baby with ACD?***

#### **Background**

The information in the first two **Learning Series** articles were to develop a general background understanding of genetics to lay the foundation for this article. As stated in previous **Learning Series** articles, ACD is suspected to be a genetic disorder by many researchers, but the real cause is not yet known. ACD could result from mutations, environmental affects or other causes. However, most research strategies are based on the assumption that ACD is genetic so this article will discuss the various ways that ACD **could be** transmitted genetically, **if** it is indeed genetic.

Many disorders can result when defective genes are inherited from the person's parents. In this case, the genetic disorder is known as a hereditary disease. There are many ways in which this can occur, but before explaining these, a brief review of some basic biology is in order to help understand the terminology.

**Humans have 46 total chromosomes, which are made up of 23 pairs of different types. One copy of each chromosome pair is inherited from the mother and one from the father.**

**Chromosomes 1 through 22 are the same in both males and females. These do not determine the sex and are called *autosomes*.**

**Chromosome pair number 23 determines the sex of the child. The sex (X and Y) chromosomes differ between the sexes. Males have one X and one Y chromosome, whereas females have two X and no Y chromosomes. Mothers contribute X chromosomes to offspring, since females only have X chromosomes. A father can contribute an X or Y chromosome to his offspring. If the child receives an X chromosome the child will be a female and if the child receives a Y chromosome then the child will be a male.**

Each chromosome is a very long, continuous piece of DNA and each DNA contains many genes which are composed of nucleotides. The Human Genome is a large and complex structure, but can be broken down into smaller parts somewhat analogous to a set of encyclopedias. If the genome is represented by a complete set of encyclopedias, then the 23 pairs of chromosomes are similar to the volumes in an encyclopedia. Similarly, DNA are the “chapters” that make up each chromosome “volume”. Likewise, the DNA chapters consists of many genes (sentences) that are formed from exons (words) which in turn are made up of the smallest components, nucleotides which are analogous to letters.

Structure of a set of Encyclopedias	Structure of the Human Genome
Encyclopedia	Genome
Volumes	Chromosomes
Chapters	DNA
Sentences	Gene
Words	Part of gene (exon)
Letters	Nucleotides

To give some perspective on the enormity of this construction, each human has 25,000 genes and each DNA is composed of  $3 \times 10^9$  (3 billion) pairs of nucleotides. DNA is often referred to as the molecule of heredity, as it is responsible for the genetic propagation of most inherited traits. During reproduction, DNA is replicated and transmitted to the offspring.

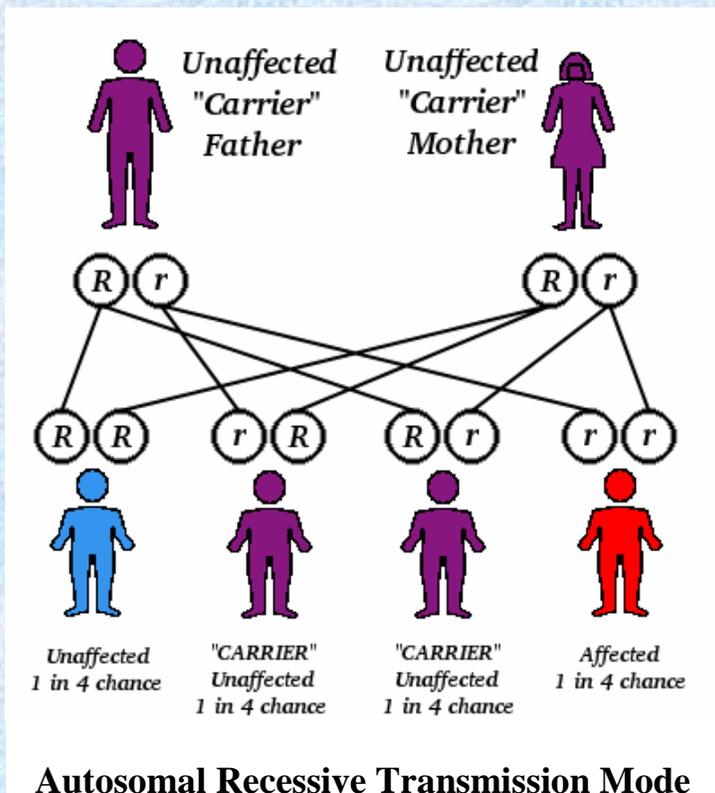
### Hereditary Transmission of Diseases

Following are brief summaries of the potential ways that ACD could be passed on to offspring along with an assessment of the likelihood that ACD is transmitted this way:

#### Autosomal Recessive<sup>1</sup>

In these genetic diseases, both the Father and Mother are carriers of a recessive trait. Because it is recessive, neither parent displays the trait, but carry the recessive gene and can pass it on their children. There are 23 pairs of chromosome in humans. Each pair consists of one chromosome from the Father and one from the Mother. Assuming that capital “R” denotes a “good” gene and lower case “r” a “bad” recessive gene, the diagram below shows the possible combinations of chromosome pairs that could occur in a couples’ offspring.

If ACD is autosomal recessive, then from the diagram it can be seen that there is a 75% chance (3 out of 4) that a baby will NOT get ACD because they are completely unaffected (1 out of 4) or just a carrier (2 out of 4). However there is a 25% chance that an offspring might inherit the recessive genes from both parents which would result in the trait being expressed by the child having ACD.



Of note is that 66% of the surviving children (2 of the 3 survivors) will carry the recessive gene. When they grow up and have a child with a mate that also carries the recessive gene, then the odds of their offspring having ACD is the same as the diagram. If an ACD carrier has a child with a mate that does not carry an ACD gene, then that child has a 50% chance of being an ACD carrier, but can not get ACD (it will be recessive and not expressed).

**Recessive inheritance means two abnormal copies of the relevant gene must be present for individual to be affected. Examples of recessive disorders include cystic fibrosis, sickle cell anemia and many forms of deafness.**

*Many geneticists suspect that ACD is an autosomal recessive disease.*

*NOTE: The chances of inherited diseases are based on statistics and statistics have no memory. It does matter how many other children (with or without the recessive problem) a couple has had. When both parents are carriers, every pregnancy has the same 1 in 4 risk of having an affected child.*

## Autosomal Dominant

An **autosomal dominant** gene is an abnormal gene on one of the autosomal (non-sex determining) chromosomes. Because it is dominant, it need only exist in the inherited chromosomes of one parent for it to cause disease. The chances of an autosomal dominant disorder being inherited are 50% if one parent has the gene. Some diseases inherit in this fashion but still affect less than 50% of the offspring; in this case the disease is termed of having *incomplete penetrance*.

**Dominant inheritance means one copy of the abnormal gene is sufficient to cause disease. Examples of dominant disorders include Huntington's disease, some forms of breast cancer and some forms of Alzheimer's disease.** <sup>4</sup>

*There is very low likelihood that ACD is autosomal dominant, unless it is incomplete penetrance.*

## X-link Inheritance

An X-linked genetic disease is one that is generally passed on from mother to son. The genetic abnormality is found on the X chromosome. Males have the sex chromosome make-up of XY. Males inherit the X chromosome from their mother and the Y chromosome from their father. Since this is the case, abnormalities on the X chromosome from the mother will usually manifest as a disease within 50% of her sons. Although rarely seen in girls and women, these diseases can affect them as well.

Since females have a chromosomal make-up of XX, inheriting an X chromosome with disease mutations in it generally will not produce the disease condition. The healthy X chromosome that the female has inherited from her other parent masks the diseased X chromosome. The female with one mutated X chromosome would be known as a carrier because she can pass the mutation onto her children, though she may not be directly affected by it. An X-linked disease could affect a female if her mother is a carrier and the disease affects her father. If her mother and her father are both affected with the disease, she will most certainly be afflicted with the disease as well. In addition, some X-linked conditions produce mild symptoms in women that are carriers.

**When an abnormal gene responsible for a recessive disorder is located on the X chromosome, then only males are primarily affected, because a female has another X chromosome that can compensate for the abnormal X chromosome. Examples of such "sex-linked" recessive disorders are hemophilia and color blindness.** <sup>4</sup>

*Since ACD appears to affect males and females equally, this is not likely the cause.*

## Mitochondrial Transmission

Because eggs destroy the mitochondria of the sperm that fertilize them, the mitochondrial DNA of an individual derives exclusively from the mother. Since all the mitochondria are from the cytoplasm in the Mother's egg, this would pass a disease from Mother to children and not from the Father to children. However, there is some evidence that mitochondria can be recombined and therefore some of the Father's mitochondria can be passed to the offspring. <sup>2</sup>

*While there is limited data, the transmission path does not appear to be solely from the Mother so this has a low probability of causing ACD.*

## Imprinting or Silencing

This is the suppression of certain genes on chromosomes, depending on from which parent they were received. When DNA is passed to daughter cells after fertilization of an egg by a sperm, certain alleles can become active only if they were received from the mother, others only if they came from the father. If a gene is suppressed through imprinting from one parent, and the allele from the other parent is not expressed because of mutation, neither can act and the child will be deficient.

Allele - One member of a pair or series of genes that occupy a specific position on a specific chromosome.

## Mutation

Any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited.<sup>3</sup>

*There are instances of ACD afflicting more than one child in a family. ACD is not likely a mutation, because for this to happen twice in one family would be like lightning striking twice in one spot.*

## Gonadal Mosaic

The parent may show no signs of disease, but may have children with some risk of inheriting the mutation because there are 2 populations (mutant and normal) of germ cells in their gonads (ovaries or testes). Normally, all body cells would have the same number of chromosomes (46). But in mosaicism, some cells may have 47 chromosomes (such as extra chromosome 21 or X chromosome in some, but not all cells). So any individual egg or sperm either has the mutation or not. Therefore, the mutation is present from conception and acts like a mutation in any typical (not mosaic) genetic disease.

## Multi-Factorial/Complex Inheritance

This condition results from a combination of one or more of the hereditary transmission modes described above.

**Complex inheritance often means that several genes combine to influence a single trait or disease and that nongenetic factors also play a role.**<sup>4</sup>

*This is a complex mode and is thus very complicated to analyze with limited data. It is a possible transmission mode for ACD transmission, but others would need to be ruled out first.*

## Conclusion

While ACD has had major impacts on our lives, medically there are relatively few documented cases of ACD and that limits the statistical accuracy of any general conclusions about what type of disease ACD is. However, as described above there are some modes of inheritance that seem to have a low probability of being the cause given the known data.

Many researchers and geneticists feel that ACD is a genetic disease with an autosomal recessive inheritance mode. This remains to be proven, but **if one accepts the currently prevailing opinion, then couples who are both carriers of ACD have a 25% chance for each pregnancy to result in an ACD affected baby. More optimistically, there is a 75% chance that the baby will not be affected, although the child could be a carrier that displays no symptoms (like each parent).**

While it is cause for great joy and celebration when subsequent children are born healthy and not affected by ACD, it must be remembered that each “healthy” child still has a 66% chance of being a carrier of ACD (if ACD is autosomal recessive). If that “healthy” child is a carrier and produces offspring with a mate that is also a carrier, then the cycle starts over again and there is a 25% of an ACD affected baby. For this reason, it is an ACDA long term goal to develop an affordable test to determine if a person is an ACD carrier. This will enable an unprecedented ability to understand potential risks prior to conception or potentially even in utero. This knowledge could reduce the heart-breaking, gut wrenching, life-changing shock of suddenly having a joyous time of birth turn into a nightmare of emptiness, despair and unanswered questions.

Only time and additional research will determine the cause of ACD and eventually provide diagnostic capabilities. The ACDA will continue to support families affected by ACD and with your support of research in the medical community, we will find the cause of ACD.

#### **Acknowledgements:**

1. [http://en.wikipedia.org/wiki/Autosomal\\_recessive](http://en.wikipedia.org/wiki/Autosomal_recessive)
2. **Recombination of human mitochondrial DNA. [Kraytsberg Y](#), [Schwartz M](#), [Brown TA](#), [Ebralidse K](#), [Kunz WS](#), [Clayton DA](#), [Vissing J](#), [Khrapko K](#). *Science*. 2004 May 14;304(5673):981**
3. [http://www.uccc.info/CancerCenter/content/CancerInfo/Details\\_g.asp?Id=CDR0000046063&Type=Glossary](http://www.uccc.info/CancerCenter/content/CancerInfo/Details_g.asp?Id=CDR0000046063&Type=Glossary)
4. <http://research.marshfieldclinic.org/genetics/Home/nutshell.asp>