ACDA NOTES

From The Alveolar Capillary Dysplasia Association

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Dear Friends and Family,

We are excited about the prospects for an ACDA letter writing campaign to raise money for our research account at NORD. We hope that one of you will volunteer your time to head up this campaign that could become an annual fundraiser for the ACDA. For others that are ready to make a difference in memory of your baby, this is a great way to get started with minimal effort and cost.

On a more personal note - This year, we have six families in the ACDA that will mark the tenth year or more since they have lost their baby to ACD. Like us, you must be wondering where the time has gone, what would my baby look like today, how would our lives be different? Our grief has never gone away; instead we have learned to manage it on a daily basis. We hope that you, as well as our other ACDA families, will continue to live your lives to include the memory of your baby and to ensure that your other children will always remember that they have another sibling. Thank you to ACDA founder, Madonna Myers, who has written a personal article about reaching this milestone (see page 2).

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INSIDE

Kick-Off for the ACDA Letter Writing Campaign

We have been inspired by the efforts of a family in our neighborhood that we have known for several years. [redacted] have a seven-year old son, [redacted], who is the same age as our daughter, [redacted]. [redacted] and [redacted] were in a playgroup together as preschoolers and now attend the same elementary school. [redacted] was born with a rare disease called Tuberous Sclerosis (TS) which is a genetic disorder without a cure. It causes benign tumors to form in the vital organs of the body including the brain, kidneys, skin, heart, eyes, lungs and liver. Every year for the last five years, [redacted] and his family have participated in a letter writing campaign to raise money for the TS Association. To date, the [redacted] have raised over $43,000 by writing a letter to friends and family members asking for a donation! For more information on [redacted] and his family's campaign, go to http://www.firstgiving.com/[redacted].

While [redacted]'s story is obviously different than our babies that we have so tragically lost, we are inspired by the [redacted]'s dedication to raising money for the TS Association. We believe the ACDA can be just as successful in raising money for our research account at NORD. We all have friends, family members, co-workers and acquaintances that would support our own fundraising efforts.

Some of you have expressed an interest in contributing to the ACDA in some way and this is a great opportunity to make a difference in memory of your child. We are looking for a volunteer to head up this letter writing campaign. Here is a list of responsibilities that we envision for that volunteer:

- Draft a sample letter that to be sent to all the families in the ACDA. We have a copy of the [redacted]'s letter to help get you started.

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A Decade After Losing [redacted]

From [redacted]

It's been ten years since we lost [redacted]. Those words have such an impact on me. Ten years ago, I could not imagine where our lives would be. We sat in support groups and heard all of the horrible statistics about how the loss of a child could tear a family apart. Not us, we would tell ourselves. Not sure how we would prevent it.

May 31st of this year should have been her 10th birthday, and it was in a way. It was a strange day for our family. The kids were celebrating their last days of school. [redacted] and I both worked that day, for the first time in ten years. To everyone outside of our home, it seemed like any other day. Inside our home that evening was a very different story. It was quiet, not mournful, but peaceful. The kids weren't bickering, the stereos weren't blaring, the televisions weren't on and not one friend arrived at the door to play; it was quiet.

In our family, the tenth birthday is a big deal. We tell the kids they are at "double digits" now. Double digits has been a right of passage for the boys, now 16 and 11. They got raises in their allowance, later bedtimes, more freedom. In our family reaching ten means you get *benefits.* But, not this year, [redacted]'s tenth birthday meant quiet. May 31, 2006 brought extra hugs and a few tears. During this last year, I had not allowed myself to consider this day. Each of [redacted]'s birthdays has come and gone with a few traditions in our family. We always had a cake and let balloons go into the sky. This year seemed like the right year to stop. We have not forgotten her by any means, but we just needed to make a new tradition. Time together, not in ritual, but in reality. Those rituals got us through some very hard times, but without a word being said, we were all ready to let them go.

We've moved away from Chicago three years ago. The cemetery is a ten hour drive away, so we don't get their more than once a year. [redacted]'s parents take care of the plot for us now. They tell us it is something they want to do. It is not a place we feel obligated to visit now. After ten years, [redacted] is in our hearts more than in that place. It is another ritual we have given up.

We still have photos of [redacted] mixed in with other families photos, so she is still a part of our lives. Instead of her Christmas stocking, we have a Christmas angel. We'll get our tenth Christmas angel this year. I don't think we are ready to give that up. It is important to the kids. We talk about her whenever the kids want. I send a letter to each classroom teacher at the beginning of the year, so that they are aware of our family history. I almost didn't do that this year, but I am so glad I did. During the holidays, a teacher lost her baby in-utero and [redacted] took it very hard. His teacher was so very helpful getting him through that time.

Through that very special teacher, [redacted] was invited to Camp Forget Me Not this year. It is a camp that the local hospice puts on for children ages 6 -12 who have lost a loved one for any reason. [redacted], who was only a year old when [redacted] was born, has always had the hardest time with his grief. He has the sweetest, most sensitive soul. I can only imagine that comes from being touched by our grief when he was so young. The camp did so much for him in four short days. He made her a memory book that is his very own to keep. I haven't worked up the courage to look at it yet, but [redacted] says it is so very sweet. Maybe tomorrow will be the day I look. I made copies of her photos for him to put in the book. Those photos, his very own, are so important to him. I wish I had known that sooner. I would have copied all of them long ago for him to keep. I think they were something I was holding onto for myself, my selfish spot.

[redacted] and I made a decision very soon after [redacted] died. We would always keep her a part of our lives. She would never be that quiet secret we couldn't talk about. Looking back over the last decade, I think that was right. We could have done it better, but I think we did OK. Our living children, [redacted] (16), [redacted] (11), [redacted] (9) and [redacted](6), are our testament to our love not only for them, but also to [redacted]. On my hard days, I have always tried to remind myself that the legacy of her life could never be a broken family. It has made me stronger than I ever thought I could be.

[redacted] turned forty just two weeks after [redacted]'s tenth birthday. We've been under attack the last few

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months with a mid-life crisis around here. Sometimes, it was funny and sometimes it was rough. Just a couple of days after [redacted]'s birthday, it seemed to go away. He looked peaceful. The lines on his face had softened; his shoulders weren't so tense. He looked at me and said how relieved he was that his birthday was finally over. Putting my chatty nature aside, I said nothing and let him talk. He smiled at me, took a deep breath and said, *I am so very grateful that no one died*. In ten years, I don't think he had ever been able to open up like that to me. We have a good marriage, but it has had a few bumps. [redacted]'s death made it hard for us to talk about our pain to one another. I don't think I can explain what his proclamation felt like on my end of the living room. It was enlightening to say the least. [redacted]'s thirtieth birthday was spent in the NICU. It was the end of the second week. [redacted]'s 30th birthday was [redacted]'s first circuit change on ECMO. We acknowledged his birthday with a piece of lemon meringue pie in the hospital cafeteria. There was no celebration, only a small time-out from our crisis. His courageous honesty has brought us to talk more and healed more in the last two weeks than in the last ten years.

I share all of this in hope that those families who are right now wondering how they will get on might know that they will. I can't tell anyone else how we have gotten on, only that we have. Ten years brings a lot of change to any family. We went through two very hard pregnancies with [redacted] and [redacted] in the years after we lost [redacted]. We moved our whole family away from [redacted] and to a new home. We've been through sick kids, trips to the emergency room, report cards, job changes, temper tantrums, driving lessons and a lot of hugs, kisses and tears. We lived through one day, and then another, and then the next one after that. We will make it through tomorrow. And next week, we will make it through the tenth anniversary of her death. And then the day after that.

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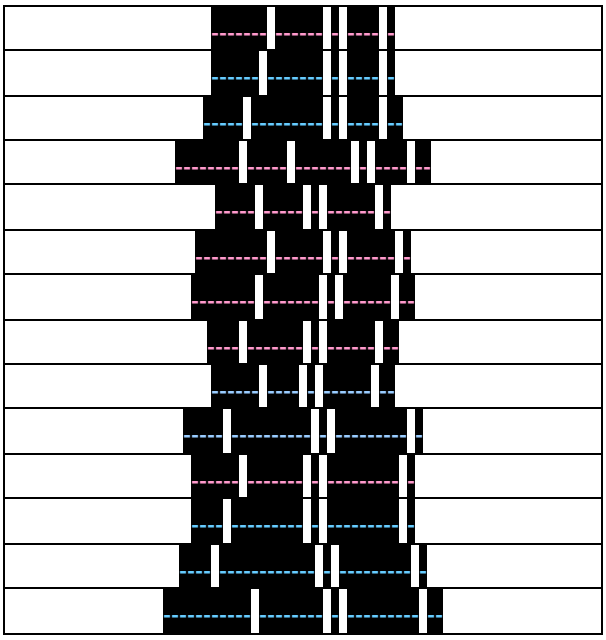
- Coordinate the efforts of our members and answer any questions they may have;
- Act as the liaison with NORD to ensure that the money raised money is earmarked for the ACD research account;
- Arrange for our international families to participate;
- Research the establishment of an on-line site at www.firstgiving.com;
- Collect all the donations and forward them to NORD;
- Coordinate with NORD to obtain receipts for tax purposes; and
- Track the amount of donations.

So, if you are interested in spearheading this effort, please let us know. As we kick off the letter writing campaign, we hope that all of you will participate. So, watch for more details to come so you can help the ACDA raise money to find a cause and cure for ACD.

Memorial Garden

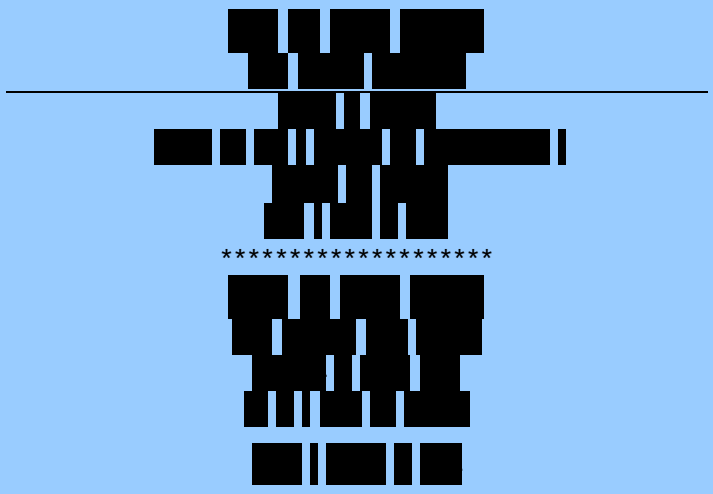
We are dedicated to remembering the birth dates of our member's babies who are not here to share our lives. Please pause to remember them.

Please let us know if we have inadvertently omitted your baby's name or if you do not wish to have your baby's name included in this section. You can email us at sdesj@verizon.net.

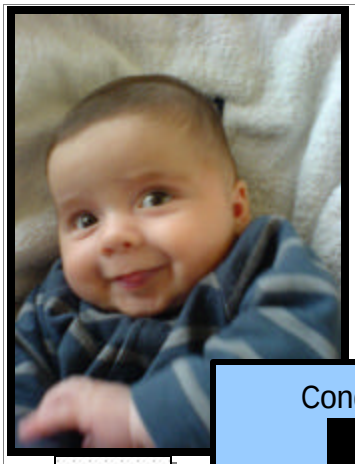


Meet our New ACDA Families

It is with mixed emotions that we introduce two new families that have contacted the ACDA since the last newsletter. Please take the time to introduce yourself, offer support and share the story of your child (children).



Safe Arrivals



[redacted]

Congratulations to the [redacted] family in [redacted] on the arrival of [redacted]!
Born on [redacted]

Congratulations to the [redacted] Family of [redacted] on the arrival of [redacted]!
Born on [redacted]

Congratulations to the [redacted] family of [redacted] on the arrival of daughter, [redacted]!
[redacted]

What's in a Name?

Thanks to [redacted] and [redacted] for sharing this story about their family!

"Shortly after the birth of our first child in June of 2003, before any problem was detected, we named him [redacted]. Then, the nightmares began and he was soon transported to [redacted] Children's Hospital where he later died at only 20 days old. Sometime between hearing of his fatal condition and the weeks following, we realized that our names went in alphabetical order – [redacted]. So, we decided that we would continue to follow the order. In September of 2004, we gave birth to a beautiful, healthy girl named [redacted], and we are now expecting another girl in October, and we will choose a name starting with the letter [redacted]. We know that [redacted] will always be a part of our family, with or without an order in names, but this helps us remember him as our lives continue. And despite the future we face, every child we have will always have a "special" spot in our family. "

******* ANNOUNCEMENTS *******

- As of June 22, 2006, the balance of the ACD Restricted Research Account at NORD was $11,355. Thank you to everyone that has contributed!
- [redacted] recently reported year-to-date donations of $1,280 to the ACD Research Fund at NORD. This amount includes sales of their cookbook, "*Recipes from the Heart*," The [redacted] fundraiser and miscellaneous private donations in memory of their daughter, [redacted].

LEARNING SERIES – Part 2

This is part 2 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 a more detailed understanding of genetics that will provide the background understanding for the discussions of hereditary transmission modes (ways that ACD could be passed from parents to child) that will be covered in the next newsletter. It also provides information about the relationships between genes and proteins to aid in understanding the "bigger picture" of the investigation into proteins that is being conducted at the Baylor College of Medicine.

NOTE: This article is about genetics. 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.

How does this article relate to the research at Baylor?

If you recall from the last Newsletter, the focus of the Baylor research under the NORD research grant is to look for differences in proteins in ACD lung tissue samples compared to "normal" lung tissue. Any observed differences in proteins between the samples could point toward a gene sequence or gene region that is likely to be responsible for ACD (this article provides some information about the relationship between genes and proteins). Finding a gene sequence or region from the protein investigation would narrow the search region(s) for the gene(s) involved with ACD and provide sharper focus for future research. Once the gene(s) is identified, then the blood samples provided by ACDA members can be reviewed to look for genetic (hereditary) links for the disease. If none are found, the focus may switch to investigating what environmental factors could logically explain the variations in the genes and therefore proteins.

Introduction

Human diseases are based on defects in single genes, like cystic fibrosis; alterations in multiple genes, like cancer; or attacks on the body's immune system, which disrupt the proper functioning of the genetic mechanism, as in multiple sclerosis. Even when a disease is triggered by environmental or behavioral factors, genes are harmed as a consequence of the exposure. Every bit of human biology, every bit of human disease is tied to genes being on or off. [1] Human disease and genetics are inseparable. All human disease ultimately is genetic, and all of the information about human health and disease resides in the complete set of genes, known as a genome.

The next sections are from the Human Genome Project website. [2] Their website is very broad and deep and we have tried to summarize the information in a kind of a Biology 101 review that we think might be of interest and provide a basic understanding some of the terms used in genetic research. It also provides a summary of the genome and provides some insight into the size and construction of the genome.

Definitions (*courtesy of the Howard Hughes Medical Institute)*

The cell nucleus Inside the cell nucleus, 6 feet of DNA are packaged in 23 pairs of chromosomes. One chromosome in each pair comes from each parent.

A chromosome Each of the 46 human chromosomes contains the DNA for thousands of individual genes, the units of heredity.

A gene Each gene is a segment of double-stranded DNA that holds the recipe for making a specific molecule, usually a protein. These recipes are spelled out in varying sequences of the four nucleotide bases in DNA: adenine (A), thymine (T), guanine (G) and cytosine (C). The bases form interlocking pairs that can fit together in only one way: A pairs with T; G pairs with C.

A protein Proteins, which are made up of amino acids, are the body's workhorses -- essential components of all organs and chemical activities. Their function depends on their shapes, which are determined by the 100,000 or more genes that reside in the cell nucleus.

The Human Genome Project

The Human Genome Project originally began in 1990 as a 15-year effort coordinated by the U.S. Department of Energy and the National Institutes of Health. Due to rapid technological advances the project was completed 2 years early in 2003. Some of the key goals were to:

- *identify* all the approximately 20,000-25,000 genes in human DNA,
- *determine* the sequences of the 3 billion chemical base pairs that make up human DNA,
- *store* this information in databases,
- *improve* tools for data analysis,

What's a genome? And why is it important?

- A **genome** is all the DNA in an organism, including its genes. Genes carry information for making all the proteins required by all organisms. These proteins determine, among other things, how the organism looks, how well its body metabolizes food or fights infection, and sometimes even how it behaves.
- DNA is made up of four similar chemicals (called bases and abbreviated A for **Adenine**, T for **Thymine**, C for **Cytosine**, and G for **Guanine**) that are repeated millions or billions of times throughout a genome. The human genome, for example, has 3 billion pairs of bases.
- The particular order of As, Ts, Cs, and Gs is extremely important. The order underlies all of life's diversity, even dictating whether an organism is human or another species such as yeast, rice, or fruit fly, all of which have their own genomes and are themselves the focus of genome projects. Because all organisms are related through similarities in DNA sequences, insights gained from nonhuman genomes often lead to new knowledge about human biology

What Does the Draft Human Genome Sequence Tell Us?

By the Numbers

- The human genome contains 3164.7 million chemical nucleotide bases (A, C, T, and G).
- The average gene consists of 3000 bases, but sizes vary greatly, with the largest known human gene being dystrophin at 2.4 million bases.
- The total number of genes is estimated at 30,000 —much lower than previous estimates of 80,000 to 140,000 that had been based on extrapolations from gene-rich areas as opposed to a composite of gene-rich and gene-poor areas.
- Almost all (99.9%) nucleotide bases are exactly the same in all people.
- The functions are unknown for over 50% of discovered genes.

The Wheat from the Chaff

- Less than 2% of the genome codes for proteins.
- Repeated sequences that do not code for proteins ("junk DNA") make up at least 50% of the human genome.
- Repetitive sequences are thought to have no direct functions, but they shed light on chromosome structure and dynamics. Over time, these repeats reshape the genome by rearranging it, creating entirely new genes, and modifying and reshuffling existing genes.
- During the past 50 million years, a dramatic decrease seems to have occurred in the rate of accumulation of repeats in the human genome.

How It's Arranged

- The human genome's gene-dense "urban centers" are predominantly composed of the DNA building blocks G and C.
- In contrast, the gene-poor "deserts" are rich in the DNA building blocks A and T. GC- and AT-rich regions usually can be seen through a microscope as light and dark bands on chromosomes.
- Genes appear to be concentrated in random areas along the genome, with vast expanses of noncoding DNA between.
- Stretches of up to 30,000 C and G bases repeating over and over often occur adjacent to gene-rich areas, forming a barrier between the genes and the "junk DNA." These CpG islands are believed to help regulate gene activity.
- Chromosome 1 has the most genes (2968), and the Y chromosome has the fewest (231).

Variations and Mutations

- Scientists have identified about 1.4 million locations where single-base DNA differences (SNPs) occur in humans. This information promises to revolutionize the processes of finding chromosomal locations for disease-associated sequences and tracing human history.
- The ratio of germline (sperm or egg cell) mutations is 2:1 in males vs. females. Researchers point to several reasons for the higher mutation rate in the male germline, including the greater number of cell divisions required for sperm formation than for eggs.

So despite all the knowledge gained through the Human Genome Project, there is still a tremendous amount of unknown information which makes genetic research very challenging. Deriving meaningful knowledge from DNA sequence will define biological research through the coming decades and require the expertise and creativity of teams of biologists, chemists, engineers, and computational scientists, among others. A sampling follows of some research challenges in genetics--what we still won't know, even with the full human sequence in hand.

- Gene number, exact locations, and functions
- Gene regulation
- DNA sequence organization
- Chromosomal structure and organization
- Noncoding DNA types, amount, distribution, information content, and functions
- Coordination of gene expression, protein synthesis, and post-translational events
- Interaction of proteins in complex molecular machines
- Predicted vs. experimentally determined gene function
- Evolutionary conservation among organisms
- Protein conservation (structure and function)
- Proteomes (total protein content and function) in organisms
- Correlation of SNPs (single-base DNA variations among individuals) with health and disease
- Disease-susceptibility prediction based on gene sequence variation
- Genes involved in complex traits and multigene diseases
- Complex systems biology including microbial consortia useful for environmental restoration
- Developmental genetics, genomics

Even though a lot is known about this enormously complex system called the genome, as noted above there is still a lot that will require additional research. This is not surprising when you consider the following for perspective:[3]

The human genome (3,000,000,000) bases of DNA, split into 24 chromosomes. This information…

- would fill a stack of paperback books 200 ft (61 m) high
- would fill two hundred 500-page telephone directories
- would take a century to recite, if we recited at one letter per second for 24 hours a day
- if spread out 1 mm apart, would extend 3000 km (1864 miles) or about 7000 times the height of the Empire State Building.

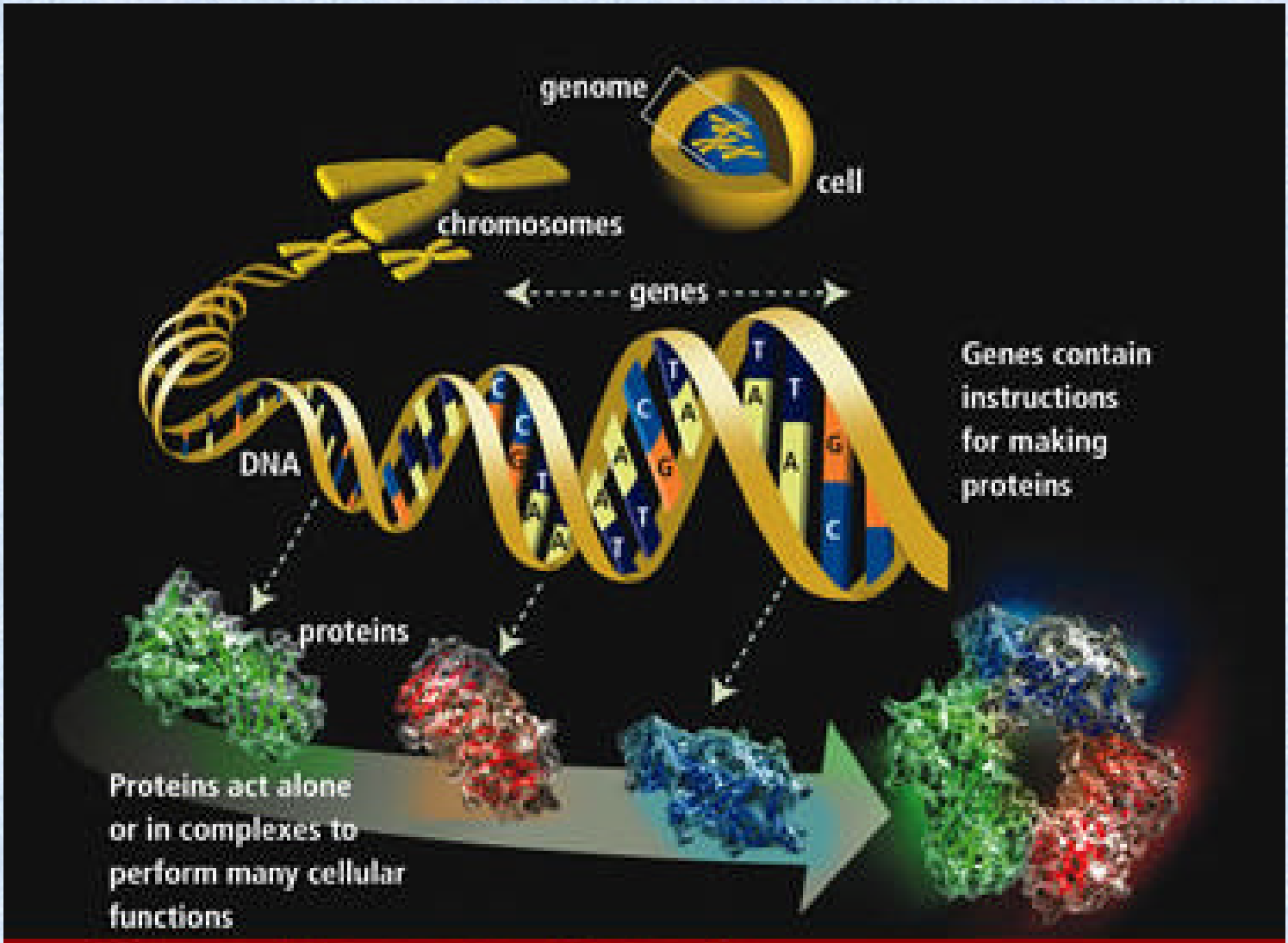
Human cells

- The human body is made up of 100 trillion cells. Each cell has at least one nucleus, which houses the chromosomes.
- There is 1.8 meter (6 foot) of DNA in each of our cells packed into a structure only 0.0001 cm (.00004 inch) across (it would easily fit on the head of a pin).
- If all the DNA in the 100 trillion cells of the human body was put end to end it would reach to the sun and back over 600 times
- Most human cells contain 46 chromosomes: pairs of chromosomes 1-22, and a pair of sex chromosomes (females have two Xs; males an X and a Y). Sperm and eggs contain one of each chromosome.

Genes and variation

- Housed along each chromosome is a selection of genes. The human genome contains about 20 000-25 000 genes.
- Between humans, our DNA differs by only 0.2 per cent, or 1 in 500 base (letters). (This takes into account that human cells have two copies of the genome.)

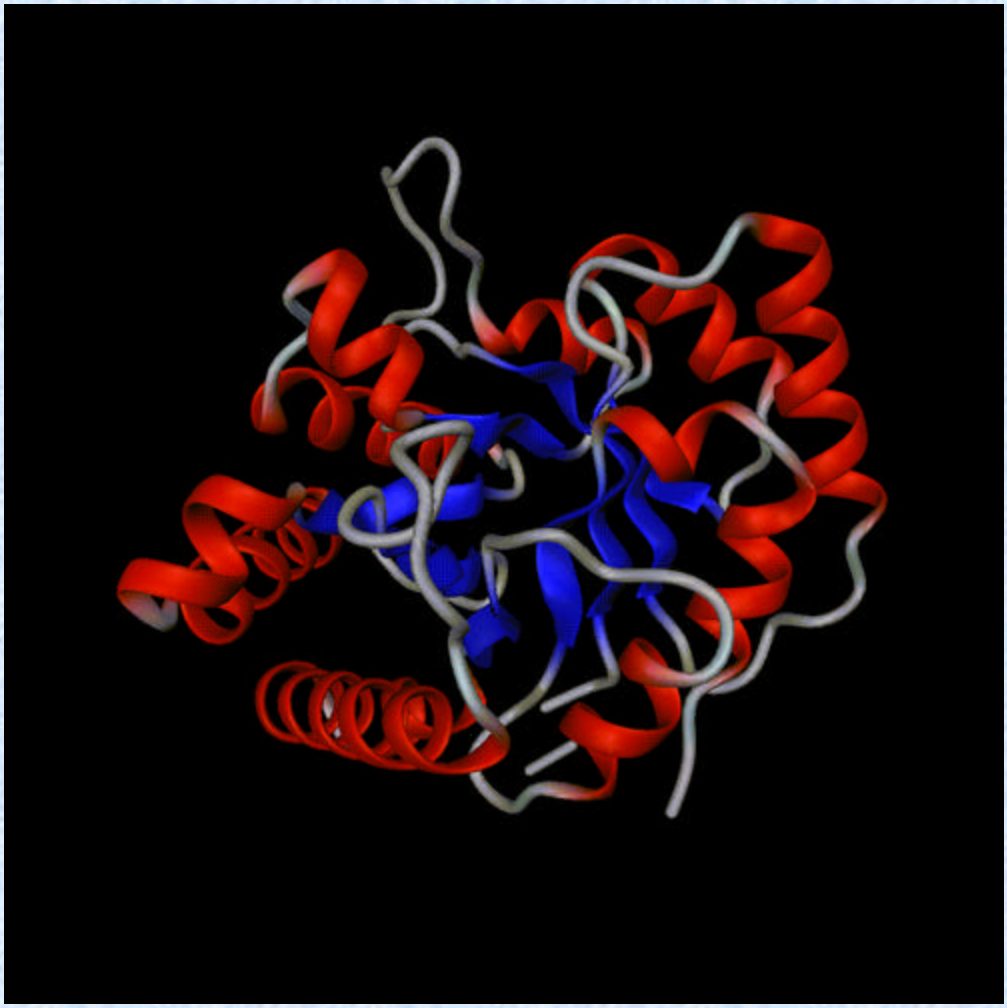
The figure [2] on the next page provides a visual reference of the components that are discussed in more detail below.



From Genes to Proteins

Explanation of the figure: All living organism are composed of many, many cells (illustrated as the sphere in the top center of the figure). Inside each of these cells are 23 pairs of chromosomes (each pair consists of one chromosome inherited from the Mother and one from the Father). The chromosomes are represented by the "X" shapes in the figure. In turn, each chromosome is made up of chains of DNA, which is a double helix shape as shown in the figure. The DNA strands for each chromosome can consist of about 50 million to 250 million base pairs. The base pairs that make up each DNA strand can be thought of as links between each helix. There are only four types of "links" A, C, G and T and their unique sequence is what defines each organism (whether a human, fly or bacteria). Genes are specific sequences of bases that provide the instructions for making proteins that control many functions of the cells.

Although genes get a lot of attention, it's the **proteins** that perform most life functions and even make up the majority of cellular structures. Proteins are large, complex molecules made up of smaller subunits called amino acids. Chemical properties that distinguish the 20 different amino acids cause the protein chains to fold up into specific three-dimensional structures that define their particular functions in the cell. Here is a "cartoon" representation of a folded protein to help visualize how complex the three dimensional folded shapes are.



The constellation of all proteins in a cell is called its **proteome**. Unlike the relatively unchanging genome, the dynamic proteome changes from minute to minute in response to tens of thousands of intra- and extracellular environmental signals. A protein's chemistry and behavior are specified by the gene sequence and by the number and identities of other proteins made in the same cell at the same time and with which it associates and reacts. Studies to explore protein structure and activities, known as proteomics, will be the focus of much research for decades to come and will help elucidate the molecular basis of health and disease.

References:

1. http://www.swmed.edu/home_pages/publish/magazine/HumanGenome/GeneResearch.html
2. http://www.ornl.gov/sci/techresources/Human_Genome/project/about.shtml
3. http://genome.wellcome.ac.uk/doc_WTD020745.html