



## "Junk DNA" That's Not Junk

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*This event in the vertebrates that created the ultra conserved elements in the birth of the vertebrate lineages was a **unique event**. ...It cannot be a coincidence that there have been so few changes in these (vertebrate 481 'junk DNA') elements over this enormous span of half a billion years. It's got to be that they are functionally important."* David Haussler, Ph.D., UC-Santa Cruz

**June 25, 2005 Santa Cruz, California** - A biomolecular engineer at the University of California in Santa Cruz was published in a recent *Science* journal stating his lab has found 481 genetic sequences that are the same in all vertebrates from humans to rats and are so important they have not changed in nearly half a billion years. But until now, those genes were considered "junk DNA."

Amazingly, 95% of the genome in all vertebrate animals - from humans to rats - is considered junk DNA. The traditional meaning of junk DNA are genes that do not code for making proteins. But another meaning might be there are a lot of genes that no one understands exactly what they do.

Now, Professor David Haussler, Professor of Biomolecular Engineering at the Howard Hughes Medical Institute, University of California - Santa Cruz, and his research team have discovered 481 previously categorized junk DNA elements which are identical in humans, rats and mice. That means those DNA elements have not changed over the past half billion years.

### Interview:

**David Haussler, Ph.D., Prof. of Biomolecular Engineering, Howard Hughes Medical Institute Investigator, University of California-Santa Cruz:** "This is actually turning out to be specific to vertebrates, which is a very small branch of life on this planet. It's an important branch because it includes us humans, all mammals, birds, fish. There are an enormous number of different species under the classification of vertebrates. But they all share a common ancestor perhaps half a billion or more, maybe 600 to 700 million years ago.

THAT IMPLIES THAT IF THIS GENOME CODE IS A COMMON DENOMINATOR TO ALL OF THESE VERTEBRATES OVER SUCH A LONG PERIOD OF TIME THAT THIS COULD NOT BE JUNK DNA? THERE HAS TO BE SOMETHING VITAL ABOUT IT?

We feel that is true. It cannot be a coincidence that there have been so few changes in these elements over this enormous span of half a billion years. It's got to be that they are functionally important.

But these are a very special subset of the junk DNA that seem to have some other important functions in these elements. We located 481 of these special elements that we call 'ultra conserved elements' in the genome.

MEANING FOR SO LONG?

Yes, the ultra conserved means they were unchanged in mammals for at least 100 million years. Then we subsequently looked to see how they changed in birds and in fish and we found that they were remarkably conserved as well between those more distant (from humans) species."

## Vertebrates

### Types of Vertebrates



**Left to right:** Amphibians, Birds, Reptiles, Dolphins and Whales, Seals.



**Left to right:** Fish, Mammals, Marsupials, Primates and Rodents.

**University of California-Berkeley Museum of Paleontology:** "Vertebrates are animals with an internal skeleton made of bone. Although vertebrates represent only a very small percentage of all animals, their size and mobility often allow them to dominate their environment. We humans coexist with many other vertebrates and are often quite aware of them in our environment. We also have many biological, social, cultural and historical ties with vertebrates. We have domesticated dogs, cats, and birds, and have used horses as a means of transportation. We have used carrier pigeons as a means of communicating over long distances. We also use many products from cows, like milk and leather.

"Vertebrates have a long history on this earth -- more than 500 million years, from the late Cambrian up to today. These first vertebrates lacked jaws, like the living hagfish and lampreys. Jawed vertebrates appeared 100 million years later, in the Silurian.

"Some have argued that many of the characters that describe vertebrates have been derived from the same set of cells, the neural crest cells. These cells appear early in development, and **only** vertebrates have them. From neural crest cells are derived the skull and jaw bones."

"IS IT TRUE, AS THE BBC QUOTED YOU, THAT YOU SAID, 'THIS ABSOLUTELY KNOCKS ME OFF MY CHAIR!'

That's true, yes. (laughs) It is an expression, so I didn't physically fall off my chair. But I was floored when my post-doc produced 481 of these sequences that were completely unchanged between human, mouse and rat, which were the three completely sequenced genomes that we had available at the time when we first did this study.

## What Do These Ultra Conserved Genes Do?

ANY HYPOTHESIS YET ABOUT WHAT THE FUNCTION IS OVER HALF A BILLION YEARS?

What we have found is that the ones we have looked at are actually controlling the function, the expression, of nearby genes. They are turning on genes that are in the neighborhood. But what is shocking about this is what we mean by 'in the neighborhood.' If you look, for most species there are these elements outside of the protein-coding region, these regulatory elements in the DNA which turn on or turn off the gene. They are usually very close to the start of the gene. But these ultra conserved elements can be up to a million base pairs away from the start of a gene that they regulate. There have been only a few examples of this in the literature that have been fully documented for conserved elements. We suspect that these ultra conserved elements will provide a large new set of such examples. And the ones we have tested so far have proven to be just that: they are very precise. They exhibit a very precise control over the gene that they regulate.

WHAT ARE THEY TURNING ON?

The genes we first noted in the *Science* journal paper that these ultra conserved elements were not randomly distributed throughout the human genome. In fact, they tend to form clusters and these clusters often surrounds a very important gene that's involved in the embryonic development of the body essentially. So during the very early stages of human or mammalian or any vertebrate development, certain genes come on at particular times to control the differentiation of the cells into the different organs and to guide the body as it takes shape. These are really critical families of genes. Their technical name is homeobox

genes. We have whole varieties of homeobox genes in our genome and other related types of what are called transcription factors which operate during development to turn on specific genes at specific times.

You have to know when and where you are going to turn on a gene that's going to make an arm. Or after you make an arm, when you make a digit. A whole brain is built on the careful orchestration of these genes as they get turned on during development. It was just these kinds of important developmental genes that we found these ultra conserved elements nearby. We have been looking at a few of these and verifying that they do in fact control the expression of the nearby developmental genes.

FROM A MICROBIOLOGY GENETIC POINT OF VIEW, WHY WOULD THOSE BE THE GENES THAT ONCE WERE CLASSIFIED AS JUNK LAST FOR NEARLY HALF A BILLION YEARS? WHY WOULD THEY BE SO ULTRA CONSERVED?

That is the \$100 question at this point. We cannot answer that definitively and our lab and other labs are working furiously to really try to answer why these segments of DNA are so conserved as compared to the other segments of DNA. They are even more conserved than the protein-coding segments that are the more typical object of study in molecular biology.

DOES THAT MEAN THAT THESE GENES YOU HAVE BEEN STUDYING HAVE SOME KIND OF IMMUNITY TO COSMIC RAYS AND RADIATION AND OTHER THINGS THAT MIGHT CAUSE MUTATIONS?

We don't think so. It seems like there is some recent evidence that they don't necessarily accumulate mutations any slower. But what happens is once if you start with a mutation it does not become fixed in the population.

IF WE HAVE 3 BILLION GENES, OR LETTERS, THAT MAKE UP A HUMAN BODY, HOW MANY OF THOSE 3 BILLION HAVE BEEN CONSIDERED JUNK DNA TRADITIONALLY? AND NOW WHAT HAS CHANGED IN THAT NUMBER?

Only 1.5% of the human genome is DNA that codes for a protein. It's a remarkably small fraction. And that is very unique. Other mammals are similar, but if you look at very simple organisms like the 1-celled yeast cell, then an enormous fraction of the DNA makes protein. And in many bacteria, even simpler organisms, the vast majority of the DNA has the job of making a protein. But in species such as humans, it's only a tiny part of the DNA that makes protein. 98%, more than 98% of the genome, does not make protein.

Now, the ultra conserved elements are only a tiny additional fraction of the genome because there are so few of them. We looked carefully at a broader class of elements that are not ultra conserved elements, but elements that look like they are changing slower than you would expect in neutral evolution. So, they are probably under some sort of Darwinian selection. And that broader class of elements accounts for 5% of the human genome, which for some people still seems remarkably small! That would leave potentially still 95% of the human genome as 'junk DNA.'

## What Could the Other 95% of the Vertebrate Genome Be Doing?

IF THE CURRENT GENOME SEQUENCE IS 3 BILLION LETTERS OF WHICH ONLY 5% ARE REALLY IMPORTANT IN CREATING A HUMAN BEING OR RAT OR MOUSE OR OTHER VERTEBRATES THEN DOES THAT MEAN THE WORD FOR HUMAN COULD BE REDUCED TO 5% OF 3 BILLION?

There is a difference between the letter not being important. Maybe some things are important just as spacers. You have to have a certain amount of space between Important Element 1 and Important Element 2 maybe there have to be several thousand bases. It doesn't matter what those are. We would call those thousand bases 'junk.' But if you deleted them, you might be in trouble because the space is missing between the two important elements that flank them is wrecked. So, I don't want to speculate that you could just take it out and you'd be fine. That's not what we are saying.

BUT JUNK DNA IS A LITTLE BIT EQUIVALENT TO THE COSMIC PHYSICIST WHO SAID THAT MOST OF THE UNIVERSE IS DARK ENERGY AND DARK MATTER AND THEY DON'T UNDERSTAND WHAT THAT IS EITHER. BUT OBVIOUSLY, IT IS IMPORTANT. AND HERE WE'VE GOT 95% OF THE HUMAN GENE SEQUENCING, OR VERTEBRATE SEQUENCING, IS NOT UNDERSTOOD AND WE CALL IT 'JUNK,' BUT COULD BE ABSOLUTELY VITAL TO THE OTHER 5%.

That's true. Actually this 'junk' DNA has been referred to as 'Dark Matter' more than once at a meeting. So you actually have anticipated something there in your comment. I've heard many a speaker say, 'Let's look at what has been called the Dark Matter in the human genome.' It is analogous.

BUT YOU COULD SAY THAT YOUR WORK IS AT LEAST SHOWING MORE TIP OF AN ICEBERG THAT WASN'T RECOGNIZED BEFORE?

Absolutely. What our work shows is that there is more inside the junk DNA than you would have expected. There are unexplored frontiers. There is no doubt about it. We have much more to learn about molecular biology, about how cells work, about how life works. We have an enormous amount left to learn. But that is different than saying that eventually we'll find that every one of the 3 billion bases is critically important in the human genome.

## Do Non-Vertebrates Have Any Similarly Ultra Conserved "Junk DNA?"

We think they probably do. It's not going to be exactly the same kind of thing. We've looked around the genes involved in the development of the body plan in flies and worms and we see different kind of elements. We don't see the same kind of ultra conserved elements that we see in the vertebrates. There are certainly highly conserved regulatory elements. But in terms of their sequence, they look completely different. And so, we have a suspicion that *this event in the vertebrates that created the ultra conserved elements in the birth of the vertebrate lineages was a unique event.*

There might have been an analogous event in flies and worms to create their regulatory systems, but we think those two systems, the vertebrates and those of flies, worms and so on, evolved independently."

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### More Information:

On June 9, 2005, the National Institutes of Health's (NIH) Mental Health and Research Resources divisions reported the following:

#### **"Rodent Social Behavior Encoded in Junk DNA**

A discovery that may someday help to explain human social behavior and disorders such as autism has been made in a species of pudgy rodents by researchers funded, in part, by the National Institutes of Health's (NIH) National Institute of Mental Health (NIMH) and National Center for Research Resources (NCRR).

The researchers traced social behavior traits, such as monogamy, to seeming glitches in DNA that determines when and where a gene turns on. The length of these repeating sequences - once dismissed as mere junk DNA - in the gene that codes for a key hormone receptor determined male-female relations and parenting behaviors in a species of voles. Drs. Larry Young and Elizabeth Hammock, Emory University, report on their findings in the mouse-like animals native to the American Midwest in the June 10, 2005 *Science*.

The discovery is the latest in a two decades-old scientific quest for the neural basis of familial behavior begun at the NIMH Intramural Research Program in the mid 1980s by now NIMH director Thomas Insel, M.D. By 1993, his team had discovered that the distribution of brain receptors that bind to the hormone vasopressin differed dramatically between monogamous and polygamous vole species and accounted for their divergent lifestyles. Yet, how such behavioral differences could have evolved in animals that otherwise appear almost identical remained a mystery.

"This research appears to have found one of those hotspots in the genome where small differences can have large functional impact," explained Insel. "The Emory researchers found individual differences not in a protein-coding region, but in an area that determines a gene's expression in the brain. This is an extraordinary example of research linking gene variation to brain receptors to behavior."

Hammock and Young were particularly intrigued with microsatellites, repeating sequences of letters in the genetic code peppered throughout these regulatory areas of the vasopressin receptor gene. "It was considered junk DNA because it didn't seem to have any function," noted Hammock. Each animal species has its own signature microsatellites; for example, the repeating letter sequences are much longer in monogamous than in polygamous vole species. But even within a species,

there are differences in the number of letters in the sequence among individuals.

The researchers first showed in cell cultures that the vole vasopressin receptor microsatellites could modify gene expression. Next, they bred two strains of a monogamous species, the prairie vole - one with a long version of the microsatellites and the other with a short version. Adult male offspring with the long version had more vasopressin receptors in brain areas involved in social behavior and parenting (olfactory bulb and lateral septum). They also checked out female odors and greeted strangers more readily and were more apt to form pair bonds and nurture their young.

"If you think of brain circuits as locked rooms, the vasopressin receptor as a lock on the door, and vasopressin as the key that fits it, only those circuits that have the receptors can be 'opened' or influenced by the hormone," added Hammock. "An animal's response to vasopressin thus depends upon which rooms have the locks and our research shows that the distribution of the receptors is determined by the length of the microsatellites."

Prairie voles with the long version have more receptors in circuits for social recognition, so release of vasopressin during social encounters facilitates social behavior. If such familial traits are adaptive in a given environment, they are passed along to future generations through natural selection.

Variability in vasopressin receptor microsatellite length could help account for differences in normal human personality traits, such as shyness, and perhaps influence disorders of sociability like autism and social anxiety disorders, suggest the researchers. The Emory researchers have found that the bonobo, an ape noted for its empathic traits, unlike its relative the chimpanzee, has a microsatellite with a sequence similar to that of humans. Two studies have found modest associations between alterations in this microsatellite and autism in some families. As subgroups of autism spectrum disorders are characterized, a stronger connection may emerge.

*Far from being junk*, the repetitive DNA sequences ... may ultimately exert their influence through complex interactions with other genes to produce individual differences and social diversity, according to Young."

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## Website:

UC-SC Reconstructing Ancestral Genome: <http://www.cbse.ucsc.edu/news/newsarchive05.shtml#ancestor>

## Credits

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