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Testimony before the House Labor, Health and Human Services and Education Subcommittee of Appropriations

By
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And

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On behalf of
the International Rett Syndrome Association (IRSA)

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Testimony of Mr. Clint Black
Before the House Labor, Health and Human Services and Education
Subcommittee of Appropriations
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Mr. Chairman, Mr. Hoyer and members of the Committee, thank you for this opportunity.

My name is Kevin Black. Like my brothers, Brian and Clint Black, I have performed in front of lots of people but never to a group of people that could have so much impact on so many lives.

My brother, Clint Black, wrote and recorded a hit song called "Put Yourself in my Shoes. That is what I'm hoping that you will do here today for me… for us.

My wife and I had the same dreams of having a normal healthy family as everyone does. Those dreams came to an end when my daughter, Cortney, was diagnosed with Rett Syndrome at the age of 15 months. By the time she reached the age of 2 years, all of her social and motor skills also came to an end. They regressed back to a stage of infancy where she lived out the rest of her 14 years. She died at the age of 16 due to complications of Rett Syndrome.

In all those years I never really knew if Cortney understood me when I said 'I love you, Cortney.' We were not prepared for the confusion, the anger, and the guilt that comes with this devastating disorder. Our decision to have more children when Cortney was young was a very difficult one. Due to the many challenges we all faced, our two boys never really had a normal childhood, either.

It is my enduring love for Cortney that brings me here today. I beg you to please consider increasing funding to the National Institutes of Health for research on Rett syndrome. It is the only way to help us find a cure for the many thousands of girls who are suffering like my Cortney did for 16 years.

I know people walk through those doors every day asking for your help and I'm no different. We have found the cause of Rett syndrome, and now we need to find the treatment and cure.

Thank you for your time and your consideration. God Bless you and God bless America.

Testimony of Dr. Alan Percy
Before the House Labor, Health and Human Services
Subcommittee of Appropriations
March 29, 2006

Chairman Regula, Mr. Hoyer and members of the Committee, thank you for allowing me to be here today and follow Mr. Black's moving testimony. My name is Dr. Alan Percy. I am the Scientific Director of the International Rett Syndrome Association (IRSA) and Professor of Pediatrics and Neurology at the University of Alabama at Birmingham. Four years ago I appeared before you with Ms. Julia Roberts to testify about research into the causes and therapies for Rett syndrome.

Since the discovery nearly seven years ago of mutations in the *MECP2* gene as the basis for Rett syndrome, we understand much more about its clinical and fundamental scientific aspects. In the process, we have improved the lives of individuals and families affected by this devastating disorder. Once thought to be restricted to girls and women, by learning more about this gene, we are now identifying boys with mutations in *MECP2*. They have a much more severe disorder with little resemblance to Rett syndrome. It is crucial that we understand their disorder as well. In many ways, *MECP2* and Rett syndrome represent a Rosetta stone, holding the key to other disorders including autism and schizophrenia.

In the past five years, crucial NIH funding has allowed development of animal models to accelerate progress in understanding the basic brain mechanisms underlying Rett syndrome and ultimately lead to effective therapies. At the same time, funding through the NIH Office of Rare Diseases and the National Center for Research Resources has established a clinical research consortium to develop natural history data on Rett syndrome, laying the groundwork for clinical trials emerging from these basic studies.

I am here today to ask that you continue to support the progress we are making in Rett syndrome Awareness AND Research by funding Mr. Hoyer's request of $300,000 for the International Rett syndrome Association (IRSA) in order to raise awareness of Rett syndrome among physicians, educators, clinicians and parents.

We also ask that you continue your very valued funding of the NIH and your direction to them to continue funding research related to Rett syndrome.

At IRSA our motto is "Care Today, Cure Tomorrow." By granting these requests, you can help us do just that. Thank you for this time.

Rett Syndrome: Rosetta Stone of Neurologic Disorders

Rett Syndrome (RS), a neurological orphan disease of children that was long relegated to obscure articles and the fervent concern of parents, might soon be adopted into a family of higher-profile neurologic disorders. This change from medical oddity to the focus of avid researchers reflects the exciting discovery of genetic similarities between RS and disorders as disparate as autism and schizophrenia. And if this early promise holds true, RS will no longer be a medical trivia question. Rather, it could become a medical Rosetta Stone for translating a tangle of genetic and biochemical evidence into a real understanding of some terrible neurological conditions. That ancient slab of writing, found in the Nile delta area in 1799, was inscribed in multiple languages--Egyptian hieroglyphics, a simpler form of Egyptian writing, and Greek. By comparing how the same messages were written in these different languages, a French scholar was able to decode the language of hieroglyphics by 1822. This monumental breakthrough in understanding an important age in ancient history occurred because the Rosetta stone shed light on the similarities between known and unknown languages. Likewise, medical scholars are now decoding the mysteries of certain brain disorders by comparing them to RS.

RS seems to be a classic example of a “chromatin disease,” a general term for a specific mutation that cripples the ability of cells to control the activity of a variety of genes. Chromatin is the “storage” form of DNA inside the nucleus of a cell. This highly condensed form of DNA lets the enormous lengths of chromosomes remain tightly packed; but it permits specific genes to be accessed and activated when the cell needs them to perform their assigned tasks. In chromatin, the long chains of DNA making up the chromosomes are wrapped around proteins called histones. This reduces the space the DNA takes up, while leaving genes available for duty in the cell. This is like a twenty-foot length of thread being wrapped around a spool, greatly reducing the space it takes up, even while leaving it available to make or repair clothes. (In the case of histones, however, the continuous length of DNA is wrapped around a series of histone proteins rather than around just one; this keeps DNA from being bunched up on a single “spool” and allows access to many genes at once.)

Chromatin disorders are attracting increased attention because of their direct link to a variety of disorders, ranging from mental illness to cancer. And RS stands at the center of the growing excitement over chromatin diseases. As investigators peel away the layers of molecular mysteries around RS, they are uncovering evidence that may help them treat other neurologic diseases.
Indeed, investigators are now hot on the trail of a cure for the blood cancer promyelocytic leukemia, based on their understanding of chromatin disorders.

The Long and Winding Road of Rett Syndrome

Clearly, RS has come a long way from the day Dr. Andreas Rett first became aware that he had some very special patients.

In 1954, Dr. Rett, a Viennese physician, first noticed this syndrome in two girls as they sat in his waiting room with their mothers. He observed these children making the same repetitive hand-washing motions. Curious, he compared their clinical and developmental histories and discovered they were very similar.

Dr. Rett checked with his nurse and learned that he had six other girls with similar behavior in his practice. Surely, he thought, all these girls must have the same disorder. Not content with

studying his own patients, Dr. Rett made a film of these girls and traveled throughout Europe seeking other children with these symptoms.

Meanwhile, in 1960, young female patients in Sweden with quite similar symptoms caught the eye of their own physician, Dr. Bengt Hagberg. Dr. Hagberg collected the records of these girls and put them aside, intending to return to them when he had more time to study this curious phenomenon.

Then, in 1966, Dr. Rett published his findings in several German medical journals, which, however well-known in that part of the world, were hardly mainstream reading for much of the rest of the world's medical community. Even after Dr. Rett published a description of the disease in English in 1977, RS remained in the backwaters of medical concern: The pre-internet world lacked the electronic information highways taken for granted in the 21st Century.

But in 1983 an article on RS appeared in the mainstream, English-language journal, *Annals of Neurology*. Written by none other than Dr. Hagberg and his colleagues, the report finally raised the profile of RS and put it on the radar screen of many more investigators. This article was a breakthrough in communicating details of the disease to a wide audience, and the authors honored its pioneering researcher by naming it Rett syndrome.

As investigators continued to chip away at the shell of mystery surrounding RS, increased research funding ensured that the work would continue. A team of scientists from Baylor University (Houston, TX) and Stanford University (Palo Alto, CA), toiled in the labs and clinics trying to pinpoint the cause of RS.

A major breakthrough occurred in 1999, when a research fellow at Baylor named Ruthie Amir discovered *MECP2*, the gene that, when mutated, causes RS. The discovery of the gene, located at the Xq28 site on the X chromosome was a triumph for the Baylor team, led by Huda Y. Zoghbi, MD, a professor in the departments of pediatrics, neurology, neuroscience, and molecular human genetics at the Howard Hughes Medical Institute. (Dr. Zoghbi's multiple department affiliations reflect the need to bring to bear the knowledge of a variety of specialties to solve the mysteries of RS.)

This discovery of the gene also vindicated the investment in Dr. Amir made by IRSA, which funded her position. Although the IRSA grant was small by the standards of other funders, such the National Institutes of Health and the Howard Hughes Medical Institute, the fact that IRSA money supported the scientist most directly involved in finding the gene (and who was the first author on the published paper announcing the discovery), demonstrated the extraordinary contributions such grass roots organizations can make to the cause of medical science.

The discovery that *MECP2* is on the X chromosome proved that RS is an *X-linked disorder.* And because only one of the two X chromosomes need have the mutation in order for it to cause the disorder, this is a *dominant disorder* as well. The fact that RS is an *X-linked dominant* disorder also helps explain why it is usually found only in girls.

Normal males and females have 23 pairs of chromosomes. One member of each pair comes from the mother; the other comes from the father. Therefore, a baby might inherit a gene for blue eyes from the mother and a gene for brown eyes from the father. Or perhaps the child may inherit two genes for brown eyes.

The two chromosomes making up the so-called sex chromosomes are also inherited from individual parents. These are the X and Y chromosomes. Girls inherit two X chromosomes; boys get one X and one Y chromosome. The X chromosome is big and has plenty of genes; the Y

chromosome is short and stubby and carries the genes needed to swing a developing fetus from the path to girlhood to the road to boyhood.

Both of the X chromosomes tend to be active. This could be deadly to girls, since duplication of gene activity would almost certainly disrupt the cell's ability to live a normal life. To prevent this, each of the body's cells turns off one of the X chromosomes. Which X chromosome gets inactivated in each cell is usually a random process. According to the laws of probability, the X chromosome with the *MECP2* mutation will be turned on in half of their cells. But enough X chromosomes with the mutation will be activated to produce the symptoms of RS. (If, by some chance, a large majority of cells express only the normal X chromosome, the girl has only mild symptoms or none at all.)

Mutations in *MECP2* are almost always sporadic, that is, they occur spontaneously rather than through heredity. That means that parents rarely pass on the disease to their children. Even if a child does inherit the mutation, however, boys don't usually get RS. That's because the father can't pass it on to them. In order for the fetus to become a boy, the father must pass on a Y chromosome, not an X chromosome. Since the *MECP2* gene is located only on the X chromosome, the boy, by virtue of being XY, avoids RS. Another reason few boys are diagnosed with RS is that most pediatricians would not have thought to check a baby boy with respiratory problems and severe encephalopathy (including abnormally small brain size) for mutations in *MECP2*.

An exception to the XY rule of boys not getting RS occurs in Klinefelter syndrome. In this disorder, boys are XXY; that is, they have an extra X chromosome, if one of these X chromosomes has the *MECP2* mutation, RS can occur. (Among other symptoms, boys with Klinefelter syndrome have disrupted development of sexual organs.)

RS is classified as a *developmental* disorder: it doesn't cause the brain to degenerate. Rather, RS interferes with maturation of specific areas of the brain.

The role of *MECP2* is to silence certain genes. In RS, the *MECP2* gene is unable to perform this task, leaving those genes to act like overzealous electricians ignoring the wiring plans for a new house. Instead of installing a network of carefully placed wires and switches, these neuronal electricians create a hodgepodge of wires that cause short-circuits and blown fuses.

The areas of the brain disrupted in RS are the frontal, motor, and temporal cortex, brainstem, basal forebrain, basal ganglia, which control many basic functions, such as movement. They are also critical to the normal development of the cortex, or higher brain functions.

Not surprisingly, investigators have recently learned that, although active *MECP2* occurs widely throughout the body, it is especially abundant in the brain. Moreover, mouse studies strongly suggest that the brain is the *main site* of action for *MECP2*. The disastrous neurodevelopmental mishaps in RS arise from the disruption of the obscure and subtle mechanism by which the normal MeCP2 protein works. This disruption is also a classic example of a chromatin disorder.