THE MIRROR

The Newsletter of
IDEAS
IsoDicentric 15
Exchange, Advocacy & Support

SPRING ■ 2004

Celebrating 10 Years of IDEAS

NICOLE CLEARY, MSS, Executive Director

Ten years ago, in the spring of 1994, Donna Bennett, mother to Joshua, and Brenda Finucane, Genetic Counselor at Elwyn, Inc., recognized that families raising children with what was then called Inverted duplication 15 needed a support and advocacy organization specifically for this disorder. The first issue of The **MIRROR** came out in Spring/Summer 1994 and it marked the official beginning of **IDEAS**. Donna wrote the first Family Portrait about her son Joshua. In that article, she wrote about the relief she felt when she first found other families raising children with Josh's disorder.

*In the years since Josh's diagnosis, I have been able to track down over a dozen other parents of children with inv dup(15), and I find that we have so much in common! Yes, there is a bond among all parents of children with special needs, but finding others whose children share Josh's exact medical condition brings that bond one step further. I only hope that through **IDEAS** we can accomplish as much for our children as other support groups have done for theirs.*

Ten years later we are well on our way! **IDEAS** is now a vibrant network of over 250 families from around the world, many of whom share the joys, sorrows, challenges, and hopes of raising a child with Isodicentric 15 and related disorders every day on the yahoogroups listserve

http://health.groups.yahoo.com/group/Inverted-Dup15

IDEAS provides families with a rich support network. Our families meet together in conferences, regional gatherings, and whenever possible with families living nearby. Each of us has a family life that is made more challenging by our child's special needs. The support found in **IDEAS** helps us recognize that while our family life may be different than we thought it would be, it can still be good —even fun at times. Along the way, we support and encourage each other over the rough spots as we share the journey of raising our special children.

IDEAS provides families with a wealth of information about what kind of therapies and educational practices will help their children reach their full potential. Ten years ago, families receiving a diagnosis of idic(15) or inv dup (15) did not have much guidance about what they should do to help their children. Today's newly diagnosed families quickly learn about the importance of therapy (speech, occupational and physical) and educational strategies and programs that can help their children. We now have the first generation of young adults identified with idic(15) and related disorders. They are establishing their adult lives and providing role models and information about options in adulthood for the families of younger children.

IDEAS helps facilitate research. Brenda Finucane and her colleagues at Elwyn have conducted surveys of our families that provide important data about seizures and the links between idic(15) and autism. **IDEAS** collaborates with researchers at Duke University, Nemours Research Programs at the Alfred I duPont Hospital for Children, University of Pennsylvania, and new research collaborations are in the works. These researchers are providing vital information for families, presenting their findings at professional meetings, and publishing their results in scientific journals. These presentations and publications are instrumental in raising awareness of idic(15) and related disorders.

Isodicentric 15 idic(15), formerly known as Inverted Duplication 15, is a disorder in which a child is born with extra genetic material from chromosome 15. Symptoms may include: poor muscle tone, developmental disability, seizures, and autism. Although the exact prevalence is not known, Isodicentric 15 is one of the most common causes of autism.

In honor of our 10 year anniversary, the MIRROR will profile what **IDEAS** is doing in each of these areas. This issue will highlight **IDEAS** activities in the area of research. You will find the results of two studies conducted by Brenda Finucane and her colleagues at Elwyn. These studies will be presented at the annual meeting of the American College of Medical Genetics in Orlando, Florida in March. This issue also contains research updates from several of our collabo-rators, and information about two exciting new research studies. Dr. Jeff Gregg at UC Davis recently received a small grant for a study entitled Identification of dysregulated genes in children with autism and idic(15). Dr. Diane Chugani at Wayne State University is preparing to launch a study that will look at GABA receptor binding in 25 individuals with duplications of 15q11-q13.

We've come a long way in 10 years. The energy and commitment of our families promises even greater levels of support, information, research and increased awareness in the years to come. **Happy Anniversary, IDEAS!**

Update on Elwyn Research Studies

BRENDA FINUCANE, MS, CGC, Genetic Counselor
Genetic Services, Elwyn Training and Research Institute, Elwyn, Pennsylvania

One of the priorities of IDEAS is to further research into Isodicentric 15 and related disorders. Families who participate in research studies do so in the hope that discoveries may help their own children, as well as future generations of children born with idic(15). It often takes months, and sometimes years, before studies are completed and the results are published. I am pleased to be able to report on the results of two such studies which we initiated a few years ago, and to once again thank those IDEAS families who participated. In March, 2004, I will have the opportunity to present the results of these studies at the annual meeting of the American College of Medical Genetics in Orlando, Florida. This conference attracts hundreds of genetics professionals from around the country and offers an excellent opportunity to get the word out about idic(15) and IDEAS. The next step will be to publish the results in a medical journal. Hopefully, these presentations and publications will stimulate interest by other researchers who can continue to make strides toward better understanding idic(15).

Follow-up Study of Idic(15) and Autism

Researchers: Brenda Finucane, Barbara Haas-Givler, and Elliott W. Simon (Elwyn Training and Research Institute, Elwyn, PA)

Numerous reports have linked autism with the Prader-Willi / Angelman Critical Region (PWACR) of chromosome 15. This area of genetic material is duplicated in people with idic(15) syndrome. In 1998, we reported a high incidence of autistic symptoms among children and young adults with idic(15) (Rineer et al., 1998. Am J Med Genet 81:428-33.) Using a standardized questionnaire called the Gilliam Autism Rating Scale (GARS), we confirmed high autism scores in 20 of 29 children and young adults studied. Because younger children with idic(15) in the group were more sociable and less likely to be autistic than older children, we questioned at the time whether the onset of autistic symptoms, particularly problems with social interaction, could be age-related. Such a progressive pattern of autistic symptoms is unusual, as sociability generally remains stable or improves with age in people with autism of other causes.

We recently contacted the IDEAS families who participated in our original study in order to see how their children were doing. Of the 9 children with idic(15) whose initial GARS scores were below the range for autism, 7 were available for follow-up study. The GARS was readministered, and on retesting 6 years after the original study, all 7 showed a significant increase in the GARS Autism Quotient, specifically due to increasing deficits in social interaction. Six of the 7 previously non-autistic children scored well within the autism range on retesting. Although the remaining non-autistic child still scored below the autistic range on retesting, his scores had significantly increased since the previous study (i.e. he had more autistic symptoms than before.)

This recent follow-up study supports the conclusion that there may be an age-related increase in the severity of autistic symptoms among individuals with idic(15) in the area of social interaction. This is different than the usual course of autism, where overall improvement in social functioning is found with increasing age. It is important to keep in mind that there is a wide range of abilities among children with idic(15), and even among those in our study, autistic features in some were much milder than in others. These are preliminary results and additional longitudinal work needs to be done to confirm this finding. If true, it could have important implications for educational intervention, strengthening the case for providing intensive autism services for young children with idic(15).

Results of the IDEAS Seizure Survey

Researchers: Brenda Finucane, Elliott W. Simon (Elwyn Training and Research Institute, Elwyn, PA), and Lawrence Brown (Children's Hospital of Philadelphia, PA)

Over the past decade, a recognizable pattern of features has started to emerge in people with duplications of the Prader-Willi/Angelman Critical Region (PWACR) on chromosome 15. The clinical "profile" (called a phenotype) of people with idic(15) syndrome includes a subtle but characteristic facial appearance, poor muscle tone, varying degrees of intellectual disability, and a high incidence of autism spectrum disorders. The PWACR is known to encompass a cluster of genes called gamma-aminobutyric acid (GABA) receptor subunit genes. These genes are known to play a role in causing epilepsy. A handful of case reports have described seizures in children with idic(15) syndrome, but until now, a systematic study of seizure prevalence and characteristics in idic(15) has not been reported.

We used a questionnaire to survey parents of children and adults with idic(15). Many of you filled out the green questionnaires which were sent in the mail, and some, including many IDEAS families from overseas, completed the questionnaire online on the IDEAS website. We received 90 responses from parents of individuals with idic(15), including 52 males and 38 females ranging in age from 9 months to 24 years. Fifty-four percent of the group surveyed had experienced at least one seizure. Age of onset of the first seizure ranged from birth through 18 years, with a mean age of 2.8 years. Fifty-five percent of those with seizures had onset by 1 year of age, with 82% having onset prior to age 5. Parents reported multiple seizure types in their children, including generalized tonic clonic (18%), absence (12%), and myoclonic seizures (11%). Sixteen percent of the group, accounting for 29% of those with seizures, had a history of infantile spasms. Many children experienced more than one seizure type, and several had severe, intractable epilepsy. When surveyed about the impact of the child's seizures on his / her quality of life and functioning, 51% of parents reported a minor impact, 16% a moderate impact, and 33% a major impact.

The results of the seizure survey confirm that seizures represent an important medical feature of idic(15) syndrome. Over half of people with idic(15) will have at least one seizure. The vast majority of those will experience their first seizure before age 5. The prevalence of infantile spasms among the surveyed group was unusually high and suggests that idic(15) syndrome could account for a significant percentage of infants experiencing those episodes. Abnormal GABA receptor gene expression is a likely contributor to seizures in people with idic(15). Additional studies are needed to further characterize seizures in idic(15) and to study the effectiveness of medications which influence the brain's GABA receptor system.

Research update on chromosome 15 duplications Idic(15) and interstitial duplications

N. CAROLYN SCHANEN, MD, PhD
Head of Human Genetics Research, Nemours Research Programs
Alfred I DuPont Hospital for Children, Wilmington DE

Our research study on *Molecular Investigations of Duplications of Chromosome 15 in Autism* is now in its 5th year. Thanks to the willingness of many families to participate in our research, we have received samples from 86 people with duplications of chromosome 15. Our team has done clinical assessments on 57 people and a total of 52 have completed both parts of the study. We will be recruiting new participants in this study through 2008, although there will be a change in strategy for families entering the study after March 1, 2004. We are concluding the enrollment into the behavioral part of the study so that most families who enroll after March 1, 2004 will only be asked to participate in the DNA study. Over the next 12-18 months, we will complete these evaluations for the families already enrolled.

We are learning a lot about the structural features of the long arm of chromosome 15 that predisposes it to rearrange and make duplication chromosomes. On chromosome 15, there are repeated regions that share nearly identical DNA sequence. Recent studies have determined that there are likely to be five main positions that are involved in the generation of duplication chromosomes. These repeated regions contain active genes, so understanding the positions that are involved in making the duplication chromosomes may help us understand the variability in the symptoms of people with duplications - the symptoms may depend on both what is duplicated and which repeat region was involved. Although the initial reports of idic(15) chromosomes suggested that the extra chromosome is symmetric and a mirror image, we have found that actually the positions of the breakpoints involved vary among kids with seemingly identical duplications (based on the clinical studies). How this affects outcome is not known at this point.

The most commonly duplicated region contains at least 20 genes. Of these, two genes are known to be expressed from the maternal copy of chromosome 15. Because maternally derived duplications tend to cause more significant developmental problems, these genes are likely to be important in duplications of chromosome 15. These two genes are *UBE3A* and *ATP10A (aka ATP10C)*. There are also 3 GABA receptor genes in the region that is commonly duplicated. Since these genes are active on both copies of the chromosome, patients with duplications are likely to have an increase in the amount of the product of the gene that is made by cells in the brain. GABA receptors are neurotransmitter receptors that are inhibitory in function and play important roles in virtually all neuronal systems. They are implicated in seizures and it is likely that the increased numbers of receptors are part of what predisposes kids with duplications of 15q11-q13 to seizures.

We have been collaborating with the research group at Duke University to examine the symptoms of kids with duplications of chromosome 15 with typically developing kids and kids that have autism but no chromosome abnormality. There is remarkable variability in how the kids are doing when they are sorted by age. In general, kids with typical interstitial duplications have milder cognitive symptoms and fewer seizures. Children with idic(15) chromosomes tend to sit and walk later, although 95% were walking by age 5 years. 14 of 41 children had their first word by age 5 years, 2 began using words between 5-10 years and one acquired their first word after age 10.

If any families would like more information or would like to enroll in our study, please contact Naghmeh Dorrani at 310-825-8084.

Happy Birthday to these special kids:

Allison G.	03/01/97	Michael H.	03/17/80	Marissa K.	04/04/88	Cody L.	04/19/93	Joelle G.	05/02/94	Jaylin L.	05/15/92
Dylan M.	03/01/94	Kathryn M.	03/18/95	Chad T.	04/08/94	Suzanne K.G.	04/20/89	Jacob M.	05/04/99	John L.	05/20/94
Fabio C.	03/01/93	Jacob G.	03/19/99	Jeffrey M.	04/10/95	Coleen S.	04/23/93	Shelby L.	05/05/93	Lindsey Y.	05/22/98
Jackson R.	03/08/94	Christina M.	03/20/85	Niklas H-H.	04/11/99	Alexis J.	04/25/02	Jillian B.	05/06/92	Brenden O.	05/24/91
Samuel C. R.	03/08/83	Joshua R.	03/21/96	Jaime Lee J.	04/12/93	Elisabeth A.	04/27/95	David W.	05/08/91	Joanne W.	05/27/88
Shawn K.	03/09/93	Joseph G.	03/21/88	Marlena H.	04/13/99	Robert M.	04/28/94	Albanelia R.	05/08/84	Jarrett S.	05/28/91
Benjamin R.	03/13/98	Jason K.	03/23/90	Bobby W.	04/14/78	Paige J.	04/28/92	Anna M.	05/09/88	Madison M.	05/31/01
Patience V.	03/15/90	Katherine C.	03/29/97	Julie R.	04/19/99	Matthew V.	04/29/88	Simon P.	05/10/83		
Jacob L.	03/16/00	Cody K.	03/31/99	Allora W.	04/19/96	Crystal O.	04/30/87	Austin E.	05/13/92		

IDEAS fundraiser event brings over $18,000

Pat and Lori George really know how to throw a fundraiser!

Lori is a Board Member and Corporate Secretary for IDEAS. Back in October, 2003, Lori and Pat, parents of Will, decided to hold a fundraising dinner for IDEAS at the Marriott Hotel in the nearby town of Burlington, Massachusetts. They reserved a hotel ballroom and invited a wide network of 150 family and friends. The evening was a smashing success! The total amount raised after expenses was more than $18,000 from dinner tickets, an auction, and donations. Lori reports, "Our family & friends supported us beyond our expectations. One of Pat's friends donated a Predo Ball which my cousin won at the Auction for $1,750, as well as a Manny Martinez Away Jersey which my nephew won for $1,100 (he told my sister after he bid, which of course she didn't mind). I'm just thrilled because I won the bid on a beautiful designer rug and the best part was Pat didn't even know I was the person bidding until my nephew said 'Hey Uncle Pat, Aunt Lori just won the rug'—not that Pat minds because, let's face it, it is truly for a good cause!"

The evening included speeches from Pat George, Will's dad, and Paul Rivard, IDEAS finance officer. They provided the audience with information to increase awareness and understanding of Isodicentric 15 and related disorders. Lori's cousin gave a really rousing speech that kicked off the auction. In addition to the generous donations, several people offered to help IDEAS in becoming a non profit and spreading the word about Isodicentric 15 and related disorders. Several left wanting to know what we are doing next year and offering to help!

Thanks so much to Lori and Pat George for organizing this fundraiser! Thanks also to Paul and Dawn Rivard who provided a lot of support, to Kathy and John Wise for getting the flowers, and to all of the participants who showed such generosity and support for IDEAS and for our kids! If any IDEAS members would like to learn more about how to host an evening dinner fundraiser, you can contact Lori and Pat George at

PL9071@aol.com

Exploring Autism Web site adds information about Isodicentric 15 and Autism

The Exploring Autism web site housed at Duke University and funded by the National Alliance for Autism have added two information pages about the association between Isodicentric 15 and autism. These web pages contain information that may be helpful for families who need resource material to share with doctors, educators, therapists, etc. The web site can be reached at

http://www.exploringautism.org/

The web page for Genetics Overview: Exploring Chromosome 15 can be found at

http://www.exploringautism.org/genetics/chrom15.htm

The web page for What is Autism?: Isodicentric Chromosome 15 can be found at

http://www.exploringautism.org/autism/iso_chr15.htm

Following is an excerpt from the **What is Autism?: Isodicentric Chromosome 15 page**

Since chromosomes carry genes that determine how our bodies grow and develop, having extra chromosomal material can alter a person's physical and mental development. Many individuals with idic(15) have delays in language development and motor skills such as walking or sitting up. Other traits may include low muscle tone (hypotonia), seizures, short stature, and mental retardation. Distinctive facial features associated with idic(15) may include epicanthal folds (skin folds at the inner corners of the eyes), a flattened nasal bridge, button nose, and a high arched palate (roof of the mouth). Some individuals with idic(15) also have features of autism, such as problems with communication, social interactions, and repetitive and stereotyped behaviors (e.g., lining up toys, playing with a toy in the same manner over and over again, hand flapping, rocking back and forth).

Isodicentric Chromosome 15 and Autism

For more than 12 years, scientists have noticed that some individuals with autism also have idic(15). In fact, idic(15) is the most frequently identified chromosome problem in individuals with autism. (A chromosome anomaly involves extra or missing chromosomal material, not changes within the genes such as Fragile X syndrome). There are now over 20 reports in the literature of individuals with both autism and idic(15). The frequency of these reports suggest that the co-occurrence of autism and idic(15) is not by chance. There may be a gene or genes in the 15q11-q13 region that is/are related to the development of autism in some individuals. Genetic research studies of individuals without chromosome anomalies also support this idea that an autism-related gene may be present in 15q11-q13. Specifically, research studies found that certain DNA markers from the 15q11-q13 region were found more often in individuals with autism than in individuals without autism. Although these DNA markers are too small to be genes, they suggest that researchers may be getting close to finding an autism gene in this region.

Candidate Genes in 15q11-q13

Researchers are currently focusing on genes in this region called the GABA receptor genes, known as GABRB3, GABRA5, and GABRG3. They are good candidates for being related to autism not just because of their location, but also because of their function. The GABA genes make proteins that carry messages between nerve cells. Several studies have found associations between GABRB3 and autism (Buxbaum, Shao, Cook), but further study is needed.

IDEAS Incorporating as an Independent Non-Profit

Since its inception 10 years ago, IDEAS has been fortunate to have the support and sponsorship of Elwyn, Inc. Elwyn is one of the nation's oldest and largest human services organizations serving adults and children with a wide range of special needs.

With a current mailing list of over 250 families and professionals, IDEAS is the only support group in the world dedicated to supporting families, raising awareness and fostering treatment and research into idic(15). At their 2003 annual meeting, the IDEAS Board determined that incorporating as an independent non-profit organization is necessary for IDEAS to continue to move forward organizationally. A team of parents came together this fall to research potential states for incorporation and provide advice to the Board on incorporating IDEAS as a non-profit.

The Board is pleased to announce that in February, 2004, IDEAS filed Articles of Incorporation in Oregon. Following is the legal description of our group under this filing: IDEAS is a non-profit, public benefit corporation dedicated to providing information, education and support to families with individuals affected by IsoDicentric 15 and related disorders; uniting families, researchers, and professionals; and promoting research, awareness and understanding of IsoDicentric15 and related disorders.

The officers of the Corporation include an Executive Director, a Finance Officer, and a Corporate Secretary. The Board has elected Nicole Cleary as the Executive Director. Nicole holds a master's degree in social service and has over 10 years experience working for non profit organizations. She has served as the Chair of the IDEAS Board since 2001. Paul Rivard will serve as the first Finance Officer for IDEAS. Paul has been instrumental in the development of IDEAS, serving as the listserve moderator, maintaining the family mailing database, chairing the fundraising committee, and working with Elwyn to manage the restricted fund they hold for IDEAS. He has served on the Board since 2001. Lori George will serve as the IDEAS Corporate Secretary. Lori has been working as an accounting and credit manager for 20 years and has served on the IDEAS Board since 2003.

Our next step is to prepare and file the federal tax exemption application. Following review of the application, the IRS will issue a "Letter of Determination" which is what grants IDEAS official non-profit, also called 501(c)(3) status. We anticipate having the federal tax exemption application completed by the end of the year.

Establishing IDEAS as a non-profit has been a big undertaking and has required hours of work. Special thanks to Todd Luchsinger, Evelyn O'Dell, Brian Gazewood, Nicole Cleary and the IDEAS Board.

UPCOMING STUDY:

Brain $GABA_A$ receptor abnormalities in children with chromosome 15q11-13 mutations

Autism is a neurodevelopmental disorder characterized by a spectrum of abnormal behaviors including profound impairment in social interaction, communication, and restrictive, repetitive and stereotyped behavior. Gamma amino butyric acid (GABA) is a major inhibitory neurotransmitter in the brain. GABAergic inhibition is mediated by two major classes of receptors: type A and B (Macdonald 1994, Bowery 1993). Impaired GABA function, especially $GABA_A$ receptor function, has been proposed to play an important role in the pathophysiology of numerous developmental and genetic disorders. As noted in the research update from Dr. Carolyn Schanen, there are 3 GABA receptor genes in the region of chromosome 15 that is commonly duplicated in people with idic(15) and int dup(15).

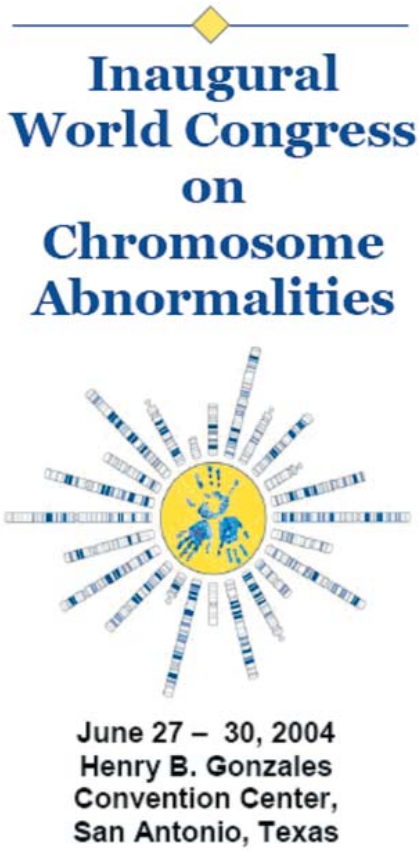
The IDEAS Board has recently voted to collaborate with a new research study, which involves PET scans of the $GABA_A$ receptor. This study is in the final planning stages. The principal investigator of the study is Diane Chugani, PhD at Wayne State University and Children's Hospital of Michigan. The central hypothesis of this proposed research is that abnormalities in the $GABA_A$ receptor binding in the brains of autistic subjects with chromosomal abnormalities in the region 15q11-13, contribute to the pathophysiology of this neurodevelopmental disorder. Understanding of $GABA_A$ receptor binding abnormalities in subjects with 15q11-13 chromosome duplications may lead to clues regarding the diverse presentation of this neurodevelopmental disorder as well as to mental retardation in these children.

We will have more information on this study in our next newsletter.

1. Bowery N. $GABA_B$ receptor pharmacology. Ann Rev Pharmacol Toxicol 1993;33:109-147.
2. Macdonald RL, Olsen RW. $GABA_A$ receptor channels. Ann Rev Neurosci 1994;17:569-602.

IDEAS is host organization for inaugural World Congress on Chromosome Abnormalities

In 2004 IDEAS will not have our own conference but we are excited to be serving as a host organization for the Inaugural World Congress on Chromosome Abnormalities in late June.



The World Congress has been organized around a central vision: Children born with chromosome abnormalities will have specific treatments so they can lead healthy and autonomous lives. The Congress is organized with three primary goals in mind:

1. Build a community of parent-advocates by creating a forum for interaction, disseminating information on topics common to many genetic disorders, and showcasing success stories.
2. Build stronger Lay Advocacy Groups for chromosome abnormalities by learning about each other's success, identifying common issues, and planning synergistic strategies.
3. Establish the nucleus of a scientific community dedicated to solving the issues faced by people with chromosome abnormalities by developing models for clinical evaluation, identifying universal research themes, and establishing "cross talk" between medical and scientific subspecialties.

Dr. Carolyn Schanen will be presenting on idic(15) at this conference. She is one of the foremost professional experts on idic(15) and heads up one of the few major research studies on our children, in addition to having met many of our children in person!

The World Congress will take place June 27 - 30, 2004 at the Henry B. Gonzales Convention Center in San Antonio, Texas. The IDEAS Board will be holding its annual meeting at the Congress. We encourage parents interested in a conference addressing chromosome abnormalities to consider attending this conference. It will be a wonderful opportunity to learn more about issues involved in raising a child with idic(15), and a chance to see how these issues are shared by parents raising children with different genetic disorders. Following is a partial listing of the preliminary program for families.

- IDEA & Your Rights
- Estate Planning
- IEP Strategy
- Skyrocketing Self Esteem
- Sibling Issues and an Actual Sib Shop
- Dad's / Mom's/ Grandparents groups
- Challenging Behavior
- Positive Exposure
- Humor through Song
- Regular Kids
- Diet & Nutrition
- Sensory Integration
- Grief and Coping
- Speech Issues
- Dental Care
- Family Dynamics & Effect on Outcomes

The Congress has arranged for a variety of activities for children who are registered for the conference. There will be an open door policy for these activities; therefore a responsible caretaker must accompany every child. The Congress will NOT provide child care or supervision. They WILL provide activity directors. Individual childcare can be arranged through the hotel or with local childcare services. Information on these services will be provided with the registration packet.

Online registration for the conference begins March 1, 2004. You can get more information about the World Congress on their web site

www.chromosome18.org/worldcongress/

New Research Study at UC Davis

Deb Lindgren, one of our IDEAS parents, noticed something interesting in her latest copy of the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute newsletter. It contained a listing of UC Davis Pilot Grant award recipients. One of the awards jumped out at her: Jeffrey P. Gregg, Pathology, for the Identification of dysregulated genes in children with autism and ID15.

The IDEAS Board contacted Dr. Gregg and he provided the following information on his study.

Specific Aims

Chromosome 15q11.2-q13 has been identified as a strong candidate for autism due to the frequent chromosomal aberrations in that region and suggestive linkage studies that have found associations in this region. Recently, the Pericak-Vance group (Shao et al., 2003) have shown through a novel linkage methodology, ordered-subset analysis (OSA), strong linkage to the region of 15q11-q13. With this evidence linking 15q11.2-q13 (idic(15)) to autism, we hypothesize that there is a gene or group of genes in this region that is dysregulated in autism and that these genes may have a direct effect (epigenetic) on the expression of other non-15q11.2-q13 genes (n15q). We believe that the 15q11.2-q13 and the n15q set of genes can be identified through comprehensive gene expression profiling on a small set of individuals with idic(15) and matched controls. We believe that the genes identified through these experiments may have relevance to individuals with autism without idic(15), as this region is heavily imprinted, and that errors in imprinting or increased maternal sharing of 15q, may result in the same dysregulated gene expression caused by idic(15). Therefore, the idic(15) experiments provide a model of identification of genes that then can be used to screen larger cohorts of children with autism for association at the gene expression level. This global hypothesis will be tested through the aims listed below.

1. Identification of cell lines with 15q11.2-q13 inverted repeat (idic(15)) families in the AGRE cell line repository and idic(15)-related families identified by Carolyn Schanen.
2. Comprehensive gene expression will be carried out with Affymetrix GeneChips, that contain over 22,000 genes, on 10 idic(15)/autism selected cell lines and 10 matched sibling controls.
3. Idic(15) regional specific and n15q genes will be identified and verified through quantitative TaqMan PCR (2002). TaqMan PCR, which is routine in our laboratory, will be performed in order to conform the identified genes.

Methods and preliminary data

The MIND Institute is obtaining the Autism Genetic Resource Exchange Repository of cell lines which includes over 335 multiplex autism families. Among this repository, approximately 5 families have idic(15) (pers. comm. Dan Geschwind). These families have been identified through chromosomal and FISH analysis completed at The University of Chicago. We have obtained one idic(15) cell line from AGRE. In collaboration with Carolyn Schanen, we are obtaining additional cell lines from families with autism and idic(15). From these two sources, we will select 10 cell lines from 10 unique individuals with autism and idic(15) and 10 cell lines from matched siblings. As this group of individuals with autism is a genetically similar idic(15), we will try to make this a more homogeneous population by selecting a phenotypic homogeneous population, if possible, based on the repetitive behavior/stereotyped patterns domain in the ADI-R, as this group has shown linkage to 15q11.2-13. We will only attempt this if we can obtain a larger of group of idic(15) with autism (n>10). RNA isolation, GeneChip hybridization, and data analysis will be performed as described in Geschwind and Gregg

The ultimate goal of the proposal is to identify a set of genes that are dysregulated in a genetic and phenotypic homogeneous population with autism and then test these selected genes on a broader cohort of children with autism (in a subsequent proposal). We believe that this initial investigation and group of genes will provide sufficient preliminary data for a R21 or R01 proposal to the National Institutes of Health within 6-9 months.

We are just about to run the arrays on 10 patients. I am very excited about the project and couldn't do it without the families and organization!

References:

Geschwind DH, Gregg JP, (eds.) (2002) Microarrays For The Neurosciences: An Essential Guide. Cambridge: The MIT Press.

Shao T, Cuccaro ML, Hauser ER, Raiford KL, Menold MM, Wolpoert CM, Ravan SA, Elston L, Decena K, Donnely SL, Abramson RK, Wright HH, DeLong GR, Gilbert JR, Pericak-Vance MA. (2003). Fine Mapping of Autistic Disorder to Chromosome 15q11.2-q13 by use of Phenotypic Subtypes. Am. J. Hum. Genet. 72:539-548

GOT NEWS?

The MIRROR welcomes the stories, insights, and ideas of all parents and professionals interested in idic(15). We'd also like to hear your suggestions for future articles.

Send correspondence to Jane True, MIRROR Editor at: JTRUE@kc.rr.com

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Jane True, Editor

Lin Neighbors, Design & Layout

Printing costs for this newsletter provided by Elwyn, Inc.

Marlena's Story

Marlena is an adorable, happy, extremely affectionate 4 year old brown-eyed girl diagnosed with IsoDicentric 15. Marlena was born April 13, 1999 and was noted as a good, quiet baby. Her first signs of concern included hypothermia and inadequate sucking skills immediately after birth.

Marlena was diagnosed with infantile spasms at 7 months of age. She received Vitamin B6, ACTH injections, and Topamax. Her spasms discontinued with ACTH injections. As part of the work-up for infantile spasms, a chromosome analysis was done and IsoDicentric 15 was diagnosed.

Her medical diagnosis includes: history of seizures, dysphagia, hypotonia, ADHD, sensory dysfunction, heart murmur, developmental delay, mild hearing loss, exotropia, mild mental retardation, and tachycardia. She displays both an auditory and visual processing disorder.

Marlena attends a special education, early childhood program for 2-1/2 hrs per day. She receives OT, PT and speech and language services. She thoroughly enjoys riding the big yellow bus driven by Ms. Paula as she picks up her school buddies. She likes going to school and regresses without the structured setting. Her biggest challenges include her short attention span, hyperactivity, and lack of self organizational skills. She has responded well to behavioral interventions and visual schedules.

She is extremely social, and greets newcomers at the classroom door, "have a seat," "come in," "how are you," "I'm Marlena," and "I'm fine." Marlena has made significant gains at school. She can identify people correctly by name and is able to answer simple and direct questions with appropriate responses. She can scribble on paper, put together a simple puzzle, and remove her clothing. Her muscle strength is improving.

Marlena's favorite activity is horse therapy. She also loves any musical activity, can memorize songs, and cooperates best if music is included in the task. She enjoys books, puzzles, PBS station on TV, and coloring-anything, especially the walls. She does, at times, show self-stimulating behavior, especially when overwhelmed or exhausted. She will turn the pages of a phone book and then can rip every page out of the entire Yellow Pages.

Auntie Lulu and Uncle Dan are her favorite relatives. She has numerous cousins to play with on a daily basis. Marlena has several brothers and she tests their patience with her unlimited energy. She enjoys waking them up early, "time to get up," "let's go downstairs" she states, not comprehending that they don't have to be up at 5:00 AM... When they get upset, she will hug them, kiss them, tell them, "I Love You" and ask, "You don't want to play with me?"

The bathroom is one of her favorite play areas. She loves to stand on the sink, look in the mirror and pretend play. "I'm pretty," she states as she covers her face with mascara. 'Needed lotion," she responds as she covers her Arthur doll with layers of hand cream. "It's a maracas, mom, and dance with me," she exclaims as she shakes a bottle of medicine and wiggles her body to the beat.

Marlena needs constant supervision. She loves to run from you, she waits for that moment where you let go of her hand, she looks at you with that look in her eye, and off she runs… then laughs as you try desperately to catch her. Perhaps it is a reaction to over stimulation or perhaps she's just being a kid, but none-the-less a real cause for concern because she has no sense of danger awareness and she runs extremely fast.

Marlena arises early, retires late in the evening and is in perpetual motion throughout the day. She was on Adderal for a year and a half, but no longer takes any ADHD mediation. She is able to recognize medical buildings, medical parking lots and now becomes hysterical at the mere sight or mention of medicine or doctors. Four years of numerous doctor appointments, tests and medications have taken its toll on her emotional well-being. Her medical appointments are now called trips to see our friends.

Life with Marlena can be very exhausting yet extremely rewarding. Listening to her say, "Mom, I love you," receiving a pat on the back with an "it's okay Mom, don't be sad," watching her accomplish a new task after months of attempts, seeing her get excited at the simplest things, observing her unconditional love people of all ethnicities and ages, and admiring her strong character has helped us focus on the important things in life. Marlena is our special angel and we are blessed to have her in our lives.

— RUTH KROSS