The Chromosome 18 Clinical Research Center Annual Report

Academic Year 2013/2014

Jannine D. Cody, Ph.D.
&
Daniel E. Hale, MD

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1. Activities and Changes during FY 2014

Organizational Chart (as of 08/01/14)

Volunteer Faculty
Child Neurology       Sid Atkinson, MD
Endocrinology         Carisse Orsi, MD
MRI                  Peter Fox, MD
ENT                  Brian Perry, MD
Ophthalmology        Martha Schatz, MD
Gait Lab             Ann Newstead, PhD
Gait Lab             Gail Walden
Immunology           Ed Brooks, MD
Cardiology           Chris Curzon, MD
Orthopedics          Travis Murray, MD
Nephrology           Mazen Arar, MD
Pulmonology          Jesus Guajardo, MD

Financial status

![Funding Sources Diagram]

Total funding for FY2014 was $480,223 ($60,843 less than FY13)
Registry - ($375,000)
100% of Erika Carter (Cytogeneticist)
100% of Patty Heard (Research Associate)
10% of Gloria Matthews (Business Manager)
30% of David Rupert (Data Manager)
50% of Courtney Sebold (Genetic Counselor)
100% of Annice Hill (Project Manager)
100% Bridgette Soileau (Social Science Research Assoc.)
100% of Minire (Mimi) Hasi (Social Science Res. Assoc.)

Registry funding support participant enrollment, medical records collection and abstraction, annual surveys and genotyping.

MacDonald gift ($104,073)
45% of Jannine Cody, PhD
2.5% of Daniel Hale, MD
15% Jon Gelfond, MD, PhD (Bioinformatics)
15% Louise O’Donnell, PhD, (Psychologist)

Personnel changes
There have been no staff changes in the last year. The newest member of the staff, Annice Hill, has been a part of the team for 7 years, making this a very cohesive group.

Students
Xi Tan, is a PhD student in Biomedical Engineering. Jack Lancaster is her mentor. She is analyzing the MRI and fMRI scans of individuals with 18q-.
Blake Novy is a fourth year medical student. He did a summer research project between his first and second years surveying 18q- families about seizure history and treatments. Hopefully he will finish this project up this year.

Space
Lab space is unchanged. The total lab space for all 3 labs is 1350 square feet. Our office space remains unchanged – we have 3 suites each with a reception area office and a total of 11 private offices and a small conference room. We share this space with Dr. Hale’s other staff (Division of Endocrinology Administration).

Enrollment

<table>
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<tr>
<th>Syndrome</th>
<th>FY2014</th>
<th>Total</th>
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<tbody>
<tr>
<td>18q-</td>
<td>18</td>
<td>320</td>
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<tr>
<td>18p-</td>
<td>12</td>
<td>104</td>
</tr>
<tr>
<td>Ring 18</td>
<td>3</td>
<td>35</td>
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<tr>
<td>Tetrasomy 18p</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>Trisomy 18*</td>
<td>4</td>
<td>34</td>
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<tr>
<td>18q+</td>
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<tr>
<td>TOTAL</td>
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<td>563</td>
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Publications
Published


In Press


Submitted
1. **Beyond dysmorphology: An examination of the spectrum of cognitive and behavioral characteristics of individuals with Tetrasomy 18p.** O’Donnell L, Soileau, B., Sebold, C., Gelfond JA, Hale DE, Cody JD.

In Preparation/revision:
4. **Effects of childhood GH treatment on adults with 18q-.**
5. **Parenting stress associated with a chromosome 18 disorder.**
6. **Understanding relationships between individuals with chromosome 18 abnormalities and their siblings.**

2. **Strategy for Making the Chromosome 18 Conditions Treatable**
Making the chromosome 18 conditions the first treatable chromosome abnormalities; how hard can it be? All we have to do is stimulate 1 gene to do the work of 2 or suppress 3 or 4 genes down to the level of 2. The approach we are taking to make the chromosome 18 conditions treatable involves 3 major aspects:

   A. Defining standards of care
   B. Understanding key genes
   C. Developing new treatments

   **A. Defining Standards of Care**
When we began this project most of what was known about the chromosome 18 conditions involved the superficial appearance of someone with the condition. There was very little information about how they develop skills, learn to interact with the world and what medical issues they may have. In addition because
chromosome abnormalities seemed too complex to sort out, little effort had been expended to understand the nature of the various medical and developmental problems.

We therefore work to develop a deeper clinical understanding of each of the conditions in order to identify standard treatments and evaluate their effectiveness. Additionally, we are monitoring and analyzing any of these treatments for complications that are unique in this population. This information is then used to create management guidelines. This is a process in continuous revision and refinement as the other aspects of our research strategy yield results.

Understanding the basis of the clinical issues is particularly challenging for chromosome abnormalities for several reasons. First, because they are rare conditions it takes many years to enroll a sufficient number of individuals to distinguish between the things that are related to the condition and the things that reflect individuality. This is why we continue to enroll participants and follow their medical, educational and life progress over many years. Secondly, because there is so little genetic uniformity between individuals with the same chromosome 18 condition, we are challenged in how we approach creating a summary of the conditions. For example, every person with 18q-, Ring 18 and half of those with 18p- have individually unique deletions involving a different set of genes. Therefore there is no average or typical group with any of these conditions. This diversity is what dictates our strategy to use a gene by gene approach to understanding the conditions. Such an approach would create an individualized syndrome description based on the specific genes involved in each person’s unique deletion or duplication. Each individual would then have their own personal “syndrome description”.

In the meantime, until we understand the role of every gene on chromosome 18 and can implement the gene-by-gene personal syndrome description, we are identifying sub-groups within each condition group that can act as reference points. Within the 18q- group we have identified 2 sub-groups; proximal interstitial deletions and the distal 18q- reference group. Within the 18p- population, half of the individuals have breakpoints at the centromere and therefore have whole p-arm deletions while the others have unique breakpoints. This allows us to create a syndrome description for those with breakpoints at the centromere as a reference group for 18p-. With regard to Ring 18, every person has a unique deletion and therefore what we learn about both 18q- and 18p- applies to them. Tetrasomy 18p is unique for two reasons. It involves the duplication of genes instead of a deletion and almost everyone has the exact same genetic abnormality. With regard to this clinical and educational descriptive work there are still clinical questions we need to address; which are somewhat different for each condition group.

For 18q-, there are several important tasks we need to accomplish in order to increase our understanding of the manifestations (phenotypes) of an 18q deletion. The group we originally described with proximal 18q deletions included only 5 individuals, whose main features included developmental delay and a lack of speech. We have enrolled an additional 6 individuals with a proximal 18q deletion and we would very much like to assess those individuals in order to have a more comprehensive picture of this condition.

As we continue to narrow in on specific genes for specific issues in people with distal 18q- we are hampered by the fact that the majority of individuals have large deletions that include numerous genes. This makes it hard to pinpoint any single gene as causative. However, we have enrolled a few people with very small deletions of 18q. If we were able to perform clinical evaluations on some of these people, it would help us narrow in on potentially identify specific genes for specific issues. Additionally, most of the small identified regions of 18q where the key genes are likely located near the end of the q arm. This is primarily because most people have a deletion of this region. However, there are several individuals who have interstitial deletions of distal 18q and whose deletions are between the end region of the chromosome and the TCF4 gene. There are 13 of these individuals and 3 of them have already been to the Research Center for
evaluation. We would like to evaluate the other 10. This will help us understand the clinical effects of deletions within the region of 18q that is between the end of the chromosome and the TCF4 gene.

With regard to 18p-, we have only evaluated 11 individuals at the Research Center out of the 104 that are currently enrolled. This leaves a huge deficiency in our knowledge base about 18p-. Since we now know that half of the people with 18p- have deletion breakpoints at the centromere, we need to learn more about this group in order to have a solid reference point. In addition, we also need to assess those with smaller deletions in order to begin to identify key genes. Because there is such a huge knowledge gap about 18p-, it is logical to begin additional clinical assessments on the oldest individuals because we can learn the most from them. There are 25 people with 18p deletions of the entire p arm and who are over the age of 15.

With regard to Ring 18 and Tetrasomy 18p, there are no emergent clinical assessment issues – at this time. As key genes are identified, these groups will need to be clinically assessed for the specific effects of those genes. This is what we are doing with regard to the five suspected dosage sensitive genes on 18p and the 18p- initiative that we started last year. More importantly, as we begin to understand the underlying physiology and biochemical consequences of key genes, we will need to assess people in these groups for the relevant findings. This type of assessment will generate the baseline information needed for use in clinical trials.

With regard to Trisomy 18, very little is known about the health and medical history of the long-terms survivors. We want to know what is different about these individuals that allows them to be the survivors. We are very interested in performing comprehensive clinical assessments on 20 individuals with Trisomy 18 who are over the age of 4. We also propose to perform exome sequencing in order to determine if there are shared genetic variants that allowed them to survive.

<table>
<thead>
<tr>
<th>Rationale:</th>
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<tbody>
<tr>
<td>1. Identify and apply standard treatments</td>
</tr>
<tr>
<td>2. Define clinical endpoints for future treatment trials.</td>
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<table>
<thead>
<tr>
<th>Ongoing:</th>
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<tbody>
<tr>
<td>1. Enrolling anyone with any chromosome 18 abnormality</td>
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<tr>
<td>2. Collecting medical records and survey information.</td>
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<table>
<thead>
<tr>
<th>Next Steps:</th>
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<tbody>
<tr>
<td><strong>18q-</strong></td>
</tr>
<tr>
<td>1. Clinical evaluation of 6 additional individuals with proximal 18q-.</td>
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<tr>
<td>2. Clinical evaluation of 10 individuals with interstitial distal 18q deletions.</td>
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<tr>
<td><strong>18p-</strong></td>
</tr>
<tr>
<td><strong>Trisomy 18</strong></td>
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<tr>
<td>4. Clinical evaluations of 20 individuals over the age of 4 with Trisomy 18.</td>
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</table>

**B. Understanding Key Genes**

Although one goal of the clinical assessments is to define the conditions and create management guides, the other is to define the specific medical or behavioral aspects (called phenotypes) so that these phenotypes can be correlated with specific genes. There are data that lead us to believe that only about 10% of genes will actually have a negative effect when there are more or fewer than the normal two copies. The other 90% of gene have no adverse consequence when deleted or duplicated. Before we can understand these key genes we have to identify them. The data from the clinical assessments of a large group of individuals with different deletions or duplications can be used to find correlations between a deletion of a chromosome region and a particular phenotype. This is called genotype phenotype correlation. So far, this has worked
well and we have identified several chromosome regions which were subsequently narrowed down to single genes.

In addition to, or complimentary with, this effort is the fact that there are rapidly expanding data about the function of many individual genes. Although other researchers are rarely trying to determine the effect of a gene when it is present in an abnormal copy number, some of their work does inform ours. For example, a common approach to understanding the function of a gene is to create mice without the gene. These are called knock-out mice. In any one colony of these mice there will be those with no copies of the gene of interest, 1 copy and two copies. Most researchers are interested in comparing the 2 copy (normal) mouse to the no copy (knock-out) mouse, but sometimes they include data in their papers about the mouse with 1 copy of the gene. This information can be very informative to us if the mouse looks and tests just like the normal or the knock-out mouse. This is one example of how the emerging scientific literature can inform our work. Therefore curating the data for each gene on chromosome 18 is an active, deliberate and ongoing process.

Other lines of helpful data include:

i. The presence of a copy number variation (deletion or duplication) of a gene within the normal population
ii. The known function and/or disease association of the gene
iii. The proximity of the gene to a region of the chromosome associated with a particular phenotype.

In addition to reviewing the literature, we can employ several techniques to help us identify key genes. We are using gene expression studies to determine if there are genes that have normal expression regardless of their gene copy number. Also, with this analysis we can determine if there are genes elsewhere in the genome that have extremely abnormal expression because of the gene deletion or duplication on chromosome 18. We do not yet know if this approach will yield consistent results across individuals, but those experiments and analyses are underway. Another similar avenue would be proteomics. We can analyze the levels of hundreds of proteins in blood or tissue samples to again determine if there are changes in people with deletions or duplications. Not only might these types of experiment help us to identify and understand the key genes, but they would give us additional insight into the biochemistry of these conditions.

We now know of one very significant gene on 18q that is responsible for serious cognitive disability, which is TCF4. In order to better understand the impact of this gene in preparation for clinical trials and to identify potential biomarkers that could eventually be used as endpoints in clinical trials, we need to evaluate people with mutations in TCF4. This evaluation would focus on physiological and biochemical measures using such things as sleep studies and blood tests.

In addition, on 18q we have several small overlapping regions of 18q linked to different phenotypes. We don’t know if these phenotypes are caused by one gene, several genes acting independently or multiple genes acting in concert. We have several genes we think could play a role and we want to test that hypothesis by evaluation of the knockout mice with a single copy of the gene deleted. We want to evaluate several of these different mice and if they do not have the same phenotypes as the people, we can make mice with a deletion of two of the genes in the region. This would tell us if there are phenotypes caused by the combination of gene deletions.

With regard to 18p-, we need to perform genotype/phenotype correlation studies for 18p-. There are 27 individuals who are over the age of 15 with different sized deletions that do not include the entire p arm of the chromosome. By comparing the medical, behavioral, social and cognitive profiles of people with these different deletions, we can start to develop a map for where the genes for the various characteristics lie on 18p.
Another aspect to identifying the key genes is to identify the modifying genes. These genes may be on other chromosomes, but some variation in how they work combined with the chromosome 18 changes expresses a new condition or phenotype. These would be things that are the less common or more extreme phenotypes. For example, now that we have identified the distal 18q- reference group, we can use this group to test various strategies for understanding the effects of abnormal gene dosage when all the genes are the same. First, there are some significant differences between the individuals in this group. One person is severely autistic, while all of the others have no or only very mild autistic (Asperger) behaviors. We assume the autism is caused by a combination of a gene deletion on 18q and another gene mutation elsewhere in the genome. We can use exome sequencing and/ or gene expression and/ or proteomic studies to determine how this one person is different from all of the others. We can also use these same data to see how this group as a whole is different from their parents. This could give us additional insight into pathways and key genes on 18q that are responsible for autism.

Rationale:
Identification of the key genes is necessary for:
1. Refining clinical correlations between a gene and a phenotype
2. Guiding the characterization of mouse models for understanding the pathophysiology
3. Development of drug screening systems

Ongoing:
1. Curation of the scientific knowledge of all the genes on chromosome 18 for the “Gene Dosage Map.”
2. Using gene expression studies to identify dosage sensitive genes.

Next steps:
1. Clinical evaluation 20 individuals with mutations in the \textit{TCF4} gene.
2. Clinical evaluation of 15 teenagers and adults with smaller 18p deletions in order to do genotype/phenotype correlations.
3. Using proteomic analysis to identify dosage sensitive genes.
4. Use exome sequencing to identify non-chromosome 18 modifying genes that could cause autism in someone who also has 18q-.

C. Developing New Treatments
It is very hard to delineate precisely where one set of experiments fits into this plan because one experimental approach may yield information in more than one component of the plan. Clinical evaluations may lead to appreciating the usefulness of a standard therapy or they could be used in genotype phenotype correlations to identify the key genes. Likewise, investigating the characteristics of the mice with a deletion of one copy of a gene or duplication of a gene can help us understand the gene’s function. But the next step is to test novel drugs in these mice to see if the drugs can normalize the phenotype. This is the first step in developing new treatments.

In addition to mice, there are other methodologies to test or screen new compounds. This includes cell-based assays. Two examples of this include our collaborations with Steve Haggarty at Harvard working on \textit{TCF4} (on 18q) and an international team based in The Netherlands working on \textit{SMCHD1} (on 18p). Our role in these collaborations is to supply DNA, or fibroblast cells (derived from skin samples) and clinical information. The ultimate goal of both of these projects is to develop drug therapies.

We are still trying to understand the exact effects and benefits of growth hormone therapy in people with 18q deletions. Given our pilot data from the group of adults with 18q- who are either taking or not taking GH, we
would propose to do a treatment trial: provide GH therapy for these individuals with 18q- who are GH deficient and do pre and post treatment cognitive testing. Since our previously published data were gathered on young children, we expect to be able to acquire more extensive data in adults and determine if the adults also benefit from starting GH therapy as adults.

When such therapies are developed and tested for safety in people, we will be conducting the clinical trials to determine effectiveness in our population. This information will then be transferred to recommendations in the clinical management guidelines.

<table>
<thead>
<tr>
<th>Rationale:</th>
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<tbody>
<tr>
<td>1. Identification of the mouse models and cell-based assays for drug screening</td>
</tr>
<tr>
<td>2. Preparation for future clinical trials</td>
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</table>

<table>
<thead>
<tr>
<th>Ongoing:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Using fibroblasts from people with TCF4 deletions or mutations to generate iPS cells and then neurons for the development of drug screening assays.</td>
</tr>
<tr>
<td>2. Using fibroblasts from people with 18p deletions to differentiate into myoblasts for testing and drug screening.</td>
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<table>
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<tr>
<th>Next steps:</th>
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</thead>
<tbody>
<tr>
<td>1. Clinical evaluation adults of with 18q- who are GH deficient, before and after GH therapy.</td>
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</tbody>
</table>

### 3. Implementation of the Strategy

The plan described above is the conceptual approach, while this section is the logistical plan for implementing the strategy. This means there are core activities that are ongoing and independent of specific research questions being addressed.

**Core Activities**

**Primary Enrollment**

We continue to enroll anyone with any chromosome 18 abnormality. As a part of the enrollment we collect:

- Medical records. These are abstracted (key information entered into the database) and copies of the original documents are scanned into the database. (Mimi)
- Whole blood. DNA is isolated and analyzed using microarrays with 248,000 features to characterize each affected person’s chromosome 18 change (Patti and Erika).
- White blood cells are isolated and used to develop permanent cell lines. These allow us to undertake a variety of other activities, some of which will be described subsequently (Patti and Erika).

**Gene Dosage Map**

One of our most important and less visible Core activities is to keep up with the literature on what is known about every gene on chromosome 18. At least once each year all of the information on every known or suspected gene on Chromosome 18 is reviewed (Cody). The purpose of this review is primarily to determine if there might be a potential effect of an abnormal copy number of each gene. Highlights of this year are summarized in the bullet points below and individual details are reflected in individual project descriptions.

- Only 27% of the 258 known genes remain in the “unknown” effects category.
- More importantly, 148 of the genes are predicted to have inconsequential effects when present in an abnormal copy number.
- 36 are potentially dosage sensitive.

Although these designations are tentative and always subject to reevaluation with the discovery of new information, this knowledge helps us prioritize which genes focus on.
Ongoing Projects

18p gene effects

From the annual review of the literature, described above, we appreciated that three potentially dosage sensitive genes on 18p are associated with adult or adolescent onset conditions. These genes and their associated conditions are:

- SMCHD1; facioscapulohumoral dystrophy type 2 (FSHD2)
- AFG3L2: spinal cerebellar ataxia 28 (SCA28)
- GNAL; dystonia.

We are continuing the process of surveying families for early symptoms, and having them follow up with their local specialists if there are any concerns about one of these conditions.

We continue to collaborate with the international group of investigators trying to understand how SMCHD1 causes FSHD2. We received a grant (our part was $30,000 for 2 years) from the FSHD Global Foundation to measure the DUX4 gene expression in the fibroblasts (skin cells) from several people with 18p deletions on whom we have both molecular and clinical data.

Another gene on 18p that may be dosage sensitive is the EMILIN2 gene. We are collaborating with Jane Hoover-Plow, PhD at the Cleveland Clinic who is studying the knockout mice for this gene and looking for correlations with the human cardiac and thrombosis phenotypes.

TCF4

Since the TCF4 gene is now appreciated to be one of the key genes responsible for a phenotype when present in 1 copy, we have intensified efforts to characterize the consequences. We have enrolled 56 participants with a deletion or mutation in the TCF4 gene. In addition, 27 families are in the enrollment process.

We are working to develop cell-based assays for the screening of potential drugs that would upregulate TCF4. We asked select people with TCF4 mutations or deletions for a skin biopsy. The samples were de-identified and sent to Steve Haggarty, PhD at Harvard. These cells have been cultured and stimulated to become induced pluripotent stem cells (iPS cells) for further differentiation into neurons so he can determine how these neurons are different from normal neurons. The next step will then be to screen these cells with a variety of drugs to see if any of the compounds can normalize the neurons with TFC4 deletions or mutations. He has pilot funding, so in order to really do these experiments we will need to write an NIH grant. The reason this might actually be fundable by the NIH is not because of Harvard or Pitt Hopkins, but because the TCF4 gene is implicated in schizophrenia.

Gene Expression as a window to gene dosage effects

Contemporary literature suggests that ~1/3 of genes are sensitive to the gene dosage (copy number). Functionally, this means that there is less mRNA (the intermediate step between DNA and functional protein) when there is one copy instead of 2. We thought we could use this information to help identify the 1/3 of the genes on chromosome 18 that are sensitive to gene dosage by simply measuring the mRNA level. We planned to first test this idea by assaying the gene expression using RNA isolated from cells from the 18q- reference group compared to their same sex parent. Those experiments have been completed and show, surprisingly, that almost all genes on distal 18q are dosage sensitive.

Since this contradicts the literature, we decided to explore this further using a different approach: to perform a gene dosage curve. Specifically, we would compare the expression of the genes on 18p in people with 1 (18p-), 2 (normal), 3 (18p+) and 4 (Tetrasomy 18p) copies of the p arm of chromosome 18 to show a
relationship between gene copy number and gene expression. The preliminary data confirms our hypothesis that the mRNA level corresponds to the gene copy number. But we only used RNA from one person in each group. We need to rerun the experiment with 4 people in each group in order to have statically significant data. The cells have been grown up and the RNA is isolated, but we did not have the funding to complete the very costly analysis experiments until the recent fundraising initiative by the Tetrasomy 18p families. The supplies are now in order and these experiments will be completed soon.

18q- Functional Imaging Project
We acquired functional MRI data on a group of adults with 18q-. A major emphasis in the upcoming year will be to determine how best to analyze these data and correlate it with behavioral data.

Mouse models
We have begun this series of experiments by establishing a colony of Neto1 knockout mice. This is a gene near the end of 18q. Based on our own data and the previously published mouse data, we think the NETO1 gene may be important for learning. More importantly there are compounds that have completed Phase 2 clinical trials in humans that are likely to counteract the effects of a deletion of this gene. We have some pilot funding for this project so that we can acquire the preliminary data to submit an NIH grant.

Grant Applications
We were not awarded the grant from PCORI (Patient Centered Outcome Research Institute) to help expand our network and to develop clinical management guides.

We were also not awarded the NIH grant for an Undiagnosed Diseases Program. This would have covered a portion of the salaries for multiple staff by having them organize the patient visits for this project.

We are currently working on a small grant application to the Pitt Hopkins Research Foundation to identify biomarkers and outcome measures for future treatment trials. This would supply the preliminary data for an NIH grant. Because the product of the TCF4 gene plays a role is so many different processes developmentally as well as in lifelong homeostasis in the realms of both the central nervous system and immune system, possible treatments that target one function will also have to be monitored for effects (positive or negative) with regard to the other functions. For this reason it is critical to develop early markers that correlate with the abnormal physiology so that any changes in response to a treatment can be monitored. This grant would allow us to gather the preliminary data necessary to apply for an NIH grant.

4. Next Steps Toward Treatments

18q-

1. Clinical evaluation of 6 additional individuals with proximal 18q-.
The cost for evaluating each family, which includes, travel, hotel, all testing and hospital costs, plus staff time to make arrangements, do data entry and compile medical reports, totals about $10,000. Since a major part of the cost is in the personnel to conduct the study, and given that the Registry already supports their salaries, the new cost to the Registry to support such a project is about $4,000 per family. Therefore this study would cost $24,000.

2. Clinical evaluation of 10 individuals with interstitial distal18q deletions.
This study would cost the Registry approximately $40,000 to conduct.

3. Clinical evaluation 20 individuals with mutations in the TCF4 gene.
This study would cost the Registry approximately $80,000 to conduct.
4. Clinical evaluation adults with 18q- who are GH deficient, before and after GH therapy. This study would cost the Registry approximately $96,000 to conduct. This study costs more because it involves study multiple visits by each participant.

5. Use exome sequencing to identify non-chromosome 18 modifying genes that could cause autism in someone who also has 18q-.
Exome sequencing costs about $1,000 per sample, plus the time of a bioinformatician to analyze the data. The cost of this project would be approximately, $30,000.

18p-

This study would cost the Registry approximately $60,000 to conduct.

7. Clinical evaluation of 15 teenagers and adults with smaller 18p deletions in order to do genotype/phenotype correlations.
This study would cost the Registry approximately $60,000 to conduct.

Trisomy 18

8. Clinical evaluations of 20 individuals over the age of 4 with Trisomy 18.
This study would cost the Registry approximately $100,000 to conduct. This project is more expensive per participant because we propose to perform exome sequencing in these participants.

All chromosome 18 conditions

This study would cost the Registry $15,000 to complete.

10. Using proteomic analysis to identify dosage sensitive genes.
A budget for this project has not yet been developed.