

THE BEAT

Winter 2008

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MARK YOUR CALENDAR

- April 1 PCD Foundation Board of Directors Election
- May 16-22 ATS Conference, Toronto, Ontario, Canada
- July 18-20 PCD Family Education Day, Durham, NC See Page 3

Go Green with PCD!!
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Human Ciliopathies: An Overview of The First One Hundred Years

By Johnny L. Carson, PhD
 University of North Carolina, Chapel Hill.
 From an abstract to be presented at the Microscopy Society of America meeting in Albuquerque, New Mexico, August, 2008.
 Dr. Carson serves on the board of directors

At the beginning of the last century, a German physician, A. K. Siewert, reported a case of bronchiectasis accompanied by the concurrent but seemingly disparate symptom of *situs inversus*. Some thirty years later, Manes Kartagener extended these observations to a triad of symptoms that included *situs inversus*, bronchiectasis, and chronic sinusitis which came to bear his name, Kartagener's Syndrome. Again, the syndrome languished in obscurity for almost a half century before Bjorn

Afzelius and others discovered that the pathophysiologic (functional changes that accompany a particular syndrome or disease) basis of Kartagener's Syndrome resided in ultrastructural anomalies of respiratory cilia and sperm flagella which caused ciliary and flagellar dysfunction. "Immotile cilia syndrome" as it was originally known, almost certainly is among the first human diseases to be identified and characterized by the advent of routine biological electron microscopy. Continuing investigations of this syndrome throughout the latter part of the 20th century, demonstrated that airway cilia were not always totally immotile but more often exhibited dyskinesia. These observations combined with the congenital nature of the syndrome led to a more correct nomenclatural change from immotile cilia syndrome to primary ciliary dyskinesia (PCD).

The revolution in biology and medicine brought about by the improved resolution of the electron microscope has been complemented by another revolution in molecular genetics from the last quarter of the 20th century to the present time. Because cilia and flagella are evolutionarily conserved across the phylogenetic (sequence of events involved in the development of a species) spectrum, the present day combination of imaging and molecular studies has further demonstrated the marked continuity of structure and function of this organelle. Indeed, many of the early studies of eukaryotic Protists (single-celled organisms) provided the foundation for current efforts to identify candidate genes associated with ciliopathic diseases.

While early studies of cilia in human disease focused on the failure of motility that conferred disease, particularly as it related to respiratory and fertility issues, more recently cilia have garnered attention for their function as sensory organelles (sensory cilia are also called "primary cilia," but are not related to PCD). The presentation of *situs inversus* among patients with primary ciliary dyskinesia led to early speculation about the possible role of cilia in positioning of the viscera during fetal life. This speculation has led to a surge of interest in mechanisms of ciliogenesis (the initial formation of cilia) and the

Continued on Page 5.

Clinical Genetic Testing for PCD: Ambry Genetics and UNC

Ambry Genetics has entered the PCD genetic testing market with the Ambry Panel PCD 61™, a molecular genetic blood screening for the 61 currently verified and published mutations (on two genes—DNAI1 and DNAH5) which have been shown to cause autosomal recessive primary ciliary dyskinesia (PCD). The panel will expand as additional mutations are verified. Ambry's Panel PCD 61™ offers an option for clinical genetic testing for PCD, in addition to the clinical and research molecular genetic testing currently offered by the University of North Carolina at Chapel Hill.

Genetic Testing for PCD: The Basics

There are known PCD-causing mutations on two genes linked to the production of outer dynein arm (ODA) protein: DNAI1 and DNAH5). Together, the mutations on these two genes account for approximately 10% of all cases of PCD and close to 30% of ODA-related PCD. Current clinical

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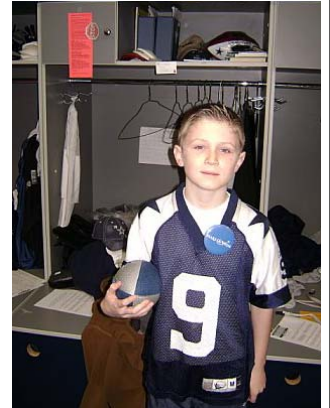
Wishes Do Come True: Paul Wettengel Meets Tony Romo!

By Mary Wettengel

Last year at the PCD Foundation Family Education Day, I met some families who told me about their experience with the Make-A-Wish (MAW) Foundation. I was surprised to hear that their children had been granted wishes based on the PCD medical condition. I had always thought that Make-A-Wish was only for terminally ill children but I later learned that any child with a life-threatening medical condition, between the ages of 2 ½ - 18 (at the time of referral) is potentially eligible for a wish. And as much as I don't always like to admit it, PCD is a life-threatening medical condition.

My son Paul, age 9, knew right away what his wish would be – to meet quarterback Tony Romo of the Dallas Cowboys. You see, even though Paul has PCD, he loves playing sports, watching sports, or anything to do with sports! Before school he watches ESPN and NFL Total Access and after school and on weekends he plays sports. He loves most all sports! Paul's father (also Paul), has been a Dallas Cowboys fan since he was very young and passed on his team spirit to all of us – as if we really had a choice!

Paul's Dad has been a Cowboys fan since he was young and so our whole family became Cowboys fans. Last year the Cowboys hadn't been doing so great but in the middle of the season they put Tony Romo in as quarterback and he was AWESOME! Paul just **really** liked him. He's a great athlete, he's funny, and he loves to play sports – just like Paul.



Paul Wettengel



Clockwise from back left: Mary Wettengel, Tony Romo, Paul Wettengel, Sr., Matthew Wettengel, Patrick Wettengel and Paul Wettengel, Jr.

Two very caring representatives from MAW, Rose Mary and Michele, came to our house to meet the boys and fill out some paperwork. They brought presents and a really cool Halloween cake that they quickly gobbled down. We could hardly believe this was happening. They asked us what dates would work well and we gave them two dates. Michele followed up and let us know that Paul would meet Tony Romo on December 14th and go to the game on December 16th. A few days before our departure, Rose Mary and Michele brought the airplane tickets, some more goodies, and documents for the trip. They were very secretive about the details regarding the trip so we didn't know what to expect.

A limousine picked us up at 5am to take us to the airport to begin Paul's wish trip. We were treated like celebrities and really couldn't believe it was happening. We arrived and were greeted by more MAW representatives, Michael and Karen Wykrent. Again, we all felt like celebrities. Michael had the rental car all ready and waiting for us and we were on our way to the Westin Galleria in Dallas.

What a beautiful hotel! It was connected to a gorgeous mall that had an ice skating rink in the center. Needless to say, the boys also got to go ice skating as part of the trip.

The next morning we were greeted by Tisha Schwartz our MAW Dallas Cowboys representative. She had been doing this for 15 years and you could tell that she was a pro! She brought us to the Valley Ranch Dallas Cowboys headquarters. Paul was in heaven! We were greeted by Emily Robins and Whitney Brandon from Dallas Cowboys public relations. They greeted the kids with adorable Dallas Cowboys bears and since it was so close to Christmas, Dallas Cowboys Santa hats. We got a tour of the facility and then went to the locker room. Yes, the locker room! The players were practicing so we got to look around the locker room. Paul saw a note on Tony Romo's locker about his MAW visit. He could hardly believe his eyes! Then it was on to the practice field to see the team in action. It had been rainy, so the team was practicing at their enclosed field (they have 3!).



Paul with #9 Tony Romo!

There were all the guys Paul had seen on TV right in front of his face. There was Wade Phillips, the coach, Jason Garrett, the assistant coach, all the players and even Troy Aikman, the former Dallas Cowboys quarterback who would be covering the game as the FOX Sports announcer. This was more than Paul had imagined and then without any notice – in walked Jerry Jones, the owner of the Dallas Cowboys. What a surprise! He came right over and shook Paul's hand and even put his Super Bowl ring on Paul's finger. He walked Paul over to the end zone and explained what the coaches were doing during practice and who the players were on the field. I thought Paul was going to pass out and he hadn't even met Tony Romo yet!

After about forty-five minutes of watching practice, Emily and Tisha led us back to have lunch and meet Tony Romo. The boys began eating their lunches when Troy Aikman walked in to get his briefcase and then Tony Romo walked in the door. Since Paul didn't pass out at this point, I knew he would be ok for the rest of the trip. He was so excited but tried to remain calm. Tony was so friendly and really welcoming. Paul had developed a list of questions to ask Tony, so Paul with the help of his brother Matthew asked the list of questions, while Patrick, Paul's youngest brother ate his lunch next to Tony.

Here are some of the questions and answers from Paul's interview with Tony:

Q: "Were you always a quarterback?"

A: "No, I didn't start playing quarterback until I was in high school and I stunk." (We didn't believe him).

Q: "Do you have any brothers or sisters?"

A: "I have two older sisters. I'm the little baby." (Then he high-fived Patrick since they're both the youngest).

Q: "What do you do to prepare for a game?"

A: "I study."

Q: "What is your favorite food?"

A: "Vegetables! Just kidding – probably pizza, I'm a pizza guy."

Q: "Why did you pick number 9 for your number?"

A: "Because of the movie *The Natural*."

Tony autographed all the Dallas Cowboys memorabilia we brought and was such a great sport about it. There were lots of laughs and smiles and before my eyes I saw Paul's wish coming true! Tony told us he would see us at the game on Sunday.



Team lunch



On the field with Tony

On Sunday, we were ready for the game wearing all our best Dallas Cowboys apparel signed by Tony Romo. Tisha arrived and surprised us with a Hummer limousine to take us to the game! We felt like celebrities and driving into the stadium, people thought we were Jessica Simpson inside the Hummer. We got to go on the sidelines before the game and even got to high-five Tony. They lost the game to the Eagles, but we didn't care. It was the best trip of Paul's life! What a wish come true.

After the game and on our way back to the hotel, Paul still couldn't believe all that had happened in these few short days. He will never forget how special he felt and what special events and details were prepared just for him. Paul will be a lifelong Dallas Cowboys and Make-A-Wish fan!

For more information about the Make-A-Wish Foundation, visit them at www.wish.org.

Check out Paul's Make-A-Wish page at: http://www.wishni.org/wish_stories/wish_stories.html

Sixth-Annual PCD Family Education Weekend

July 18-20, 2008 Marriott Triangle Park, Durham, NC

Registration forms are now available for the PCDF 6th Annual Family Education Weekend (aka "Family Day"). The format and program will be similar to past meetings. Specific details will be posted as soon as they are available. Check online for updates. Access forms at: www.pcdfoundation.org or email/call the PCDF at info@pcdfoundation.org or 623-215-2032.

WE NEED YOU!

PCD Foundation Open Election for
Board of Directors, April 1, 2008

We are looking for a few good people to join our busy PCDF Board of Directors. Your skills as a parent, patient or professional dedicated to advancing the cause of PCD research and awareness will help us attain our important goals. For more information, please check the website at:

www.pcdfoundation.org/forms/PCDFApplicBOD.pdf
or contact the PCD Foundation at 623-215-2032.

Airway Clearance Ideas: The National Jewish Medical & Research Center Experience

Please note—the following is not intended as an endorsement of any particular form of airway clearance or specific protocol, but is provided for informational purposes only. CONSULT YOUR PHYSICIAN PRIOR TO MAKING ANY CHANGES IN YOUR TREATMENT REGIMEN.

At a recent conference about nontuberculous *Mycobacterium* (NTM) sponsored by National Jewish Medical & Research Center (NJ), a respiratory therapist presented information about NJ's preferences for airway clearance therapy, highlighting the need for diligent, daily therapy. This talk was given in the context of patients with bronchiectasis and NTM infections, but much of what was presented applies equally well to people with PCD.

At NJ, the basic airway clearance recommendation calls for high-frequency-chest-wall-oscillation (HFCWO; aka "vest") therapy. There are several options for HFCWO, including Hill-Rom (The Vest®), Electromed (SmartVest®) and RespirTech (InCourage™). In addition, they encourage patients to use a positive expiratory pressure (PEP) device with their vest treatments. There are several PEP devices on the market (details below) and any one of them will work. NJ's preference is the Acapella®, a handheld device that does not require positioning on the part of the user. They recommend the blue (for pediatric or low lung volume patients) or the green (adult) original versions of the Acapella®. They do not use the Acapella® Choice (the cleanable one) for now, because it tends to break easily. The manufacturer is working on this and hopefully will be able to come up with a solution to the breaking issue.

The speaker cautioned that she was presenting the regimen that NJ feels has been most successful, but that any form of airway clearance is better than nothing and each individual needs to work with their physician to determine the most effective therapy for them individually. She provided details about their recommended regimen as an example. NJ feels that they have had the most success with a protocol of vesting for 10 minutes (using the pressure and frequency prescribed for you), followed by five blows (exhaling only) on the Acapella® or other PEP device, followed by huff-coughing.* Repeat x 1 for a total of 20 minutes of vesting. NJ does not generally prescribe IPV (intrapulmonary percussive ventilation) devices for patients with bronchiectasis because, in their experience, the "jack hammer" effect can lead to hemoptysis (bleeding in the lungs). However, this is a widely accepted option in certain regions of the country so check with your own doctor before making a decision about IPV use.

Because bronchiectatic airways become "floppy" and can collapse from the pressure of coughing and trap mucus, NJ recommends not relying on cough alone for airway clearance—even if you have a vigorous cough. PEP devices (see below) essentially use positive pressure to stent the airway open, so mixed with the Vest to loosen secretions and cough to clear them out you may get better results. Also, the speaker emphasized the importance of not confusing lack of productive cough during airway clearance therapy with failure of treatment and suggested that airway clearance is happening with therapy regardless of whether you notice a demonstrable result.

Postural drainage (PD) is strategic positioning or tipping to facilitate the movement of mucus by gravity. It works great for some people and is used at NJ to help people get sputum samples up. However, not everyone can tolerate head-down positioning and you need to be sure you don't have any reflux issues before embarking on a postural drainage regimen. It is always a good idea to do PD on an empty stomach to prevent aspiration.

PEP-py Options**

In addition to the Acapella®, there are other options for PEP therapy, including the Flutter®, a handheld device that provides PEP therapy by the user blowing against resistance—a small steel ball, and Quake®, a PEP device that allows the user to control the amount of oscillatory vibration using a hand-turned crank that looks a bit like a fishing reel. All three are single-user devices (should not be shared!) that work during exhalation. Quake® provides percussion on inhalation and exhalation, but inhalation is not generally recommended for patients with infectious organisms. Acapella® devices are position and technique-independent. Both the Flutter® and Quake® require a minimal amount of user coordination—either with positioning or with being able to exhale and turn a crank simultaneously. None of these devices can be boiled or sterilized, which leads us to :

Keeping it clean*

Respiratory equipment can harbor infectious organisms, particularly organisms that reside in the respiratory tract of the person using the equipment. To avoid re-infection, it is important to clean equipment daily. Most PEP devices cannot be boiled or sanitized, so it is important to remember to only exhale into them—don't inhale. Check the manufacturer's recommendations for cleaning and clean and air dry daily. Your clinic may have cleaning equipment cleaning guidelines, as well. And don't forget to clean your vest device! Surfaces and tubing on most of these devices can be cleaned, but check with your specific manufacture to be sure.

*Directions for huff-coughing and tips for device cleaning are available on the National Jewish website at: <http://www.nationaljewish.org/disease-info/treatments/Using-Acapella-DM-DH.aspx>

**Link to a review of airway clearance technologies: http://www.rtmagazine.com/issues/articles/2006-07_06.asp

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genetic testing is limited to these known mutations. For this reason, clinicians who are interested in ordering a clinical genetic test for PCD should contact Ambry Genetics or the UNC Molecular Genetics Laboratory prior to ordering the test.

Interpreting the Results

Because PCD is a recessive disorder, genetic confirmation of the diagnosis requires positive identification of two known PCD mutations. When two mutations are identified, there is high specificity for a diagnosis of PCD. *However, a negative result or a result positive for only a single mutation does not rule-out a diagnosis of PCD, nor does it suggest that a clinical diagnosis of PCD is incorrect.* Individuals may harbor disease causing mutations not yet identified, therefore not detectable with current genetic panels. In this case, patients and their physicians may want to explore ongoing research studies which are seeking to identify additional disease causing mutations in these and possibly other genes. It is very important that genetic testing be part of a comprehensive clinical evaluation.*

Who Should Consider Genetic Testing?*

Ambry Genetics PCD Panel 61™ suggests that clinical genetic testing for PCD is appropriate for the following indications:

- Known or suspected PCD
- Chronic sinusitis or bronchiectasis not due to cystic fibrosis
- Suspected PCD with heterotaxy, situs ambiguus, or situs inversus (aka Kartagener syndrome)
- Congenital heart defect associated with recurrent respiratory disease or heterotaxy
- Chronic otitis media with effusion
- Male infertility with other signs of PCD
- Idiopathic respiratory distress in full-term neonates
- Carrier status determination for relatives of patients with known mutations

The decision to pursue genetic testing cannot be taken lightly. Interpretation of inconclusive results and access to genetic counseling regardless of the results, are factors to be considered before making the decision. Both Ambry Genetics and the UNC Molecular Genetics Laboratory are committed to working with patients and clinicians to ensure that appropriate candidates for testing are identified and that necessary follow-up is available to patients and ordering clinicians. For more information and contacts, please visit the following sites or contact the PCD Foundation:

Ambry Genetics PCD Panel 61™:

http://www.ambrygen.com/ts/ts_pcd.aspx

University of North Carolina, Chapel Hill, Molecular Genetics Laboratory:

<http://www.pathology.unc.edu/common/weck.htm>

<http://www.unchealthcare.org/site/labs/forms/dnah5>

**Adapted in whole or part from Ambry Genetics Fact Sheet on PCD Panel 61™*

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possible sensory role of primary cilia in the pleiotropic (having multiple any and varied effects) nature and pathophysiology of a variety of diseases.

While congenital ciliopathies have captured much research attention and have contributed considerably to our understanding of the role of cilia in development, a separate group of ciliary defects deriving from infection, irritant exposure, and inflammation also have been characterized. Unlike the homogeneity (showing a consistent, uniform, identifiable pattern) characteristic of congenital ciliary anomalies, acquired ciliary defects are more heterogeneous (varied and inconsistent) affecting ciliary membrane integrity and microtubular organization. Nonetheless, these secondary anomalies of cilia represent a component of the spectrum of ciliopathic disease that contributes to human morbidity and mortality.

Future research in the ciliopathies no doubt will benefit from improvements and innovations in imaging technologies as well as the emergence of new data from coordinated molecular genetic studies of cilia and flagella.

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News From the Primary Ciliary Foundation

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*The PCD Foundation
Education & Advocacy for
People with Primary Ciliary
Dyskinesia*

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Journal Watch NEW ARTICLES OF INTEREST TO THE PCD COMMUNITY

The National Library of Medicine (NLM) maintains a database of peer-reviewed articles from international medical journals. The peer-review process means that the article is subject to vigorous critical review by a panel of experts prior to being accepted for publication. This information can be accessed by the public at:

<http://www.ncbi.nlm.nih.gov/PubMed> or by typing "entrez pubmed" into your internet provider search function.

Bush A, Chodhari R, et al. *Primary ciliary dyskinesia: current state of the art*. Arch Dis Child. 2007 Dec;92(12):1136-40.

Tan SY, Omran H., et al. *Heterotaxy and complex structural heart defects in a mutant mouse model of primary ciliary dyskinesia*. J Clin Invest. 2007 Dec;117(12):3742-52

Schwabe GC, Hoffman K., et al. *Primary ciliary dyskinesia associated with normal axoneme ultrastructure is caused by DNAH11 mutations*. Hum Mutat. 2008 Feb;29(2):289-98.

Fliegauf M, Benzing T, Omran H. *When cilia go bad: cilia defects and ciliopathies*. Nat Rev Mol Cell Biol. 2007 Nov;8(11):880-93.

Lie H, Ferkol T. *Primary ciliary dyskinesia: recent advances in pathogenesis, diagnosis and treatment*. Drugs. 2007;67(13):1883-92.