United Mitochondrial Disease Foundation

MITOCHONDRIAL NEWS

Volume 8 • Issue 3 • Summer 2003

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The Genetics of Mitochondrial Disorders

Amy C. Goldstein, M.D.
(pictured left with Chuck Mohan at the 1st Annual UMDF 5K Walk/Run in Pittsburgh)
Carolyn Bay, M.D.
Pittsburgh Pediatric Neurology Association, Pittsburgh, PA and Children's Hospital of Pittsburgh, Department of Medical Genetics, Pittsburgh, PA

INTRODUCTION

Understanding the genetics of mitochondrial disorders is challenging. Indeed, it can be difficult to sort out the complexity of biochemical pathways and the different clinical symptoms, as well as the inheritance patterns of the different disorders.

To gain a basic understanding of mitochondrial genomics, a patient or family needs to learn about four aspects. These are:

1. The basic structure and mechanics of mitochondrial and nuclear DNA.
2. The process of identifying and understanding defects in the DNA.
3. The impact different defects have on the electron transport chain.
4. Significant disorders with complex inheritance patterns.

MITOCHONDRIAL GENOMICS

The human mitochondrial genome (mtDNA) is a circular DNA composed of 16,569 base pairs (bp) that encode for 13 protein subunits of the respiratory chain complexes, 22 tRNA (transfer RNA), and 2 rRNA (ribosomal RNA). tRNA and rRNA are genetic material required for the production of proteins. mtDNA is inherited only from the mother, as sperm do not contribute their mitochondria to the fertilized egg, only their nuclear DNA. A common misnomer about mitochondrial disorders is that they are inherited only through the mother. While a handful of disorders are maternally inherited, the vast majority of mitochondrial disorders are autosomal recessive in nature. For an excellent primer on the basics of genetics and inheritance patterns, refer to the UMDF web site at www.umdf.org (go to Information Center - Genetics).

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IMPORTANT NOTICE

UMDF Conference ☆ DATE CHANGE ☆

Mitochondrial Medicine 2004
Westin Hotel-Convention Center, Pittsburgh, PA

The UMDF recently learned that the scheduled dates for the 2004 symposium in Pittsburgh (previously publicized as September 16-19) include the two days of Rosh Hashanah. Holding the meeting on these dates would greatly reduce attendance. We will have the new 2004 date in the Fall issue. **We will also post the date change on www.umdf.org.**

Ask the Mito Doc

Living with mitochondrial disease presents many twists and turns - a maze of questions. UMDF is pleased to offer answers to some of those questions. All questions and responses are taken from www.umdf.org -- Ask the Mito Doc. Please note that information contained in Ask the Mito Doc is for informational and educational purposes only. Such information is not intended to replace, and should not be interpreted or relied upon, as professional advice, whether medical or otherwise.

Responders for this issue: Richard G. Boles, M.D., Children's Hospital of Los Angeles, CA and Brian H. Robinson, Ph.D., The Hospital for Sick Children, Toronto, Canada

The Question Is:

My son has mito complex 3. He is 26 and has had chest pain for over four years. Echo proved normal and all tests have shown no problems. It was decided he probably has esophageal dysmotility and was prescribed Prilosec and Carafate for over a year with no improvement and chest pain has become worse. Could there be any other explanation for chest pain and what type of specialist should he see next? He also recently sporadically developed purple splotches on his ankles and feet. Could this be related?

Response From:
Richard Boles, M.D.

Your son's physicians were correct in first considering gastroespheageal reflux disease (GERD) (because it is common) and heart disease (because it can be severe, even if it is not a common cause of chest pain). However, as you suggest, there are many other potential causes of chest pain, including those that are more common in individuals with mitochondrial disease.

Muscle pain is not uncommon in mitochondrial disease, and the legs (and arms) are the most common locations. However, I have seen cases in which pain mostly resided in the chest, side or back. I believe that often this is a neurovascular abnormality. As in many of these cases intermittent/transient changes in skin color (red, white or blue/purple), temperature (hot or cold) or size (mild swelling) can be seen. Again, these changes typically occur in the limbs, but not always. Many cases also have migraine, abdominal pain, and/or cyclic vomiting. If this is what the problem is, then treatment with amitriptyline (Elavil) or cyproheptadine (Periactin) might be helpful, and you should discuss this with your son and his physician.

The chest pain may not be related to mitochondrial disease; inflammation of the rib/cartilage joint (costochronditis) is the most common cause of chest pain in young adults. GERD is very common and often quite difficult to treat, and still may be the culprit here. There are also many rarer causes of chest pain.

If the purple blotches do not move or fade, even when putting pressure on them with your fingers (no blanching), then this is a problem with blood clotting or blood vessel rupturing. The chest pain could be due to the same process, and may be serious.

The Question Is:

I am about five weeks pregnant and a carrier of the t-c 8993 mitochondrial DNA mutation with 81% mutant mitochondria. I have one mildly affected daughter with 87% mutant mitochondria and one totally unaffected son, negative for the mutation. I have a CVS procedure scheduled in December and was wondering if this test will give me some idea as to the presence of the mutation and to the extent of the percentage of mutant mitochondria. I have read conflicting information on prenatal genetic testing and was curious if this test or possibly an amniocentesis would be helpful.

Response From:
Brian H. Robinson, Ph.D.

There is no definitive answer to the questions that this patient is asking, but there are some general guidelines for the T8993C and T8993G mutations which seem to be useful. First of all, in mothers with a high percentage of heteroplasmy, the chances of producing a child who will always be asymptomatic with a low heteroplasmy are lower than in mothers with low heteroplasmy. Results obtained prenatally either by CVS or amniocyte analysis have some predictive value although the correlates are not absolute. So, a result with low heteroplasmy in prenatal samples will have good indications for the fetus; higher values may be harder to interpret.

United Way and YOU!

It's that time of year again. Anyone interested in designating UMDF as the recipient for their gifts to the United Way, please email toni@umdf.org for guidance.

Chairman's Report

Two brothers decided to dig a deep hole behind their house. As they were working, a couple of older boys stopped by to watch.

"What are you doing?" asked one of the visitors.

"We plan to dig a hole all the way through the earth!" one of the brothers volunteered excitedly.

The older boys began to laugh, telling the younger ones that digging a hole all the way through the earth was impossible. After a long silence, one of the diggers picked up a jar full of spiders, worms and a wide assortment of insects. He removed the lid and showed the wonderful contents to the scoffing visitors. Then he said quietly and confidently, "Even if we don't dig all the way through the earth, look what we found along the way!"

Their goal was far too ambitious, but it did cause them to dig. And that is what a goal is for -- to cause us to move in the direction we have chosen; in other words, to set us to digging!

But not every goal will be fully achieved. Not every job will end successfully. Not every relationship will endure. Not every hope will come to pass. Not every endeavor

6th Annual Pittsburgh UMDF Golf Outing raises $28,441. Chuck Mohan presents UMDF's Pittsburgh Humanitarian Award to Anderson Interiors, accepted by Paul Quinn.

will be completed. Not every dream will be realized. When you fall short of your aim, perhaps you can say, "Yes, but look at what I found along the way! Look at the wonderful things which have come into my life because I tried to do something!"

It is in the digging that life is lived. And I believe it is joy in the journey, in the end, that truly matters. Every day poses new challenges as well as new opportunities but we have to be a participant, a player in the game of life, to see the challenges and seize the opportunities.

In 2002 the UMDF Trustees decided to "dig a hole all the way through the earth." The Trustees approved by motion and majority vote a more aggressive approach to encouraging and supporting research by increasing our annual research grants to:

2002:	250k	Awarded
2003:	500k	Awarded
2004:	1m	To be awarded in June/July
2005:	1.5m	To be awarded in June/July
2006:	2m	To be awarded in June/July

To the amazement of many we have been successful in our commitment and have awarded $750,000. This early success has already produced amazing results. The number of grant applications and the quality of those applications has risen significantly;

Continued on page 12

UMDF MISSION

To promote research for cures and treatments of mitochondrial disorders and to provide support to affected individuals and families.

Chapter Activities

ARIZONA CHAPTER

Phoenix, AZ
President: Karen Lipps
Phone: 623-694-5151
Email: AZChapter@umdf.org

Ashton Anderson Potluck Dinner

SPECIAL THANKS to . . .

Juli Pritsos, President of Orthodox Parent Association, Holy Trinity Greek Orthodox Cathedral, for her efforts coordinating the "Together We Can Make A Difference" - Ashton Anderson Potluck Dinner on April 5, 2003. The dinner raised $1010 for the Arizona Chapter.

And to Jessica and Mackenzie Lipps, along with their mother, Karen, for sharing their mito experiences with those in attendance.

Thank YOU...

The following guest speakers gave incredible information to the AZ Chapter. The chapter members appreciate their support and hope they'll visit them again in the future!

Adrian Lopez - Make A Wish Foundation

Renaldo Fowler - Arizona Center for Disability Law

Traci Jones - Muscular Dystrophy Association

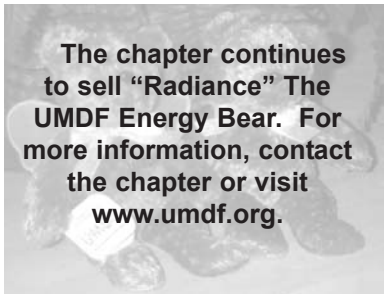
Sheryl Kelly - Children's Center for Neurodevelopmental Studies

Shelley Douglas - Children's Rehabilitative Services

Thank you for taking time to share your experiences and expertise with the AZ families.

AZ Chapter Members

Thanks to our chapter members who have gone above and beyond volunteering their time, energy and support: **Ben & Margot Anderson, Becky Lowe, Trudie Jones, Linda Kolze, Mike & Amanda Flitsch, Jane & JD Shumaker, Dee Straker, John Sheedy, and Daisy Dwyer**.



SOUTHERN CALIFORNIA CHAPTER

Lakewood, CA
President: Christine Trojahn
Phone: 562-438-5883
Email: SCalChapter@umdf.org

Southern California Chapter Welcomes New Officers as of July 1, 2003

President: Christine Trojahn
Vice President: Kathy Fares
Co-Vice President: Dave Fares
Secretary: Jen DeMeo
Treasurer: Alison DeVriendt
Membership Coordinator: Lee DeMeo
Fundraising: Laura Maese
Spanish Speaking Liaison: Luis & Norma Pina

Dear Families:

The torch of service is being passed to your new team, and what a team they are!!

THANK YOU - Christine, Alison, Kathy, Laura, Dave and Jennifer for stepping up to the plate and saying "yes" to service on a whole new level with the UMDF family.

God bless Christine, your new chapter president. I said jokingly to her, "Bring a truck, when you come to my home to get all the chapter files, paperwork and supplies." We had planned our 'pass the torch meeting.' Thank God she really had a truck, because we really needed one! I was amazed at all of the paperwork and files we had generated in just two years. I had a range of emotions handing over the goods. I realized what a big part the UMDF has played in my life, in helping me to maintain my hope, faith and positive attitude - simply by getting out of myself and BEING of service.

I am CERTAIN I have gotten back more than I have given.

I will miss my involvement with the Southern California Chapter.

From the bottom of my heart, I want to thank my sidekick and partner in crime - Linda Cooper. Her dedication went above and beyond the call of duty. Linda served as my Vice President, Secretary (for a period), AND Treasurer. One of the greatest gifts to come out of this is our friendship. Mark Clayton, our secretary - thank you for giving us precious energy on days that were rough for you and doing an excellent job to boot. Lissa Mirand - you have always done a great job; we have always appreciated your efforts and support.

As for me, I am moving to Arizona this August. I will remain as Chair of the 2004 Pittsburgh Symposium.

And forever and a day . . . I will carry gratitude in my heart towards the UMDF for allowing me to be of service.

Yours In Service Toward a Cure,

Sharon Shaw

Sharon Shaw

Chapter Activities

The Pisani Family, members of the NY Metro Chapter, have been very busy this year. On April 12th, they organized the Walk to Create Awareness and Health Awareness Picnic, raising $8,200. On June 7, they held a 50's Dance and raised another $1,205 to benefit the UMDF. Special thanks to the band, Smokin' Joe, for donating their services at the Knights of Columbus hall in North Haven.

The chapter would also like to thank Kids for Kids, Dancing for Life, Inc. for donating $1,000 to the UMDF.

NEW YORK METRO CHAPTER

Manhattan, NY
President: Joe Rice
Phone: 631-862-8975
Email:NYMetroChapter@umdf.org

The rain did not dampen the spirits of the NY Metro Chapter or the North Haven community on April 12th

NEW ENGLAND CHAPTER

Boston, MA
President: Justine Fargo
Phone: 781-396-4286
Email: NEngChapter@umdf.org

Friends of Cameron Picnic raised $8,427.53 on June 21st. The Genie Family organized this first-time picnic which included lunch, games for children, DJ, Chinese auction, and raffles. The picnic took place at the Moose Lodge in Chicopee, MA and more than 150 people attended - even in the rain!

Mark Your Calendars NOW!
4th Annual Mito-What?
5K Walk/Run

Sunday, October 5, 2003 in Longmeadow, MA, at Baypath College on Route 5

For more Walk/Run info, please contact: Jackie Tyler at 413-567-5435 or visit www.mitowhat.org.

Final total for Boston Bruins 50/50 Raffle was $10,847
Well DONE!

DELAWARE VALLEY CHAPTER

Philadelphia, PA
President: Maripat Shelly
Phone: 215-256-0273
Email: DelValChapter@umdf.org

DelVal Chapter's 4th Annual Shelly's Heroes 5K Run 1 Mile Walk and the Blosky Blast-off Family Fun Day raised more than $22,000 on May 10th, and the Hair Cuttery in Flourtown, PA held its second Cut-a-Thon to benefit UMDF, raising $1,444 on June 8th.

For more race pictures, see page 9.

Amanda Polsky shares her Pretzels with Pizzazz!

Looking ahead:

- 4th Annual Del Val UMDF Family Picnic is August 23, 2003
- 6th Annual *You Go, Girl!* Golf Outing, October 8, 2003
- 2nd Annual Fashioning Hope for UMDF, November 8, 2003

OHIO CHAPTER

Cleveland, OH
President: Jennifer Lyman
Phone: 330-929-4430
Email: OHChapter@umdf.org

On May 18th, the Junior Child Care Association (JCCA) President, Suzann Klein, presented Kevin Adelstein with a check for $1,000 to establish a JCCA Family Scholarship Progam "To Brighten the Lives of Children with Special Needs." The scholarship fund will be used to help Ohio families attend UMDF symposia.

UMDF Apparel

The Ohio Chapter is once again selling UMDF apparel including adult nylon hooded pullovers, baseball hats, and sweatshirts for all ages.

Order forms are available via the web site at www.umdf.org. If you prefer the form via fax or postal mail, please email the chapter at ohchapter@umdf.org or leave a message at 330-929-4430. Or contact the national office at 412-793-8077.

Below is a sample of the nylon pullover and the baseball hat.

Special Thanks to family and friends for sending donations (totaling $3,286) in memory of Larry Van Horn - loving grandfather of Caroline Lyman and constant inspiration to his daughter, Jennifer Lyman.

You never said I'm leaving,
You never said goodbye.
You were gone before I knew it,
And only God knew why.
A million times I've needed you,
A million times I've cried.
If love alone could have saved you,
You never would have died.
In life I loved you dearly,
In death I love you still.
In my heart you hold a place
No one could ever fill.
It broke my heart to lose you,
But you didn't go alone.
For part of me went with you
The day God took you home.

Author unknown

Check out all of the upcoming events for the chapter nearest you at www.umdf.org and help spread the word about mitochondrial disease in your community!

Tomato Face Foods™

Tomato Face Foods, a Division of A&B Cuisine, LLC, continues to grow. According to creator, Barbara Bruck, the no fat spaghetti sauce is available in the following: Heinen's Supermarkets (14 stores) in Northeast, Ohio; Jungle Jim's International Market (1 store) in Fairfield, Ohio; West Point Market (1 store) in Akron, Ohio; Ukrop's Supermarkets (26 stores) in Richmond, Virginia; Woodman's Food Markets (8 stores) in Wisconsin and (1 store) in Rockford, Illinois; Kroger's Supermarkets (63 stores in the NATURAL FOOD SECTION) in Indiana- (Indianapolis,Bloomington, Fort Wayne, South Bend, Lafayette) and in Illinois - (Peoria, Rockford, Decatur); Pipkin's Fruit and Vegetable Market (1 store) in Cincinnati, Ohio. Watch out Paul Newman - here we come!!!!

To date, the A&B has submitted over $800 to UMDF and the awareness raised in the media has been priceless!

Pictured left is Barbara Bruck and Chris Rice, UMDF Executive Director.

Vacation Toward a Cure

Courtesy of

AmericanAirlines®

Official Airline of the United Mitochondrial Disease Foundation

You Could Win ...

- Round Trip Coach Air Transportation for four to any American Airlines/American Eagle destination in the Caribbean, courtesy of American Airlines.
- $1,000 American Airlines Vacations Gift Certificate toward any affiliated hotel in the Caribbean.

All proceeds to benefit the United Mitochondrial Disease Foundation. Drawing Date: **November 15, 2003**. Drawing will take place at the UMDF Annual Meeting in Philadelphia, PA.

$5 per ticket

$25 for book of 6 tickets

For more information on buying or selling the tickets, please contact UMDF at 412-793-8077. Contest rules are available on the UMDF web site and/or noted on the raffle tickets.

Individuals who sell eight books of tickets will win a UMDF t-shirt (hunter green)!

Attention Groups and Chapters: Sell Vacation Toward a Cure Tickets and WIN!!!

Grand Prize
Group or Chapter selling the most raffle tickets (at least $5,000 wins)

$1,000 in scholarship money for members of your support group/chapter to attend the 2004 UMDF Symposium

Caribbean Celebration in a BOX!
For all groups and/or chapters selling at least $1,000 in raffle tickets.
Your group sells together and then can celebrate with a box full of goodies at your next meeting!

Future UMDF Symposia

We Want to Hear from YOU!

The 2004 date in Pittsburgh will be determined in the next few weeks based on space availability. However, UMDF would like your feedback for future years.

Best time for symposia

(please check all that apply):

☐	January	☐	August
☐	February	☐	September
☐	March	☐	October
☐	April	☐	November
☐	May	☐	December
☐	June	☐	No Preference
☐	July		

Please complete this form and send it to the UMDF, 8085 Saltsburg Road, Suite 201, Pittsburgh, PA 15239. You may also email to kara@umdf.org or fax to 412-793-6477.

UMDF Takes...

One Step

Together, We Can Make a Difference!

Closer to

A

Cure!

5K UMDF

On May 31, 2003, mitochondrial disease touched the lives of thousands in Ohio and Western Pennslyvania. The Ohio Chapter held its second annual walk/run and Pittsburgh held its first annual event to take UMDF "One Step Closer to a Cure."

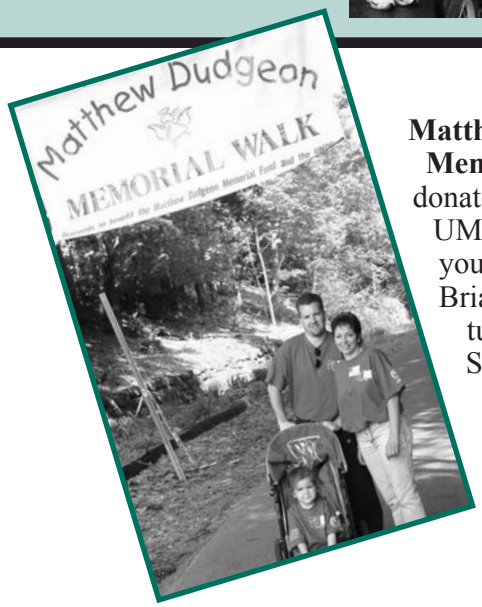
It rained, and rained, and rained -- but spirits of our UMDF members were high and dry! Friends, families, sponsors, volunteers, local media, and running enthusiasts helped UMDF raise more than $130,000 in one day -- Ohio leading the way with more than $113,000.

Plans are underway for 2004 for both Pittsburgh and Cleveland. The date is already set for both groups for Saturday, June 5, 2004 -- who else will join us?

More than dollars were generated on May 31st. Friendships have grown stronger and new friendships formed. Families gathered to share support and watch their children take pride in making a difference in the lives of loved ones.

Fundraisers

Raffle/In Loving Memory of Aspyn Block - family and friends organized a raffle and raised $3,984. Pictured left to right, Bev Block, Wayne Block, Stacy Block, Brenda Wiese, Tiffany Hanson, Rhonda Block and Fr. Cyprian of the Spirit of Life Church (in the back row).



Matthew Dudgeon Memorial Trust donates $23,000 to UMDF! Thank you Gina, Jim, Brian (not pictured) and Stephanie.

Fundraisers

4th Annual Ohio Golf Outing nets more than $94,000 for UMDF!

Pictured from right to left is Stan Davis, *Event Chairman and UMDF Trustee*, Jill Platt, and Amy Rogoff.

Delaware Valley Chapter's 4th Annual Shelly's Heroes 5K Walk/Run raises more than $22,000 on April 5, 2003. Kevin Shelly entertains the crowd with MAGIC!

New Groups Seeking Chapterhood

Indianapolis Mitochondrial Support Group raises $8,900 to benefit UMDF during the Indianapolis Ice "Pack the House Night."

Kansas City Mitochondrial Support Group held a benefit sale that resembled a one day flea market to raise money for UMDF. Special thanks go to Commercial Federal Bank for the facility use and assistance, the IAFF Local 2195 for their kind sponsorship and tremendous volunteers the day of the sale, and so many others. The benefit sale raised $10,252 for UMDF.

Gabriella Atchley pulls the winning raffle tickets

The Cans for Ashley Anderson continues its can recycling program in Fort Smith, AR. Thanks Randi, Sandi and Ashley!

Corvette Cruise 2003 - $300 in May, Monroeville, PA

Tierney Holiday Golf Tournament - $4,448, Philadelphia, PA

Kites for Kristen/St. Daniels - Pat Charleston strikes again and raises $10,129.77 to benefit UMDF. Keep up the great work, Pat!!!!

Events come in all shapes, sizes and ALL make a difference!

Baylee's Ball Bash (pictured above) for the UMDF raised $1,200 in its first year. Baylee's parents (Jody and Gary Thompson), family and friends held the tournament June 7th and 8th in Cannelville, Ohio. Planning to make it annual!

The Kuk Sool Won Kick-a-thon and Demo, organized by the Sibbaluca Family, of Petaluma, California, and Kuk Sool Won Academy took place on Saturday, June 21, 2003 from 10:00 a.m. to 3:30 p.m. at Lucchesi Park in Petaluma. They ended up doing 3025 kicks in the sun, raising $3400 -- they were TIRED and we were all impressed.

Annual Gibson Barbecue raises $4,265 in memory of Heidi Marie Daniel in Utica, CA

The Genetics of Mitochondrial Disorders

Continued from page 1

In any one cell, there can be a varying number of mtDNA copies, between one and 100,000, with an average of 1000 to 5000. Homoplasmy is a term that means that each copy of mitochondrial DNA (abbreviated as mtDNA) in a cell is identical; heteroplasmy means that there are variations in the sequence of mtDNA within the same cell. The degree of heteroplasmy correlates with the mutant load of the cell. A mutation can be pathologic (causing disease), or a polymorphism (a naturally occurring difference that is thought to be benign).

TESTING AND DIAGNOSIS

We can test for a number of disease causing genetic disturbances in either the mtDNA or the nuclear DNA. Blood can be analyzed (via Southern blot) for point mutations, deletions/ duplications, and depletions in the mtDNA. Skin fibroblasts and muscle biopsy samples (as well as other organ samples, for example: liver, or GI tract) can be analyzed for genetic mutations as well as measuring the enzyme activity of the complexes of the electron transport chain. Once a deficiency of enzymatic activity of one or more of the complexes is identified, the molecular basis for the deficiency can be further studied, looking for the most common causes of that particular deficiency. Not all causes are currently known, but each year more and more mutations in genes are identified, furthering our understanding of both the molecular basis, and the genetics, of the disease.

When an individual receives a genetic diagnosis, the family often has questions, including:

- What are the chances of having another child with the disease?
- Will my existing children develop the disease?
- Is there any increased risk that I will develop the disease?
- How is this disease transmitted to future generations?
- Is this disease identifiable prenatally (before birth)?

Before answering these questions, a doctor should thoughtfully research genetic evaluation and counseling of disorders of energy metabolism and mitochondrial disorders. Significant attempts should be made to identify the genetic etiology if possible on a DNA or molecular basis. Often one starts with enzyme activity testing, but accurate genetic counseling is best provided when DNA and molecular test results are available in addition to the enzymatic test results.

Unfortunately, we don't have testing for all mitochondrial disorders or disorders of energy metabolism. However, all testing that is currently available should be considered. That is why genetic counseling requires a true "team approach." Testing can be ordered by physicians of many backgrounds, particularly with experience in the evaluation and diagnosis of mitochondrial disorders and/or disorders of energy metabolism.

Once a DNA or molecular diagnosis is made, the team determines the most likely inheritance pattern and informs the family of the known inheritance patterns, known genetic risks, and whether prenatal diagnosis is possible. Occasionally, no abnormal molecular or enzymatic test result is obtained, but a clear pattern of inheritance can be discerned by careful analysis of a family tree. In those instances, genetic counseling can be provided. Ideally, the team consisting of a clinical geneticist experienced with the diagnostic evaluation of mitochondrial disorders, working with a certified genetic counselor, also experienced in the counseling of mitochondrial disorders and energy metabolism, can provide the most accurate and up-to-date information on genetic risks and options to interested family members.

Prenatal diagnosis is often possible in disorders that are due to abnormalities of regular nuclear DNA. It is more difficult however, in disorders caused by abnormalities of mtDNA, due to the difficulty in accurately predicting whether an individual will have symptoms, and how significant those symptoms will be.

Some researchers have considered prenatal diagnosis for two common mtDNA mutations (White et al. 1999). While prenatal diagnosis is possible, major concerns are:

- variable heteroplasmy in different tissues
- the possibility that the degree of heteroplasmy could increase over time
- the variation in the clinical disorders

The same genetic disease may have different clinical presentations, while the clinical picture may be identical in genetically distinct disorders (referred to as the genotype/phenotype correlation). This is an area that is being researched and individuals with questions in this area should seek individual genetic counseling sessions.

THE ELECTRON TRANSPORT CHAIN

To better understand the genetics of mitochondrial disease, we need to look at the "machinery" for which the DNA provides the blueprints. This is the electron transport (respiratory) chain, which is located in the inner mitochondrial membrane. Through its components, energy in the form of ATP is produced. In a lab, the

membrane can be treated with detergents to release 5 complexes:

- **Complex I (or NADH-coenzyme Q reductase)**
- **Complex II (or succinate coenzyme Q reductase)**
- **Complex III (or coenzyme Q H2-cytochrome c reductase)**
- **Complex IV (or cytochrome c oxidase)**
- **Complex V (or ATP synthetase)**

Each of the complexes is made up of multiple protein building blocks (called polypeptides) which are encoded for by either the nuclear DNA or the mtDNA.

Complex I deficiency

Complex I consists of at least 36 nuclear-encoded and 7 mitochondrial-encoded subunits. Mutations in either the nuclear genome or the mitochondrial genome can lead to complex I deficiency. Most cases of isolated complex I deficiency in children are caused by mutations in nuclear DNA and are of autosomal recessive inheritance.

Complex I deficiency was reviewed by Smeitink and van den Heuvel (1999), and they reported Complex I deficiency resulting from mutation in any one of several nuclear genes, including NDUFV1 (double mutation and single-amino acid substitution), NDUFS1, NDUFS2, NDUFS4 (duplication), NDUFS7, and NDUFS8 (double mutation). Other researchers (Triepels et al. 2001) reviewed Complex I deficiency and found that mtDNA mutations cause only a minority of cases.

Complex II deficiency

Complex II has four or five polypeptides, all encoded by the nuclear genome. Complex II deficiency can be caused by multiple mutations involving the flavoprotein gene and has autosomal recessive inheritance.

Complex III deficiency

Complex III has nine or ten components. Only cytochrome b (MTCHYB) is encoded by the mtDNA. Some researchers have confirmed that cytochrome b alterations cause isolated complex III defects in humans by analyzing the MTCYB gene in patients with mitochondrial disease (some with an isolated complex III defect and some without an isolated complex III defect) and healthy control subjects (Legros et al. 2001). On examining variations in the MTCYB gene sequence, two mutations were found in patients with complex III deficiency and both mutations were heteroplasmic and restricted to skeletal muscle. Both patients had symptoms of exercise intolerance.

Defects in complex III are reported as an autosomal dominant inherited form of mitochondrial myopathy. Mutations in MTCYB also contribute to Leber hereditary optic neuropathy (LHON).

It has been noted by some researchers that mutations in the MTCYB gene are often sporadic and can arise early in embryonic development, affect a limited number of cells and result in tissue-specific symptoms (Andreu et al. 1998, 1999). Some have also identified a point mutation in the MTCYB gene that was associated with histiocytoid cardiomyopathy (Andreu et al. 2000).

Complex IV deficiency (COX deficiency)

Complex IV has 13 subunits, 3 of which are encoded by the mtDNA. Deficiency of cytochrome c oxidase causes a variety of disorders in childhood and adulthood and can result from either nuclear or mitochondrial mutations. Cytochrome c oxidase deficiency can be caused by mutations in the SURF1, SCO2, COX10, or SCO1 genes, and result in different manifestations of the disorder, including Leigh syndrome, fatal infantile cardioencephalomyopathy, tubulopathy and leukodystrophy, and early-onset hepatic failure and neurologic disorder.

Researcher Eric Shoubridge provided a comprehensive review of cytochrome c oxidase deficiency in a 2001 article. He concluded that most isolated COX deficiencies are inherited as autosomal recessive disorders; mtDNA mutations for COX subunits are relatively rare.

Complex V deficiency

Complex V (ATP synthase) has 12 to 14 components, of which two (ATPase 6 and ATPase 8) are encoded by the mtDNA. Complex V deficiency can cause NARP (neuropathy, ataxia, and retinitis pigmentosa), Leigh syndrome, and Leber optic atrophy.

NARP is a maternally inherited disorder, due to mutations in the ATP synthase mtDNA gene.

OVERVIEW OF SELECT MITOCHONDRIAL DISORDERS

Maternally Inherited Mitochondrial Disorders

Two disorders that are due to maternally inherited point mutations are MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged-red fibers). There is marked clinical variability in these disorders, and this may be due to the degree of heteroplasmy, and what tissues are the most affected. Maternally inherited disorders are most likely due to a point mutation, where a single amino acid is substituted, therefore

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UMDF Board Decisions

The UMDF Board met by conference call on May 14, June 17, and July 16, 2003. Here are the significant decisions from those meetings:

- Initiated discussions with the Mitochondrial Medicine Society and Mitochondrial Research Society. UMDF wants to work more closely with both groups.
- Approved $500,108 in grants to six researchers. See page 13 for more details.
- Approved revised chapter bylaws. The revisions aligned the chapter bylaws with the UMDF bylaws and the chapter affiliation agreement.
- Approved a research commitment up to $1 million for 2003-04. This will be the funding for the grant program and other research approved by the Board.
- Approved an operating budget of $1,734,356 for 2003-04. This is the total planned expenses for the year, including the research commitment, member and group support, physician education, and office operations.
- Approved a position paper titled "The Establishment of Mitochondrial Centers and Clinical Trials." The document will be used in outreach and awareness activities with researchers, funders, and government agencies.
- Approved group and chapter operations requirements.

Chairman's Report *(continued from page 3)*

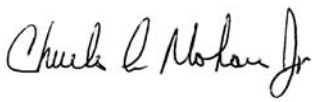
research in the development of techniques for early diagnosis has increased, as well as discoveries of new mitochondrial disorders. And perhaps most importantly, the number of new researchers in the field of mitochondrial disease is increasing. These are all measurable and tangible results we have found while "digging" our way to a cure!

Our immediate goal of raising an additional 4.5 million by 2006, with 1 million needed by 2004, sometimes gets sidetracked because uppermost in our minds is the final destination — the cure. Once we get there, our dreams will have come true, and the pieces of our lives will fit together like a jigsaw puzzle. How restlessly we pace the aisles, damning the minutes for loitering -- waiting, waiting, waiting for the destination, the cure.

What can you do, or more importantly, what have you done and what will you continue to do while waiting for the cure? There is much to see and experience on our way to the cure and there is no time to wait. We need more and more diggers pitching in along the way. We need you to make your days count rather than counting your days. We all need to continue to strive to "seek a common good beyond our comfort." We must all stretch beyond our individual comfort levels and do what we must rather than what we can.

There is no such thing as a small fundraiser or a small donation. They all become important pieces of the puzzle. Be part of the journey, pick up your shovels and dig! Who knows, you may be surprised at what you find along the way.

Yours toward a cure



Charles A Mohan, Jr.
Chairman, UMDF

I am only one, but still I am one;
I cannot do everything, but still I
can do something;
And because I cannot do
everything I will not refuse
To do the something I can do.
-Edward E. Hale

Mito Adults Corner

Calling all Mito Adults: The Mitochondrial News Needs YOU!

The UMDF has been fortunate to have some very helpful ladies contributing to the Adults Corner. Tara Collyer, Kathy Graff, Patsy Ann Kniel, Melissa Nixon, and Jean Shepherd have been doing a great job providing articles for the past three issues. THANK YOU!!!

However, as any mito patient knows, crashes tend to come on suddenly and many times (as with this issue), no one had the energy to submit an article. The following ideas were sent to the office by the committee and/or other UMDF members:

- Coping Strategies - On the Job
- Coping Strategies - On the Homefront
- Muscle Biopsies: Step by Step Experience or a Q & A
- Caregiving for your Loved One
- Applying for Disability Benefits

Our committee could use more helpers. Join the committee, submit an article for consideration or send us your experiences with the above mentioned topics. Or, maybe you have a topic of interest! If you are willing to help, please email Kara Strittmatter at kara@umdf.org or call 412-793-8077, ext. 106. We look forward to hearing from you!

Research Update

By Mark Fleming

UMDF Vice-Chairman, Research Coordinator and SAB Liaison

We are pleased to announce the UMDF 2003 grant cycle is complete and we awarded a total of $500,180 to some very exciting projects. This brings our total funding of research into mitochondrial medicine to more than $1,000,000 since the inception of the UMDF. Next year we are planning to double that amount by awarding up to $1,000,000 toward mitochondrial medicine research. Considering the economic times, the UMDF board realizes this may be a stretch. But we know the only way to beat this disease is to pour money into research. We welcome your participation in this effort.

Stan Davis, UMDF Trustee, presents check to Dr. Giovanni Manfredi. Also pictured (left to right) is Tom Shubeck (of NY Metro Chapter), Dr. M. Flint Beal, Joe and Patricia Rice (of the NY Metro Chapter).

With the addition of these projects to the four carry-over projects from 2002, we are now actively funding 10 projects. We are funding more concurrent projects than ever before. Of course, none of this would be possible if it weren't for the many supporters willing to give their time, energy and money. Thank you for your dedication and keep up the good work.

Please visit the UMDF web site at www.umdf.org for more details about the 2003 grant recipients. Researchers interested in the 2004 grant cycle may contact the UMDF for a grant packet or download it via the web site.

SAB Update

Our Scientific Advisory Board (SAB) continues to grow in size and activity. The following doctors have accepted the UMDF Board's invitation to join the SAB:

- Annette Feigenbaum, MB ChB, FRCPC, Hospital For Sick Children, Toronto, Canada
- Andrea Gropman, MD, National Institutes of Health, Bethesda, MD and Georgetown University Medical Center, Washington, DC
- David Nicholls, PhD, Buck Institute for Aging, Novato, CA
- Russell P. Saneto, DO, PhD, Oregon Health Sciences Center, Portland, OR
- Jan Smeitink, MD, PhD, Nijmegan Center for Mitochondrial Disorders, the Netherlands
- David Whiteman, MD, Mayo Clinic, Rochester, New York

2003 Grant Recipients

Researcher	Affiliation	Project Title
Giovanni Manfredi, M.D., Ph.D.	Weill Medical College of Cornell University	MtDNA Complementation and Recombination in Mitochondrial Disorders
Matthew Freeman, Ph.D.	Laboratory Molecular Biology M.R.C.	Role of Rhomboid Proteolysis in Optic Atrophy
Koji Okamoto, Ph.D.	University of Utah	Molecular Basis of Mitochondrial Membrane Dynamics: a New Paradigm of Human Disease
Immo Scheffler, Ph.D.	University of California, San Diego	Application of RNA Interference in the Study of NADH-ubiquinone Oxidoreductase (Complex I) Assembly in Mammalian Mitochondria
Bernard Lemire, Ph.D.	University of Alberta	The Use of the Yeast CYB2 Gene As Therapy for Complex I Mutations in a C. Elegans Model System
Mikhail Alexeyev, Ph.D.	University of South Alabama	Selective Elimination of Defective Mitochondrial Genomes as an Approach to the Reversal of NARP and MILS Syndromes, Heritable Mitochondrial Disorders

Continued from page 11

potentially changing the gene product.

Mitochondrial Depletion Syndrome

Several groups have defined mitochondrial depletion syndrome as a disease that involves overall depletion of the amount of mtDNA in affected tissues (up to 98%), while unaffected tissues have relatively normal levels of mtDNA (Moraes et al. 1991; Mazziotta et al. 1992; and Tritschler et al.1992).

Investigators have found no evidence of a mtDNA mutation or evidence of maternal inheritance, but suggested that mtDNA depletion may be of autosomal recessive inheritance, autosomal dominant with incomplete penetrance, or a combination of nuclear and mitochondrial factors.

Two main forms have been described, a hepatocerebral form and a myopathic form. The hepatocerebral form results from a mutation in mitochondrial deoxyguanosine kinase, while the myopathic form is associated with mutations in mitochondrial thymidine kinase (Moraes et al. 1991).

A reversible mitochondrial DNA depletion can be caused by certain medications, for example, an anti-retroviral medication used in HIV/AIDS patients. (Moraes et al. 1991).

Patients with mtDNA depletion in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome have been found to have mutations in the thymidine phosphorylase gene.

Mitochondrial Deletion/Duplication Syndromes

Identical deletions of mtDNA have been reported in Kearns-Sayre syndrome (KSS), Pearson syndrome, and chronic progressive external ophthalmoplegia (CPEO). For each disease, the mutant mtDNA is found in different tissues; in Pearson syndrome all tissues are affected, in KSS the muscle and the central nervous system are most affected, and in CPEO the mutations are localized to certain skeletal muscles.

Children who survive Pearson syndrome may develop KSS as the abnormal mtDNA decreases in blood and accumulates in muscle. The genetic mutations in Pearson/KSS are very complex and seem to involve both deletion and duplications of mtDNA.

X-Linked Disorders

Pyruvate dehydrogenase Complex deficiency due to a mutation in the E1alpha subunit is one of the most common genetic disorders of energy metabolism. The gene for this disorder is located on the X chromosome. Because of this, the disease most often affects boys. However, females also can be affected. Females with mutations on one of their two X chromosomes usually are asymptomatic carriers of the disorder, and are at risk for having sons with severe disease. However, some females, instead of being carriers, have very severe symptoms as well. Researchers are working currently on prenatal testing for this X-linked disorder.

SUMMARY

The best approach in understanding the genetics of mitochondrial disorders and how it relates to your particular diagnosis is the team approach. Review the clinical diagnosis and any inheritance patterns with a genetic counselor and, ultimately, pull together a team to assist in obtaining the most accurate and up-to-date information on the genetic risks and options to interested family members.

REFERENCES CITED

UMDF web site www.umdf.org

OMIM (Online Mendelian Inheritance in Man): #252010, 252011, 124000, 516020, 220110, 251880, 157650, 550000, 530000

Legros et al. *Europ. J. Hum. Genet.* 9: 510-518, 2001.

Mazziotta et al. *J. Pediat.* 121: 896-901, 1992.

Moraes et al. *Am. J. Hum. Genet.* 48: 492-501, 1991.

Smeitink, J.; van den Heuvel, L.: *Am. J. Hum. Genet.* 64: 1505-1510, 1999.

Triepels et al. *Am. J. Med. Genet.* 106: 37-45, 2001.

White et al. *Prenatal Diag.* 19:1165-1168, 1999.

Melas Angels Book For Sale

Joseph Yu and Joyce Yip-Li recently published a book called *Melas Angels* which tells the true stories of two brave girls (Angela Yu and Betty Yip-Li) and their struggle against mitochondrial disease. Joseph graciously donated 50 *Melas Angels* books to the Block Family for their raffle (see fundraiser on page 8). Interested in purchasing the *Melas Angels* book? Contact the UMDF office for more information at 412-793-8077.

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NEWSLETTER FEEDBACK FORM

Mitochondrial News contains the following sections in every issue. Please rate your interests in these sections, 5 = high interest and 1 = least interest (Circle one for each).

Sections	Rating				
Lead Medical Article	1	2	3	4	5
Ask the Mito Docs	1	2	3	4	5
Chapter Activities	1	2	3	4	5
Adult Corner	1	2	3	4	5
Secondary Article	1	2	3	4	5
(Research Updates, UMDF Development, Various Topics of Interest)					
Fundraisers	1	2	3	4	5
Chairman's Report	1	2	3	4	5
Donor Acknowledgements	1	2	3	4	5
(from past issues-NOT IN THIS ISSUE)					

Please provide topics of interest to you and your family:

_____

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Donor Acknowledgements

The UMDF deeply appreciates the ongoing support from our many contributors. Please watch for a new publication at the end of the year that will list ALL of our donors - from $5 to $500,000. This new publication will be coupled with our Annual Report.

The *Mitochondrial News* is intended to inform our members about mitochondrial disease, upcoming conferences, chapter events and activities, fundraisers and annoucements. It is our sincere hope that this transition will be well received by our supporters.

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We're Here to Help You! 412-793-8077

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Upcoming Fundraising Events

- September 27, 2003 - 2nd Annual Cooper Golf Open, Portsmouth, NH
- September 28, 2003 - 3rd Annual Cruisin' Toward a Cure, Pittsburgh, PA
- October 5, 2003 - 4th Annual Mito-What? Walk-Run, Longmeadow, MA
- October 8, 2003 - 6th Annual *You Go, Girl!* Golf Outing, Philadelphia, PA
- October 24, 2003 - Benefit Dinner, Nunno Family, Rutherford, NJ
- November 8, 2003 - 2nd Annual Fashioning Hope for UMDF, Philadelphia, PA

Check www.umdf.org for more upcoming events!

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UMDF MISSION
To promote research for cures and treatments of mitochondrial disorders and to provide support to affected individuals and families.

Deadline for next issue is 9/8/03