

FALL



PFIC.org Newsletter

Volume 4

October 2006

INSIDE THIS ISSUE:

The Inspiring Story of the Gayle Family	1-3
CETT Lab	3
Birthdays	3
PFIC 3 "MDR3 deficiency", or "ABCB4 disease"	4-6
Florida Organ Donor License Plate	7
Transplant Anniversary	7
Indoor Kid Fun	8

The Inspiring Story of the Gayle Family

By Kurk Gayle

Note:

When I heard Anna was diagnosed with liver disease I needed inspiration. Not just a little feel good story but a story that would inspire faith in miracles. I did not have to look far. A co-worker had a friend whose daughter was just that, a miracle. The Gayle family has been my inspiration. Hallie as a very young child had liver cancer. Why then put a cancer story as the front page of the PFIC newsletter? Originally the story was going to be on the benefits of blood donation. Julie, Hallie's Mom works at Carters Blood Bank and we had spoken about having a blood donation story. I think the real story here isn't about donating blood but how miracles unfold. What better story to put on the front page?

Robin Marceca

By Kurk Gayle

It's Personal

My good friend Gerry recently asked why I donate blood. He saw the bright green band wrapped around my arm, and was curious as to why someone with a full and hectic schedule would take time to give blood. "Is it for all the free T-shirts you get?" he asked.

"That's the short answer," I replied. But he already knew the long answer, the one much closer to my heart. He knew because Gerry and I often talk about our families, our kids, especially our daughters. They're at that age that has us both mystified and feeling slightly left out.

These days it's my daughter's friends, her cell phone, the computer and a hair straightener that get all the attention. I try, but my attempts at conversation usually result in a good eye-roll, which is something she's amazingly good at. Gerry says this is typical behavior for a 13-year-old girl. And he's probably right. But to me, my daughter Hallie is anything but typical. This year marked the ninth year of her cancer survivorship. And that's how the long answer begins



It's Personal

In May, 1994, Hallie was only 20 months old when my wife, Julie, brought her into the pediatrician for a fever. She had not been her typical funny, energetic self. "It's probably just a virus," the pediatrician said. But in just a week, the high temperature continued and our baby's stomach was swollen. The second time at the doctor's office, Julie phoned me: "Please come fast. They think Hallie has a tumor."

Stunned and close to fainting, I sped to the clinic. (Thank God for adrenaline to wake a man from anemic shock.) Hours after Hallie endured pokes, and X-rays, and exploratory surgery, we found ourselves in the cold boardroom of the children's hospital, surrounded by physicians whose somber faces denied us a single sign of reassurance. And then they spoke the word -- that dreaded "C" word: "We're afraid your child has cancer."

The Fight

The specific diagnosis was hepatoblastoma, a rare liver cancer found in less than 100 children a year in the United States. "A dreadfully poor diagnosis" was the way one oncologist phrased it. Treatment would require several rounds of chemotherapy and then, if possible, the surgical removal of the tumor. But the chemotherapy guaranteed only an initial attack on the cancer cells and a certain poisoning of healthy cells as well.

Hallie's beautiful red hair was the first casualty the first visible casualty that is. Inside, she also endured mouth sores, aches in her tiny legs, and the loss of red blood cells and platelets. So she wore fancy hats. We swabbed her ulcers and watched the lab charts as her numbers dropped. Eventually, her rosy cheeks and lips grew ashen from the lack of oxygen supplied by healthy red blood cells.

My fighter fought on. She didn't choose this battle, but she was always brave, maybe a little stubborn. As her ally chemotherapy brought her to the lowest points, I was glad when physicians ordered blood transfusions. Exhausted in her hospital bed, Hallie would usually sleep as the ruby red cells were slowly transfused into her body from a bag hung nearby. The entire process took no more than two hours, and by the end of the transfusion, she was back in true form, jumping on the bed, making it difficult for the nurses and her mother to disconnect her from the IV pump. I never counted the number of units of blood and platelets Hallie received throughout treatment. I do know the transfusions became routine, and in her fight against cancer, were invaluable reinforcements.



Transplant

After eight months of chemotherapy, there was the radical, surgical attempt to remove Hallie's cancer. For a few months, it seemed a success, until the deadly tumor came back. The last hope was a liver transplant, a long shot. Liver transplants in children were uncommon. Worse than that, a study of one dozen transplanted cancer kids in 1995 showed a death rate of 50%. There wasn't a life-after-cancer champion to be found. The live-strong Lance Armstrong was still four years away from his own first encounter with the deadly disease and more than a decade away from his unprecedented seven consecutive victories in the Tour de France. For Hallie, such a great hero might as well have been a hundred years away. She was destined to her own uncharted triumphs.

I was honored to play a role in this champion's story. In addition to being her *Daddy*, I was given the rare opportunity to be my daughter's liver donor. When it came time for a transplant, Hallie's oncologist, Dr. Paul Bowman (of Cook Children's Medical Center in Fort Worth) referred her to Dr. Jean Emond (of the University of California at San Francisco Medical Center), who is a pioneer in living-related liver-donor transplants, a procedure considered experimental at the time. Dr. Emond and his extraordinary team found me (and the left lobe of my liver) to be a suitable match for Hallie. I was delighted that this might be her cancer cure.

And we were all thrilled the blood supply was strong, because (according to University of Iowa estimates) "the average liver transplant patient needs 40 pints of red blood cells, 30 pints of platelets, 20 bags of cryoprecipitate, and 25 pints of fresh frozen plasma." Both my wife and my father donated blood for Hallie's surgery. Although I never knew the

exact number of units used for her transplant, I do know that having the blood available was critical to its success.

A Beautiful Reason to Give

The long story short does end happily ever after. Today Hallie is, in my opinion, a beauty. She's physically strong, willfully strong and deeply compassionate. Hallie is an A student, a loyal friend, a fun sister, and a daughter who makes me proud -- even when I get the eye roll.

So, I wear my Carter BloodCare T-shirts with pride, and I've even convinced my friend to give blood, despite his busy schedule. He joins me -- because he knows my story, and he has a daughter, and we know the blood we give will make a difference in some remarkable life.

Collaboration, Education, and Test Translation (CETT) LAB

The CETT lab application to set up the translational genetic tests for PFIC has recently been approved and funded. In October Dr Wong will be setting up the Clinical Laboratory Improvement Amendments (CLIA) approved clinical service. CETT will be working with CLiC researchers to provide clinical diagnosis to treating physicians. PFIC.org has been asked to be the advocacy group for the CETT lab. As more information is received look for it to be posted in the PFIC.org Forum page. For more information on what CETT is check out their web-site <http://www.cettprogram.org/>

A Special Day to Celebrate

Happy Birthday Caden

Caden will be 2 on Nov 23rd.



PFIC 3 “MDR3 deficiency”, or “ABCB4 disease

By Alex Knisely, MD

Consultant Histopathologist

Institute of Liver Studies

King's College Hospital

Some persons will have come to this website to learn more about a disorder called “PFIC-3.” A more precise, and less confusing, name for the disorder is “MDR3 deficiency”, or “ABCB4 disease.” Just different spoonfuls of alphabet soup, I can hear people saying – but let me try to set out why I think the distinctions matter.

The shorthand name for one of the clinical-laboratory studies, or “blood tests”, done to monitor children with liver disease is “GGT”. GGT stands for “gamma-glutamyl transpeptidase.” This is an enzyme, a protein that speeds up a chemical reaction. Samples of blood serum (what is left of blood after clotting has occurred and the clot is separated out) contain some GGT. The concentrations of GGT activity in serum can be measured in different ways; the values obtained are used to track the severity of cholestasis. In all but a few forms of cholestasis, GGT values rise in parallel with bilirubin values. (Bilirubin is the yellow substance that gives jaundice its color.)

“PFIC” was originally defined as the class of rare inherited childhood liver disorders in which GGT values did *not* rise in parallel with bilirubin values. “PFIC-1” was the first member of that class to be described, the original “Byler disease”, and the first member for which a responsible gene was identified. “PFIC-2” was the second member to be distinguished, and the second member for which a responsible gene was identified. The search continues for others.

In “PFIC-3”, however, GGT values are not low. They are high.

So confusion has been great. Doctors and nurses are puzzled – can there be a “high-GGT” form of PFIC, when the definition of PFIC requires that GGT values be low? (In my opinion: No; logically there can't.) Many other inherited childhood liver disorders, as well as even more acquired childhood liver disorders, are characterized by high GGT values. More puzzlement – my patient or my family member, who has a small child, has “high-GGT” liver disease; does (s)he have “PFIC-3”? (Not necessarily.)

Those puzzled questions, I think, are the result of a misleading name, one that has got even medical professionals muddled. I'd rather that the terms used to describe any disorder be clear and specific, and that's why I prefer the designations “MDR3 deficiency” and “ABCB4 disease” to “PFIC-3.”

What, then, are “MDR3” and “ABCB4”?

MDR3 is an officially approved abbreviation for an enzyme called “multidrug resistance protein 3.” (The third identified member of a set, that is, of proteins that in structure resemble “multidrug resistance protein 1”, which acts to push various substances out of liver cells.) Yes, there are committees of scientists that track, evaluate, and assign names to newly discovered substances, to ensure that everyone sings from the same page of the hymnbook. The officially approved abbreviation for the gene encoding MDR3 (providing the cell with instructions on how to make MDR3) is *ABCB4*, short for “ATP-binding cassette gene class B, member 4.” Defects in *ABCB4* – gene designations are put in *italics*, if you were wondering – lead to complete or partial lack of working MDR3. This lack then causes disease of the liver, including the bile ducts.

How does that happen? To explain that, I have to describe what MDR3 does in the healthy liver.

MDR3 contributes to forming bile. Bile is a mix of water, and salts, and bilirubin pigment, and wastes or toxins that the liver has partly broken down, and fatty substances called lipids, and detergents called bile acids. Without MDR3, the bile is deficient in one of those fatty substances, a lipid called phosphatidylcholine. The tiniest branches of the biliary tract (the bile canaliculi) have walls made of parts of liver cells (hepatocytes). Those walls, or membranes, are two layers thick. MDR3 in the hepatocyte spans the inner and outer layer of the canalicular membrane and

PFIC 3 “MDR3 deficiency”, or “ABCB4 disease –Continued

moves phosphatidylcholine from the inner layer to the outer layer.

A quick digression about “detergents.” That oil and water don’t mix is proverbial. Detergents, however, let such substances mingle with one another. Laundry detergent breaks up grease and lets it disperse in water. Bile acids inside the small intestine break up the fat in what we’ve eaten and let it disperse in the mix (mostly water) of partly digested food. Once the fat is dispersed, the cells that line the intestinal wall can take it up. Without bile acids, we can’t absorb fat, or fat-soluble substances like some vitamins, from our diet. This is why cholestatic children require vitamin supplements: Bile acids in such children aren’t making the journey from hepatocytes to small intestine.

Let’s head back to the membranes that line the biliary tract. If MDR3 is present in the canalicular wall, and if the MDR3 present is working normally, the outer layer of the canalicular membrane will contain phosphatidylcholine. Under the influence of bile acids, then, phosphatidylcholine can float out of the membrane and into the bile, like a grease spot out of a work shirt and into the wash water. In the bile the phosphatidylcholine forms a complex with the bile acids and acts as a “chaperone.”

The action of phosphatidylcholine as a chaperone – sticking close to the bile acids and keeping them from causing trouble, like teachers watching rowdy teenagers on Prom Night – is essential because bile acids are very corrosive substances. The canalicular membranes, and the membranes of the cells that line the bile ducts, contain large quantities of lipids. If bile acids in the bile are not chaperoned by phosphatidylcholine, they will attack the membranes and injure them by leaching lipids away. This sort of injury can lead to cell death or dysfunction. Cell death and dysfunction in the hepatobiliary system lead to jaundice, and itching, and inflammation, and scarring, which eventually may be fatal without a liver transplant.

And that is the sequence proceeding from mutation in *ABCB4* (or *ABCB4* disease) to absence or malfunction of MDR3 (or MDR3 deficiency) to unhappy, undergrown, scratching, yellowish, miserable children on the transplant waiting list.

Why are GGT values high in MDR3 deficiency? Because GGT is present in large quantities in the canalicular and bile-duct membranes (mostly canalicular). When those are damaged, GGT is released into the bile. GGT then leaks across the wall of the biliary tract into the blood and the concentrations of GGT activity in the serum rise.

Why are GGT values low in PFIC-1? Because GGT is lacking in the canalicular membranes in that disorder – if it isn’t there, it can’t be released.

Why are GGT values low in PFIC-2? Because bile acids are not normally pumped into bile in that disorder – although GGT is present in the canalicular membranes, without the detergent action of bile acids the GGT can’t be released.

MDR3 deficiency has a broad clinical spectrum. In total deficiency, the effects are quite severe, often are evident in early childhood, and can require liver transplantation for relief. In partial deficiency, the effects are milder. They may include gallstones, or off-and-on itching, and may show up only in adulthood or even middle age. When MDR3 deficiency is suspected in adults, two principal approaches to diagnosis exist. When it is suspected in young children, a third approach also can be useful.

Most definitive, of course, is analysis of *ABCB4*, looking for gene changes that can be predicted to disrupt gene function. This is expensive and takes a long time. In some cases, the abnormalities found are not clear-cut, and additional studies must be done. It is most useful for families who want to take advantage of prenatal diagnosis.

A reasonable tack to take is to analyze bile itself to learn if phosphatidylcholine is deficient. Such deficiency can be inferred, if other things fit the picture, to be the result of lack of MDR3, or of subnormal MDR3 function. (Sampling bile, however, is not an easy business, particularly in the very young.) Bile analysis can permit the diagnosis of *functional* deficiency of MDR3.

PFIC 3 “MDR3 deficiency”, or “*ABCB4* disease –Continued

Genetic analysis and bile analysis can be used in diagnosis of both severe and mild forms of MDR3 deficiency. For severe forms, immunohistochemical studies of liver biopsy materials also can be conducted. Antibodies that tag MDR3 protein are used in this approach. If no MDR3 protein can be demonstrated in liver tissue, as shown in Figure 1, *actual* (rather than functional) MDR3 deficiency can be diagnosed. If the antibodies react, and if the pattern of reaction is appropriate, then MDR3 is present, as shown in Figure 2. This does not give any information, however, on how well the MDR3 actually functions. Persons with disease manifest after infancy likely have some MDR3 protein – protein that works, but that that does not work very well. Immunohistochemical studies are not conclusive in such cases. Persons with disease manifest in infancy, that is, with severe clinical signs and symptoms, are more likely to lack all MDR3 protein, and are better candidates for immunohistochemical study of liver biopsy materials.

So far, to my knowledge, no one has been found who has functional severe MDR3 deficiency, as demonstrated by analyses of bile that show phosphatidylcholine to be almost totally absent – and who has documented *ABCB4* mutations – and who has no lack, on immunohistochemical study, of MDR3 protein along canaliculi in a liver biopsy specimen. But such a person will almost certainly be found, because some mutations in other genes like *ABCB4* lead cells to make forms of proteins that are normally handled by the cell, going to the right places and reacting properly with antibodies, but do not perform their usual function at all. In my opinion, it is just a matter of time till a person with this sort of *ABCB4* disease shows up. When immunohistochemical studies demonstrate no MDR3 protein, the test has given a clear answer: “Severe MDR3 deficiency is present.” When they demonstrate MDR3 protein, the answer can only be: “This study does not support the idea that severe MDR3 deficiency is causing this patient’s disease. However, it also does not disprove that idea.”

Figure 1. Antibodies against MDR3 did not react in this liver biopsy specimen from a boy with itching, mild jaundice, high serum GGT activity values, and a family history of liver disease. The diagnosis of severe MDR3 deficiency can be made. Compare with Figure 2.

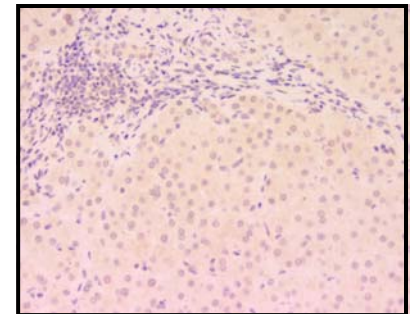


Figure 1

Figure 2. The fine network of canaliculi – little canals – among hepatocytes is well demonstrated in this liver specimen from an adult (who required liver surgery for a tumor but was not jaundiced). Antibodies against MDR3 were allowed to incubate with tissue sections; then another antibody, bearing a pigmented tag, was used to show where the first antibodies had united with the tissue. The walls of the canaliculi mark well for MDR3. Compare with Figure 1.

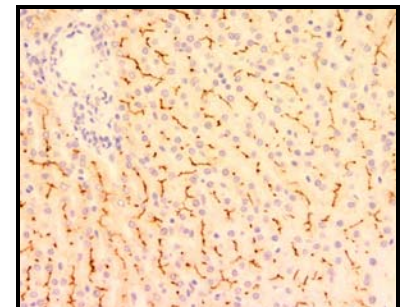


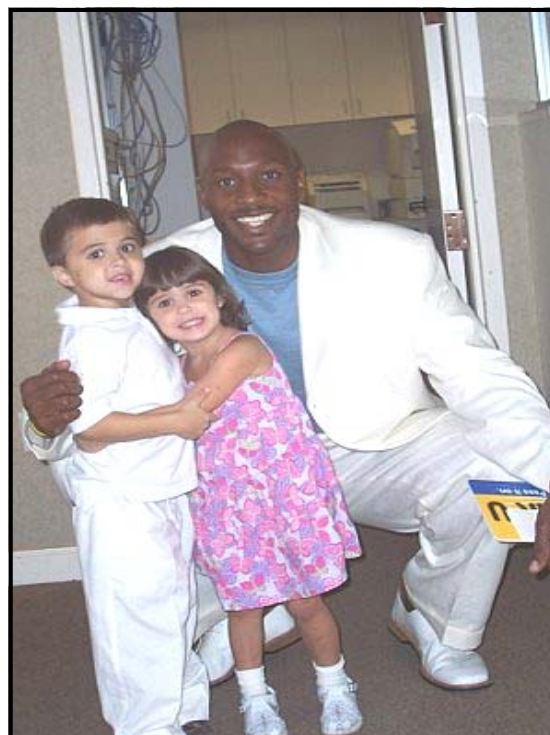
Figure 2.

Florida's Ad for Organ Donor License Plate

The kids, Gilbert and Gabby, took some pictures today with Alonzo Mourning from the Miami Heat. Alonzo received a kidney transplant a few years ago. The state of Florida is finally getting an organ donor license plate and the kids with Zo will be in the ad campaign.

Also please help me wish both Gilbert and Gabby Happy Birthday! Gilbert turned 7 years old Sept 3rd and Gabby will be 4 years old Dec 16th.

By Mom Susan



Donate Organs-Pass it On

Specialty License Plate

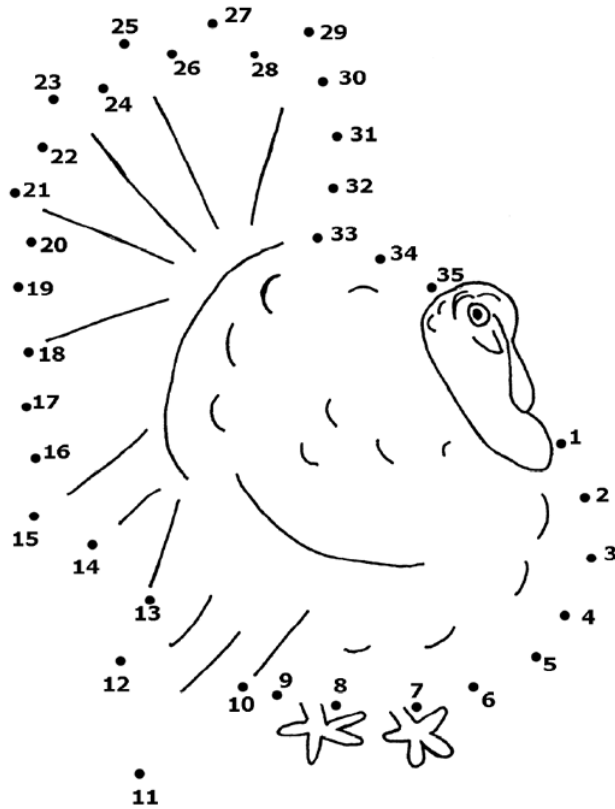


A Special Anniversary

On December 21st, Anna will celebrate her 3 year liver transplant anniversary. She will be giving out organ donor lapel pins and organ donor cards to celebrate.



Turkey Fun



Gobbler Groaners

Q. If April showers bring May flowers, what do May flowers bring? A. Pilgrims

Q. Why do turkeys go "gobble, gobble"? A. Because they never learned good table manners

Q. What kind of music do Pilgrims listen to? A. Plymouth rock

Q. How do you make a turkey float?

A. Get two scoops of ice cream, add some root beer and a turkey.

Q. What do you get when you cross a turkey with an octopus?

A. Lots of drumsticks for Thanksgiving dinner



Handprint and Footprint Turkey for Indoor Fun

Materials:

- paper, construction paper, or gift wrap
- scissors
- glue
- something to color with
- Optional decorations, glitter, plastic eyes,

Directions:

Trace around child's foot on brown paper or a brown paper bag. Cut out foot this will be the turkey body.

Trace around child's hands on multiple sheets of colored paper and cut them out. These will be the feathers. For a family turkey try tracing the whole family's hands for the feathers.

Glue the hand prints to the turkey body.

Design and cut out the turkey beard, beak, and feet. Glue these on too.

Now glue on or color on the eyes.

Decorate if desired

Your Turkey is complete!

