MEDICAL EXPERT REPORT FOR

Jianhua Xie

16 May 2014

EXPERT CONSULTANT(S)

Barbara Kay Burton

Best Doctors®

Table of Contents

Report Summary 3

Expert Findings 4

Clinical Overview 8

Report Summary for Jianhua Xie, 16 September 2012

This Best Doctors' Report Summary highlights and clarifies the key points of your Expert report(s). You can use this as an aid when you read the report(s) and in the future when you review and discuss the report(s) with your treating physician(s). We are always available to you and your treating team should there be any additional questions or concerns.

Dr. Burton recommends that you and your treating physician(s) review and consider the following assessment and options:

- The diagnosis of Jianhua's micronodular cirrhosis remains unclear.
- Many disorders have been effectively ruled out, but it remains possible that he has some type of rare underlying metabolic disorder.
- A fatty acid oxidation disorder is very possible, particularly as he has apparently responded to a low fat diet with medium chain triglycerides (MCT). Additionally, a fatty acid oxidation disorder is made more likely by the fact that Jianhua had not seemingly been exposed to an MCT containing formula prior to the abnormal urine organic acid testing on 4/11/2013.
- It is recommended that Jianhua's geneticist contact Dr. Jerry Vockley at the Children's Hospital of Pittsburgh to determine if he could assay ACAD9 enzyme activity in skin fibroblasts. This would allow determination if he has ACAD9 deficiency with a 2nd undetectable mutation.
- Continuing his current diet, which has reportedly been helpful, is recommended.

Expert Findings for Jianhua Xie, 16 September 2012

6 May 2014

To: Dr. Lewis Levy, MD, VP of Corporate Medical Quality Best Doctors
From: Dr. Barbara Kay Burton, MD, Best Doctors Expert Consultant
Re: Jianhua Xie, DOB 16 September 2012

Dear Dr. Levy,

I have reviewed the case summary and laboratory data provided to me on Jianhua Xie. Jianhua is a 20 month old boy who presented with fulminant hepatic failure and was found on liver biopsy to have micronodular cirrhosis of undetermined etiology. Liver transplant was considered but function has since improved so this is on hold. Extensive testing failed to yield a definitive diagnosis to explain the liver disease. Whole exome testing did reveal some findings of uncertain significance. The parents are concerned about the possibility of a fatty acid oxidation disorder and have treated Jianhua with a low fat diet supplemented with MCT. He has been seen by a biochemical geneticist who reviewed the whole exome results and did not feel there was convincing evidence for a fatty acid oxidation disorder. The specific questions posed to me and my responses are as follows:

1. What is your overall assessment of the patient's condition? **The patient's diagnosis is unclear. He has had an extensive evaluation with no definitive diagnosis suggested by the tests obtained thus far. I think it is possible that he has an underlying metabolic disorder. If so, it is one that is rare or difficult to identify since many metabolic disorders have been effectively ruled out by the testing conducted thus far.**

2. Jianhua's family asks about the significance of his newborn screen test results. Some of the values appear high when compared to normal ranges on subsequent testing. **This comparison is not valid. Normal ranges for all metabolites vary by age of the patient. We do not expect the same levels in newborns as we see in older children. Similarly, normal ranges vary in different laboratories. Therefore, the newborn screen results can only be compared to the normal ranges for newborns established by the laboratory that did the newborn screening testing. Since all of the newborn screening tests were interpreted as normal, this would indicate that the values fell within their normal ranges.**

Jianhua's family notes that his urine organic acids from 4/11/13 showed very high levels of adipic , seberic and sebacic acids and want to know if this could be related to a mitochondrial fatty acid oxidation defect. **This is a non-specific finding. It can be seen in fatty acid oxidation defects but can also be seen in patients who are ingesting medium chain triglycerides (MCT) in the diet.**

4. Looking specifically at thea acylcarnitine profile and urine organic acids, is any metabolic disorder suggested , including a fatty acid oxidation defect? **NO**

5. The family notes that whole exome sequencing noted a mutation in the ACAD9 gene. In the final column, it states "tolerated/probably damaging". What is the significance of this? **The ACAD9 gene has a role in fatty acid oxidation and in assembly of complex I in the mitochondria, which has a major role in cellular energy production. A mutation is a change in the alphabet of the gene. It may or may not change the function of the gene. If it does not, it is not disease causing and is a harmless or benign change and is "tolerated". If it alters or knocks out the function of the gene, it may cause disease and is said to be pathogenic or damaging. Often changes in genes are detected where there is no information on how they affect the function of the gene since they have**

not been found in other patients. In these cases, computer programs or other systems can be used to try to "guess" how the change would affect gene function. Sometimes the answer is unclear as apparently was the case with the ACAD9 gene mutation detected in Jianhua I think we should assume it is damaging since a problem with this gene could be consistent with the clinical findings. However, two mutations in this gene are usually required to cause disease. Testing was done to try to determine if there was a second mutation in the other ACAD9 gene. A search was done for a deletion or duplication in that gene and none was found. However, it is still possible that a second mutation is present since none of the available testing is able to detect all mutations.

6,. What additional testing do you recommend? **I recommend that Jianhua's geneticist contact Dr. Jerry Vockley at the Childrens Hospital of Pittsburgh to determine if he could assay ACAD9 enzyme activity in cultured skin fibroblasts.This would allow him to determine if Jianhua has ACAD9 deficiency with a second undetectable mutation. The fact that he has apparently responded to a low fat diet with MCT is suggestive of a fatty acid oxidation disorder and patients with ACAD9 deficiency can have a normal acylcarnitine profile. If this testing can be done, then Jianhua will need a skin biopsy with fibroblast culture.**

7. Based on the available testing, can any specific treatments or diet supplements/restrictions be recommended? **No. However, since Jianhua has apparently done well on his current diet, I would continue it with supervision by a metabolic nutritionist.**

8. How would you recommend following this patient? **He should be followed regularly by a hepatologist, metabolic specialist (biochemical geneticist) and by his pediatrician.**

9. Please provide any further recommendations you believe will aid in understanding the patient's findings. **No further recommendations.**

10. Please provide any scientific references that support your assessment and which may be helpful to the treating physician. **None**

In summary, Jianhua is a 20 month old boy who presented with acute liver failure accompanied by hypoglycemia. He was found to have micronodular cirrhosis of undetermined etiology. Whole exome sequencing identified one mutation in the ACAD9 gene and the patient has improved on a low fat diet with MCT supplementation. I recommend that there be further efforts to evaluate the possibility that Jianhua has ACAD9 deficiency by assaying ACAD9 activity in cultured skin fibroblasts. In the interim, he should continue on his current dietary restrictions.

Sincerely,

Barbara K. Burton, MD

Professor of Pediatrics

Northwestern University Feinberg School of Medicine

Division of Genetics, Birth Defects and Metabolism

Ann and Robert H. Lurie Children's Hospital of Chicago

Dear Doctor Barbara Kay Burton,

Regarding this case you had reviewed for us, could you please provide some additional insight on the following:

When Jianhua initially presented to the hospital with fulminant hepatic failure, he was on a soy based formula (Isomil). Once he was safely able to feed, Isomil formula was restarted on the morning of 4/10/2013. Records indicate that he was to be changed to Nutramigen formula at some point on 4/11/2013, but the exact timing is not clear. His parents note that he had a CT scan performed and a PICC line placed on 4/11/2013 and was therefor NPO for much of the day. As such, they are confident that he did **NOT** receive Nutramigen formula prior to the urine organic acids being collected at 21:00 on 4/11/2013.

You note in your anser to question #3 that his pattern of dicarboxylic acid elevation in the urine from 4/11/2013 could be seen in fatty acid oxidation defects **OR** infants that are receiving medium chain triglycerides. Does this additional bit of information about the probable lack of exposure to a formula other than Isomil change your interpretation of the aforementioned urine organic acid testing? Does it change your assessment of the probability of a fatty acid oxidation defect or other metabolic disorder?

Thank you again for your time and expertise!

This information increases the likelihood of a fatty acid oxidation defect since there was apparently no exposure to MCT. However, it is not diagnostic of such a condition. These dicarboxylic acids are occasionally found in the urine of children who have other diagnosis (such as mitochondrial defects in oxidation phosphorylation) or no specific diagnosis.

Clinical Overview

The following information was provided to the Best Doctors Medical Expert(s) for review. It is a clinical summary of your medical records, tests, reports and intake session with your Best Doctors Member Advocate.

Clinical Overview for Jianhua Xie, 16 September 2012

Case Snapshot

20 mo old boy with fulminant hepatic failure who has been diagnosed with micronodular cirrhosis of undetermined etiology. His work-up has been extensive, including a large number of metabolic studies and whole exome sequencing.

Case Overview:

20-month-old boy with micronodular cirrhosis of undetermined etiology. The family is particularly concerned about the possibility of a disorder of fatty acid oxidation. They are seeking a Best Doctors consultation regarding the diagnosis and treatment plan.

History of Present Illness:

Jianhua was in his usual state of good health until early April 2013, when he presented with a 3 day history of vomiting, diarrhea, increasing abdominal distension, periorbital and lower extremity edema, and increased work of breathing. He was seen in the emergency department of an academic children's hospital on 4/10/2013, where he was found to be febrile to 40 degrees Celsius. Anasarca and splenomegaly were noted on examination. He did not appear encephalopathic. Labs revealed evidence of fulminant hepatic failure, with an INR of 5.6, a conjugated bilirubin of 4 mg/dL, and mildly elevated AST/ALT (around 100 IU/L). At that time, his initial blood glucose was normal.

Of note, Jianhua's father had had some symptoms of vomiting and diarrhea just prior to this acute presentation. Additionally, Jianhua had had a chronic history of greasy, pale stools ("like olive oil"). There was no history of travel, medications, or herbal supplements.

Jianhua was resuscitated with 30-cc/kg normal saline and given broad-spectrum antibiotics after cultures were obtained. He was admitted to the pediatric intensive care unit for ongoing care, with the diagnosis of acute hepatic failure. His coagulopathy was not responsive to parenteral vitamin K administration. Hypoglycemia ensued, requiring intravenous dextrose administration. A PICC line was placed. For progressive anemia and coagulopathy, Jianhua received multiple transfusions of cryoprecipitate, packed red blood cells, and fibrinogen. He was treated with diuretics, antibiotics, fat-soluble vitamin supplementation (significant deficiencies discovered on testing), and a high MCT formula (Pregestamil).

An extensive work-up to determine the etiology of for his liver failure was unrevealing. Imaging revealed moderate intraperitoneal fluid, mild splenomegaly, evidence of portal hypertension, and multiple small, echogenic foci throughout the right lobe of the liver. Please see below for full details. A urine toxin screen was negative, and a serum acetaminophen level was undetectable. Testing for autoimmune hepatitis associated antibodies was negative.

An infectious disease consultation was obtained, and evaluation for a number of pathogens was negative (EBV, CMV, HSV, and Hepatitis A/B/C). Blood cultures were negative. A catheterized urine culture grew between 1,000-10,000 cfu/mL of E coli, which was treated with antibiotics.

Hematology was consulted to rule out an infiltrative process. A serum ferritin and triglyceride level were both normal, arguing against hemophagocytic lymphohistiocytosis. By report, soluble IL-2 testing was unremarkable. Leukemia was felt to be extremely unlikely, given the normal neutrophil count. The labs and imaging were not felt to be consistent with lymphoma or a primary liver malignancy. Neuroblastoma was felt unlikely given the imaging findings, and a normal VMA level provided additional support in that regard.

Metabolics/genetics was consulted as well. Carbohydrate deficient glycoprotein, serum amino acids, and urine organic acids were reportedly unremarkable (formal results not available in reviewed medical records). A urinalysis showed trace reducing substances, but subsequent galactosemia screening was reportedly negative (results unavailable). A fecal elastase showed "severe exocrine pancreatic insufficiency (see below)." It appears that this was felt to be a false positive, given what was described as creamy consistency stool. Pancreatic enzyme supplements were not started. Genetic testing ('JaundiceChip' at Cincinnati Children's Hospital) revealed no mutations in the genes involved with alpha-1 antitrypsin deficiency, Alagille syndrome, PFIC-2, or PFIC-3. There was a clinical variant of unknown significance in 1 allele of the PFIC-1 gene (please see lab reports below for full details). A urine bile acid profile was

unremarkable (full report listed in labs below).

Jianhua had a normal ophthalmologic exam, without any ocular evidence to suggest a specific metabolic or genetic disease.

He underwent a laparoscopic liver biopsy on 4/18/2013, revealing an established micronodular cirrhosis with bile ductular proliferation. The etiology of the cirrhosis was of unclear etiology.

The liver transplant team followed Jianhua closely during his inpatient stay, and he was listed for transplantation after lengthy discussions with the family and consulting services. However, his clinical condition improved. By discharge in late April, his jaundice had resolved, and his INR was stable at 2.5 (without the need for any corrective products).

Jianhua has since been followed closely by the transplant team as an outpatient, initially weekly, then every other week, and subsequently every 2-3 months. He has been removed from the active transplant list, as his liver disease has stabilized. The last available clinic note is from 1/15/2014. At that time, the impression was micronodular cirrhosis of unknown etiology, likely a congenital finding. “His labs continue to improve.” His bilirubin (total and direct) was normal, and his transaminases were just minimally elevated (see below). His PT/INR has long since normalized. He was continuing on Pregestimil plus MCT, as well as a number of different foods that are listed below. Ursodiol and fat-soluble vitamin supplementation was continued. His spironolactone was stopped, given a resolution of his ascites.

The work-up for an underlying etiology for his micronodular cirrhosis and history of fulminant hepatic failure has continued post hospitalization. He has had extensive metabolic testing performed, as well as whole exome sequencing. Please see below for the full results, which have not been conclusive for any specific diagnosis.

Jianhua was seen in biochemical genetics on 4/11/2014. At that time it was noted that the family was feeding him a low fat diet that was restricted as much as possible from long chain fats, given their concern that he may have a long chain fatty acid oxidation disorder of some type. He was drinking 22 ounces per day of Pregestimil, in addition to measured amounts of carrots, celery, white winter melon, chicken, white mushrooms, and MCT oil. At that visit, his previous workup was reviewed. Rather than attempt to summarize the details, clinical documentation is pasted here:

I then discussed at length with his parents their questions regarding their suspicion that he may have an underlying fatty acid oxidation disorder. We discussed possibilities of him having LCHAD (long chain 3-hydroxyacyl-coA dehydrogenase deficiency or ACAD9 deficiency. This is based on evidence of his liver dysfunction and then after his treatment in the hospital, he developed acute hypoglycemia on the morning of 4/12/2013. He had a glucose of 30 at 5:42 in the morning. This was then corrected and by 11:30 that morning his glucose had actually become slightly high at 117. At that morning as well he then had some diagnostic testing with an acylcarnitine profile done at 10:25 in the morning of 4/12. On this, he had some trace to mild elevations of C16-1-acylcarnitine of 0.10 (normal between 0-0.8), and a mild elevation of C16-acylcarnitine of 0.26 (normal between 0-20.24 micromoles). He had no other elevations in his hydroxyl species or other long chain or short chain acylcarnitines. His parents are concerned that this laboratory was not collected at his original presentation. We discussed that at original presentation, he did not have presentation of hypoglycemia at that point in time. It may not have been collected initially at that point in time as part of evaluation liver dysfunction because was either not clinically indicated or suspected or possibly was ordered and it was not able be collected due to blood volume results, but I cannot speak to the specifics of this at this point in time. The acylcarnitine profile that was drawn, though, approximately 5 hours after his hypoglycemic event, even though his glucose had normalized, I would not expect his acylcarnitine profile to quickly correct. This is based on reasoning that he would have had a severe form of a fatty acid oxidation disorder that would be causing this severe liver disease and that was present and then progressed during that period of time. Individuals with severe liver disease, if it was due to a fatty acid oxidation disorder should have much more significantly elevated abnormalities on their acylcarnitine profiles. More specifically, they should have abnormalities that are consistent with a particular disorder and he only had isolated elevations of C16 and C 16:1 acylcarnitine. If he had VLCAD

deficiency, we would expect elevations of C14s and C16s at minimum. IF he had CPT2 or CACT deficiency, we would expect elevations of C16 and C18 concurrently. He had and LCHAD or TFP deficiency we would expect elevations of 3-hydroxyacylcarnitine species and not the C16 ___ elevations which he had. If he had GA2 deficiency or it MADD deficiency, we would expect elevations of all of these various long chain acylcarnitines. This being said he was treated for hypoglycemia and soon thereafter he was placed on MCT supplemented diet and has been continued on a low-fat and MCT supplemented diet over the past year by his family. He has shown constant improvement in his liver disease since that period of time with improvement in his developmental milestones as well, which his parents to do attribute to his diet. We did discuss that this is a positive sign and in a particular situation could be suggestive of some sort of improvement or response to a treatment of a fatty acid oxidation disorder, so if we did further testing for fatty acid oxidation disorder based on these initial results and we would then recommend DNA sequencing. Jianhua had DNA sequencing which included a whole exome analysis which did not demonstrate any sequence mutations that were detectable on this exome analysis in any of the fatty acid oxidation disorder genes with the exception of ACAD9. As we previously discussed, he does have a single heterozygous finding in ACAD9 with sequence change C.998A>C. He is heterozygous though we have not been able to determine that he has a second variant or mutation. This sequence change is also thought to be either tolerated or probably damaging and is not highly suspicious for being a pathogenic causing type of mutation. We then arranged to have the Baylor MitoMet Microarray performed looking for deletions and duplications in the ACAD9 gene as well as other fatty acid oxidation genes here in the past few months. This testing did not find any deleterious mutations on this microarray in the ACAD9 gene or any other FAO genes or any other variants in areas that this microarray covers. This is further reassuring that he does not have a fatty acid oxidation disorder, given he has had normal DNA sequencing. While whole exome sequencing is certainly a young technology used ___ in use in the clinical realm, t would be very unlikely that he could have 2 pathogenic disease causing mutations that would have been missed by this technology. We must further consider that he has had additional repeat acylcarnitines done here in the past, one in February and one in March 2014 as well as repeat urine organic acids. The acylcarnitine profiles have both been normal with no elevations in any of the long chain acylcarnitine species. His urine organic acids only demonstrated very mild elevations in dicarboxylic acids. His parents asked further questions regarding some research they found regarding elevations of 3-hydroxydicarboxylic acids for LCHAD deficiency which they have found some literature written by Dr. Charles Row. We discussed that there is no comment of these elevations of 3-hydroxydicarboxylic acids in his organic acid profiles. They requested if we could obtain for the specific profiles so they can review of the raw data. I discussed that I would send this request to the laboratory but I do not know if this is hospital policy to release that kind of information or if this information is still on file. If it is, we can at least have the laboratory go back and rereview this profile to ensure there were no other elevations of 3-hydroxydibicarboxylic acids. If they were, they were likely at a very mild level or not clinically significant and these acids are not routinely reported out in a quantified specific manner as the suberic and sebacic and adipic are as we see on the current organic acid reports. If they are slightly present, this may to be normal or I suspect due to some sort of larger more generalized mitochondrial dysfunction which may have been causing secondary dysfunctions in some of the fatty acid disorder genes as well as some in the urea cycle genes given he had some mild hyperammonemia at that point in time as well and this certainly could be seen with any type of liver disease causing hepatocellular dysfunction which causes mitochondrial dysfunction which would then cause these secondary enzyme abnormalities. These would not expect it to be permanent abnormalities indicative of a specific diagnostic disorder.

We discussed that he is continuing on his low-fat and MCT supplemented diet. I mentioned to them that I would like to have our metabolic nutritionist review this to make sure he is having no nutritional deficiencies in his current diet. ___ may contact with his family over the phone here in the next few weeks to review the details of this to see if we need to make additional recommendations or changes to his nutrition in order sure he is having no nutritional deficiencies on his current dietary formulization. His parents were interested in proceeding with this. We also may have some point in the future need to do more specific detailed dietary log but we can wait and see how his initial review proceeds.

Her parents also had questions regarding the elevations that were described as "modest" in the literature by Dr. Row. These may be ranging from elevations that may be over 100% of normal to may be 200%-300%-400% normal depending on the specific analytes. It is hard to interpret exactly what modest means as far as an exact percentage increase because their interpretation of these analytes should always be taken in context with the larger clinical information that is present in the patient so that any elevations in any organic acids of acylcarnitine should be interpreted together with the patient's clinical status in order to provide a more accurate diagnosis. Specific interpretation of a specific analyte on organic acids or acylcarnitines should not be taken in isolation.

I also previously briefly had a chance to speak with his parents regarding the mutation found in the gene TNFRSF13B. Disease causing mutations in this gene have been associated with common variable immune deficiency type 2 (MIM240500) and immunoglobulin A deficiency type 2 (MIM reference #609529). CVID (common variable immunodeficiency) type 2 may present with recurrent infections, splenomegaly, hepatomegaly and decreased IgG, IgM, and IgA levels. Individuals may have recurrent upper respiratory tract types of infections. I also discussed there may be IgA deficiencies which could ___. These can be associated with recurrent sinopulmonary infections. I discussed with his parents the possibility that may be Jianhua's ongoing viral infections he has had here recently and it may be also going back to his presentation last year, could be associated with some sort of viral or other type of infection resulting from these immune deficiencies. We have now documented that he has values at the low end of normal for IgG, IgM and low end of normal for IgA. I think it would be important to repeat these in quantitative immunoglobulin levels and perhaps also have him seen by an immunologist who could further give us insight into if he is at risk for having complications from recurrent infections associated with CVID2 or IgA deficiency. While this mutation is seen in his mother, these disorders often have a significant variable clinical phenotype and may be mild in her and that is something we would have to further more establish a later point time. (This comment about his mother I was not able to share with them during the clinic visit due to time limitations were running out at that point in time).

I encouraged his parents to consider everything that we have discussed and I would be happy to see them back here in clinic in 2-3 weeks later this month, so we continue to further discuss his exome findings. His parents were interested in continuing this discussion at this next clinic visit.

I spent 80 minutes obtaining the interval history, examination, and discussion with greater than 50% of the time spent in counseling and coordination of care in this extended clinic visit.

Jianhua has exhibited some mild developmental delays and has been followed in neurodevelopmental pediatrics.

Currently, Jianhua takes in roughly 30 ounces per day of Pregestamil formula per day. In a day, he will also eat 120

grams of skinless chicken breast, 100 grams carrot, 120 grams celery, 150 grams winter gourd, 50 grams mushroom, 20 mLs MCT oil, and 40 mLs white flour. All of the above are stewed with 200 mL of water. The stew is then processed to soup and separated into 3 meals.

He has 2-3 brownish or greenish-brown stools per day. It appears oily once every couple of days. There is no blood or mucus.

There is no vomiting. There is no jaundice.

When he sweats, it “has a strong fishy odor.”

Jianhua’s parents desperately want to understand the etiology of his liver disease. They are particularly concerned about the possibility of a fatty acid oxidation disorder. With this in mind, they are requesting a Best Doctors consultation regarding the diagnosis and optimal treatment plan moving forward.

Past Medical History:

- Former 38.5-week gestational age infant. During the pregnancy, Jianhua’s mother had an abnormal maternal serum screen and therefore underwent amniocentesis. This reportedly demonstrated a double Y chromosome in 10 of 20 cultures. Jianhua was vaginally, without any delivery complications. His birth weight was 7 pounds 5 ounces. He had a normal newborn screen
- History of RSV bronchiolitis x 2
- Presumed milk protein intolerance. He had a history of emesis and diarrhea early in life that resolved upon changing to a soy-based formula.
- Inguinal hernia

Past Surgical History

- Laparoscopic liver biopsy, 4/18/2013

Current Medications:

- Ursodiol 18 mg (3.2 mL) PO BID
- AquaDEKs 1 mL PO daily
- Vitamin D3 1000 units (0.2 mL) PO daily
- Aquasol E 50 units (0.3 mL) PO daily
- Pregestamil formula 30 ounces PO daily
- MCT oil 3.33 mL PO TID

Allergies:

- Eggs have caused wheezing and shortness of breath

Family History:

- Both parents are of Chinese ethnicity. The mother had a heart murmur when she was a young child but is otherwise healthy. The father is healthy. Jianhua has 3 older siblings, all of whom are healthy. There is no family history of liver disease.

Social History

- Jianhua lives with his parents and siblings in the Pacific Northwest.

Physical Examination:

Weight – 10.08 kg (19th percentile)

Height – 30 inches per parental intake

Examination from biochemical genetics visit on 4/11/2014:

PHYSICAL EXAMINATION: Temperature 37.2 degrees Celsius. Weight of 10.08 kg places him at the 19th percentile, showing proportionate weight gain. Height not obtained today. Head circumference of 48 cm, places him just below the 50th percentile, showing proportionate growth. Blood pressure 133/82, pulse of 130. He was very upset during times of a blood pressure measurement. During exam, he was crying fairly consistently, although briefly does console appropriately when held in his mother's arms and when consoled by his father. Head is normocephalic, straight black hair, normal distribution. Eyes show copious tears, no conjunctival injection. Nares are patent and clear. Some clear discharge secondary to his crying. Ears are normally set. He has normal tympanic membrane landmarks. There is no erythema. Oral exam demonstrates no erythema, exudate, or lesions seen in mouth or anterior pharynx but full examination of his throat and posterior pharynx is not possible for him today. Neck is supple, with normal range of motion. He has some shotty posterior cervical lymphadenopathy bilaterally. Heart: Regular rate and rhythm, S1, S2 sounds without murmurs. Lungs: Clear to auscultation bilaterally, no increased work of breathing. No wheezes or crackles are heard. Abdomen is soft, nontender with positive bowel sounds. No palpable hepatosplenomegaly. Skin is warm and he is slightly flushed. No visible rashes on limited exam due to compliance. Cranial nerves are symmetrical. Sensory exam is grossly intact to touch. He has normal strength and tone. Moves all 4 extremities spontaneously. Other detailed neurological testing, possible at the present time due to his being upset and appears uncomfortable.

Laboratory Testing:

- *Newborn screen #1 and #2:*

HAVTRN: NICU:
Antibiotics: Steroids:

1st screen

Submitter
EVERGREEN HEALTH (H0164)
12040 NE 128TH ST, KIRKLAND, WA 98034
Phone: (425) 899-1000 Fax: (425) 391-3915

Physician
AMY CARTER (P48372)
22635 NE MARKET PL DR, STE 120, REDMOND, WA 98053
Phone: (425) 898-7408 Fax: (425) 898-7409

DISORDER	MNEMONIC	STATUS	TEST	VALUE
PTSH	NORM	Normal	PTSH	17.01
MCADD	NORM	Normal	C8	0.06
			C8/C2	0
			C8/C10	0.66
			C10:1	0.07
PKUMS	NORM	Normal	Phe	59
			Phe/Tyr	0.92
GAL	NORM	Normal	GAL	8.17
BIO	NORM	Normal	BIO	
MSUD	NORM	Normal	Leu	77
			Val	82
			Leu/Ala	0.38
			Leu/Phe	1.31
			Val/Phe	1.4
HCYS	NORM	Normal	Met	25
			Met/Phe	0.42
HGB	FA	Normal	HB-IEF	
CF	NORM	Normal	IRT	18.02
CAH	NORM	Normal	CAH	8.18
ASA	NORM	Normal	CITa	9.67
			ASA	1.7
			Cit/Arg	2.69
			Asa/Arg	0.47
CIT	NORM	Normal	CITc	9.67
TYR-I	NORM	Normal	SUAC	0.36
			Tyr	63.33
HMG	NORM	Normal	C5OHh	0.09
			C5OH/C8	1.37
BKT	NORM	Normal	C5:1	0.01
GA-I	NORM	Normal	C5DC	0.03
			C5DC/C5OH	0.32
			C5DC/C8	0.44
			C5DC/C16	0.01
IVA	NORM	Normal	C5	0.08
			C5/C0	0
			C5/C2	0
			C5/C3	0.03
MMAs/PROP	NORM	Normal	C3	2.36
			C3/C2	0.1
			C3/C16	0.8
MCD	NORM	Normal	C5OHm	0.09
CUD	NORM	Normal	C0	37.46
LCHAD/TFP	NORM	Normal	C16OH	0.02
			C16OH/C16	0.01
VLCAD	NORM	Normal	C14	0.32
			C14:1	0.19
			C16	2.96
			C18	0.9
			C18:1	1.01
			C14:1/C16	0.07

HAVTRN: NICU:
Antibiotics: Steroids:

2nd screen

Submitter
PEDIATRIC ASSOCIATES - REDMOND RIDGE (C2051)
22635 NE MARKET PL DR, STE 120, REDMOND, WA 98053
Phone: (425) 898-7408 Fax: (425) 898-7409

Physician
JULIE WEN (P44842)
22635 NE MARKET PL DR, STE 120, REDMOND, WA 98053
Phone: (425) 898-7408 Fax: (425) 898-7409

DISORDER	MNEMONIC	STATUS	TEST	VALUE
PTSH	NORM	Normal	PTSH	3.12
MCADD	NORM	Normal	C8	0.04
			C8/C2	0
			C8/C10	0.48
			C10:1	0.06
PKUMS	NORM	Normal	Phe	37
			Phe/Tyr	0.56
GAL	NORM	Normal	GAL	7.36
BIO	NORM	Normal	BIO	
MSUD	NORM	Normal	Leu	169
			Val	122
			Leu/Ala	0.74
			Leu/Phe	4.53
			Val/Phe	3.3
HCYS	NORM	Normal	Met	24
			Met/Phe	0.65
HGB	FA	Normal	HB-IEF	
CF	NORM	Normal	IRT	26.43
CAH	NORM	Normal	CAH	4.19
ASA	NORM	Normal	CITa	10.48
			ASA	1.1
			Cit/Arg	1.84
			Asa/Arg	0.19
CIT	NORM	Normal	CITc	10.48
TYR-I	NORM	Normal	SUAC	0.16
			Tyr	66.28
HMG	NORM	Normal	C5OHh	0.09
			C5OH/C8	2.15
BKT	NORM	Normal	C5:1	0.01
GA-I	NORM	Normal	C5DC	0.01
			C5DC/C5OH	0.12
			C5DC/C8	0.25
			C5DC/C16	0.01
IVA	NORM	Normal	C5	0.17
			C5/C0	0
			C5/C2	0.01
			C5/C3	0.18
MMAs/PROP	NORM	Normal	C3	0.95
			C3/C2	0.05
			C3/C16	0.55
MCD	NORM	Normal	C5OHm	0.09
CUD	NORM	Normal	C0	36.32
LCHAD/TFP	NORM	Normal	C16OH	0.02
			C16OH/C16	0.01
VLCAD	NORM	Normal	C14	0.24
			C14:1	0.26
			C16	1.72
			C18	0.67
			C18:1	1.28
			C14:1/C16	0.15

- *Urine culture, 4/9/2013:*

PROCEDURE: Urine Culture
SOURCE: U Foley Cath
FREE TEXT SOURCE: Plated by core

COLLECTED: 04/09/2013 23:05
RECEIVED: 04/10/2013 04:48
ACCESSION: 13-099-1240

*** FINAL REPORT ***

Final Report
Between 1,000 and 10,000 cfu/ml Escherichia coli
<1,000 cfu/ml Gram Negative Flora

Verified:04/11/2013 18:17

*** PRELIMINARY REPORT ***

Preliminary Report
Between 1,000 and 10,000 cfu/ml Escherichia coli
<1,000 cfu/ml Gram Negative Flora
, Final Report to Follow.

Verified:04/11/2013 02:51

*** SUSCEPTIBILITY RESULTS ***

	Escherichia coli
	Interp
Augmentin	Suscept
Ampicillin	Suscept
Amikacin	Suscept
Ceftazidime	Suscept
Ceftriaxone	Suscept
Cefuroxime IV Use	Suscept
Cefuroxime Oral use	Suscept
Cefazolin	Suscept U
Cefepime	Suscept
Nitrofurantoin	Suscept
Gentamicin	Suscept
Meropenem	Suscept
Trimethoprim/sulfamethoxazole	Suscept
Pip/Tazo	Suscept
Comments(1)	Yes

- *Urinalysis, 4/9/2013:*

Collected Date	04/22/2013	04/11/2013	04/09/2013		
Collected Time	06:15:00	21:00:00	23:05:00		
Procedure				Units	Ref Range
Urine Color			Orange		
Urine Specific Gravity			1.021		[1.001-1.035]
Urine pH			<= 5.0		[4.5-8.0]
Urine Leukocyte Esterase			Negative		[Negative]
Urine Nitrite			Negative		[Negative]
Urine Protein Qualitative			Trace *		[Negative]
Urine Glucose Qualitative			Negative		[Negative]
Urine Ketones i			Trace *		[Negative]
Urine Urobilinogen			1.0		
Urine Bilirubin			See Note		[Negative]
Urine Occult Blood			Negative f		[Negative]
Urine Reducing Substances		Trace *			[Negative]
Urine Collection Type			I/O Cath		
Urine Microscopic			Done		
Urine Cultured?			Yes		
Urine Volume			3.0	mL	
Urine RBC			0-2	/HPF	[None]
Urine WBC			0-5 *	/HPF	[None]
Urine Bacteria			Not Seen	/HPF	
Urine Epithelial Cells			Few *	/LPF	[None]
Renal Tubular Cells			1-5		
Urine Amorphous Crystals			Few *	/LPF	
Hyaline Casts			Rare	/LPF	
Notes On UA			See Note f		
Urine Bile Acid Profile i	See Below				

- *Fecal elastase, 4/10/2013:*

Collected Date	04/10/2013	04/10/2013		
Collected Time	10:17:00	04:45:00		
Procedure			Units	Ref Range
Pancreatic Elastase 1 (PE1)		<50.0	mcgE1/g	
Stool Alpha 1 Antitrypsin	<0.5		mg/g	[0.1-3.0]
Stool Occult Blood		Negative		[Negative]
Pancreatic Elastase 1 Interp, Stool		See Comments f		

04/10/2013 04:45:00 Pancreatic Elastase 1 Interp, Stool:
Severe exocrine pancreatic insufficiency*

*Please Note: This specimen was creamy/mucous-like in consistency. A formed stool should be tested for more accurate results.
Reference Values For Pancreatic Elastase in Stool

200 to >500 ug Elastase/g stool = Normal

100 to 200 ug Elastase/g stool = Moderate to slight exocrine pancreatic insufficiency

<100 ug Elastase/g stool = Severe exocrine pancreatic insufficiency

- *JaundiceChip Resequencing Array, 4/15/2013:*

HL-13-00155

JaundiceChip Resequencing Array

Collection Date and Time: 4/15/2013 4:27 PM
Laboratory Accession # : **HL-13-00155**
Specimen : 2.0mL blood/good
Ordering Physician : Phelan, Rachel
Received Date and Time : 4/17/2013 12:43 PM
Ethnicity : Asian

Genes Tested:

***SERPINA1* (a1-antitrypsin deficiency)**
Allele 1: No Mutation Identified
Allele 2: No Mutation Identified

***JAG1* (Alagille syndrome)**
Allele 1: No Mutation Identified
Allele 2: No Mutation Identified

***ATP8B1* (PFIC1)**
Allele 1: 2364 A>C (E788D)
Allele 2: No Mutation Identified

***ABCB11* (PFIC2)**
Allele 1: No Mutation Identified
Allele 2: No Mutation Identified

***ABCB4* (PFIC3)**
Allele 1: No Mutation Identified
Allele 2: No Mutation Identified

RESULT: Variant of uncertain clinical significance

We have completed the sequence analysis of the five most common genes associated with heritable liver disease in childhood. This patient is heterozygous for a previously unreported sequence variant in the *ATP8B1* gene. Its relationship with the patient's liver disease is uncertain at this time. This patient does not have an identified mutation in any of the other genes related to heritable liver disease specified above.

CLINICAL SIGNIFICANCE

We have no clinical history on this patient. This patient is heterozygous for a missense variant of uncertain clinical significance in the *ATP8B1* gene. The presence of this variant in this individual neither confirms nor excludes this variant as a causative factor in the patient's disease.

GENETIC SIGNIFICANCE

This variant, 2364 A>C, results in the substitution of aspartic acid for glutamic acid at amino acid 788. This amino acid sequence is not conserved across mammalian species examined in our laboratory. Our laboratory has not identified other symptomatic patients with this sequence variant. This variant is listed in the EntrezGene dbSNP (rs#77317429), but no minor allele frequency is available. According to the Grantham scale, this amino acid substitution is predicted to be conservative. In addition, through the use of mutation prediction software, this amino acid substitution is predicted to be "tolerated" and "benign". The accuracies of various in silico prediction methods are in the range of 0.60-0.82 (Thusberg et al 2011). **Based on all of the available information, we are unable to predict whether this sequence variant represents an unrecognized disease-causing mutation or a benign polymorphism.**

Genetic counseling is recommended for this family.

CLINICAL RECOMMENDATIONS

At this point, we recommend completion of the diagnostic evaluation as directed by the referring physician.

If you have any questions about this test result or its implications, please contact the Molecular Genetics Laboratory at 513-636-4474.

- *Plasma amino acids, 4/9/2013:*

Amino Acids Quant Interp Plasma	Amino Acids Quant Interp Plasma	
Taurine Quantitative	H 147	(30 - 133)
Aspartic Acid Quantitative	9	(0 - 20)
Hydroxyproline Quantitative	46	(0 - 50)
Threonine Quantitative	189	(45 - 205)
Serine Quantitative	143	(60 - 200)
Asparagine Quantitative	90	(20 - 90)
Glutamic Acid Quantitative	65	(15 - 100)
Glutamine Quantitative	473	(325 - 825)
Proline Quantitative	195	(60 - 360)
Glycine Quantitative	320	(105 - 385)
Alanine Quantitative	449	(145 - 495)
Citrulline Quantitative	29	(6 - 40)
Valine Quantitative	135	(75 - 350)
Cystine Quantitative	20	(15 - 50)
Methionine Quantitative	H 213	(10 - 45)
Isoleucine Quantitative	L 22	(27 - 120)
Leucine Quantitative	76	(45 - 160)
Tyrosine Quantitative	H 247	(30 - 127)
Phenylalanine Quantitative	H 100	(30 - 91)
Ornithine Quantitative	H 188	(22 - 115)
Lysine Quantitative	146	(60 - 240)
Histidine Quantitative	100	(45 - 118)
Arginine Quantitative	62	(25 - 125)

- *Urine organic acids, 4/11/2013:*

Result Type: Succinylacetone, Urine
Result Date: 11 April 2013 21:00
Result Status: Auth (Verified)
Performed By: Jack, Rhona , PhD on 16 April 2013 16:36
Verified By: Jack, Rhona , PhD on 16 April 2013 16:36
Encounter info: 94243980, CHMC, Inpatient, 4/9/2013 - 4/25/2013

*** Final Report ***

Organic Acids, Urine

Urine equivalent to 0.7 mg creatinine was extracted, derivatized and separated by gas chromatography/mass spectrometry to identify organic acids present in the sample submitted.

Organic Acid	Approximate concentration (mg/g creat)		Reference Range 1 MO-1 YR
LACTIC	20		<95
*PYRUVIC	17		<60
3-OH-BUTYRIC	36		<150
ACETOACETIC	ND		<59
ETHYLMALONIC	10		<26
FUMARIC	ND		<40
GLUTARIC	ND		<28
3-METHYLGLUTARIC	ND		<10
3-METHYLGLUTACONIC	TR		<45
ADIPIC	104	H	<64
2-KETOGLUTARIC	12		<544
SUBERIC	85	H	<46
SEBACIC	31	H	<25

Interpretation: In this sample there was moderate elevation of dicarboxylic acids (adipic, suberic, sebacic), which is most likely secondary to dietary supplementation with medium chain triglycerides. In addition, tyrosine metabolites (P-OH-phenyllactate and P-OH-phenylpyruvate) were mildly elevated, suggestive of liver dysfunction. There was no succinylacetone detected; this should rule out tyrosinemia type 1.

- *Labs, 4/17/2013:*

Result Type: Acylcarnitine Profile, Blood
Result Date: 12 April 2013 10:25
Result Status: Auth (Verified)
Performed By: Jack, Rhona , PhD on 17 April 2013 14:09
Verified By: Jack, Rhona , PhD on 17 April 2013 14:09
Encounter info: 94243980, CHMC, Inpatient, 4/9/2013 - 4/25/2013

*** Final Report ***

Acylcarnitine Profile/Tandem Mass Spectrometry

Acylcarnitine	Conc mcmole/l	Ref Range >1mo	Acylcarnitine	Conc mcmole/l		Ref Range >1mo
free carnitine	17.11	16-65	C-12:1	0.11		0-0.18
C-2 (acetyl)	22.67	2-24	C-12	0.15		0-0.17
C-3 (propionyl)	0.18	0-0.9	C-6-dicarboxylic	0.04		0-0.08
C-4 (butyryl)	0.13	0-0.7	C-14:2	0.05		0-0.11
C-5:1	0.01	0-0.08	C-14:1	0.10		0-0.18
C-5	0.06	0-0.38	C-14	0.11		0-0.12
C-6	0.09	0-0.23	C-14-hydroxy	0.02		0-0.04
C-5-hydroxy	0.02	0-0.14	C-16:1	0.10	H	0-0.08
C-7	0.02	0-0.06	C-16	0.26	H	0-0.24
C-8:1	0.17	0-0.66	C-16:1-hydroxy	0.02		0-0.03
C-8 (octanoic)	0.21	0-0.27	C-16-hydroxy	0.02		0-0.03
C-3-dicarboxylic	0.09	0-0.15	C-18:2	0.11		0-0.17
C-10:2	0.03	0-0.08	C-18:1	0.26		0-0.33
C-10:1	0.16	0-0.33	C-18	0.05		0-0.15
C-10	0.22	0-0.36	C-18:2-hydroxy	0.01		0-0.03
C-4-dicarboxylic	0.02	0-0.1	C-18:1-hydroxy	0.01		0-0.04
C-5-dicarboxylic	0.1	0-0.11	C-18-hydroxy	0.01		0-0.03

Testing done in plasma
Interpretation: The mild elevation of C16 and C16:1 is non-specific. Repeat is recommended if clinically indicated.

- *Labs, 4/10-25/2013 (during his inpatient stay):*

	Collected Date	04/23/2013	04/14/2013	04/12/2013		
	Collected Time	05:00:00	04:20:00	05:00:00		
Procedure					Units	Ref Range
Vitamin D, 25-OH Total Level i		7 L	7 L		ng/mL	[30-100]
Vitamin D2 Level		<2	<2		ng/mL	
Vitamin D3 Level		7	7		ng/mL	
Vanilmandelic Acid				8	ng/mL	[<=20]
Homovanillic Acid				58 H	ng/mL	[<=30]

	Collected Date	04/23/2013	04/22/2013	04/21/2013		
	Collected Time	05:00:00	06:25:00	04:55:00		
Procedure					Units	Ref Range
Phosphorus Serum		5.2	4.9	5.2	mg/dL	[3.9-6.5]
Bilirubin Total			4.3 H		mg/dL	[0.1-1.3]
Bilirubin Conjugated		0.0	0.0	0.1	mg/dL	[0.0-0.3]
Bilirubin Unconjugated		2.6 H	2.7 H	2.9 H	mg/dL	[0.0-1.1]
Bilirubin Delta			1.7 H		mg/dL	[0.0-0.2]
AST (SGOT)		87 H		107 H	IU/L	[3-74]
ALT (SGPT)		79 H		88 H	IU/L	[6-45]
Alkaline Phosphatase, Serum		1229 H		1342 H	IU/L	[95-380]
Gamma Glutamyltransferase		34		37	IU/L	[15-85]
Ammonia, Blood Venous		53 H	82 H	105 H	mcmol/L	[9-33]
Lactic Acid Blood, Venous		0.9		1.4	MMOL/L	[0.5-2.2]
Albumin Level		3.3	3.2	3.9	g/dL	[2.9-5.5]
Vitamin A Level		38 L			mcg/L	[125-300]
Vitamin E Level		2.5 L			mg/L	[5.0-18.0]
Zinc Level		1.53 Hf			mcg/mL	[0.60-1.20]
Retinol Binding Protein		<1.2 L			mg/dL	[2.3-3.4]

Procedure				Units	Ref Range
Phosphorus Serum	5.2	4.9	5.2	mg/dL	[3.9-6.5]
Bilirubin Total		4.3 H		mg/dL	[0.1-1.3]
Bilirubin Conjugated	0.0	0.0	0.1	mg/dL	[0.0-0.3]
Bilirubin Unconjugated	2.6 H	2.7 H	2.9 H	mg/dL	[0.0-1.1]
Bilirubin Delta		1.7 H		mg/dL	[0.0-0.2]
AST (SGOT)	87 H		107 H	IU/L	[3-74]
ALT (SGPT)	79 H		88 H	IU/L	[6-45]
Alkaline Phosphatase, Serum	1229 H		1342 H	IU/L	[95-380]
Gamma Glutamyltransferase	34		37	IU/L	[15-85]
Ammonia, Blood Venous	53 H	82 H	105 H	mcmol/L	[9-33]
Lactic Acid Blood, Venous	0.9		1.4	MMOL/L	[0.5-2.2]
Albumin Level	3.3	3.2	3.9	g/dL	[2.9-5.5]
Vitamin A Level	38 L			mcg/L	[125-300]
Vitamin E Level	2.5 L			mg/L	[5.0-18.0]
Zinc Level	1.53 Hf			mcg/mL	[0.60-1.20]
Retinol Binding Protein	<1.2 L			mg/dL	[2.3-3.4]

	Collected Date	04/14/2013	04/14/2013	04/14/2013	04/14/2013		
	Collected Time	16:23:00	10:40:00	08:00:00	04:24:00		
Procedure						Units	Ref Range
Bilirubin Unconjugated		6.9 H				mg/dL	[0.0-1.1]
AST (SGOT)		91 H				IU/L	[3-74]
ALT (SGPT)		71 H				IU/L	[6-45]
Alkaline Phosphatase, Serum		729 H				IU/L	[95-380]
Gamma Glutamyltransferase		45				IU/L	[15-85]
Ammonia, Blood Venous		44 H				mcmol/L	[9-33]
Lactic Acid Blood, Venous		1.4				MMOL/L	[0.5-2.2]
Albumin Level		2.5 L				g/dL	[2.9-5.5]

	Collected Date	04/10/2013	04/09/2013	04/09/2013	04/09/2013		
	Collected Time	02:51:00	22:20:00	22:15:00	20:35:00		
Procedure						Units	Ref Range
Sodium Level			134 L	135	135	mEq/L	[135-145]
Potassium Level			5.0	5.1	5.2	mEq/L	[3.5-5.5]
Chloride Lvl			110			mEq/L	[96-110]
CO2 Lvl			17 L			mEq/L	[18-27]
Anion Gap			12.0			mEq/L	[8.0-22.0]
Glucose Level				89	120 H	mg/dL	[60-105]
BUN			9			mg/dL	[6-20]
Creatinine			0.2			mg/dL	[0.1-0.4]
Total Protein		4.1 L				g/dL	[5.6-7.2]
Calcium Ionized		1.15 L		1.28	1.27	MMOL/L	[1.16-1.45]
Magnesium Serum			2.4			mg/dL	[1.8-2.4]
Phosphorus Serum			3.4 L			mg/dL	[3.9-6.5]
Ferritin Lvl		93				ng/mL	[10-95]
Bilirubin Conjugated		4.0 H				mg/dL	[0.0-0.3]
Bilirubin Unconjugated		10.3 H				mg/dL	[0.0-1.1]
AST (SGOT)		107 H				IU/L	[3-74]
ALT (SGPT)		91 H				IU/L	[6-45]
Alkaline Phosphatase, Serum		1270 H				IU/L	[95-380]
Uric Acid		4.3				mg/dL	[2.0-6.0]
Gamma Glutamyltransferase			54			IU/L	[15-85]
Triglycerides i		47 L				mg/dL	[60-135]
Amylase Serum			<30			IU/L	[0-115]
Lipase Level			<10 L			IU/L	[25-120]
Lactate Dehydrogenase		810				IU/L	[425-975]
Lactic Acid Blood, Venous				2.1	3.1 H	MMOL/L	[0.5-2.2]
Albumin Level		2.3 L				g/dL	[2.9-5.5]
C Reactive Protein			<0.8			mg/dL	[<=0.8]

Procedure	Collected Date / Collected Time				Units	Ref Range
	04/25/2013 04:30:00	04/24/2013 05:30:00	04/23/2013 05:00:00	04/22/2013 06:25:00		
Prothrombin Time	**28.5 H**	25.3 H	**24.1 H**	**24.4 H**	second(s)	[12.5-15.2]
International Normalized Ratio	2.5	2.4	2.3	2.3		
APTT	**>150 Cf**	**62 H**	**68 H**	**69 H**	second(s)	[25-35]
Fibrinogen Level	**137 L**	**125 L**	**125 L**	**139 L**	mg/dL	[230-450]
Thrombin Time				**20 H**	second(s)	[14-17]

Procedure	Collected Date / Collected Time				Units	Ref Range
	04/21/2013 04:55:00	04/20/2013 04:55:00	04/19/2013 04:40:00	04/18/2013 05:46:00		
Prothrombin Time	**23.7 H**	**23.6 H**	**23.7 H**	**18.3 H**	second(s)	[12.5-15.2]
International Normalized Ratio	2.2	2.2	2.2	1.6		
APTT	**>150 Cf**	**77 H**	**52 Hf**	**44 H**	second(s)	[25-35]
Fibrinogen Level	**159 L**	**162 L**	**156 L**	**204 L**	mg/dL	[230-450]
Thrombin Time	79 H		17		second(s)	[14-17]

Procedure	Collected Date / Collected Time				Units	Ref Range
	04/14/2013 04:20:00	04/13/2013 16:45:00	04/13/2013 03:45:00	04/12/2013 20:00:00		
Prothrombin Time	**21.0 H**	**38.4 Cf**	**33.7 Cf**	**31.8 Cf**	second(s)	[12.5-15.2]
International Normalized Ratio	1.9	4.1	3.5	3.2		
APTT	**40 H**	**62 H**	**54 H**	**55 H**	second(s)	[25-35]
Fibrinogen Level	**183 L**	**89 L**	**121 L**	**134 L**	mg/dL	[230-450]
Thrombin Time		**20 Hf**			second(s)	[14-17]

Procedure	Collected Date / Collected Time		Units	Ref Range
	04/10/2013 11:00:00	04/10/2013 02:51:00		
Prothrombin Time	**46.3 Cf**	**48.6 Cf**	second(s)	[12.5-15.2]
International Normalized Ratio	5.3	5.6		
APTT	**69 Hf**	**75 H**	second(s)	[25-35]
Fibrinogen Level	**80 L**	**60 L**	mg/dL	[230-450]
Thrombin Time	**19 Hf**		second(s)	[14-17]

Procedure	Collected Date / Collected Time			Units	Ref Range
	04/14/2013 10:40:00	04/13/2013 16:45:00	04/13/2013 11:16:00		
Respiratory Viral PCR Battery Result i	Negative				
Specimen, Viral culture (VCS)			STOOL f		
Result, Prelim culture (VCS)			SEE COMMENTS f		
Result, Final culture (VCS)			SEE COMMENTS f		
Specimen, Hepatitis B Viral DNA Qnt		Serum f			
Hepatitis B DNA Quant		SEE COMMENTS f			
Hepatitis B Result PCR Quant		None detected.		IU/mL	[NDET]
HBV DNA IU/mL (Log 10)		Not Calculated			

Procedure	Collected Date / Collected Time		Units	Ref Range
	04/11/2013 16:40:00	04/11/2013 00:20:00		
Human Herpes Virus 6 by PCR	SEE COMMENTS f			
HH6 Result PCR Quant	None detected.		copies/mL	[NDET]
HH6 DNA Copies/mL (Log 10)	Not Calculated			
Specimen, HSV PCR	Plasma f			
Result, HSV PCR	None detected.		copies/mL	[NDET]
HSV DNA Copies/mL (Log 10)	Not Calculated			
HSV Interpretation PCR Quant	SEE COMMENTS f			
Hepatitis B surface antigen	See Below			
Hepatitis B Surface Antibody	See Below			
Hepatitis C Antibody	See Below			
HIV Ag and Ab Interpretation	SEE COMMENTS f			
HIV Ag and Ab Result	Nonreactive			[NREAC]
CMV IgG		See Below		
CMV IgG		Positive		[Negative]
CMV IgM		See Below		
CMV IgM		Negative		[Negative]
EBV IgG result		Positive		[Negative]
EBV IgM result		Negative		[Negative]
Epstein Barr Nuclear Antibody		Positive		[Negative]
Epstein Barr Early Antigen Antibody		Negative		[Negative]
Interpretation, EBV		See Below		

04/11/2013 16:40:00 Hepatitis B surface antigen
Nonreactive; No evidence of hepatitis B surface antigen. HBsAg can be detected in serum 30-60 days after exposure to hepatitis B virus.

04/11/2013 16:40:00 Hepatitis B Surface Antibody
Nonreactive, <5.0 mIU/mL Antibody to surface antigen is the major protective antibody against hepatitis B virus. It is detected following recovery from HBV, and inoculation with hepatitis B vaccine. A nonreactive antibody test indicates lack of immunity to hepatitis B.

04/11/2013 16:40:00 Hepatitis C Antibody
Nonreactive. Approximately 45% of patients are positive for anti-HCV within 6 weeks of illness; the remainder may not have detectable antibody until 6 months later. Nonreactive HCV tests should be repeated for up to one year if clinical symptoms suggest HCV infection.

04/11/2013 00:20:00 CMV IgG
IgG antibody to CMV detected. This indicates a current or past CMV infection.

04/11/2013 00:20:00 CMV IgM
No significant level of detectable CMV IgM antibody. No current infection with CMV.

04/11/2013 00:20:00 Interpretation, EBV
Evidence of past EBV infection.

	Collected Date	04/10/2013	04/10/2013	04/10/2013		
	Collected Time	11:00:00	04:45:00	02:51:00		
Procedure					Units	Ref Range
Rotavirus			Negative			[Negative]
Specimen, CMV PCR		Plasma f				
CMV by PCR, QUANTitative		SEE COMMENTS f			IU/mL	[NDET]
CMV PCR Quant Result (IU/mL)		None detected				
CMV DNA IU/mL (Log 10)		Not Calculated				
Specimen, Epstein Barr Virus PCR		Plasma f				
EBV quant PCR blood/CSF		SEE COMMENTS f			copies/mL	[NDET]
EBV PCR Quant Result (Copies/mL)		None detected.				
EBV DNA Copies/mL (Log 10)		Not Calculated				
Hepatitis A IgM				See Below		
Hepatitis A Total Antibody				See Below		

04/10/2013 02:51:00 Hepatitis A IgM
Nonreactive. A nonreactive IgM anti-HAV test and a positive Total anti-HAV is consistent with past infection or immunization with hepatitis A vaccine. This indicates immunity to HAV.

04/10/2013 02:51:00 Hepatitis A Total Antibody
Reactive. Total antibody to hepatitis A virus tests for immunoglobulins G and M. A reactive test result is an indicator of recent, past infection or immunization with hepatitis A vaccine and immunity to HAV. IgM anti-HAV will be performed. The presence of maternal antibodies could also cause a reactive test, and may not indicate long term immunity.

	Collected Date	04/10/2013			
	Collected Time	02:51:00			
Procedure			Units	Ref Range	
Acetaminophen Level		<10	mcg/mL	[10-20]	

	Collected Date	04/12/2013	04/12/2013	04/11/2013		
	Collected Time	10:25:00	05:00:00	16:40:00		
Procedure					Units	Ref Range
Anti Nuclear Antibody Screen		Negative				[Negative]
Aspergillus galactomannan Index			0.073 f			[0.000-0.499]
Result, Aspergillus galactomannan EIA			SEE COMMENTS f			
Leptospira Antibody			Negative f			[Negative]
Liver Kidney Microsomal Antibody				Negative		[Negative]

Procedure		Units	Ref Range
Immunoglobulin G Level	479	mg/dL	[156-829]
Anti Smooth Muscle Antibody	Negative		[Negative]

- *Acylcarnitine profile, 4/12/2013:*

Result Type: Acylcarnitine Profile, Blood
Result Date: 12 April 2013 10:25
Result Status: Auth (Verified)
Performed By: Jack, Rhona , PhD on 17 April 2013 14:09
Verified By: Jack, Rhona , PhD on 17 April 2013 14:09
Encounter info: 94243980, CHMC, Inpatient, 4/9/2013 - 4/25/2013

*** Final Report ***

Acylcarnitine Profile/Tandem Mass Spectrometry

Acylcarnitine	Conc mcmole/l	Ref Range >1mo	Acylcarnitine	Conc mcmole/l		Ref Range >1mo
free carnitine	17.11	16-65	C-12:1	0.11		0-0.18
C-2 (acetyl)	22.67	2-24	C-12	0.15		0-0.17
C-3 (propionyl)	0.18	0-0.9	C-6-dicarboxylic	0.04		0-0.08
C-4 (butyryl)	0.13	0-0.7	C-14:2	0.05		0-0.11
C-5:1	0.01	0-0.08	C-14:1	0.10		0-0.18
C-5	0.06	0-0.38	C-14	0.11		0-0.12
C-6	0.09	0-0.23	C-14-hydroxy	0.02		0-0.04
C-5-hydroxy	0.02	0-0.14	C-16:1	0.10	H	0-0.08
C-7	0.02	0-0.06	C-16	0.26	H	0-0.24
C-8:1	0.17	0-0.66	C-16:1-hydroxy	0.02		0-0.03
C-8 (octanoic)	0.21	0-0.27	C-16-hydroxy	0.02		0-0.03
C-3-dicarboxylic	0.09	0-0.15	C-18:2	0.11		0-0.17
C-10:2	0.03	0-0.08	C-18:1	0.26		0-0.33
C-10:1	0.16	0-0.33	C-18	0.05		0-0.15
C-10	0.22	0-0.36	C-18:2-hydroxy	0.01		0-0.03
C-4-dicarboxylic	0.02	0-0.1	C-18:1-hydroxy	0.01		0-0.04
C-5-dicarboxylic	0.1	0-0.11	C-18-hydroxy	0.01		0-0.03

Testing done in plasma
Interpretation: The mild elevation of C16 and C16:1 is non-specific. Repeat is recommended if clinically indicated.

- *Lysosomal lipase for Wolman Disease/Cholesteryl Ester Storage Disease, 4/16/2013:*

Result Type: Acid Lipase Level
Result Date: 15 April 2013 5:00
Result Status: Auth (Verified)
Performed By: Jack, Rhona , PhD on 16 April 2013 15:57
Verified By: Jack, Rhona , PhD on 16 April 2013 15:57
Encounter info: 94243980, CHMC, Inpatient, 4/9/2013 - 4/25/2013

*** Final Report ***

Lysosomal Acid Lipase for Wolman Disease/Cholesteryl Ester Storage Disease

Gene	Enzyme	Patient Results (pmole/hr/spt)	Normal Reference Range
LIPA	Lysosomal Acid Lipase Blood Spot	68	40 - 600

Interpretation: Normal enzyme activity in blood spots. This rules out a defect in the LIPA gene as a cause for Wolman Disease or Cholesteryl Ester Storage Disease (CESD). Affected patients typically have undetectable activity.

Comment: Lysosomal Acid Lipase (LAL) deficiency presents as a clinical spectrum from early onset in infancy (Wolman phenotype), to childhood or adult onset (CESD phenotype). Deficiency or marked reduction of LAL activity results in accumulation of lipids leading to hepatosplenomegaly, liver dysfunction and fibrosis, hyperlipidemia, and malabsorption.

Rhona Jack, Ph.D.
Biochemical Genetics Laboratory

- *Urine bile acid profile, 4/22/2013:*

Bile Acids

FAB No: 12089

Client Patient Chart/Ref#: 1275567

Referring Physician/Lab:

Seattle Childrens Hopsital
Sendout Lab - A-6901
4800 Sand Point Way NE
Seattle, WA 98105

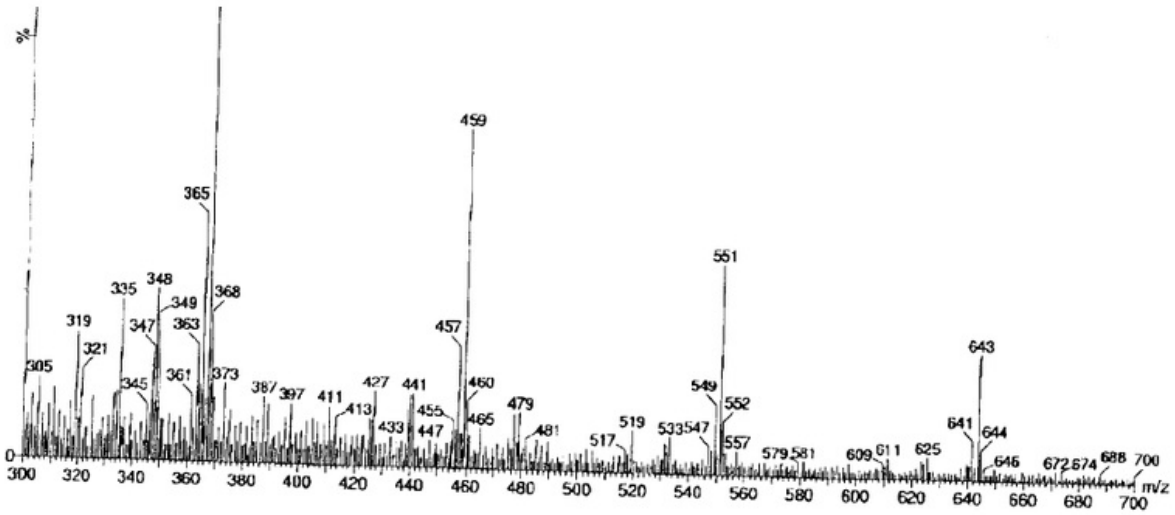
Sample received: April 24th 2013
Urine volume: 11.6 mL

A urine sample, collected April 22nd 2013 from the above named patient, has been analyzed using fast atom bombardment ionization mass spectrometry for the detection of potential inborn errors in the cholesterol-bile acid biosynthetic pathway.

The negative ion FAB-MS spectrum of the urine from this patient is attached and is unremarkable. The profile indicates a normal urinary bile acid profile, with no evidence for a cholestatic condition. Based upon this analysis, there is no indication for a defect in the cholesterol-bile acid biosynthetic pathway, or any abnormality in peroxisomal beta-oxidation of bile acid intermediates.

If you require any further information, please contact me at 513-636-4548.

This test was developed and its performance characteristics were determined and validated by the Clinical Mass Spectrometry Laboratory at Cincinnati Children's Hospital Medical Center. It has not been cleared or approved by the U.S. Food and Drug Administration. This laboratory is certified under the Clinical Laboratory Improvement



- *Labs, 5/15/2013*

Collected Date 05/15/2013
Collected Time 14:10:00

Procedure		Units	Ref Range
Sodium Level	140	mEq/L	[135-145]
Potassium Level	4.7	mEq/L	[3.5-5.5]
Chloride Lvl	108	mEq/L	[96-110]
CO2 Lvl	21	mEq/L	[18-27]
Anion Gap	15.7	mEq/L	[8.0-22.0]
Glucose Level	78	mg/dL	[60-105]
BUN	9	mg/dL	[6-20]
Creatinine	0.2	mg/dL	[0.1-0.4]
Estimated GFR (Schwartz Bedside)	>120 f	mL/min/1.73 m2	
Calcium Level, Total	9.9	mg/dL	[8.7-10.7]
Magnesium Serum	2.4	mg/dL	[1.8-2.4]
Phosphorus Serum	4.8	mg/dL	[3.9-6.5]
Bilirubin Total	1.3	mg/dL	[0.1-1.3]
Bilirubin Conjugated	0.0	mg/dL	[0.0-0.3]
Bilirubin Unconjugated	0.6	mg/dL	[0.0-1.1]
Bilirubin Delta	**0.7 H**	mg/dL	[0.0-0.2]
AST (SGOT)	**95 H**	IU/L	[3-74]
ALT (SGPT)	**58 H**	IU/L	[6-45]
Alkaline Phosphatase, Serum	**1047 H**	IU/L	[95-380]
Gamma Glutamyltransferase	24	IU/L	[15-85]
Albumin Level	3.7	g/dL	[2.9-5.5]

Procedure		Units	Ref Range
Sodium Level	140	mEq/L	[135-145]
Potassium Level	4.7	mEq/L	[3.5-5.5]
Chloride Lvl	108	mEq/L	[96-110]
CO2 Lvl	21	mEq/L	[18-27]
Anion Gap	15.7	mEq/L	[8.0-22.0]
Glucose Level	78	mg/dL	[60-105]
BUN	9	mg/dL	[6-20]
Creatinine	0.2	mg/dL	[0.1-0.4]
Estimated GFR (Schwartz Bedside)	>120 f	mL/min/1.73 m2	
Calcium Level, Total	9.9	mg/dL	[8.7-10.7]
Magnesium Serum	2.4	mg/dL	[1.8-2.4]
Phosphorus Serum	4.8	mg/dL	[3.9-6.5]
Bilirubin Total	1.3	mg/dL	[0.1-1.3]
Bilirubin Conjugated	0.0	mg/dL	[0.0-0.3]
Bilirubin Unconjugated	0.6	mg/dL	[0.0-1.1]
Bilirubin Delta	**0.7 H**	mg/dL	[0.0-0.2]
AST (SGOT)	**95 H**	IU/L	[3-74]
ALT (SGPT)	**58 H**	IU/L	[6-45]
Alkaline Phosphatase, Serum	**1047 H**	IU/L	[95-380]
Gamma Glutamyltransferase	24	IU/L	[15-85]
Albumin Level	3.7	g/dL	[2.9-5.5]

Procedure		Units	Ref Range
White Blood Cell Count	9.5	K/mm3	[6.0-17.5]
Platelet Count	**102 L**	K/mm3	[250-600]
Hematocrit	37.2	%	[33.0-39.0]
Hemoglobin	12.5	g/dL	[10.5-13.5]
Red Blood Cell Count	4.12	M/mm3	[3.70-5.30]
MCV	**90.3 H**	fl	[70.0-86.0]
MCH	30.3	pg	[23.0-31.0]
MCHC	33.6	%	[30.0-36.0]
RDW	**14.8**	%	[11.0-16.0]
Mean Platelet Volume	10.9	fl	[8.9-12.4]
Nucleated Red Cells	0	/100 WBC	
Polys, Absolute	1938	/mm3	[1,500-5,000]
Lymphocytes, Absolute	6384	/mm3	[1,500-8,500]
Monocytes, Absolute	**674 H**	/mm3	[0-500]
Eosinophils, Absolute	**456 H**	/mm3	[0-300]
Basophils, Absolute	38	/mm3	[0-50]
Immature Granulocytes, Absolute i	10	/mm3	[0-50]
Absolute Neutrophil Ct Cal	1938	/mm3	[1,500-5,400]
Polys, %	20.4	%	[15.0-45.0]
Lymphocytes, %	67.2	%	[30.0-75.0]
Monocytes, %	7.1	%	[0.0-10.0]
Eosinophils, %	**4.8 H**	%	[0.0-4.0]
Basophils, %	0.4	%	[0.0-1.0]
Immature Granulocytes, % i	**0.1 H**	%	[<=0.0]
RBC /Platelet Morphology	Normal for Age		

Procedure		Units	Ref Range
Prothrombin Time	**18.1 H**	second(s)	[12.5-15.2]
International Normalized Ratio	1.6		

- *Labs, 5/23/2013:*

Collected Date	05/23/2013		
Collected Time	14:45:00		
Procedure		Units	Ref Range
Vitamin D, 25-OH Total Level i	**11 L**	ng/mL	[30-100]
Vitamin D2 Level	<2	ng/mL	
Vitamin D3 Level	11	ng/mL	

- *Labs, 6/6/2013:*

Collected Date	06/06/2013		
Collected Time	12:24:00		
Procedure		Units	Ref Range
Sodium Level	140	mEq/L	[135-145]
Potassium Level	4.2	mEq/L	[3.5-5.5]
Chloride Lvl	105	mEq/L	[96-110]
CO2 Lvl	22	mEq/L	[18-27]
Anion Gap	17.2	mEq/L	[8.0-22.0]
Glucose Level	70	mg/dL	[60-105]
BUN	8	mg/dL	[6-20]
Creatinine	0.4	mg/dL	[0.1-0.4]
Estimated GFR (Schwartz Bedside)	**69 Lf**	mL/min/1.73 m2	
Calcium Level, Total	9.7	mg/dL	[8.7-10.7]
Magnesium Serum	2.1	mg/dL	[1.8-2.4]
Phosphorus Serum	5.0	mg/dL	[3.9-6.5]
Bilirubin Total	0.9	mg/dL	[0.1-1.3]
Bilirubin Conjugated	0.0	mg/dL	[0.0-0.3]
Bilirubin Unconjugated	0.3	mg/dL	[0.0-1.1]
Bilirubin Delta	**0.6 H**	mg/dL	[0.0-0.2]
AST (SGOT)	**86 H**	IU/L	[3-74]
ALT (SGPT)	**47 H**	IU/L	[6-45]
Alkaline Phosphatase, Serum	**912 H**	IU/L	[95-380]
Gamma Glutamyltransferase	23	IU/L	[15-85]
Ammonia, Blood Venous i	33	mcmol/L	[9-35]
Albumin Level	3.5	g/dL	[2.9-5.5]

Procedure		Units	Ref Range
Prothrombin Time	**16.6 H**	second(s)	[12.5-15.2]
International Normalized Ratio	1.4		

Procedure		Units	Ref Range
White Blood Cell Count	11.5	K/mm3	[6.0-17.5]
Platelet Count	**159 L**	K/mm3	[250-600]
Hematocrit	**37.3**	%	[33.0-39.0]
Hemoglobin	12.7	g/dL	[10.5-13.5]
Red Blood Cell Count	4.42	M/mm3	[3.70-5.30]
MCV	84.4	fl	[70.0-86.0]
MCH	28.7	pg	[23.0-31.0]
MCHC	34.0	%	[30.0-36.0]
RDW	**13.4**	%	[11.0-16.0]
Mean Platelet Volume	11.1	fl	[8.9-12.4]
Nucleated Red Cells	0	/100 WBC	
Polys, Absolute	2852	/mm3	[1,500-5,000]
Lymphocytes, Absolute	7199	/mm3	[1,500-8,500]
Monocytes, Absolute	**1116 H**	/mm3	[0-500]
Eosinophils, Absolute	264	/mm3	[0-300]
Basophils, Absolute	46	/mm3	[0-50]
Immature Granulocytes, Absolute i	**23**	/mm3	[0-50]
Absolute Neutrophil Ct Cal	2852	/mm3	[1,500-5,400]
Polys, %	24.8	%	[15.0-45.0]
Lymphocytes, %	62.6	%	[30.0-75.0]
Monocytes, %	9.7	%	[0.0-10.0]
Eosinophils, %	2.3	%	[0.0-4.0]
Basophils, %	0.4	%	[0.0-1.0]
Immature Granulocytes, % i	**0.2 H**	%	[<=0.0]
RBC /Platelet Morphology	Performed		
Schistocytes	1+ *		
Burr Cells	1+ *		
Reactive Lymphocytes	3+ *		

- *Whole exome sequencing extended report, 8/27/2013:*

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MEDICAL GENETICS LABORATORIES / WHOLE GENOME LABORATORY

2450 Holcombe Blvd - Houston, TX 77021 / One Baylor Plaza, Houston, TX 77030
1-800-411-4363 Fax: 713-798-2787 - www.bcmgeneticlabs.org - genetictest@bcm.edu

Patient Name:	**JIANHUA XIE**			Evelyn Hsu, M.D.	
Date of Birth:	September 16, 2012	Lab Number:	563848		
Gender:	M	Family #:	353253	Tel No. :	206-987-5662
Hospital/MR #:	1275567	Date Collected:	August 27, 2013	Fax No:	206-729-3068
Accession #:	13-239-0681	Date Received:	August 30, 2013		
Sample Type:	EXT DNA	Date Ordered:	December 18, 2013		
Test Code:	1510	Date Reported:	December 21, 2013		
Indication:	Symptomatic				

Whole Exome Sequencing: Expanded Report

The focused whole exome sequencing report for this individual was released on 12/16/2013. We have received a request from the referring center to issue the expanded report of whole exome sequencing. The expanded report includes deleterious mutations and variants in genes unrelated to the patient's phenotype or with no known disease association and may include information on adult-onset conditions. It should be noted that heterozygous unclassified variants associated with recessive disorders are reported only when two or more changes in the same gene are detected (Table 7). It should also be noted that the sequence changes included in the expanded report have not been confirmed by Sanger sequencing. If there is a sequence change listed in this report that is of particular interest, please contact the laboratory for further information.

Table 6: Deleterious Mutations in Disease Genes Unrelated to Clinical Phenotype

Heterozygous mutations causing recessive disorders, for which no clinical testing is currently available, are also included in this table

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Monilethrix [MIM:158000]	AD	KRT81	Chr12: 52685183	NM_002281	exon1	c.66delC	p.P22fs	Het	Novel mutation	N/R N/R	N/A/ N/A
Xeroderma pigmentosum, group C [MIM:278720]	AR	XPC	Chr3: 14220068	NM_004628	exon1	c.1A>G	p.M1V	Het	Novel mutation	N/R N/R	Damaging/ Benign

Table 7: Variants of Unknown Clinical Significance in Disease Genes unrelated to Clinical Phenotype

Heterozygous unclassified variants associated with recessive disorders will not be reported unless a second change in the same gene is also detected.

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Amelogenesis imperfecta, hypomaturation-hypoplastic type, with taurodontism [MIM:104510]; Trichodontoosseous syndrome [MIM:190320]	AD	DLX3	Chr17: 48069006	NM_005220	exon3	c.736G>C	p.D246H	Het	Seen in 1000 Genome database	N/R N/R	Tolerated/ Possibly damaging
Arrhythmogenic right ventricular dysplasia 11 [MIM:610476]	AD	DSC2	Chr18: 28651658	NM_024422	exon13	c.2038C>A	p.R680S	Het	Novel variant	N/R N/R	Tolerated/ Benign
Arthrogryposis, distal, type 1B [MIM:614335]; Lethal congenital contracture syndrome 4 [MIM:614915]	AD	MYBPC1	Chr12: 102078205	NM_002465	intron31	c.3535+3A>G	N/A	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
Birbeck granules deficiency	AD	CD207	Chr2: 71060983	NM_015717	exon3	c.359G>A	p.R120H	Het	rs180679087	N/R N/R	Tolerated/ Benign
Cardiomyopathy, familial hypertrophic 1 [MIM:613873]	AD	JPH2	Chr20: 42744874	NM_020433	exon4	c.1441G>A	p.E481K	Het	Novel variant	N/R N/R	Tolerated/ Benign
Carney complex variant [MIM:608837]; Trismus-pseudocamptodactyly syndrome [MIM:158300]	AD	MYH8	Chr17: 10318674	NM_002472	exon8	c.676G>A	p.A226T	Het	rs140408926	N/R N/R	Tolerated/ Possibly damaging
Cerebellar ataxia, nonprogressive, with mental retardation [MIM:614756]	AD	CAMTA1	Chr1: 7798423	NM_015215	exon16	c.4063C>T	p.P1355S	Het	rs186530445	N/R N/R	Tolerated/ Benign
Corneal dystrophy, Avellino type [MIM:607541]; Corneal dystrophy, Groenouw type I [MIM:121900]; Cornea dystrophy, Reis-Bucklers type [MIM:608470]; Corneal dystrophy, Thiel-Behnke type [MIM:602082];	AD	TGFBI	Chr5: 135391397	NM_000358	exon11	c.1439C>T	p.A480V	Het	rs192398905	0/3156 2/6654	Tolerated/ Possibly damaging
Duane-radial ray syndrome [MIM:607323]; IVIC syndrome [MIM:147750]	AD	SALL4	Chr20: 50406732	NM_020436	exon2	c.2290T>C	p.S764P	Het	rs150549656	0/3738 2/7018	Tolerated/ Benign
Ehlers-Danlos syndrome, type IV [MIM:130050]	AD	COL3A1	Chr2: 189871110	NM_000090	exon43	c.3133G>A	p.A1045T	Het	PMID 22001912; rs149722210	2/3736 0/7020	Tolerated/ Probably damaging
Erythrocytosis, familial, 3 [MIM:609820]	AD	EGLN1	Chr1: 231557623	NM_022051	exon1	c.12C>G	p.D4E	Het	rs186996510	0/2196 1/4565	Damaging/ Benign
Holoprosencephaly-3 [MIM:142945]; Microphthalmia with coloboma 5 [MIM:611638]; Schizencephaly [MIM:269160]; Single median maxillary central incisor [MIM:147250]	AD	SHH	Chr7: 155596114	NM_000193	exon3	c.869G>A	p.G290D	Het	PMID 10556296, 19533790	N/R N/R	Tolerated/ Possibly damaging
Hydrocephalus, nonsyndromic, autosomal recessive 2 [MIM:615219]	AD	MPDZ	Chr9: 13219593	NM_003829	exon8	c.1051C>T	p.L351F	Het	rs3739757	0/3338 1/6751	Tolerated/ Benign
Keratosis palmoplantaris striata I [MIM:148700]	AD	DSG1	Chr18: 28914025	NM_001942	exon8	c.865G>A	p.E289K	Het	Seen in ESP5400 database	0/3736 1/7003	Tolerated/ Benign
Marfan syndrome [MIM:154700]; MASS syndrome [MIM:604308]; Ectopia lentis familial [MIM:129600]; Aortic aneurysm, ascending, and dissection; Stiff skin syndrome [MIM:184900]	AD	FBN1	Chr15: 48779506	NM_000138	intron29	c.3463+3A>G	N/A	Het	rs80344206	1/3737 1/7019	N/A/ N/A
Mental retardation, autosomal dominant 3 [MIM:612580]	AD	CDH15	Chr16: 89259961	NM_004933	exon12	c.1939C>T	p.L647F	Het	Novel variant	N/R N/R	Tolerated/ Benign
Muscular dystrophy, limb-girdle, type 1E [MIM:603511]	AD	DNAJB6	Chr7: 157178324	NM_005494	exon8	c.710G>A	p.R237H	Het	Seen in ESP5400 database	1/3737 3/7017	Tolerated/ Benign

Osteogenesis imperfecta, type V [MIM:610967]	AD	IFITM5	Chr11: 299466	NM_001025295	exon1	c.25G>A	p.D9N	Het	Novel variant	N/R N/R	Tolerated/ Possibly damaging
Periodic fever, menstrual cycle dependent [MIM:614674]	AD	HTR1A	Chr5: 63257124	NM_000524	exon1	c.423G>T	p.K141N	Het	Seen in ESP5400 database	0/3738 2/7016	N/A/ N/A
Pityriasis rubra pilaris [MIM:173200]	AD	CARD14	Chr17: 78178838	NM_024110	exon18	c.2403C>T	p.S801S	Het	rs189286068	N/R N/R	N/A/ N/A
Retinoblastoma [MIM:180200]	AD	RB1	Chr13: 49033848	NM_000321	exon20	c.1985T>A	p.L662Q	Het	Novel variant	N/R N/R	Damaging/ Probably damaging
Spermatogenic failure 10 [MIM:614822]	AD	SEPT12	Chr16: 4833992	NM_144605	exon5	c.452G>A	p.R151H	Het	Novel variant	N/R N/R	Damaging/ Benign
Spinocerebellar ataxia 15 [MIM:606658]; Spinocerebellar ataxia 29, congenital nonprogressive [MIM:117360]	AD	ITPR1	Chr3: 4699845	NM_002222	exon12	c.989G>A	p.R330Q	Het	Novel variant	N/R N/R	Tolerated/ Benign

Thrombophilia due to heparin cofactor II deficiency [MIM:612356]	AD	SERPIND1	Chr22: 21134136	NM_000185	exon2	c.536C>T	p.S179L	Het	rs186996599	0/3738 1/7019	Tolerated/ Benign
Townes-Brocks syndrome [MIM:107480]	AD	SALL1	Chr16: 51175324	NM_002968	exon2	c.809C>T	p.P270L	Het	rs140827311	1/3737 0/7020	Tolerated/ Benign
Treacher Collins syndrome 1 [MIM:154500]	AD	TCOF1	Chr5: 149759278	NM_001135243	exon17	c.2842G>T	p.A948S	Het	rs181102251	N/R N/R	Tolerated/ Probably damaging
Van der Woude syndrome	AD	WDR65	Chr1: 43719693	NM_001195831	exon24	c.3683A>C	p.N1228T	Het	Novel variant	N/R N/R	N/A/ N/A
Wiedemann-Steiner syndrome [MIM:605130]	AD	KMT2A	Chr11: 118373860	NM_001197104	exon27	c.7253A>G	p.N2418S	Het	Novel variant	N/R N/R	Tolerated/ Benign
Wiedemann-Steiner syndrome [MIM:605130]	AD	KMT2A	Chr11: 118375998	NM_001197104	exon27	c.9391G>A	p.G3131S	Het	rs150804738	N/R N/R	Tolerated/ Probably damaging

Acrocapitofemoral dysplasia [MIM:607778]; Brachydactyly, type A1 [MIM:112500]	AD/AR	IHH	Chr2: 219924953	NM_002181	exon1	c.237G>C	p.K79N	Het	Novel variant	N/R N/R	Tolerated/ Probably damaging
Bethlem myopathy [MIM:158810]; Ullrich congenital muscular dystrophy [MIM:254090]	AD/AR	COL6A3	Chr2: 238280476	NM_004369	exon9	c.4184G>A	p.R1395Q	Het	PMID 15689448, 20981092; rs80272723	1/3737 3/7017	Tolerated/ Possibly damaging
Cardiomyopathy; Myopathy; Muscular dystrophy; [MIM:603689], [MIM:613765] [MIM:604145], [MIM:600334], [MIM:608807], [MIM:611705]	AD/AR	TTN	Chr2: 179518052	NM_001267550	intron198	c.38708-4T>C	N/A	Het	Novel variant	N/R N/R	N/A/ N/A
Cardiomyopathy; Myopathy; Muscular dystrophy; [MIM:603689], [MIM:613765] [MIM:604145], [MIM:600334], [MIM:608807], [MIM:611705]	AD/AR	TTN	Chr2: 179526573	NM_001267550	intron180	c.37202-4T>C	N/A	Het	Seen in ESP5400 database	5/1651 28/2880	N/A/ N/A
Central core disease [MIM:117000]; Minicore myopathy with external ophthalmoplegia [MIM:255320]; {Malignant hyperthermia susceptibility 1 [MIM:145600]	AD/AR	RYR1	Chr19: 38995413	NM_000540	exon51	c.8093T>C	p.M2698T	Het	rs185021599	N/R N/R	Tolerated/ Benign
Charcot-Marie-Tooth disease, type 1F [MIM:607734]; Charcot-Marie-Tooth disease, type 2E [MIM:607684]	AD/AR	NEFL	Chr8: 24813803	NM_006158	exon1	c.227T>C	p.V76A	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A

Emery-Dreifuss muscular dystrophy 4, autosomal dominant [MIM:612998]; Spinocerebellar ataxia, autosomal recessive 8 [MIM:610743]	AD/AR	SYNE1	Chr6: 152690102	NM_033071	intron62	c.9828+5C>T	N/A	Het	rs185350092	N/R N/R	N/A/ N/A
Hyperthyroidism, familial gestational [MIM:603373]; Hyperthyroidism, nonautoimmune [MIM:609152]; Hypothyroidism, congenital, nongoitrou [275200; Thyroid carcinoma with thyrotoxicosis	AD/AR	TSHR	Chr14: 81575012	NM_001142626	exon9	c.812G>A	p.S271N	Het	Seen in 1000 Genome database	N/R N/R	Tolerated/ Benign
von Willebrand disease, type 1 [MIM:193400]; von Willebrand disease, types 2A, 2B, 2M, and 2N [MIM:613554 von Willibrand disease, type 3 [MIM:277480]	AD/AR	VWF	Chr12: 6167131	NM_000552	exon14	c.1613C>T	p.P538L	Het	rs139196998	1/3737 0/7020	Tolerated/ Possibly damaging
46XY sex reversal 8 [MIM:614279]; Obesity, hyperphagia, and developmental delay	AR	AKR1C2	Chr10: 5037668	NM_001354	exon9	c.689C>A	p.P230Q	Het	Novel variant	N/R N/R	Tolerated/ Benign
46XY sex reversal 8 [MIM:614279]; Obesity, hyperphagia, and developmental delay	AR	AKR1C2	Chr10: 5040855	NM_001354	exon7	c.532A>C	p.N178H	Het	Novel variant	N/R N/R	Damaging/ Probably damaging
Adams-Oliver syndrome 2 [MIM:614219	AR	DOCK6	Chr19: 11339635	NM_020812	exon29	c.2795G>C	p.W932S	Het	Seen in 1000 Genome database	N/R N/R	Damaging/ Probably damaging
Adams-Oliver syndrome 2 [MIM:614219	AR	DOCK6	Chr19: 11348985	NM_020812	intron15	c.1644-5C>G	N/A	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
Adams-Oliver syndrome 2 [MIM:614219	AR	DOCK6	Chr19: 11322772	NM_020812	exon36	c.4547C>T	p.T1516M	Het	rs181639639	N/R N/R	Damaging/ Probably damaging
Albinism, oculocutaneous, type VI [MIM:113750]	AR	SLC24A5	Chr15: 48431319	NM_205850	exon7	c.1025C>T	p.A342V	Het	Seen in 1000 Genome database	N/R N/R	Tolerated/ Probably damaging
Ciliary dyskinesia, primary, 3, with or without situs inversus [MIM:608644]	AR	DNAH5	Chr5: 13919366	NM_001369	exon7	c.894C>G	p.N298K	Het	rs116995413	N/R N/R	Tolerated/ Possibly damaging
Ciliary dyskinesia, primary, 3, with or without situs inversus [MIM:608644]	AR	DNAH5	Chr5: 13911508	NM_001369	exon12	c.1631C>T	p.T544I	Het	rs118026202	N/R N/R	Tolerated/ Benign
Fanconi anemia, complementation grou I [MIM:609053]	AR	FANCI	Chr15: 89838293	NM_001113378	exon24	c.2604A>C	p.E868D	Het	rs118031800	0/702 2/2530	Tolerated/ Benign
Fanconi anemia, complementation grou I [MIM:609053]	AR	FANCI	Chr15: 89835937	NM_001113378	exon21	c.2011A>G	p.I671V	Het	rs139814895	0/3738 5/7015	Tolerated/ Benign
Beckwith-Wiedemann syndrome	imprinted/ep igenetic	NLRP2	Chr19: 55493970	NM_017852	exon6	c.904G>C	p.E302Q	Het	rs3745904	1/3737 1/7019	Tolerated/ Benign
Blue cone monochromacy [MIM:303700]; Colorblindness, deutan [MIM:303800]	X-linked	OPN1MW	ChrX: 153490455	NM_000513	exon2	c.194T>C	p.I65T	Hem	rs1065419	N/R N/R	Tolerated/ Benign
Mental retardation, X-linked 89 [MIM:300848]	X-linked	ZNF41	ChrX: 47326826	NM_153380	exon2	c.55C>T	p.R19C	Hem	Seen in 1000 Genome database	N/R N/R	Tolerated/ Possibly damaging
Mental retardation, X-linked 97 [MIM:300803]	X-linked	ZNF711	ChrX: 84510499	NM_021998	exon4	c.314A>G	p.E105G	Hem	Novel variant	N/R N/R	Tolerated/ Probably damaging

Table 8: Deleterious Mutations in Genes with no Known Current Association with Disease

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2

		AGAP5	Chr10: 75434461	NM_001144000	exon8	c.1957C>T	p.R653X	Het	Seen in ESP5400 database	4/690 0/2490	N/A/ N/A
		ANKRD35	Chr1: 145561822	NM_144698	exon10	c.1510C>T	p.R504X	Het	rs139177747	4/3734 0/7020	N/A/ N/A
		ASB15	Chr7: 123267310	NM_080928	exon7	c.844C>T	p.R282X	Het	rs116956332	4/3734 4/7016	N/A/ N/A
		C2orf57	Chr2: 232458461	NM_152614	exon1	c.800delG	p.S267fs	Het	Novel mutation	N/R N/R	N/A/ N/A
		C2orf57	Chr2: 232458458	NM_152614	exon1	c.796_797insGT	p.A266fs	Het	rs61631859	N/R N/R	N/A/ N/A
		CCDC38	Chr12: 96273421	NM_182496	intron13	c.1142+1G>A	N/A	Het	rs191253798	0/3738 1/7019	N/A/ N/A
		CD209	Chr19: 7810932	NM_021155	exon4	c.220C>T	p.Q74X	Het	Novel mutation	N/R N/R	N/A/ N/A
		CDHR3	Chr7: 105655641	NM_152750	exon10	c.1310delC	p.A437fs	Het	Novel mutation	N/R N/R	N/A/ N/A
		CGREF1	Chr2: 27325449	NM_001166239	exon3	c.89_90del	p.30X	Het	Novel mutation	N/R N/R	N/A/ N/A
		CLEC5A	Chr7: 141635690	NM_013252	exon5	c.269C>A	p.S90X	Het	rs117965702	N/R N/R	N/A/ N/A
		DDX49	Chr19: 19035115	NM_019070	exon7	c.850C>T	p.Q284X	Het	Novel mutation	N/R N/R	N/A/ N/A
		HAP1	Chr17: 39890576	NM_001079871	exon1	c.311G>A	p.W104X	Het	rs181373328	N/R N/R	N/A/ N/A
		HELB	Chr12: 66715790	NM_033647	exon8	c.2218C>T	p.Q740X	Het	rs191467977	N/R N/R	N/A/ N/A
		HIST4H4	Chr12: 14923934	NM_175054	exon1	c.85_86insT	p.G29fs	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
		HIST4H4	Chr12: 14923935	NM_175054	exon1	c.84_85insG	p.Q28fs	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
		LILRA3	Chr19: 54803664	NM_006865	exon3	c.160G>T	p.E54X	Het	PMID 16501917; rs138741442	0/3724 3/6747	N/A/ N/A
		LRP3	Chr19: 33698023	NM_002333	exon7	c.1855C>T	p.R619X	Het	Novel mutation	N/R N/R	N/A/ N/A
		MAD1L1	Chr7: 2020106	NM_003550	exon15	c.1487_1488insG	p.E496fs	Het	Novel mutation	N/R N/R	N/A/ N/A

		NDUFB4	Chr3: 120315225	NM_004547	exon1	c.19A>T	p.K7X	Het	Novel mutation	N/R N/R	N/A/ N/A
		OR2T2	Chr1: 248616730	NM_001004136	exon1	c.633_636del	p.V214fs	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
		OR5H6	Chr3: 97983365	NM_001005479	exon1	c.238_239del	p.G80fs	Het	Novel mutation	N/R N/R	N/A/ N/A
		OXGR1	Chr13: 97639879	NM_080818	exon4	c.134delT	p.L45fs	Het	rs145685926	N/R N/R	N/A/ N/A
		PCDHGA6	Chr5: 140755048	NM_032086	exon1	c.1399delA	p.R467fs	Het	rs140643836	N/R N/R	N/A/ N/A
		PHC1	Chr12: 9085218	NM_004426	exon8	c.1165C>T	p.Q389X	Het	Seen in 1000 Genome database	N/R N/R	N/A/ N/A
		PRLHR	Chr10: 120354113	NM_004248	exon2	c.644G>A	p.W215X	Het	Novel mutation	N/R N/R	N/A/ N/A
		SDR39U1	Chr14: 24909363	NM_020195	exon6	c.808C>T	p.Q270X	Het	rs17844876	N/R N/R	N/A/ N/A
		SNX31	Chr8: 101608881	NM_152628	exon10	c.963delG	p.W321fs	Het	rs145643740	N/R N/R	N/A/ N/A
		SPRR2D	Chr1: 153012715	NM_006945	exon2	c.108C>A	p.C36X	Het	rs143912640	1/3737 0/7014	N/A/ N/A
		TET2	Chr4: 106158550	NM_017628	exon3	c.3451G>T	p.E1151X	Het	rs141975400	N/R N/R	N/A/ N/A
		THOC3	Chr5: 175388069	NM_032361	exon5	c.876delT	p.I292fs	Het	Novel mutation	N/R N/R	N/A/ N/A
		USP17L1P	Chr8: 7190747	NM_001256873	exon1	c.840delG	p.L280fs	Het	Novel mutation	N/R N/R	N/A/ N/A
		ZSWIM2	Chr2: 187693359	NM_182521	exon9	c.1238_1253del	p.I413fs	Het	Novel mutation	N/R N/R	N/A/ N/A

METHODOLOGY:

See the Methodology section on the focused report .

The WES report now includes minor allele frequency (MAF) data for variants reported in the NHLBI GO Exome Sequencing Project (ESP) ESP5400 database. For example, "1/3738 3/7017" in "ESP5400 AA/EA" column means for the variant listed, the minor allele was observed one time, the major allele was observed 3738 times in African Americans (AA), while the minor allele was observed three times, the major allele was observed 7017 times in Europeans (EA). N/R in the "ESP5400 AA/EA" column denotes "Not Reported".

The WES report also includes in silico predictions for nonsynonymous (missense) changes by SIFT (reference 6) and PolyPhen-2 (reference 7). The predictions are listed in the "SIFT/PolyPhen-2" column with predictions from SIFT (Damaging, Tolerated or N/A) listed first followed by predictions from PolyPhen-2 (Probably damaging, Possibly damaging, Benign or N/A). N/A denotes predictions that cannot be obtained. The N/A situation applies to nonsynonymous changes for which the algorithm used failed to output a prediction or changes not classified as nonsynonymous, for example, nonsense or frameshift mutations. It should be noted that in silico prediction results may vary depending on the algorithm and databases used at the time and should only be used as a guide but not solely relied upon for variant classifications.

Christine M. Eng, M.D.
Medical Director

Yaping Yang, Ph.D.
Laboratory Co-Director

This test was developed and its performance determined by this laboratory. It has not been cleared or approved by U.S. Food and Drug Administration. Since FDA is not required for clinical use of this test, this laboratory has established and validated the test's accuracy and precision, pursuant to the requirement of CLIA '88. This laboratory is licensed and/or accredited under CLIA and CAP. (CAP# 2109314 / CLIA# 45D0660090 WGL CAP# 8004250 / CLIA# 45D0927450). * performed at the Whole Genome Laboratory; ** performed at both the Medical Genetics Laboratories and the Whole Genome Laboratory.

- *Whole exome sequencing focused report, 8/27/2013:*

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MEDICAL GENETICS LABORATORIES / WHOLE GENOME LABORATORY

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Patient Name:	JIANHUA XIE			Sendouts,	
Date of Birth:	September 16, 2012	Lab Number:	563848	Seattle Children's Hospital Laboratory	
Gender:	M	Family #:	353253	Tel No. :	206-987-2563
Hospital/MR #:	1275567	Date Collected:	August 27, 2013	Fax No:	206-987-3840
Accession #:	13-239-0681	Date Received:	August 30, 2013		
Sample Type:	EXT DNA	Date Ordered:	September 4, 2013		
Test Code:	1500	Date Reported:	December 16, 2013		
Indication:	Symptomatic				

Whole Exome Sequencing: Focused Report

563848-1170985

HETEROZYGOUS MUTATION IN THE TNFRSF13B GENE AND OTHER VUS DETECTED, POSSIBLY RELATED TO PATIENT'S CLINICAL PHENOTYPE

According to clinical information submitted by the referring center, this individual has features include micronodular liver cirrhosis, which is associated with coagulopathy, mild jaundice, pruritus, anemia, hyperammonemia, splenomegaly, and failure to thrive. Family history indicates a significant maternal family history of gall bladder issues. In addition, the patient has one sister with GI issues including possible dairy intolerance and a low platelet count, and his mother has a history of heart murmur as a child and hypothyroidism. Previous testing at a different laboratory have identified a heterozygous missense variant of unknown significance in the ATP8B1 gene. We were requested to perform whole exome sequencing on extracted DNA sample from this individual. We also received blood samples of the mother (Sample# 563849) and father (Sample# 563850).

1. Deleterious mutations in disease genes related to clinical phenotype (Table 1)

A heterozygous c.777G>A (p.W259X) mutation in the TNFRSF13B gene was detected in this individual. This mutation is categorized as deleterious according to guidelines (ACMG Recommendations for Standards for Interpretation and Reporting of Sequence Variations: Revision 3567. Genet Med 3568:10:294). Defects in TNFRSF13B are the cause of Immunodeficiency, common variable, 2 (CVID2) [MIM:240500], a primary immunodeficiency characterized by antibody deficiency, hypogammaglobulinemia, recurrent bacterial infections, hepatomegaly, splenomegaly, diarrhea, and an inability to mount an antibody response to antigen. Defects in TNFRSF13B are also the cause of Immunoglobulin A deficiency 2 (IGAD2) [MIM:609529]. The inheritance for both disorders related to TNFRSF13B defects can be autosomal dominant or recessive. This individual is heterozygous for this mutation, which was confirmed by Sanger sequencing. Sanger sequencing also showed that the mother is heterozygous for this change, the father is negative. a second mutation or variant was not detected in the gene, however, the presence of a large or small deletion or duplication cannot be ruled out. It is recommended that correlation of these findings with the clinical phenotype be performed.

2. Variants of unknown clinical significance in disease genes related to clinical phenotype (selected variants are discussed below, see Table 2 for the complete list)

Heterozygous variant(s) of unknown clinical significance (VUS) in other gene(s) were detected in this individual (see Table 2). For dominant disorder(s), the variant(s) in the gene(s) were inherited from a parent. For recessive disorder(s), a second mutation or variant was not detected in the gene(s), however, the presence of a large or small deletion or duplication cannot be ruled out. It is recommended that correlation of these findings with the clinical phenotype be performed.

3. Medically actionable mutations in disease genes unrelated to clinical phenotype (Table 3):

None detected

4. Carrier Status for Recessive Mendelian Disorders (Table 4):

5. Pharmacogenetic Results (Table 5)

See Table 5.

6. Whole Mitochondrial Genome Sequencing

No large deletion or deleterious mutations were detected.

RECOMMENDATION SUMMARY:

It is recommended that correlation of these findings with the clinical phenotype be performed. Please note that the focused report is limited to genes predicted to be related to the clinical phenotype, medically actionable mutations, as well as carrier status for autosomal recessive conditions recommended for carrier screening by professional organizations such as ACMG or ACOG. An expanded report of the Whole Exome Sequencing Test is available. The Expanded Report will give additional information on mutations and variants in genes which cause disease unrelated to the indication for testing and predicted deleterious mutations in genes with no known current association with disease. It is available at no additional cost if requested within 6 months of the date of the Focused report. The turn-around time for the Expanded Report is 4 weeks. To order, please visit our website at www.bcmgeneticlabs.org and complete the Whole Exome Expanded Report Requisition (Test Code 1510) and FAX to 713-798-2787

RESULT TABLES

Table 1: Deleterious Mutations in Disease Genes Related to Clinical Phenotype

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Immunodeficiency, common variable, 2 [MIM:240500]; Immunoglobulin A deficiency 2 [MIM:609529]	AD/AR	TNFRSF13B	Chr17: 16842966	NM_012452	exon5	c.777G>A	p.W259X	Het	Novel mutation; Proband confirmed by Sanger, mother is heterozygous, father is negative.	N/R N/R	N/A N/A

Table 2: Variants of Unknown Clinical Significance in Disease Genes Related to Clinical Phenotype

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
HEM skeletal dysplasia [MIM:215140]; Pelger-Huet anomaly [MIM:169400]; Reynolds syndrome [MIM:613471]	AD/AR	LBR	Chr1: 225600276	NM_002296	exon8	c.964G>A	p.V322M	Het	rs145104817; Proband confirmed by Sanger sequencing, mother is negative, father is heterozygous.	N/R N/R	Damaging/ Benign
ACAD9 deficiency [MIM:611126]	AR	ACAD9	Chr3: 128622934	NM_014049	exon10	c.988A>C	p.K330Q	Het	rs79530903	2/3736 3/7017	Tolerated/ Probably damaging
Cholestasis, benign recurrent intrahepatic [MIM:243300]; Cholestasis, intrahepatic, of pregnancy, 1 [MIM:147480]; Cholestasis, progressive familial intrahepatic 1 [MIM:211600]	AR	ATP8B1	Chr18: 55329769	NM_005603	exon21	c.2364A>C	p.E788D	Het	rs77317429	N/R N/R	Tolerated/ Possibly damaging
Crigler-Najjar syndrome, type I [MIM:218800], Crigler-Najjar syndrome, type II [MIM:606785], Hyperbilirubinemia, familial transcient neonatal [MIM237900]	AR	UGT1A1	Chr2: 234681073	NM_000463	exon5	c.C1470T	p.D490D	Het	PMID 22710376; rs114123636	0/3738 2/7018	N/A/ N/A
Developmental delay, multifocal epilepsy & abnormal liver function	AR	NGLY1	Chr3: 25824791	NM_018297	exon1	c.91G>A	p.A31T	Het	Novel variant	N/R N/R	Tolerated/ Probably damaging
Hypercholanemia, familial [MIM:607748]	AR	BAAT	Chr9: 104133522	NM_001701	exon2	c.165C>G	p.F55L	Het	Novel variant	N/R N/R	Tolerated/ Benign
Meckel syndrome 7 [MIM:267010]; Nephronophthisis 3 [MIM:604387]; Renal-hepatic-pancreatic dysplasia 1 [MIM:208540]	AR	NPHP3	Chr3: 132432006	NM_153240	exon6	c.1082C>G	p.S361C	Het	rs146250226	N/R N/R	Damaging/ Probably damaging

Table 3: Medically Actionable Deleterious Mutations in Disease Genes Unrelated to Clinical Phenotype
No mutation/variant detected

Table 4: Carrier Status for Recessive Mendelian Disorders
No mutation/variant detected.

Table 5: Pharmacogenetic Profile Variant Alleles

Drug	Allele	Zygosity	References/Comments
Anti-depressants, anti-epileptics, Plavix	CYP2C19*3	Het	Non-functional allele, PMID 8195181, www.pharmgkb.org/gene/PA124; rs4986893
Anti-depressants, anti-epileptics, Plavix	CYP2C19*2	Het	Non-functional allele, PMID 8195181, www.pharmgkb.org/gene/PA124, CYP2C19*2; rs4244285
Warfarin	VKORC1-1639G>A	Hom	Decreased expression, PMID 21900891, www.warfarindosing.org, www.pharmgkb.org/gene/PA133787052; rs9923231

METHODOLOGY:

1. Whole exome sequencing (WES)*: for the paired-end pre-capture library procedure, genome DNA is fragmented by sonicating genomic DNA and ligating to the Illumina multiplexing PE adapters. The adapter-ligated DNA is then PCR amplified using primers with sequencing barcodes (indexes). For target enrichment/exome capture procedure, the pre-capture library is enriched by hybridizing to biotin labeled VCRome 2.1 (reference 3) in-solution Exome Probes at 47°C for 64 - 72 hours. For massively parallel sequencing, the post-capture library DNA is subjected to sequence analysis on Illumina HiSeq platform for 100 bp paired-end reads. The following quality control metrics of the sequencing data are generally achieved: >70% of reads aligned to target, >95% target base covered at >20X, >85% target base covered at >40X, mean coverage of target bases >100X. SNP concordance to genotype array: >99%. This test may not provide detection of certain genes or portions of certain genes due to local sequence characteristics or the presence of closely related pseudogenes. Gross deletions or duplications, mutations from repetitive sequences may not be accurately identified by this methodology.
2. As a quality control measure**, the individual's DNA is also analyzed by a SNP-array (Illumina HumanExome-12v1 array). The SNP data are compared with the WES data to ensure correct sample identification and to assess sequencing quality.
3. Data analysis and interpretation by Mercury 1.0**: The output data from Illumina HiSeq are converted from bcl file to FastQ file by Illumina CASAVA 1.8 software, and mapped by BWA program. The variant calls are performed using Atlas-SNP and Atlas-indel developed in-house by BCM HGSC. The variant annotations are performed using in-house developed software: HGSC-SNP-anno and HGSC-indel-anno. Synonymous variants, intronic variants not affecting splicing site, and common benign variants are excluded from interpretation unless they were previously reported as deleterious mutations. The variants were interpreted according to ACMG guidelines (reference 5) and patient phenotypes. Mutations/variants related to patient phenotypes are usually confirmed by Sanger sequencing for patients and if available, parents. Sanger confirmation is noted in the "References/Comments" section of the tables if performed. It should be noted that the data interpretation are based on our current understanding of genes and variants at the time of reporting.
4. The focused report contains results of genes related to the patient's clinical phenotype. This interpretation is based on the clinical information provided by the referring center. Results reported in the focused report should be carefully correlated to the individual's clinical findings by the referring physician. Results of carrier status for autosomal recessive conditions are limited to disorders which are recommended for carrier screening by professional societies such as ACMG or ACOG. Pharmacogenetic variants are limited to CYP2C9*2, CYP2C9*3, CYP2C9*5, CYP2C9*6, VKORC1-1639G>A, CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*8, CYP2C19*10, and CYP2C19*17.
5. The WES test also includes a mitochondrial genome screening*. The mitochondrial genome is amplified by a long-range PCR reaction and subjected to paired-end library construction and Illumina HiSeq 2000 sequencing analyses as described above. The mean depth of coverage for targeted bases is greater than 25,000X by this assay. Only deleterious point mutations and large structural rearrangements with heteroplasmy greater than 20%, i.e. clinically relevant mutations, will be reported. The Revised Cambridge Reference Sequence (RCRS) and the reported polymorphisms and mutations listed in http://mitomap.org database are used as references.
6. The WES report includes minor allele frequency (MAF) data for variants reported in the NHLBI GO Exome Sequencing Project (ESP) ESP5400 database. For example, "1/3738 3/7017" in "ESP5400 AA/EA" column means for the variant listed, the minor allele was observed one time, the major allele was observed 3738 times in African Americans (AA), while the minor allele was observed three times, the major allele was observed

7017 times in Europeans (EA). N/R in the "ESP5400 AA/EA" column denotes "Not Reported".
7. The WES report also includes in silico predictions for nonsynonymous (missense) changes by SIFT (reference 6) and PolyPhen-2 (reference 7). The predictions are listed in the "SIFT/PolyPhen-2" column with predictions from SIFT (Damaging, Tolerated or N/A) listed first followed by predictions from PolyPhen-2 (Probably damaging, Possibly damaging, Benign or N/A). N/A denotes predictions that cannot be obtained. The N/A situation applies to nonsynonymous changes for which the algorithm used failed to output a prediction or changes not classified as nonsynonymous, for example, nonsense or frameshift mutations. It should be noted that in silico prediction results may vary depending on the algorithm and databases used at the time and should only be used as a guide but not solely relied upon for variant classifications.

References:

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4. Li H. and Durbin R. (2009) Fast and accurate short read alignment with Burrows-Wheeler Transform. Bioinformatics, 25:1754-60. PMID:19451168.
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6. Kumar P, Henikoff S, Ng PC (2009). Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc. 2009;4:1073-1081. PMID:19561590.
7. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR (2010). PolyPhen-2. Nat Methods 7:248-249. PMID:20354512.

Christine M. Eng, M.D.
Medical Director

Yaping Yang, Ph.D.
Laboratory Co-Director

This test was developed and its performance determined by this laboratory. It has not been cleared or approved by U.S. Food and Drug Administration. Since FDA is not required for clinical use of this test, this laboratory has established and validated the test's accuracy and precision, pursuant to the requirement of CLIA '88. This laboratory is licensed and/or accredited under CLIA and CAP. (CAP# 2109314 / CLIA# 45D0660090 WGL CAP# 8004650 / CLIA# 45D2027450). * performed at the Whole Genome Laboratory; ** performed at both the Medical Genetics Laboratories and the Whole Genome Laboratory

- *Labs, 1/7/2014:*

Collected Date	01/07/2014		
Collected Time	14:03:00		
Procedure		Units	Ref Range
Prothrombin Time	13.6	second(s)	[12.5-15.2]
International Normalized Ratio	1.1		

- *Labs, 1/22/2014:*

Patient: XIE, JIANHUA DRACO — Flowsheet Print Request — Printed by: Nguyen, Tra
MRN: 1275567 — Date Range: 4/24/2013 0:00 - 2/3/2014 0:00 — Printed on: 2/3/2014 13:5

Event Date	Event	Result	Ref. Range	Status
1/22/2014 11:50	Sodium Level	140	(135 - 145)	
	Potassium Level	5.0	(3.5 - 5.5)	
	Chloride Lvl	104	(96 - 109)	
	CO2 Lvl	25	(18 - 27)	
	Anion Gap	16.0	(8.0 - 22.0)	
	Glucose Level	78	(60 - 105)	
	BUN	11	(6 - 20)	
	Creatinine	H 0.5	(0.1 - 0.4)	
	Estimated GFR (Schwartz Bedside)	* L 63		
	Calcium Level, Total	10.4	(8.7 - 10.7)	
	Magnesium Serum	2.2	(1.8 - 2.4)	
	Phosphorus Serum	5.7	(3.9 - 6.5)	
	Bilirubin Total	0.2	(0.1 - 1.3)	
	Bilirubin Conjugated	0.0	(0.0 - 0.3)	
	Bilirubin Unconjugated	0.0	(0.0 - 1.1)	
	Bilirubin Delta	0.2	(0.0 - 0.2)	
	AST (SGOT)	H 78	(5 - 41)	
	ALT (SGPT)	H 49	(6 - 40)	
	Alkaline Phosphatase, Serum	H 458	(95 - 380)	
	Gamma Glutamyltransferase	22	(15 - 85)	
	Albumin Level	4.7	(3.8 - 5.4)	
	White Blood Cell Count	10.9	(5.0 - 15.5)	
	Platelet Count	255	(250 - 600)	
	Hematocrit	H 41.2	(33.0 - 39.0)	
	Hemoglobin	13.4	(10.5 - 13.5)	
	Red Blood Cell Count	4.99	(3.70 - 5.30)	
	MCV	82.6	(70.0 - 86.0)	
	MCH	26.9	(23.0 - 31.0)	
	MCHC	32.5	(30.0 - 36.0)	
	RDW	13.5	(11.0 - 16.0)	
	Mean Platelet Volume	9.9	(8.6 - 12.0)	
	Nucleated Red Cells	0		
	Polys, Absolute	2572	(1500 - 7500)	
	Lymphocytes, Absolute	H 6965	(1500 - 5000)	
	Monocytes, Absolute	H 959	(0 - 450)	
	Eosinophils, Absolute	H 360	(0 - 250)	
	Basophils, Absolute	22	(0 - 50)	
	Immature Granulocytes, Absolute	* 22	(0 - 50)	
	Absolute Neutrophil Ct Cal	2572	(1500 - 7800)	
	Polys, %	23.6	(15.0 - 70.0)	
	Lymphocytes, %	63.9	(30.0 - 70.0)	
	Monocytes, %	8.8	(0.0 - 10.0)	
	Eosinophils, %	3.3	(0.0 - 4.0)	
	Basophils, %	0.2	(0.0 - 1.0)	
	Immature Granulocytes, %	* H 0.2	(- <=0.0)	
	RBC /Platelet Morphology	Normal for Age		
	Reactive Lymphocytes	R 2+		

- *Acylcarnitine profile, 3/17/2014:*

Laboratory Text Results

Collected Date/Time 03/17/2014 01:18
Procedure Acylcarnitine Profile, Blood

Acylcarnitine Profile/Tandem Mass Spectrometry

Acylcarnitine	Conc mcmole/l	Ref Range >1mo	Acylcarnitine	Conc mcmole/l	Ref Range >1mo
free carnitine	20.56	16-65	C-12:1	0.04	0-0.18
C-2 (acetyl)	9.56	2-24	C-12	0.03	0-0.17
C-3 (propionyl)	0.23	0-0.9	C-6-dicarboxylic	0.02	0-0.08
C-4 (butyryl)	0.11	0-0.7	C-14:2	0.01	0-0.11
C-5:1	0.01	0-0.08	C-14:1	0.03	0-0.18
C-5	0.04	0-0.38	C-14	0.03	0-0.12
C-6	0.05	0-0.23	C-14-hydroxy	0.01	0-0.04
C-5-hydroxy	0.02	0-0.14	C-16:1	0.02	0-0.08
C-7	0.01	0-0.06	C-16	0.09	0-0.24
C-8:1	0.05	0-0.66	C-16:1-hydroxy	0.01	0-0.03
C-8 (octanoic)	0.09	0-0.27	C-16-hydroxy	0.01	0-0.03
C-3-dicarboxylic	0.03	0-0.15	C-18:2	0.02	0-0.17
C-10:2	0.01	0-0.08	C-18:1	0.06	0-0.33
C-10:1	0.06	0-0.33	C-18	0.03	0-0.15
C-10	0.13	0-0.36	C-18:2-hydroxy	0.01	0-0.03
C-4-dicarboxylic	0.03	0-0.1	C-18:1-hydroxy	0.00	0-0.04
C-5-dicarboxylic	0.03	0-0.11	C-18-hydroxy	0.00	0-0.03

Testing done in plasma

Interpretation: Normal acylcarnitine profile.

Jane A. Dickerson, Ph.D.
Biochemical Genetics Laboratory

- *Serum amino acids, 3/17/2014:*

Genetics Non-Text Results

Collected Date 03/17/2014
Collected Time 01:18

Procedure	See Below	Units	Ref Range
Amino Acids Quant Interp Plasma			
Taurine Quantitative	81	mcmol/L	(30-133)
Aspartic Acid Quantitative	9	mcmol/L	(0-20)
Hydroxyproline Quantitative	24	mcmol/L	(0-50)
Threonine Quantitative	55	mcmol/L	(45-205)
Serine Quantitative	103	mcmol/L	(60-200)
Asparagine Quantitative	52	mcmol/L	(20-90)
Glutamic Acid Quantitative	37	mcmol/L	(15-100)
Glutamine Quantitative	600	mcmol/L	(325-825)
Proline Quantitative	134	mcmol/L	(60-360)
Glycine Quantitative	176	mcmol/L	(105-385)
Alanine Quantitative	224	mcmol/L	(145-495)
Citrulline Quantitative	12	mcmol/L	(6-40)
Valine Quantitative	134	mcmol/L	(75-350)
Cystine Quantitative	39	mcmol/L	(15-50)
Methionine Quantitative	18	mcmol/L	(10-65)
Isoleucine Quantitative	40	mcmol/L	(27-120)
Leucine Quantitative	81	mcmol/L	(45-160)
Tyrosine Quantitative	52	mcmol/L	(30-127)
Phenylalanine Quantitative	107 H	mcmol/L	(30-91)
Ornithine Quantitative	34	mcmol/L	(22-115)
Lysine Quantitative	93	mcmol/L	(60-240)
Histidine Quantitative	68	mcmol/L	(45-118)
Arginine Quantitative	73	mcmol/L	(25-125)

03/17/2014 01:18 Amino Acids Quant Interp Plasma
Interpretation: No significant abnormalities in the amino acid profile.

Rhona M. Jack, Ph.D
Biochemical Genetics Lab

Imaging Studies/Diagnostic Reports:

- *Chest and abdominal X-rays, 4/9/2013:*

Impression:

1. Colonic thumbprinting could indicate infectious or inflammatory colitis. An infiltrative process cannot be completely excluded on the basis of these radiographs.
2. No gross evidence of small bowel obstruction or ileus, although a paucity of gas in the bowel makes evaluation somewhat difficult.
3. Possible mild intraperitoneal free fluid.

- *Abdominal ultrasound, 4/9/2013:*

Findings:
The liver is normal in size and echogenic texture. There is no focal hepatic mass. The gallbladder is normal in size. Gallbladder wall demonstrates mild diffuse thickening. There is no cholelithiasis. There is no pericholecystic fluid. The common bile duct measures 1.2 mm. There is no intrahepatic biliary dilatation.

There is mild splenomegaly, measuring 8.5 cm. (normal range 5.2-7.0 cm). Splenic echogenic texture is normal.

The pancreas is poorly visualized, but demonstrates no gross abnormality. The right kidney measures 5.6 cm in length. The left kidney measures 6.0 cm in length. Normal renal length for age is 6.2 cm +/- 1.3 cm. There is trace bilateral pelviectasis. Renal parenchyma is unremarkable. The urinary bladder is decompressed, but demonstrates no focal abnormality. There is no distal ureteral distention.

Visualized images of the abdominal aorta and IVC are unremarkable.

There is a moderate amount of intraperitoneal free fluid.

Impression:

1. Moderate intraperitoneal free fluid.
2. Mild diffuse gallbladder wall thickening without cholelithiasis or pericholecystic fluid, likely related to volume overload with third spacing of fluid.
3. Mild splenomegaly.
4. Trace bilateral pelviectasis (SFU grade 1).

- *Abdominal ultrasound with Doppler, 4/10/2013:*

Impression:

1. Edematous appearance to the liver with interval development of multiple small echogenic foci throughout the right lobe of the liver, the latter findings suggesting a diffuse inflammatory etiology including septic emboli. Differential diagnosis for the echogenic hepatic foci includes metastatic lesions and the possibility of hemorrhagic infarcts.

2. Persistent splenomegaly.
3. Contracted gallbladder likely reflecting nonfasting state.
4. Trace central pelviectasis right kidney, decreased from prior.
5. Small amount of anechoic free intraperitoneal fluid.
6. Abnormally elevated resistive indices measuring 1.0 throughout the liver.
7. Recanalization/patency of the umbilical vein, a finding which, in conjunction with splenomegaly, suggests portal hypertension.

- *Transthoracic echocardiogram, 4/10/2013:*

Summary:

1. No intracardiac vegetation.
2. No intracardiac shunting.
3. Normal valvular structure and function.
4. No pericardial effusion.
5. Indirect markers for impaired relaxation of the left ventricle include abnormal annular and septal tissue Doppler patterns, 'a' wave reversal in pulmonary venous Doppler.
6. There is mild increase in velocity across aortic, pulmonary and mitral valves, indicating hyperdynamic or fluid overloaded status.

- *CT angiogram of the abdomen, thorax, and pelvis, 4/11/2013:*

Impression:

1. Diffuse hazy mesentery could represent edema in the setting of stigmata of portal hypertension including recanalized paraumbilical vein, minimal gastric varices and moderate splenomegaly as well as diffuse subcutaneous edema. Additional diagnostic considerations include infectious processes of the mesentery given coexisting bowel wall thickening and mucosal hyperenhancement of the sigmoid colon or possibly an infiltrative process of the mesentery such as lymphoma or leukemia.

2. Numerous small hypodense hepatic lesions are too small to further characterize and are thus indeterminate. However, diagnostic considerations should include infection or metastases. Fat density is seen within several lesions and therefore fat containing metastases such as liposarcoma can produce this pattern although there is no evidence of primary tumor on the current exam, benign fat-containing lesions such as angiomyolipomas, xanthomas could be included in the differential of fat containing lesions.

3. Sigmoid colon and rectal wall thickening with mucosal hyperenhancement could represent infectious colitis.

4. Bilateral dependent airspace opacities are most compatible with atelectasis, although infectious etiology cannot be completely excluded.

Pathology Reports:

- *Liver biopsy, 4/18/2013:*

Gross Description:

Received fresh labeled LIVER BIOPSY is a single needle core biopsy fragment measuring 0.1 cm in diameter x 1.3 cm in length. The specimen is placed in formalin then wrapped and submitted in its entirety in a single cassette designated A1. [MA]

Microscopic Description:

H&E stained sections show a cirrhotic liver with bridging fibrosis and marked bile ductular proliferation. There is moderate inflammation in the portal tracts with scattered neutrophils, lymphocytes, and eosinophils. Bile ducts are present, although difficult to see with the marked portal expansion and ductal proliferation. Lobular inflammation is variable and predominantly lymphocytic in nature. There is variable cholestasis, with some nodules showing canalicular plugging and others showing only mild intracellular cholestasis. Acidophil bodies are readily identified. Hepatocytes are swollen with lacy cytoplasm and reactive appearing nucleoli. Rare areas show features of early hepatocyte necrosis with the blurring of cell junctions and hypereosinophilia. There is patchy mild macrosteatosis (<5%). A trichrome stain highlights the presence of bridging fibrosis, as well as pericellular fibrosis. Periodic acid shift stains with a without diastase reveal no diastase resistant globules.

Slide and stain summary: H&E 3 slides; PAS 1 slide; PAS-D 1 slide; trichrome 1 slide

Electron Microscopy Findings:

Toluidine blue stained thick sections reveal cirrhotic liver with both periportal and pericellular fibrosis. There is mild portal inflammation. Examination by transmission electron microscopy shows mild cholestasis, and occassional hepatocytes with membranous debris but no evidence of storage disease. Bile canaliculi show normal microvillous architecture, without Bylers-type bile. Probable peroxisomes are identified. Mitochondria are present in normal numbers, and are without circular or paracrystalline arrays of cristae.

Final Diagnosis:

LIVER, NATIVE, CORE BIOPSY: CIRRHOSIS AND BILE DUCTULAR PROLIFERATION, SEE COMMENT

Comment

The biopsy shows established cirrhosis with marked bile ductular proliferation and variable cholestasis. There is ongoing hepatocyte injury, with scattered apoptotic cells, as well. PASd stain reveals no evidence of alpha-1 antitrypsin deficiency, and no abnormal mitochondria, bile or storage-type material are seen on electron microscopy. A definitive etiology for the patient's chronic liver failure is not evident from this biopsy.

- The pathology slides were reviewed as consults at Massachusetts General Hospital. The MGH review ***clarified*** the diagnosis, with the following interpretation:

FINAL PATHOLOGIC DIAGNOSIS

Micronodular cirrhosis with cholestasis, moderate macrovesicular steatosis and PAS/D positive globules. See note

Note:
The trichrome stain shows nodules composed of hepatocytes and surrounded by fibrosis. A keratin 19 immunohistochemical stain was evaluated. The stain shows marked bile ductular reduplication. In addition, native bile ducts are also identified arguing against a diagnosis of paucity of bile ducts. An iron stain is negative.

A copper stain shows a diffuse increase in intracellular copper. However this finding does not necessarily indicate a diagnosis of Wilson's disease. Elevated copper levels are often found in other chronic diseases of the liver particularly in children as well as in individuals with significant fibrosis as in this instance. Nevertheless, if clinically indicated, further evaluation to exclude a diagnosis of Wilson's disease is suggested.

A PAS/D stain shows numerous periseptal hepatocellular globules. However, these globules are not typical for out of A1AT deficiency. Nevertheless, an immunohistochemical stain for AIAT also shows the presence of periseptal globules. This data raises the possibility of A1AT deficiency and appropriate investigations to either support or exclude this possibility are required. The diagnosis of other heritable metabolic disorders would require appropriate testing and cannot be excluded based on this material alone.

Treating Physician's Assessment and Plan:

Jianhua is a 20 month-old boy that presented in April 2013 with fulminant hepatic failure. He has subsequently been diagnosed with micronodular cirrhosis of undetermined etiology. After initially being listed for liver transplant, his clinical status has improved significantly and he is currently on hold for transplant. He continues to be followed closely by the liver transplant team at his local quaternary children's hospital. His work-up has been extensive, including a large number of metabolic studies and whole exome sequencing. The results have included several abnormalities of unclear clinical significance. His parents understandably want to do everything possible in order to clarify what the

underlying cause for his liver disease. In particular, they are suspicious about a fatty acid oxidation disorder. With this in mind, they are seeking a Best Doctors consultation regarding the diagnosis and treatment plan.

Questions:

1. What is your overall assessment of the patient's condition? What is the differential diagnosis for this patient? Is a fatty acid oxidation disorder a possibility and why (or why not)? What do you think is the most likely diagnosis and why?
2. Jianhua's family asks about the significance of his newborn screen (pasted first in the labs above). They note that "his C-18, C-18:1, and C-16 are extremely high (6X, 3X, and 10X compared to the maximum normal values noted on subsequent testing.) However, other acylcarnitine values are quite normal (only C-3 at 1X)." They question, "Does these mean that he is more likely to have long/very-long chain fatty acid oxidation disorders (FAODs)?"
3. Jianhua's family notes that his urine organic acids from 4/11/2013 showed "very high adipic, suberic, and sebacic acid levels." They ask if this points to a mitochondrial oxidation defect?
4. Looking specifically at his acylcarnitine profile and urine organic acids, is any metabolic disorder suggested, including a fatty acid oxidation defect?
5. His family notes that the whole exome sequencing noted a mutation in the ACAD9 gene. In the final column, they note it states "tolerated/probably damaging." What is the significance of this?
6. What additional diagnostic testing do you recommend?
7. Based upon the available testing, can any specific treatments or dietary supplements/restrictions be recommended?
8. How would you recommend following this patient?
9. If not addressed by the questions above, please provide any further recommendations that you believe will aid in understanding this patient's findings or in guiding future therapeutic decisions.
10. Please provide scientific references that support your assessment/recommendations and which may be helpful to the treating physician.