UPMC LIFE CHANGING MEDICINE

September 25, 2014

Yong Xie
21743 NE 105th PL
Redmond, WA 98053

Dear Mr. Xie,

Thank you for giving me the opportunity to evaluate your son for a second opinion. My opinion that further diagnostic studies for a fatty acid oxidation disorder are not indicated or of benefit to Jianhua came after reviewing Jianhua's history, medical record, my examination, and consultation with the genetics team here in Pittsburgh which includes the world expert in ACAD9 deficiency, which was the purpose of your visit.

I understand from your recent emails that you have chosen not to accept our clinical judgment that Jianhua's clinical presentation is not consistent with ACAD9 deficiency or another fatty acid oxidation disorder and this is your right. In this case I could only recommend that you follow up with his local physicians for his ongoing medical care.

The University of Pittsburgh Physicians Department of Pediatrics will retain your son's medical records as required by law. Enclosed with this letter is a form titled Authorization for the Release of Protected Health Information should you need a copy of his records, or should you wish that a copy of his records be forwarded elsewhere. The second opinion process has been completed and this letter will officially end our correspondence.

Sincerely,

Areeg El-Gharbawy, MD
UPP, Department of Pediatrics
Division of Medical Genetics

Enclosure – Authorization for the Release of Protected Health Information
cc: Gerard Vockley, MD, PHD, Division Chief Medical Genetics

* Final Report *

Result Type:	Medical Genetics (dictated)
Event Date:	29 July 2014 0:00
Result Status:	Final
Result Title:	Evaluation
Performed By:	EL-GHARBAWY, AREEG H on 29 July 2014 19:48
Encounter info:	0574504284210, CHP, Outpatient, 07/29/14 - 08/02/14
Contributor system:	ESCRIPTION

* Final Report *

Evaluation

*******FINAL REPORT*******
Medical Genetics Evaluation

XIE, JIANHUA
MRN 970819723
DOB 09/16/2012
DOS 07/29/2014

GENETIC COUNSELOR: Elena Infante

CHRONOLOGICAL AGE: 22 months

PEDIATRICIAN: Dr. Reggy Kulpa

INDIVIDUALS PRESENT AT THE VISIT: The patient as well as his mother, father and sister.

CHIEF COMPLAINT: History of liver failure and liver cirrhosis. He is coming for a second opinion to evaluate the possibility of liver disease being due to a fatty acid oxidation disorder.

HISTORY OF PRESENT ILLNESS: Jianhua is a 22-month-old male child who has a history of liver failure diagnosed at the age of 6 months when he presented with generalized anasarca, abdominal distention in the form of ascites with bilateral edema in the lower extremities and jaundice as well as emesis and diarrhea. At that time an extensive genetic and GI workup was done and lab test results including a liver biopsy showed evidence of liver failure of unclear etiology. He was worked up for the possibility of sepsis versus biliary obstruction. He was noted to have anemia and received blood transfusions. The liver pathological report showed evidenc suggestive of chronic liver cirrhosis with cholestasis. He was listed for transplant at the age of 7 months given a picture of acute on top of chronic liver failure; however, he did not receive a transplant and was taken off the transplant list after his liver condition stabilized and improved. Per the parents, he had a fishy body odor at that time and his labs showed multiple abnormalities including dicarboxylics in the urine. Due to the length of his extensive files and my concern of missing any study without indicating it here in the dictation it would be best to refer for details of the

studies that were done to the paperwork file that have been scanned in Cerner. In the interim the parents placed him on a diet composed of carbohydrates, MCT oil and white meat in the form of chicken with limited red meat portions. They attributed improvement in his liver functions to the MCT in the diet and kept him on it since then, as well as all other medications he recieved during his illness (fat solubale vitamins and Ursodiol). The parents believe that MCT oil caused improvement in his liver functions and linked that to their son having a fatty acid oxidation disorder, particularly after he had an extensive workup and exome sequencing that showed a heterozygous variant of unknown significance in ACAD9. The same exome study showed a known pathogenic mutation (heterozygous mutation) in the TNFRSF13B gene which is a deleterious mutation according to the ACMG guidelines that the family refused to believe was disease causing. Defects in this gene cause immunodeficiency common variable type 2, which is a primary immunodeficiency characterized by an antibody deficiency , hypogammaglobulinemia, recurrent bacterial infections, hepatomegaly, splenomegaly, diarrhea and inability to mount an antibody response to antigen. Defects in this gene also cause immunoglobulin A deficiency. The inheritance by report can be autosomal dominant or recessive and this individual is heterozygous for the mutation which was confirmed by Sanger sequencing. A second mutation/ del/dup was not detected. Since then, the patient, has had a history of repeated infections, what appears to be viral or respiratory syncytial virus for the first half of a the year. The parents denied the pathogenic mutation was real because the mother is heterozygous for the same change and does not have any symptoms. Although, they were counseled that variability of expression is known in this disorder.

PAST MEDICAL HISTORY: In terms of maternal pregnancy history, mom's pregnancy history is G5 P3. Age of mother at delivery of the child was 38 years old. Ultrasounds were done during the first trimester and showed bilateral caliectasis and this resolved on followup. First trimester testing was done. CVS was done and revealed a 47,XYY/46 XY mosaic change. The father does not believe that it is true.

BIRTH HISTORY: The child was delivered by normal spontaneous vaginal delivery at Evergreen Hospital in Washington. Gestational age was 38.4 weeks. Apgars were 8 and 8. Birth length was 20-1/2 inches. Birth weight was 7 pounds and 5 ounces. Expanded newborn screen was all normal and he passed his hearing test.

PREVIOUS SURGICAL HISTORY: In April 2013 he had a liver biopsy.

PREVIOUS HOSPITALIZATIONS: in April 2013 for liver failure.

MEDICATIONS: He is on vitamin D 2000 International Units daily, multivitamin, vitamin E, ursodiol, acetaminophen and MCT oil.

ALLERGIES: NONE. He takes rice, flour, oats, chicken, turkey, cod, coconut oil and fruit.

FEEDING AND DIETARY HISTORY: The parents restrict him from long chain fatty acids and placed him on MCT oil.

DEVELOPMENTAL AND BEHAVIORAL HISTORY: He walked at the age of 14 to 15 months and he has refused Early Intervention and feels that he is developing normally. He has not gone to school and the parents are concerned about sending him to daycare or school because of his underlying condition.

SOCIAL HISTORY: He lives with his parents and Social Work is involved.

REVIEW OF SYSTEMS: A 14-point review of systems was done and the following are the pertinent positives. He gets sicker than others with routine illness.
GASTROINTESTINAL: He has a history of diarrhea, especially when they decrease the amount of MCT oil or change the type of diet that he is eating.
GASTROINTESTINAL: He has a history of liver failure .
NEUROLOGIC: He has mild developmental delay.
SKIN: No abnormalities.
PULMONARY: He has had a history of repeated upper respiratory tract infections.

PHYSICAL EXAMINATION: His weight is 12.2 kg. His height is 85 cm. Head circumference is 48.5.
HEENT: He is normocephalic, atraumatic. Forehead is wide. Facies are normal. Hair, eyebrows and eyelashes are normal. He has mild hypertelorism and bilateral epicanthal folds. Eye movement is normal. Ears are normal in architect, size, and position. Nose shows mild flattening of the nasal bridge. Philtrum, upper lip and lower lip are normal. Palate was difficult to see. Tongue is moist. Mucous membranes are moist. Chin is normal. Neck showed no thyromegaly or lymphadenopathy.

CARDIOVASCULAR: Shows normal heart sounds with no murmur, gallop, or rub.
ABDOMEN: Soft, nontender, nondistended with no organomegaly.
GENITAL: Deferred.
CHEST: No abnormalities.
BACK: Appears to be normal.
LUNGS: Breath sounds were heard bilaterally equal with no wheezes or crackles.
EXTREMITIES: Hands show normal fingers. Palmar creases are normal. Feet are normal.
NEUROLOGIC: He was asleep and woke up. There is no evidence of clonus or ataxia. He did not walk in front of me so it was difficult to assess his gait. Reflexes were 1+ bilaterally.

CLINICAL IMPRESSION AND PLAN: Jianhua is a 22 month old male patient who has a history of chronic liver disease with liver cirrhosis and a history of acute on top of chronic liver failure that improved without the need for a liver transplant. The parents are here for a second opinion, and to do further studies to rule in a fatty acid oxidation defect because they are convinced that their child has a FAOD disorder. This strong conviction

about the diagnosis was depsite they rceieved detailed genetic counseling and GI expert view Seattle Children's hospital who made it clear to the family that there was no indication of a fatty acid oxidation disorder or any other metbolic condition that could explain his underlying liver disease. However, he does have a pathogenic mutation in a gene related to immune deficiency that may present in autosomal recessive or dominant form. The gene is the TNFRSF13B which is associated with common variable type 2 immunoglobulin deficiency, which is a primary immune deficiency characterized by antibody deficiency, hypogammaglobulinemia, recurrent bacterial infections, hepatomegaly, splenomegaly, diarrhea, and inability to mount an antibody response to antigens. The patient's mom also carries the same mutation but has no signs or symptoms of infections; however, variable expressivity is known in this condition. The parents are in disagreement that the immunodeficiency gene has anything to do with his phenotype, although it certainly has contributing features, especially the diarrhea, the repeated upper respiratory tract viral infections and repeated immune infections. I had a very long discussion; about 2 hours with the family and during this time we reviewed why his conditon is not a fatty acid oxidation disorder, and that further testing in this direction would be invasive and not necessary. I had several discussions about Jiahhua among the whole metabolic group here in genetics clinic conference based on the family's request with Dr. Vockley and Dr. Schneider involved in all. The final decision based on our group evaluation is that there is no indication from the evaluation done here in Pittsburgh or at Seattle of a fatty acid oxidation disorder. Therefore we do not recommend any type of further testing to pursue this diagnosis. Any biopsies to pursue a non existent diagnosis would raise a concern for medical abuse and we refuse to be part of this. Our recommendation would be that the patient continue to follow up with the hepatology and metabolic team in Seattle, and to pursue testing for the immune dysfunction.

The parents brought up a question about doing whole genome testing in case whole exome (including the expanded report) missed the diagnosis. I indicated to them that this could happen, however, if they were concerned about this possibility , it would have to be done through the Seattle genetic team since they requested the initial testing and sent out the sample to the lab that did the testing. Mr. Xie sent me a metabolome testing link for a recent test that is offered by Baylor asking if it would be helpful for his son; however, becaue the metabolome link specifically mentions that the patient should not be on any dietary intervention the parents did not want to pursue this avenue because it meant taking him off MCT oil which they refuse to do.

Today, I recommended the following labs: acylcarnitine profile, comprehensive metabolic panel including INR and PT, essential fatty acids, plasma amino acids, urine organic acids, carnitine level, CPK level as well as CDG and immunoglobulin quantitative testing. I also recommended that the patient is referred to Immunology and I recommended that the parents continue to follow him in terms of his general progress and keep close with the team that follows him. No followup visit is indicated at this time since they are from Seattle and we recommend that they continue follow up locally. A copy of the results of the testing here will be sent in a seperate note. The family specifically asked to have a copy of this note sent to them, and that they would give a copy to the treating physicians

because this was a second opinion. I recommended that a copy be predeneted specifically to the genetic metabolic group to be able to follow up on further labs- specifically the immune testing, and essential fatty acids (this will require follow up over time).

A total of 120 minutes was spent in face-to-face interaction with the patient and the family. During this time, we reviewed the medical history. A 14-point review of systems was done. The pedigree was reviewed since it has been constructed in the past through the Genetics group that they saw before and we had a report of the study. I performed a full physical examination. More than 1 hour was spent to discuss with them the findings as well as to address their questions and concerns because they had many. They will be seeing Dr. Shneider for his liver condition tomorrow.

Areeg Hassan El-Gharbawy, MD
Division of Medical Genetics

D: 07/29/2014 07:48PM, AE T: 07/30/2014 02:18PM, rc R: 08/20/2014 02:53AM
Confirmation #: 1850791 / Document ID: 4928473

cc: Benjamin Shneider MD, Primary Care Physician
Gerard Vockley MD, Referring Physician

Electronically signed by: Areeg Hassan El-Gharbawy, MD on 08/26/2014 at 05:18 AM

Completed Action List:
* Perform by EL-GHARBAWY, AREEG H on 29 July 2014 19:48
* Sign by EL-GHARBAWY, AREEG H on 26 August 2014 5:18 Requested on 30 July 2014 14:19