Shodair CHILDREN'S HOSPITAL

GeneMaP
Genetics for Montana Providers

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Children's Miracle Network Hospitals Helping Local Kids

Shodair Children's Hospital is Montana's only Children's Miracle Network affiliated hospital. Children's Miracle Network is a non-profit organization dedicated to saving and improving the lives of children by raising funds for premier children's hospitals across North America. For more information, visit: www.cmn.org

Please direct your ideas or comments regarding this newsletter to:
mtgene@shodair.org

Welcome!

Welcome to the GeneMaP, genetics news for Montana providers. This is the first edition of a quarterly electronic newsletter distributed by the Genetics Department at Shodair Children's Hospital in Helena. Through this newsletter, we'll keep you up to date on the services we provide, as well as share some interesting cases. This issue will provide you with news about our Newborn Screening Follow-up Program, as well as a case study of a family with a history of colon cancer who was seen at Shodair.

Shodair's Genetics Department offers a variety of services. In addition to the Newborn Screening Follow-up Program, we provide clinical and laboratory services for patients of all ages. Our outreach genetic clinics are held throughout the state, where we see prenatal, pediatric, and adult patients. Our laboratory services include cytogenetics, prenatal serum screening, DNA testing, prenatal diagnosis, and pharmacogenetic testing.

We hope you enjoy this newsletter; please feel free to forward it your colleagues. To request additions / removals from our email list, contact us at mtgene@shodair.org.

Expanded Screening Good News for Montana's Infants

By Anne Seliskar, R.N.

Last January, Montana joined the majority of states across the nation by implementing expanded screening of its newborns for 29 genetic conditions.

Starting in 1961 with Dr. Robert Guthrie's test for Phenylketonuria (PKU), the newborn screening program added three other conditions and for years consisted of phenylketonuria (PKU), galactosemia, hemoglobinopathies, and congenital hypothyroidism. Although the test screened for four conditions, it was referred to as the "PKU Test." It is now referred to as the "Newborn Screening Test."

With advances in technology, the Tandem Mass Spectrometer (MS/MS) has changed universal newborn screening. MS/MS allows for screening of multiple metabolic disorders, including fatty oxidations disorders, organic acid disorders, and amino acid disorders.

Additionally, the conditions of biotinidase, cystic fibrosis, congenital adrenal hyperplasia, and hearing were added to newborn screening, because they meet the following criteria:

1. The condition can be identified at a phase (24-48 hours after birth) at which it would not ordinarily be presenting.
2. A screening test with appropriate sensitivity and specificity is available.
3. There are demonstrated benefits of early detection, timely intervention, and efficacious treatment of the condition being tested.
4. A test that can be offered at a low cost is available.

Newborn Screening continued

Newborn screening is done at all Montana birth centers. It consists of a blood spot test, ideally collected between 24 and 48 hours of birth. Montana's State Laboratory in Helena receives these blood spot cards and takes enough from the card to test for phenylketonuria, galactosemia, hemoglobinopathies, congenital hypothyroidism, and cystic fibrosis. The remaining samples on the cards are then sent to the Wisconsin Newborn Screening Laboratory, which runs the other metabolic tests.

Once these results are reported to Montana's State Laboratory, its staff and that of Children's Special Health Services notify the baby's primary care physician of any out of range results, send what is called an ACT sheet which gives additional information on the disorder and treatment, and requests a re-screen.

The Newborn Screening Follow-up Program (NBSFP), located in the Department of Medical Genetics at Shodair Children's Hospital, becomes involved when the second screen has an out of range value. The NBSFP staff consists of a nurse care coordinator, a genetic counselor, a nutritionist, and medical geneticists.

The NBSFP is available to assist in gaining a confirmatory diagnosis, or confirm that the diagnostic test is negative and therefore normal. The NBSFP also ensures that the newborn is receiving appropriate initial care for a confirmed diagnosis. The program is a valuable resource for the physicians of Montana.

The second facet of the NBSFP is assurance of a "medical home" for each patient with a diagnosis as a result of the screening program. The medical home, which is an approach for providing comprehensive primary health care, consists of many people working together. An example of a medical home may consist of the baby's family, primary care physician, and the pediatric specialty clinic, which includes a nutritionist, social worker, nurse and laboratory staff. Together, this team promotes a relationship in which family members and professionals work to ensure the best services for the child and family.

Long term follow-up data collection will be in place to determine that the newborn screening system is accomplishing the intended goal of improving health outcomes for Montana's children.

Each year, 4.1 million newborns are screened for congenital disorders in the United States. Of them, 4,000 infants are diagnosed as having a significant condition; it is estimated that 1,000 infants have conditions that go undetected.

In 2008, 12,318 newborns received the expanded newborn screening in Montana. Approximately 260 initial positive screens were reported to the NBSFP; 40 of them were diagnosed with a congenital disorder and are receiving treatment as the condition requires.

The following disorders were diagnosed in Montana last year as a result of the Expanded Newborn Screening:

- 1 Phenylketonuria
- 1 Carnitine Acylcarnitine Translocase Deficiency
- 1 Isovaleric Acidemia
- 1 Duarte Galactosemia
- 9 Congenital Hypothyroidism

Newborn Screening continued

- 1 Sickle Cell Anemia
- 2 Cystic Fibrosis *(plus one screened in Washington State and transferred to Montana)*
- 23 Hemoglobin Traits, either S or D or C trait
- 151 had a negative second screen.
- 15 had a positive second screen and diagnostic tests were negative.

For more information on the Newborn Screening Follow-Up Program, contact:

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You may also contact one of our Medical Geneticists:

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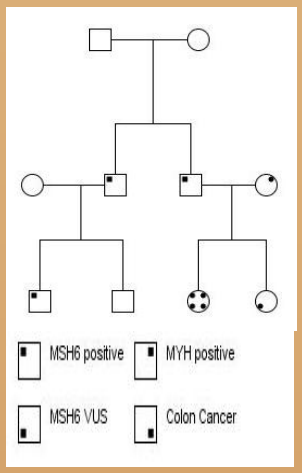
Genetic Testing for Colon Cancer:
An Easy Familial Case?
By Tessa Pitman, MS, Genetic Counselor

A family came to Shodair's Genetics Department with questions regarding genetic testing for a known family mutation that causes Hereditary Non-Polyposis Colon Cancer (HNPCC). As you may know, HNPCC is a hereditary cancer syndrome with an increased risk for colon, endometrial, and other cancers. The colon cancers usually arise from polyps without the polyposis seen in Familial Adenomatous Polyposis (FAP), an early onset colon cancer syndrome that carpets the colon with polyps. The cancer risk in HNPCC is inherited in an autosomal dominant pattern and is caused by a change in one of five known genes: MSH2, MLH1, PMS1, PMS2, MSH6.

The father of this family was a known carrier for an MSH6 deleterious gene mutation; his two sons were interested in being tested for this mutation. Maternal cancer family history was unremarkable. Although this looks like a straight forward case of testing the two sons, after taking a detailed family history, other questions precipitated.

It turns out that the father's niece had developed colon cancer at the extremely young age of 13, which reoccurred at age 24. Due to the early onset, in addition to fewer polyps than what would be expected to be identified at this age for a FAP diagnosis, genetic testing was done on the niece for both the genes associated with HNPCC and MYH Associated Polyposis (MAP). MAP is a newly discovered type of hereditary colon cancer that falls somewhere between FAP and HNPCC in regard to age of onset and the number of polyps normally associated. MAP is also unique in that it is transmitted in an autosomal recessive manner, unlike the typical autosomal dominant transmittance of most hereditary cancers.

There are two common mutations in the MYH gene known to be associated with cancer. Tests results indicated she was positive for the known deleterious MSH6 gene mutation in the family as well as several variants of uncertain significance in the MSH6 gene.



Genetic Testing for Colon Cancer continued

She was also positive for one of the two common MYH mutations. Thus, she was compound heterozygous for MYH and MSH6 gene mutations.

Variants of uncertain significance are changes in a gene that are not know if they are associated with cancer risk or normal variation in the population (a polymorphism). In general, sequence analysis of the genes in question is performed on the first person in a family pursuing genetic testing for a hereditary cancer syndrome. If a gene mutation is identified, subsequent testing involves targeted mutation analysis for other family members. So the parents were tested as well, but given the testing strategy, only for the specific MYH and MSH6 gene mutations in question, not any of the variants of uncertain significance. So although we can deduce who carries the MYH and MSH6 gene mutation through parental testing, it is unknown where the variants of uncertain significance come from. The mother was found to be a carrier of the MYH gene mutation. The father did not pursue testing; however, he is assumed to be positive for the MSH6 gene mutation. Neither parent has a personal history of cancer.

What caused the early onset of colon cancer in this family? Was it the MSH6 deleterious mutation in addition to one of the variants of uncertain significance? Or was it the compound heterozygosity of the MSH6 with MYH? The answer to this question could potentially identify those at risk for developing colon cancer at an unusually early age and help tailor preventative screening and surveillance practices.

The testing laboratory tracks the variants of uncertain significance over time to hopefully reclassify variants as a deleterious or a polymorphism. So the answer to whether or not the variants of uncertain significance are causing the early onset cancer may be answered in the future. As for the MYH mutation, it is estimated that as many as one in every 100 people may carry a single mutation in the MYH gene, although the incidence has not yet been fully established.

Given the carrier frequency for MYH, however, the family was reasonably concerned about the chances of their two sons also being compound heterozygotes of MSH6 and MYH. Given that we know one parent carries an MSH6 gene mutation, each son has 50% chance of inheriting the MSH6 gene mutation. However, assuming each parent has a 1% chance of carrying an MYH mutation (the general population risk), each son has a 2% chance of also carrying an MYH mutation. Thus, if they were to be positive for the MSH6 mutation, there is a 2% risk that they would be a compound heterozygote for the MYH mutation.

We found that one son does carry the deleterious MSH6 mutation and one son does not. Testing for an MYH mutation has not been performed. The son with the MSH6 mutation may be at a higher risk for an early onset cancer if he does carry an MYH mutation. The son without the MSH6 mutation may also carry an MYH mutation, but would not be at increased risk for cancer if he does.

This case illustrates that taking a complete family history is extremely important in all cancer cases. What seemed like straight forward testing for a known mutation in a family turned out to be a case of multiple genes involved with cancer in the family, with the possibility of an earlier onset of cancer than would have been expected.

Shodair's Genetics Department is available to see any of your patients with cancer who have a concern for a hereditary cancer syndrome, both for the seemingly straight forward cases as well as the more complicated ones. Call us today at 1-800-447-6614 or (406) 444-7530 and we'll be happy to schedule an appointment at one of our statewide outreach clinics or at our Helena campus.

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