

## Sickle Cell Trait and Sickle Cell Disease: A Case Study, Part I

### REQUIRED READING

Clinical narrative (below)

### LEARNING OBJECTIVES

By the end of this case discussion, students should be able to:

1. Determine which genetic testing methods are most informative and most efficient in different clinical scenarios. Compare and contrast the use of molecular genetic testing and biochemical hemoglobin testing in establishing the diagnosis of sickle cell disease.
2. Assess the power and limitations of genetic testing as well as the necessity of testing family members' DNA under certain circumstances.
3. Discuss the influence of compound heterozygosity on clinical outcome and management decisions.
4. Describe the social and ethical issues associated with a new diagnosis of sickle cell disease.
5. Explain issues of carrier testing for hemoglobinopathies as they relate to ethnic minority groups and minors.

## Sickle Cell Disease Case Study

Mr. N had just finished his first year at Boston University School of Medicine when he had an acute medical incident upon arriving for his summer international health experience in Quito, Ecuador. Almost immediately after disembarking from the plane, Mr. N began to experience severe pain on the left side of his abdomen, diarrhea, and vomiting. To treat these symptoms, Mr. N began a regimen of ciprofloxacin as well as over the counter medications, but the extreme pain and discomfort were not going away. Mr. N's second day in Quito was the start of his international health program, and not wanting to miss out on this experience, he dragged himself to class where he and the program directors decided to go to the ER the following day if he continued to feel ill. Unfortunately, Mr. N's symptoms persisted, so on his third day in Quito, he checked in to the Hospital Metropolitano, a hospital of gleaming modern conveniences, in stark contrast to the clinics where he was to do his medical outreach work! Mr. N was seen within minutes, and the initial ultrasound suggested an issue with his kidney or spleen. At first, the doctors suspected a clot in his kidney, but a follow up MRI suggested significant splenic damage. They wondered if this might be the result of some physical trauma such as an accident or fight, but no events of this nature seemed to trigger this

incident for Mr. N. Putting this aside for the moment, the physicians recommended an emergency splenectomy to remove Mr. N's now highly inflamed spleen. After phoning home and securing the surgery payment in the form of a gracious loan from the program director, Mr. N had his spleen removed and finally received some relief from his extreme pain.

Mr. N awoke in the Intensive Care Unit of Hospital Metropolitano on the morning of his fourth day in Quito feeling much better. He was transferred to a luxurious recovery room with amazing views of the city, and on his fifth day in Quito, he was visited by the Hospital's hematologist. As part of his work up, Mr. N's blood had been examined by isoelectric focusing (IEF), a specialized form of electrophoresis, and this analysis showed presence of both HbA and HbS forms of his hemoglobin  $\beta$  chain.

**QUESTION 1: GIVEN THAT QUITO IS SITUATED AT AN ELEVATION ABOVE 9,000 FEET, WHAT IS MR. N'S GENOTYPE, AND WHY WOULD HE SHOW SYMPTOMS IN QUITO BUT NOT IN BOSTON?**

Once Mr. N's initial diagnosis was determined, he called home to share the news. Initiating this discussion prompted Mr. N's mother to share some key aspects of his family history. Mr. N's father was the youngest of five children, and he had two older sisters and two older brothers. Mr. N's mother is one of 6 children, and she had four older brothers and one younger sister. Both Mr. N's mother and father are of African American descent, and the extended family has not generally traveled to locations that might challenge underlying genetic conditions. Interestingly, Mr. N's father had a daughter with another woman prior to starting a family with Mr. N's mother. This young woman, Mr. N's half-sister, has a family of her own with her African American husband. Notably, her son has sickle cell anemia and received extensive blood transfusions through age 4. He is now 14 years old, and his condition is relatively well-managed. Her younger daughter appears healthy.

**QUESTION 2: DRAW A PEDIGREE SHOWING THE FAMILY HISTORY DESCRIBED. ON THE PEDIGREE, BE SURE TO INDICATE WHICH, IF ANY, INDIVIDUALS ARE OBLIGATE HETEROZYGOTES. WHAT IS THE PROBABILITY OF MR. N'S NIECE BEING A HETEROZYGOTE? WHAT IS THE PROBABILITY OF HIS HALF-SISTER CONCEIVING ANOTHER AFFECTED CHILD?**

After Mr. N recovered from his surgery, he was advised to return home as soon as possible. Unfortunately, there was not much the physicians could do to keep him healthy in Quito and allow him to engage in his summer clinical experience. Mr. N confirmed that it was safe for him to travel home by air, since planes flying at typical altitudes are pressurized to the rough equivalent of 5000 feet above sea level, so Mr. N could fly home within a few days.

When he returned home, Mr. N's primary care physician ordered tests to confirm his status with respect to sickle cell disease and initiated a management program to help Mr. N stay healthy as an asplenic patient.

**QUESTION 3: IN TERMS OF TESTING, COMPARE AND CONTRAST THE BENEFITS OF USING BIOCHEMICAL TESTS FOR SICKLE CELL DISEASE (E.G. ISOELECTRIC FOCUSING AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY) WITH GENETIC TESTS IN THIS SCENARIO. WHICH TYPE OF TEST WOULD BE MORE SUITABLE FOR MR. N'S SICKLE CELL INQUIRY AT THIS STAGE?**

Because Mr. N's repeat testing confirmed his status with respect to sickle cell disease, his primary care physician was able to design a management plan that allowed him to lead a normal life – and to choose clinical outreach destinations that wouldn't challenge his system!

On one of these trips, Mr. N came to know Ms. P, a medical student hailing from Cyprus. Because of their shared passion for reaching out to underserved populations, they began to spend more time together and eventually began to plan a life together. They were able to match to residencies in the same city, and before long, the two were planning a wedding and a family of their own. At this stage, Mr. N's primary care physician recommended a meeting with a genetic counselor to fully assess the couple's risk profile.

**QUESTION 4: SHOULD THIS COUPLE BE OFFERED MOLECULAR GENETIC TESTS IN THE PRE-CONCEPTION STAGE AND WHY? IF SO, WHICH TESTS WOULD BE APPROPRIATE? WOULD A HEALTH INSURANCE PROVIDER TYPICALLY COVER THIS TYPE OF ANALYSIS? IF TESTING WAS RECOMMENDED AND RESULTS WERE NEGATIVE FOR THE PANEL OF MUTATIONS TESTED, WOULD THERE BE ANY RESIDUAL RISK OF HAVING AN AFFECTED CHILD?**

Based on the information provided by the genetic counselor, the couple declines to undergo carrier testing, in part because they realize that they would be unwilling to make use of prenatal testing or preimplantation genetic diagnosis in their future pregnancies.

A few years pass, and Mr. N and Ms. P, have two children, a five-year-old daughter and a seven-month-old son. The seven-month-old has suggestions of mild anemia in his medical history including episodes of pain and swelling of his feet and a mildly enlarged spleen, but his newborn screening results by isoelectric focusing (IEF) came back showing presence of both HbA and HbS. Given Mr. N's family history of sickle cell disease, the pediatrician specifically wants to look more carefully into the infant's sickle cell status.

**QUESTION 5: IS FURTHER TESTING WARRANTED AT THIS POINT, CONSIDERING THE INFANT HAS ALREADY UNDERGONE ROUTINE NEWBORN SCREENING? IF SO, WHAT IS THE APPROPRIATE TESTING RECOMMENDATION FOR THE FAMILY AT THIS POINT? WOULD A BIOCHEMICAL TEST OR A GENETIC TEST BE MORE SUITABLE FOR A SICKLE CELL INQUIRY AT THIS STAGE? DISCUSS THE PROS AND CONS OF EACH TESTING APPROACH.**

## Sickle Cell Trait and Sickle Cell Disease: A Case Study, Part II

The testing recommended above confirmed that the infant son carried both an HbS allele from his father and a HBB -149C>T ( $\beta^+$  thalassemia) allele from his mother. Naturally, they are very concerned about this diagnosis and its implications for the family. This diagnosis indicates that this child may have chronic health problems, with potential social, emotional, and financial burdens for the family. The family may need ample opportunities to ask questions and learn more about sickle cell disease /  $\beta^+$  thalassemia, over time, as they adjust to this new circumstance.

**QUESTION 6: DOES THE GENETIC TEST RESULT FOR THE INFANT, WITH TWO DIFFERENT MOLECULAR MUTATIONS IN *HBB* (THE  $\beta$ -GLOBIN GENE), SUPPORT A PHYSICAL DIAGNOSIS FOR SICKLE CELL DISEASE?**

In a follow-up visit with the genetic counselor, Ms. P indicates that she also has a younger sister who is also thinking about starting a family.

**QUESTION 7: UPDATE YOUR ORIGINAL PEDIGREE TO REFLECT THE NEW FAMILY MEMBERS OF MR. N AND MS. P. REGARDING MS. P'S SISTER, WHAT IS THE APPROPRIATE TESTING STRATEGY FOR HER TO INFORM HER OWN FAMILY PLANNING?**

**QUESTION 8: WHAT ADDITIONAL INFORMATION SHOULD THE GENETIC COUNSELOR PROVIDE TO MR. N AND MS. P WITH REGARD TO HEMOGLOBINOPATHY RISK IN FUTURE PREGNANCIES?**

### Key Reference Numbers

Race	<i>African American</i>	<i>Cypriot / Mediterranean</i>
<i><math>\beta</math>-Thalassemia carrier rate</i>	<i>1/75</i>	<i>1/12</i>
<i>Targeted mutation testing panel</i>	<i>6 unique mutations</i>	<i>6 unique mutations</i>
<i>Mutation detection rate with targeted panel</i>	<i>75-80%</i>	<i>91-95%</i>
<i>Fraction of <math>\beta</math>-Thalassemia carriers who are also HbS carriers</i>	<i>1/21</i>	

## Resources

### GeneTests Online Medical Genetics Information Resource

**GeneReviews, GeneTests Online Medical Genetics Information Resource.** Sickle Cell Disease and B-Thalassemia GeneReviews

**Teaching Case-Genetic Tools** *Cases designed for teaching genetics in the primary care setting.* Case 34. Sickle Cell Disease Identified in Newborn Screening Case 35. A Mother Finds out that She and her Son are Sickle Cell Carriers

## References

American Academy of Pediatrics (2001) Policy statement: ethical issues with genetic testing in pediatrics. Committee on Bioethics. *Pediatrics* 107:1451-5 [[Medline](#)]

ACMG/ASHG (1995) [Points to consider](#): ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet* 57:1233-41

Aetna (2007) Clinical Policy Bulletin: Genetic Testing. [[Aetna](#)]

Mastenbroek S, Twisk M, van Echten-Arends J, Sikkema-Raddatz B, Korevaar JC, Verhoeve HR, Vogel NE, Arts EG, de Vries JW, Bossuyt PM, Buys CH, Heineman MJ, Repping S, van der Veen F. (2007) In vitro fertilization with preimplantation genetic screening. *N Engl J Med.* Jul 5;357(1):9-17.

Titinalli JE, Kelen GD, Stapczynski S, Ma OJ, and Cline DM. (2004) Emergency Medicine: A Comprehensive Study Guide, 6<sup>th</sup> ed.

# Sickle Cell Trait and Sickle Cell Disease: A Facilitator's Guide, Part I

## Abstract

This case is a classical example of an African American individual who is a heterozygous for sickle cell disease and who does not manifest any symptoms until he encounters extreme physical conditions. This case explores:

- the initial presentation of sickle cell symptoms in a heterozygote
- the assembly of a pedigree and calculation of genetic risk for transmission of the mutation
- the biochemical and genetic testing options that are available for diagnostic and pre-conception genetic testing in sickle cell disease
- the strategies governing newborn screening for hemoglobinopathies and their limitations
- the genetic concept of compound heterozygosity as it relates to sickle cell and thalassemia mutations in  $\beta$ -globin.
- and ethical, legal, and societal ramifications of available types of testing strategies.

## LEARNING OBJECTIVES

By the end of this case discussion, students should be able to:

1. Determine which genetic testing methods are most informative and most efficient in different clinical scenarios. Compare and contrast the use of molecular genetic testing and biochemical hemoglobin testing in establishing the diagnosis of sickle cell disease.
2. Assess the power and limitations of genetic testing as well as the necessity of testing family members' DNA under certain circumstances.
3. Discuss the influence of compound heterozygosity on clinical outcome and management decisions.
4. Describe the social and ethical issues associated with a new diagnosis of sickle cell disease.
5. Explain issues of carrier testing for hemoglobinopathies as they relate to ethnic minority groups and minors.

## CASE DISCUSSION SEQUENCE

Prior to in-class discussion of the case, students should have some familiarity with sickle cell disease,  $\beta$ -thalassemia, the mutations that cause each, the ethnicities in which these mutations are prevalent, and what testing options

would identify individuals harboring these genetic alterations. Thus, the case integrates many fundamental concepts covered in most medical genetics courses and may be placed towards the end of the class in order to promote this type of integrative thinking.

It is recommended that the first part of the case, with the thought questions omitted, is distributed to the students in advance. Part II of the case is withheld until the students complete part I in class. When the students come to class prepared to discuss the case, versions of part I including the thought questions can be shared with the students. This case has been utilized in rooms of 30 students and one facilitator with 5 teams of 6 students each. It may alternately be used in rooms with fewer students working in a single team, as in the traditional PBL model of 7-8 students per room, in which case the facilitator may choose to verbally contribute the thought questions to guide the discussion.

Generally, the case discussion, including parts I, part II, and a facilitator recap, takes roughly 90 minutes of class time. It is helpful to have flip charts or black boards on hand for students to sketch pedigrees in order to promote discussion.

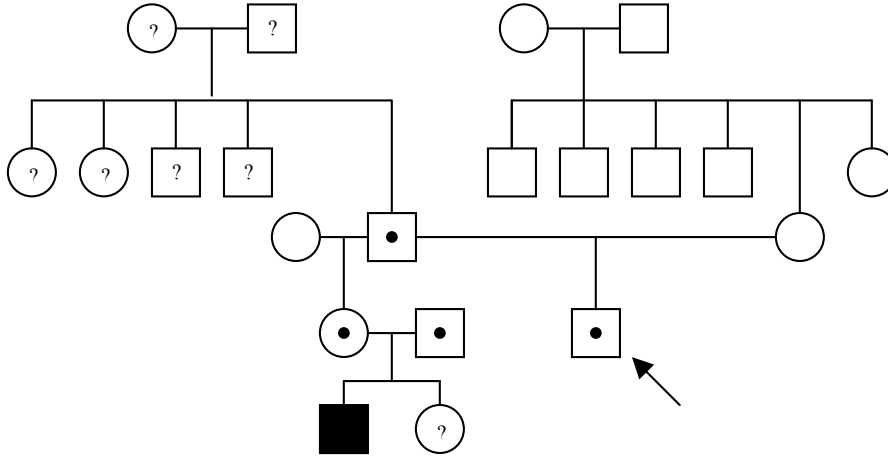
## Sickle Cell Disease Case Study

**QUESTION 1: GIVEN THAT QUITO IS SITUATED AT AN ELEVATION ABOVE 9,000 FEET, WHAT IS MR. N'S GENOTYPE, AND WHY WOULD HE SHOW SYMPTOMS IN QUITO BUT NOT IN BOSTON?**

*Mr. N has sickle cell trait, and his genotype is heterozygous (A/S) for the  $\beta$ -globin gene. Normally, this would not lead to any detectable phenotype, but under conditions of high altitude and low oxygen pressure in Quito, Mr. N's red blood cells began to take on a sickle shape, and he experienced a sickle cell crisis. Boston, of course, is located at sea level, so oxygenation of Mr. N's hemoglobin was high, and he hadn't experienced a sickle cell crisis as a result.*

*In a heterozygous individual with sickle cell trait, the normal (A) and sickle (S) versions of  $\beta$ -globin are co-dominantly expressed in the red blood cells at the molecular level. Usually, the presence of the normal hemoglobin allows the cell to function normally overall (that is the A phenotype is dominant to the S phenotype at the cellular and physiological levels), but under extreme conditions, including high elevation or deep sea diving, individuals with sickle cell trait may begin to manifest some of the symptoms typically associated with sickle cell anemia.*

**QUESTION 2: DRAW A PEDIGREE SHOWING THE FAMILY HISTORY DESCRIBED. ON THE PEDIGREE, BE SURE TO INDICATE WHICH, IF ANY, INDIVIDUALS ARE OBLIGATE HETEROZYGOTES. WHAT IS THE PROBABILITY OF MR. N'S NIECE BEING A HETEROZYGOTE? WHAT IS THE PROBABILITY OF HIS HALF-SISTER CONCEIVING ANOTHER AFFECTED CHILD?**



● = obligate HbS heterozygote  
? = potential HbS heterozygote

Mr. N's half-sister and her husband are obligate heterozygotes since they had an affected son. Mr. N's father must also be the heterozygote who passed on the sickle cell allele to both Mr. N and his half-sister.

Since Mr. N's niece is healthy, we can rule out the homozygous sickle cell anemia genotype, SS, from the Punnett square below. The Punnett square reflects the fact that both Mr. N's half-sister and her husband are heterozygotes (AS).

	A	S
A	AA	AS
S	AS	SS

Therefore, their daughter has a 2/3 chance of being a heterozygote (AS). This is significantly higher than the general probability (1/12) that an individual of African American descent is a heterozygote for the sickle cell mutation.

Furthermore, since each conception is an individual event, the risk of them having another affected child (SS) is 1/4.

**QUESTION 3: IN TERMS OF TESTING, COMPARE AND CONTRAST THE BENEFITS OF USING BIOCHEMICAL TESTS FOR SICKLE CELL DISEASE (E.G. ISOELECTRIC FOCUSING AND HIGH PERFORMANCE LIQUID CHROMATOGRAPHY) WITH GENETIC TESTS IN THIS SCENARIO. WHICH TYPE OF TEST WOULD BE MORE SUITABLE FOR MR. N'S SICKLE CELL INQUIRY AT THIS STAGE?**

The diagnosis of sickle cell disease or confirmation of carrier status can actually be established by either biochemical or genetic methods.



*The biochemical methods that are typically used to detect the presence of HbA and/or HbS are most often isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). IEF is essentially a qualitative measure looking for presence or absence of the different forms of hemoglobin. HPLC is more accurate in terms of quantitative measures and can help compare relative amounts of normal and variant hemoglobins. HPLC is slightly more technically demanding and more expensive than IEF, so for large scale testing, such as newborn screening, many states choose to utilize IEF. A confirmation of abnormal results, however, may be carried out by HPLC.*

*Genetic testing can also be utilized to screen for the typical glu6val mutation that causes sickle cell anemia. This targeted mutation analysis can be carried out by techniques such as allele specific hybridization or PCR-based techniques, for example. Utilization of genetic testing is especially helpful when seeking confirmation of a specific molecular lesion and when assessing familial risks associated with this disorder.*

**QUESTION 4: SHOULD THIS COUPLE BE OFFERED MOLECULAR GENETIC TESTS IN THE PRE-CONCEPTION STAGE AND WHY? IF SO, WHICH TESTS WOULD BE APPROPRIATE? WOULD A HEALTH INSURANCE PROVIDER TYPICALLY COVER THIS TYPE OF ANALYSIS? IF TESTING WAS RECOMMENDED AND RESULTS WERE NEGATIVE FOR THE PANEL OF MUTATIONS TESTED, WOULD THERE BE ANY RESIDUAL RISK OF HAVING AN AFFECTED CHILD?**

*Mr. N and Ms. P are a classic example of candidates for pre-conception genetic testing. We have already determined that Mr. N has sickle cell trait (A/S genotype at the  $\beta$ -globin gene), but if this was determined with a biochemical test, now would be a good time to confirm this result with a genetic test. Testing could then be extended to Ms. P, as an individual whose spouse has a family history of sickle cell. Notably, many insurance companies would cover genetic testing for couples who are planning a pregnancy, regardless of ethnicity (e.g. Aetna Clinical Policy Bulletin: Genetic Testing), with evidence of a family history for a particular disorder.*

*It is important to note that in this case, we are concerned not only about transmission of the sickle cell trait but also of a  $\beta$ -thalassemia mutation. Recall that  $\beta$ -thalassemia also arises from a mutation in the  $\beta$ -globin gene. Furthermore,  $\beta$ -thalassemia is prevalent among Mediterranean individuals, particularly Cypriots. For this reason, it is important to consider testing Ms. P for the Mediterranean panel of  $\beta$ -thalassemia mutations (6 mutations, 91-95% carrier detection rate) and Mr. N for the African American panel of  $\beta$ -thalassemia mutations (6 mutations, 75-80% detection rate). Indeed, to simplify this complex analysis and to compare apples to apples, a more extensive sequence analysis of the  $\beta$ -globin gene for both Mr. N and Ms. P may be preferable as well.*

*If both Mr. N and Ms. P were tested for a limited panel of mutations and didn't carry any of the classical mutations in the panels, they would retain some reduced risk of having an affected child, on the basis that they may carry a  $\beta$ -globin mutation that is not part of the testing panel. Given that the  $\beta$ -thalassemia carrier rates among the Mediterranean*

population (1/12) and the African American population (1/75) are known, the relative risk can be calculated. This probability, assuming the higher end of the detection rate range, would be  $0.05 \times (1/12) \times (1/2) \times (1/2)$  (probability that Ms. P is an undetected carrier and passes on the mutation not in the testing panel and that Mr. N passes on his HbS allele) +  $0.05 \times (1/12) \times (1/2) \times 0.2 \times (1/75) \times (1/21) \times (1/2)$  (probability that Ms. P is an undetected carrier and passes on the mutation not in the testing panel and that Mr. N is an undetected compound carrier and passes on a  $\beta$ -thalassemia mutation not in the testing panel) = 0.00104. Given this low probability of having an affected child when utilizing the targeted mutation testing, some clinicians and patients will be comfortable with this option.

**QUESTION 5: IS FURTHER TESTING WARRANTED AT THIS POINT, CONSIDERING THE INFANT HAS ALREADY UNDERGONE ROUTINE NEWBORN SCREENING? IF SO, WHAT IS THE APPROPRIATE TESTING RECOMMENDATION FOR THE FAMILY AT THIS POINT? WOULD A BIOCHEMICAL TEST OR A GENETIC TEST BE MORE SUITABLE FOR A SICKLE CELL INQUIRY AT THIS STAGE? DISCUSS THE PROS AND CONS OF EACH TESTING APPROACH.**

Because the newborn screening was carried out by IEF, a qualitative test looking for presence of various hemoglobin variants, it can confirm that the infant inherited HbS from Mr. N, but it does not rule out the possibility that the child inherited a  $\beta$ -thalassemia mutation ( $\beta^+$ ) from Ms. P. The  $\beta^+$  mutation results in a reduction of the amount of HbA produced, and therefore, the predominant form of  $\beta$ -globin in an HbS/ $\beta^+$  compound heterozygote would actually be the sickle cell form once the infant begins to switch to  $\beta$ -globin production from  $\gamma$ -globin (a subunit of fetal hemoglobin). This switch usually takes place around 6 months of age and is coincident with the onset of symptoms in the case of this infant. At this time, symptoms of sickle cell disease can manifest in infants or young children as “hand-foot syndrome” which involves painful swelling of the hands and feet, jaundice, pallor, pneumococcal sepsis or meningitis, severe anemia leading to an enlarged spleen, or acute chest syndrome.

To confirm the infant’s status with respect to  $\beta$ -thalassemia, either a quantitative biochemical test for hemoglobins (e.g. HPLC) or a molecular genetic test would be recommended. In order to avoid complicated analysis that may result from residual expression of  $\gamma$ -globin, molecular genetic analysis would provide the most straightforward result. In contrast, molecular genetic testing would not provide an analysis of the relative contributions of each hemoglobin subunit in the infant at that time.

For this family, molecular genetic testing may be advantageous for the following reasons:

- Test results may provide some information about the child's prognosis because some mutations are associated with a milder course.
- If both  $\beta$ -globin mutations are identified, molecular genetic testing could be used

*to determine whether siblings are also affected (for example, in this case, if the older sibling shows some mild symptoms of sickle cell).*

- If both mutations are identified, the carrier status in other relatives could be clarified through molecular genetic testing.*
- If both mutations are identified, prenatal diagnosis of subsequent pregnancies for Mr. N and Ms. P would be available.*

*Naturally, care must be taken when engaging in genetic testing of minor children. If Mr. N and Ms. P would like to pursue molecular genetic testing for sickle cell disease in their older child, they should be counseled ahead of time that there are three possible results: the child could be determined to be affected, unaffected, or a sickle cell or  $\beta$ -thalassemia carrier.*

*There is an ethical concern regarding carrier testing in minors: such testing can reveal the child's future reproductive risks, potentially causing unnecessary anxiety or other psychosocial harm, and represents information would not be of value until later in the child's life [ACMG/ASHG 1995]. Importantly, there are numerous historical precedents for misuse of this type of information, especially in the case of sickle cell disease and in the African American population. In general the identification of a carrier state in children is recommended only if that information directly benefits the health of the child at the time of testing. If there is no direct and timely benefit to the minor child, then it is recommended that carrier identification should not be completed until the child becomes competent and capable of engaging in informed consent [AAP 2001].*

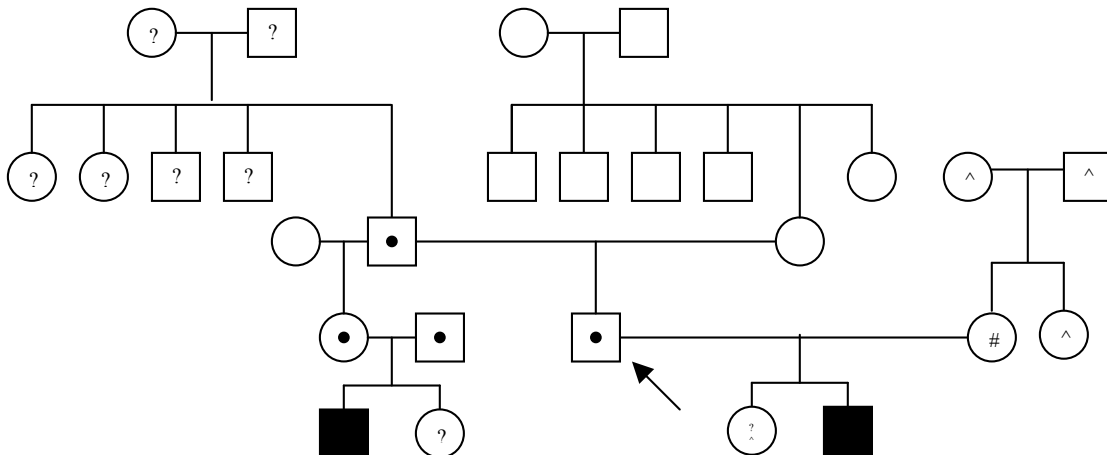
*However, in the present case, assuming that two HBB ( $\beta$ -globin) mutations have been identified in her brother, molecular genetic testing represents an effective method to determine whether the daughter has a hemoglobinopathy. Prior counseling will allow the parents to consider the possibility that the test may identify their daughter as a carrier. One possible approach would be for the parents to use their discretion in to determining at what age they will share the carrier information with their child, but in practice, this is a very complex option for both the parents and the daughter. Alternatively, if the parents express concern about the psychosocial effects of identifying their child's carrier status, they could be offered another option: reporting the molecular test results solely in terms of whether the child has sickle cell disease, with carrier identification not reported*

## Sickle Cell Trait and Sickle Cell Disease: A Facilitator's Guide, Part II

**QUESTION 6: DOES THE GENETIC TEST RESULT FOR THE INFANT, WITH TWO DIFFERENT MOLECULAR MUTATIONS IN *HBB* (THE  $\beta$ -GLOBIN GENE), SUPPORT A PHYSICAL DIAGNOSIS FOR SICKLE CELL DISEASE?**

Yes, the mutations do not need to be identical to contribute to sickle cell disease. This infant is what is known as a compound heterozygote, and he carries two different mutations in his copies of the *HBB* gene. Although only one of the alleles is a classic sickle cell allele, since both copies are mutated, the disease phenotype will manifest. This is because the non-sickle allele of *HBB* is mutated in such a way as to reduce  $\beta$ -globin production from this allele. Therefore, the ratio of HbS to HbA is high. Notably, his clinical presentation may differ from the S/S norm since one of the mutations ( $\beta^+$ ) is associated with non-classical symptoms. For instance, if the HbS allele is somewhat balanced by the reduced production of HbA, the extensive intervention (including antibiotic prophylaxis, regular transfusion, and treatment for acute episodes) required for typical patients with sickle cell anemia (S/S) may not be necessary.

**QUESTION 7: UPDATE YOUR ORIGINAL PEDIGREE TO REFLECT THE NEW FAMILY MEMBERS OF MR. N AND MS. P. REGARDING MS. P'S SISTER, WHAT IS THE APPROPRIATE TESTING STRATEGY FOR HER TO INFORM HER OWN FAMILY PLANNING?**



- = obligate HbS heterozygote
- ? = potential HbS heterozygote
- # =  $\beta^+$  thalassemia carrier
- ^ = potential  $\beta^+$  thalassemia carrier

Since the mutations in Ms. P's son have been identified, we can presume that his HbS allele came from Mr. N and that his *HBB* -149C>T ( $\beta^+$  thalassemia) allele came from

*Ms. P. Naturally, this could be confirmed in Ms. P and her sister with targeted mutation testing for this allele. If the sister is found to be a carrier, then additional testing can be offered to her in the form of  $\beta$ -thalassemia carrier screening for her spouse and, if necessary, prenatal or preimplantation genetic diagnosis.*

**QUESTION 8: WHAT ADDITIONAL INFORMATION SHOULD THE GENETIC COUNSELOR PROVIDE TO MR. N AND MS. P WITH REGARD TO HEMOGLOBINOPATHY RISK IN FUTURE PREGNANCIES?**

*This open-ended question is meant to launch discussion on any number of topics that the students may still have questions on. Some examples of areas to explore are below.*

*The hemoglobinopathies of concern in this family are inherited in an autosomal recessive manner, and thus children of this couple have a 25% risk of being affected. They should be informed about prenatal testing options (particularly, amniocentesis and CVS) and preimplantation genetic diagnosis. However, with regard to preimplantation genetic diagnosis, special attention must be given to controversial emerging data that suggests PGD may adversely affect a couple's ability to conceive (Mastenbroek et al, 2007).*

**Support** - *The family should have access to a team of health professionals in order to be fully educated on their options. The genetic counselor will often be involved in helping families assemble this team of health professionals, and families further benefit if they have access to coordinated centers of excellence, such as a regional Sickle Cell Center. These Centers can provide multidisciplinary care focused on sickle cell disease and streamline management of the condition in an affected individual. Moreover, the family should make use of patient support groups and therapeutic counseling services to help everyone cope with the diagnosis. Individuals and families living with the disorder may be in the best position to address the family's fears. Furthermore, a social worker may be able to provide additional types of psychosocial support for the family.*

**Sharing information** – *Because these diagnoses are genetic, findings in one family member often have significant implications for other members of the family. Mr. N and Ms. P may choose to share their own molecular genetic test results with their family members in order to allow them to obtain targeted mutation testing for their own health management and potentially for reproductive counseling to determine if they are at risk of having a child with sickle cell or  $\beta$ -thalassemia. Of note, no current laws create legal obligations for either the family member or the physician to inform other family members about the hereditary nature of this condition, but there is a potentially an ethical claim to encourage family members to do so. In terms of informing family members and making reproductive decisions, these complex choices are ultimately the patient's to make, and clinicians must provide respectful, non-directive counseling in these matters.*

## Key Reference Numbers

Race	African American	Cypriot / Mediterranean
<i>β-Thalassemia carrier rate</i>	1/75	1/12
<i>Targeted mutation testing panel</i>	6 unique mutations	6 unique mutations
<i>Mutation detection rate with targeted panel</i>	75-80%	91-95%
<i>Fraction of β-Thalassemia carriers who are also HbS carriers</i>	1/21	

## Resources

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**Teaching Case-Genetic Tools** Cases designed for teaching genetics in the primary care setting. Case 34. Sickle Cell Disease Identified in Newborn Screening Case 35. A Mother Finds out that She and her Son are Sickle Cell Carriers

## References

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