

## Punnett Squares: Mendelian Genetics of Fanconi Anemia and HLA type

### Acknowledgements

The activity itself is based on genotype information found in V. Verlinsky et al, 2001, Preimplantation Diagnosis for Fanconi Anemia Combined with HLA Matching, *JAMA*: 285, 3130-3133. and

S. Grewal et al, 2004, Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA-genotype-identical sibling selected using preimplantation genetic diagnosis, *Blood*: 3, 1147-1151

Note: the Nash family is not identified in the above papers, so although we discussing the case of the Nash family in today's workshop, the genotype information may not be that of the Nash family.

### Introduction

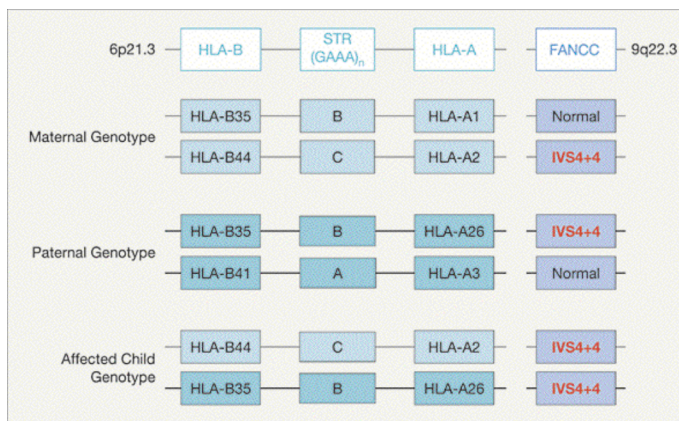
In this activity you will use Punnett Squares and/or math skills to calculate the frequency at which you would expect any additional children to be FA-free and an HLA match for an affected child.

### Background

The most important HLAs to match for a bone marrow transplant are HLA-A, HLA-B, and HLA-DRB1. These HLA genes (and all others) are located close to one another on chromosome 6. During meiosis, crossing over rarely occurs between the different HLA genes, so for purposes of this exercise assume that HLA-A, HLA-B and HLA-DR are all inherited together.

The FANCC gene is located on chromosome 9.

Below is shown a portion of the genotype for the different family members. Information on the HLA-DR locus is not given in this chart.



### Overview

When predicting frequency of offspring for traits on two separate chromosomes you are essentially doing a dihybrid cross. You can calculate the frequency in one of two ways.

1. Draw two separate Punnett squares, one for HLA type and one for FA and then multiple the frequencies obtained together.
2. Draw a Punnett square for a dihybrid cross.

### Method 1

Draw a Punnett Square representing the assortment of HLA genes in a monohybrid cross. You will use the parents' genotypes in the square.

The mom's genotype could be abbreviated

B35A1, B44A2

In the space below, write the dad's genotype in a similar fashion

Next fill in the Punnett Square


Circle the box(es) that represent a child with the same HLA type as the affected child. What is the percentage of offspring that would have the same HLA type as the affected child?

Next you will use a Punnett Square to predict the percentage of future children that would not have FA.

Remember that both of the parents are carriers of FA.  
Their genotype can be represented as

Normal,  $ivs4+4$

Next fill in the Punnett Square


Circle the box(es) that represent a child would not have FA.  
What is the percentage of offspring that would not have FA?

Finally, calculate the predicted frequency of children who would be FA-free and could serve as an HLA-matched donor.

(Hint: Multiply the two frequencies together).

**Method 2**

A Punnett Square for a dihybrid cross can also be used to determine the frequency with which any additional children would be expected to be HLA matched and FA free.

The cross can be represented as follows

B35A1, B44A2; normal, ivs4+4 X B35A26, B41A3; normal, ivs4+4


Circle the box(es) representing the children who would be an HLA match for the affected child and who would not have FA.

What percentage of offspring would be an HLA match for the affected child and would not have FA?

In the case presented today, 41 embryos were created by in vitro fertilization and tested by preimplantation genetic testing. 8 of these embryos were FA-free and an HLA match for the affected child. 7 of these embryos were implanted (5 separate attempts). One of them resulted in the birth of a second child whose cord blood was used to perform a successful bone marrow transplant on the affected child.

How does the frequency of FA-free HLA-matched possible donor embryos compare with the expected frequency?