Further Explanation of Biasing Systems

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Implementation

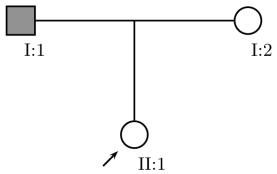
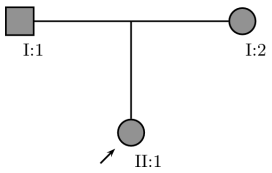
1. Autosomal Recessive

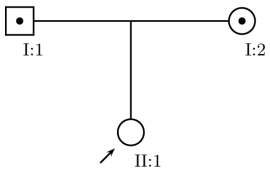
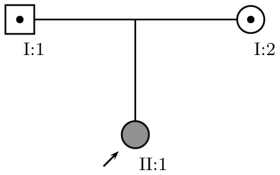
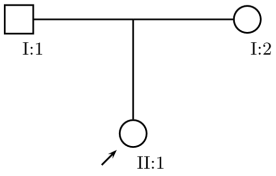
My methodology for assigning values to individuals is as follows:

1. If neither of the I generation are affected, we assume both to be Carriers.
2. If one of the I generation is affected, we assume their mate is Homozygous Dominant.
3. If given data on the I generation, we use that instead.
4. Assume outsiders to be Homozygous Dominant.
5. Homozygous Dominant are assigned a bias of -1.
6. Carriers are assigned a bias of 0.
7. Homozygous Recessive are assigned a bias of +1.
8. If the phenotype of the child is affected, immediately assign it a bias of 1.
9. Otherwise, sum up the numbers in the two parents and divide by two for the bias of the children.
10. **Heterozygotes are a complicated case**
    - In the case that two heterozygotes produce an unaffected child, we assign it a bias of -0.33. This is because we know that there is a $\frac{2}{3}$ chance that the child is a carrier, and a $\frac{1}{3}$ chance that the child is totally unaffected. $\frac{0+0-1}{3} = \frac{-1}{3}$ = -0.33
    - In the case that two heterozygotes produce an affected child, we assign it a bias of 1 (Self-Correcting Property).
    - In the case that we have to heterozygotes but their child phenotype is unknown, we assign it a value of 0. This is because the sum of the *possible* biases will equal 0.

Here, I have documented 5 cases that are **essential** to the correctness of this system. If any of these cases fail, then this system will not work.

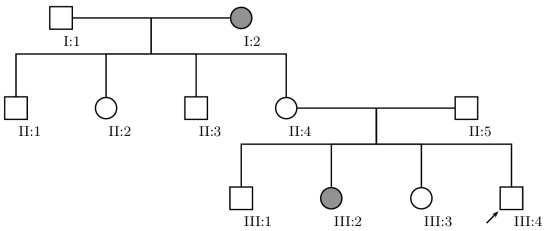
Table 1: Common Cases for Autosomal Recessive.

I Description	Affected Parent, Nonaffected Parent	Both Affected Parents
II Description	Carrier	Affected Child
		
Parental Bias	I-1(+1), I-2(-1)	I-1(+1), I-2(+1)
Child Bias	II-1 = $\frac{(1-1)}{2} = 0$	II-1 = $\frac{(1+1)}{2} = +1$

Carrier Parents	Carrier Parents	Unaffected Parents
Unaffected Child	Affected Child	Unaffected Child
		
I-1(0), I-2(0)	I-1(0), I-2(0)	I-1(-1), I-2(-1)
II-1 = $\frac{-1}{3}$ = -0.33	II-1 = +1	II-2 = $\frac{-1-1}{2}$ = -1

Test Case: Running the algorithm on Autosomal Recessive (e.g. Cystic Fibrosis):

Figure 1: The left pedigree is purely phenotypic, the right pedigree also contains genotypic information.



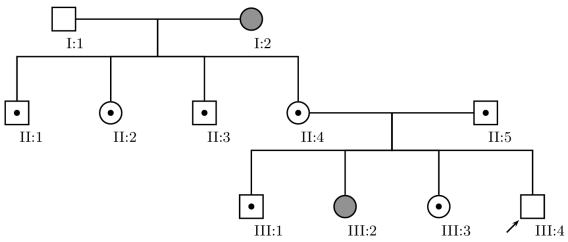
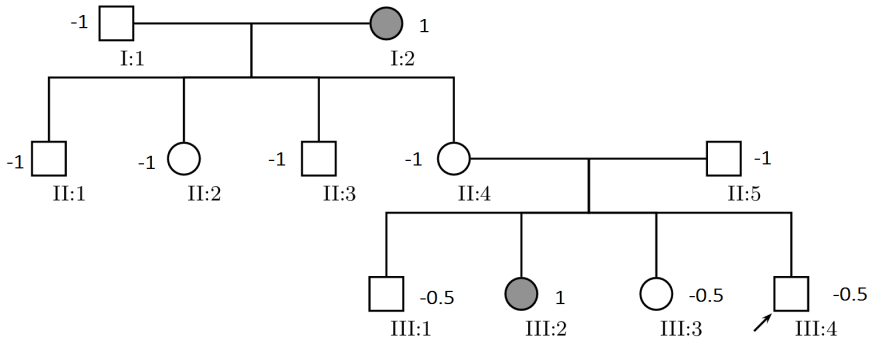


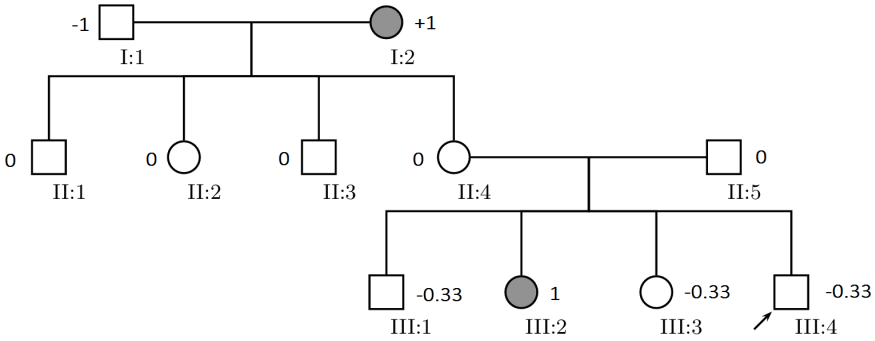
Figure 2: Attempted fit without corrections.



From this numerical system, it is easy to see that II-4 and II-5 are incorrect. We can do a quick correction by making II-5 a heterozygote, since that mating pair clearly follows the carrier parents system.

This is an example of the **Self-Correcting Property**. I will omit this step in subsequent representations.

Figure 3: Attempted fit with corrections.



Much better.

2. Autosomal Dominant

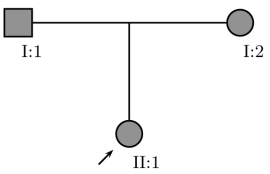
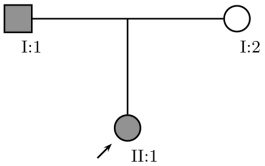
Autosomal Dominant is perhaps the least ambiguous of all the models I will present, due to heterozygotes being affected.

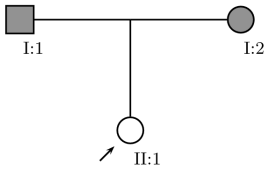
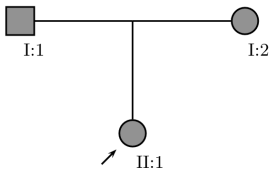
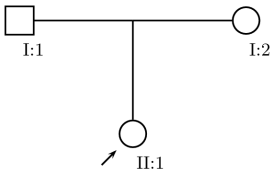
My methodology for assigning values to individuals is as follows:

1. If either of the I generation are affected, we assume them to be Heterozygotes.
2. Assume unknown affected individuals are Heterozygous.
3. If given data on the I generation, we use that instead.
4. Homozygous Dominant are assigned a value of +2.
5. Heterozygotes are assigned a value of +1.
6. Homozygous Recessive are assigned a value of 0.
7. Sum up the numbers in the two parents and divide by two when we move down a generation for the bias of the children.
8. **Heterozygotes are a complicated case**
    - In the case that two heterozygotes produce an affected child, we assign it a bias of +1.33. This is because we know that there is a $\frac{2}{3}$ chance that the child is a heterozygote, and a $\frac{1}{3}$ chance that the child is Fully Affected. $\frac{2+1+1}{3} = \frac{4}{3} = +1.33$
    - In the case that two heterozygotes produce an Unaffected child, we assign it a bias of 0 (Self-Correcting Property).
    - In the case that we have to heterozygotes but their child phenotype is unknown, we assign it a value of +1. This is because the sum of the *possible* biases will equal +1.

Here, I have documented 5 cases that are **essential** to the correctness of this system. If any of these cases fail, then this system will not work.

Table 2: Common Cases for Autosomal Dominant.

I Description	Both Fully Affected Parents	Fully Affected Parent, Unaffected Parent
II Description	Fully Affected Child	Affected Child
		
Parental Bias	I-1(+2), I-2(+2)	I-1(+2), I-2(0)
Child Bias	II-1 = $\frac{(2+2)}{2} = 2$	II-1 = $\frac{(2+0)}{2} = +1$

Heterozygous (Affected) Parents	Heterozygous (Affected) Parents	Unaffected Parents
Unaffected Child	Affected Child	Unaffected Child
		
I-1(1), I-2(1)	I-1(1), I-2(1)	I-1(0), I-2(0)
II-1 = 0	II-1 = $\frac{4}{3} = +1.33$	II-2 = $\frac{0+0}{2} = 0$

Test Case: Running the algorithm on Autosomal Dominant (e.g. Huntington's Chorea):

Figure 4: Sample Pedigree for an Autosomal Dominant trait.

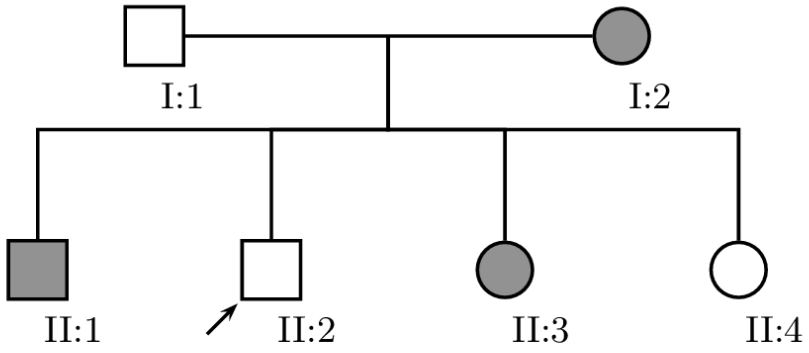
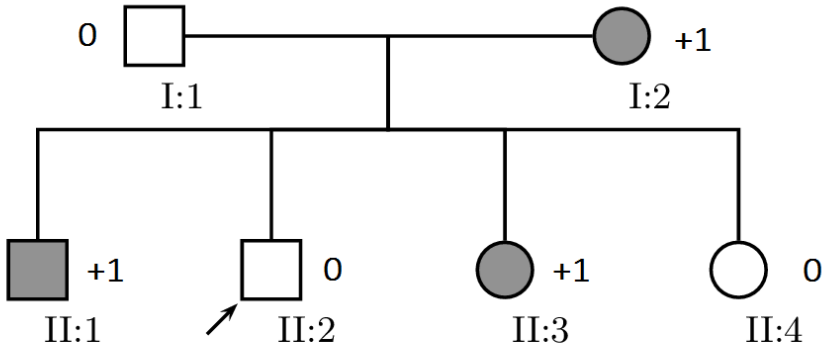


Figure 5: Attempted Fit using Autosomal Dominance.



The application on Autosomal Dominant seems trivial, but with only information about I-1 and I-2, we can accurately generate biases of the next generation. Summing and dividing I-1 and I-2 results in 0.5, therefore half of the child generation will be affected. We could go on and use this bias to calculate the children of the II generation. This abstraction of generations allows us to make predictions even without comprehensive data.

3. X-Linked Recessive

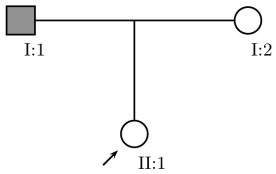
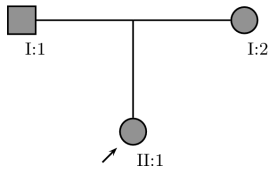
X-linked recessive bears much resemblance to Autosomal Recessive. Therefore, I will shorthand the rules that are identical. Different rules will be at the beginning.

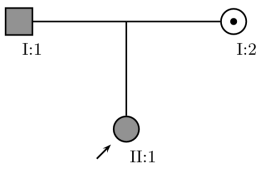
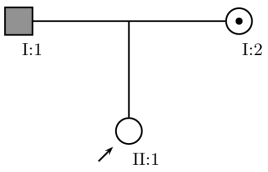
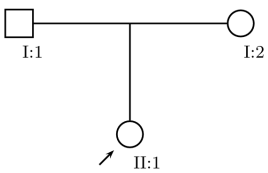
My methodology for assigning values to individuals is as follows:

1. Males will only have values +1 or -1.
2. If the child is a female, then we take the sum of both parents' biases and divide by 2.
3. If the child is male, then we assign it the same bias as its mother.
4. If we do not know the child's gender, then we assign it the average of its male biases and female biases.
5. Handling of the I generation is identical, except that the father will hold a value of 1 or -1.
6. Homozygous Dominant, Carriers, and Homozygous Recessive are represented by the same numerical system as Autosomal Recessive (+1, 0, -1).
7. Carrier females are handled differently than Autosomal Recessive. (-0.5 if Unaffected, +1 if Affected, -0.33 if Unknown)

Here, I have documented 5 cases that are **essential** to the correctness of this system. If any of these cases fail, then this system will not work. These will contain the male child calculation too.

Table 3: Common Cases for X-Linked Recessive.

I Description	Affected Father, Unaffected Mother	Both Affected Parents
II Description	Carrier/Unaffected Child	Affected Child
Example w/ II-2 ♀		
Parental Bias	I-1(+1), I-2(-1)	I-1(+1), I-2(+1)
Child Bias (Female)	II-1 = $\frac{(1-1)}{2} = 0$	II-1 = $\frac{(1+1)}{2} = +1$
Child Bias (Male)	II-1 = -1	II-1 = +1

Carrier Parents	Carrier Parents	Unaffected Parents
Affected Child	Unaffected Child	Unaffected Child
		
I-1(+1), I-2(0)	I-1(+1), I-2(0)	I-1(-1), I-2(-1)
II-1 = +1	II-1 = $\frac{-1+0}{2}$ = -0.5	II-2 = $\frac{-1-1}{2}$ = -1
II-1 = +1	II-1 = -1	II-1 = +1

Test Case: Running the algorithm on X-Linked Recessive (Ex. Hemophilia):

Figure 6: Sample Pedigree 1 & 2 for an Autosomal Recessive trait.

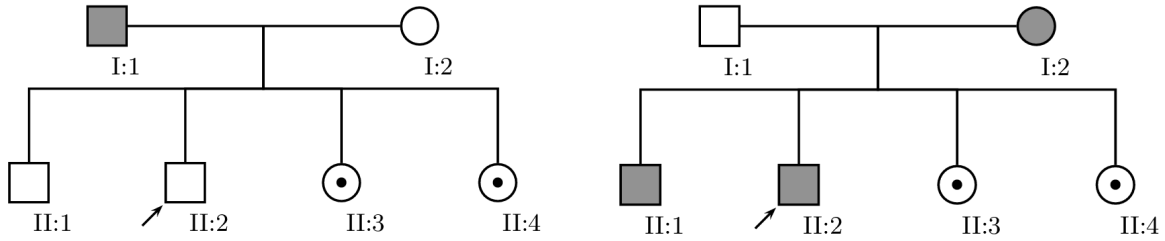
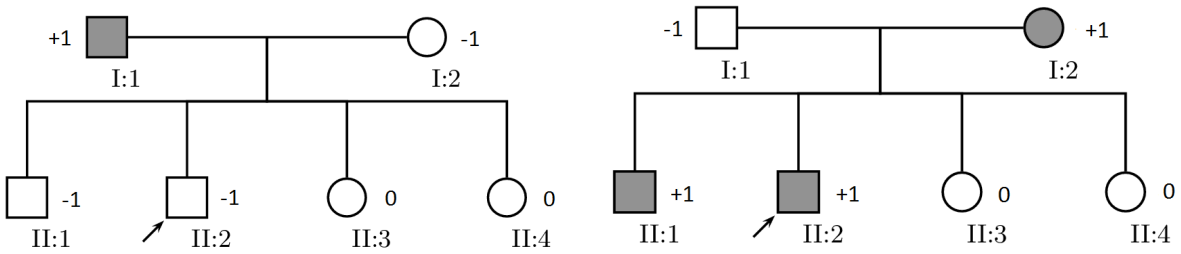


Figure 7: Attempted Fit using X-Linked Recessive on Sample Pedigrees 1 & 2.



After running the algorithm, the results are consistent with the actual results of the pedigree, even though this algorithm was given no information about II3 or II4 being carriers. The males in the tree are handled perfectly, despite using a different bias inheritance system.

Suppose we wanted to calculate the bias of a child of the left pedigree from parents I-1 and I-2. This algorithm simplifies it greatly:

$$\text{Bias} = \frac{-0.5+0}{2} = -0.5$$

This negative bias means that the child will never be affected. There is a $\frac{1}{2}$ chance that the child will receive none of the recessive gene. If we do the calculation manually, we reach the same result. Let X^R be dominant and unaffected, and X^r be recessive and affected. If the child is male, it will always inherit X^R from its mother. If the child is female, it will always inherit X^R from its mother, and X^r from its father. Since a child has a 50/50 chance of being male or female, the expected number of recessive genes inherited is $\frac{1}{2} + \frac{0}{2} = \frac{1}{2}$.

4. X-Linked Dominant

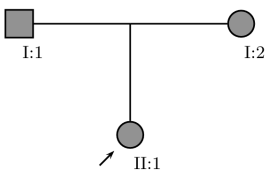
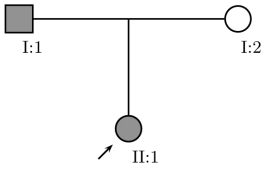
X-linked recessive bears much resemblance to Autosomal Dominant so I will continue to shorthand rules. Different rules will be at the beginning.

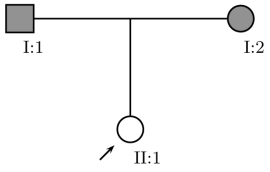
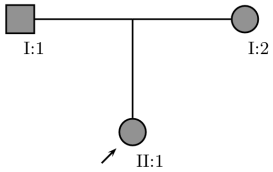
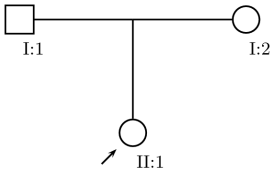
My methodology for assigning values to individuals is as follows:

1. Males will only have values +2 or 0.
2. If the child is a female, then we take the sum of both parents' biases and divide by 2.
3. If the child is male, then we assign it the same bias as its mother.
4. If we do not know the child's gender, then we assign it the average of its male biases and female biases.
5. Handling of the I generation is identical, except that the father will hold a value of +2 or 0.
6. Homozygous Dominant, Heterozygotes, and Homozygous Recessive are represented by the same numerical system as Autosomal Dominant (+2, +1, 0).
7. Heterozygous females are handled differently than Autosomal Dominant. (+1.5 if Affected, 0 if Unaffected, +1.33 if Unknown)

Here, I have documented 5 cases that are **essential** to the correctness of this system. If any of these cases fail, then this system will not work.

Table 4: Common Cases for X-Linked Dominant.

I Description	Both Fully Affected Parents	Fully Affected Father, Unaffected Mother
II Description	Fully Affected Child	Affected Child/Unaffected Child
Example w/ II-2 ♀		
Parental Bias	I-1(+2), I-2(+2)	I-1(+2), I-2(0)
Child Bias (Female)	II-1 = $\frac{(2+2)}{2}$ = +2	II-1 = $\frac{(2+0)}{2}$ = +1
Child Bias (Male)	II-1 = +2	II-1 = 0

Heterozygous (Affected) Parents	Heterozygous (Affected) Parents	Unaffected Parents
Unaffected Child	Affected Child	Unaffected Child
		
I-1(1), I-2(1)	I-1(1), I-2(1)	I-1(0), I-2(0)
II-1 = 0	II-1 = +1.5	II-2 = $\frac{0+0}{2}$ = 0
II-1 = 0	II-1 = +2	II-2 = 0

Test Case: Running the algorithm on X-Linked Dominant (Ex. Fragile X Syndrome):

Figure 8: Sample Pedigree for an X-Linked Dominant trait.

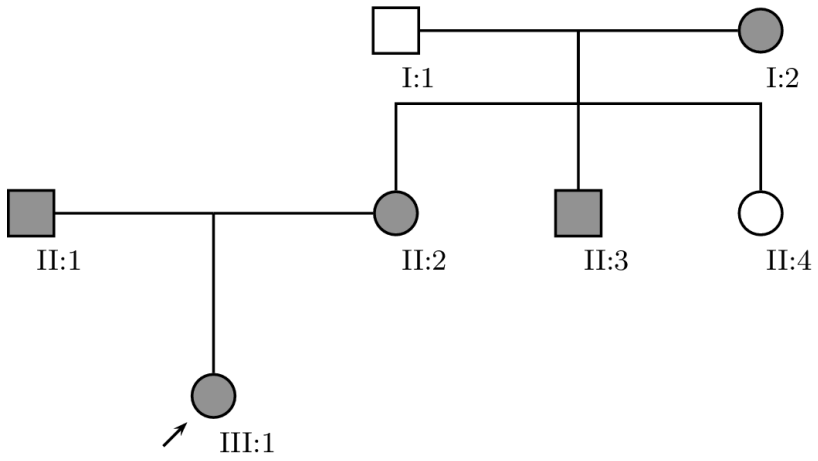
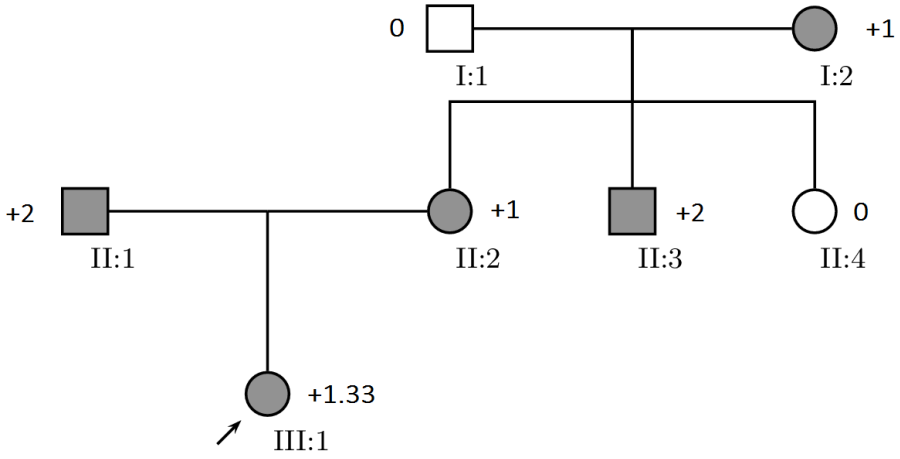


Figure 9: Attempted Fit using X-Linked Dominant on a Sample Pedigrees.



The biases are as we expected. One thing to note: the bias of III-3 (+1.33). This is significant because it tells us that III-3 *might* be Homozygous Dominant, without even looking at the parents of III-3.

5. Y-Linked

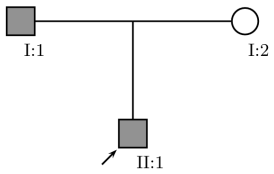
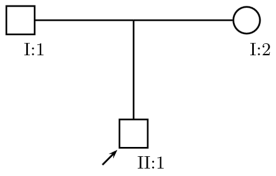
This case is highly unique.

My methodology for assigning values to individuals is as follows:

1. Males will only have values +2 or 0.
2. Females always have the value 0.
3. If the child is male, then we assign it the same bias as its father.
4. If the child is female, assign it a 0.
5. In the impossible case that a female is affected, assign it infinity.

Here, I have documented 2 cases that are **essential** to the correctness of this system. If any of these cases fail, then this system will not work.

Table 5: Common Cases for Y-Linked.

I Description	Affected Father, Unaffected Mother	Unaffected Parents
II Description	Unaffected Child/Affected Child	Unaffected Child
Example w/ II-2 ♂		
Parental Bias	I-1(+2), I-2(0)	I-1(0), I-2(0)
Child Bias (Female)	II-1 = 0	II-1 = 0
Child Bias (Male)	II-1 = +2	II-1 = 0

Test Case: Running the algorithm on Y-Linked (Ex. Y chromosome infertility):

Figure 10: Sample Pedigree for Y-Linked trait.

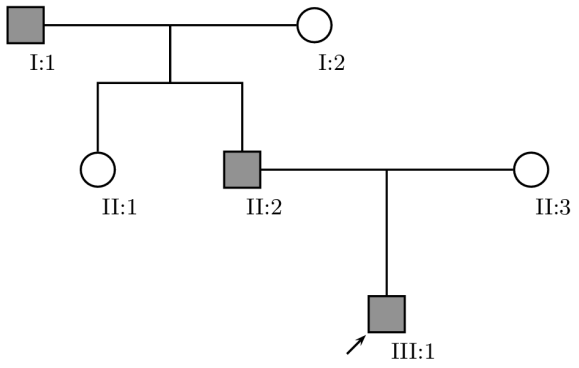
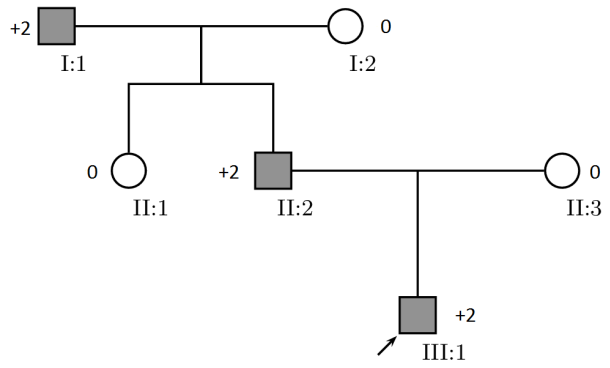


Figure 11: Attempted Fit using Y-Linked on a Sample Pedigrees.



I believe these results to be straightforward, so I will not elaborate.

Further Explanation of Autosomal Heterozygotes

The handling of Heterozygotes in these systems can be easily explained using a Punnet Square of two heterozygotes. Let R be Dominant, and r be Recessive.

Table 6: Punnet Square for a Heterozygote.

	R	r
R	RR	Rr
r	Rr	rr

We can see that we expect 1 RR, 2 Rr and 1 rr from a sample of 4 offspring.

Recessive:
Only rr will be affected. In our recessive schemes, affected is given a bias of +1. Now, we focus on the 3 other possibilities. RR is fully unaffected, and Rr is a carrier. There is a $\frac{2}{3}$ chance of being a carrier, and a $\frac{1}{3}$ chance of being fully unaffected. Since fully unaffected carries a bias of -1, and a carrier carries a bias of 0, if an individual is unaffected, their bias will be the composite of these biases, multiplied by their probability. Bias = $\frac{1}{3}$ * -1 + $\frac{1}{3}$ * 0 + $\frac{1}{3}$ * 0 = -0.33.

Dominant:
Only rr will be unaffected. In our dominant schemes, unaffected is given a bias of 0. Now, we focus on the 3 other possibilities. RR is fully affected, and Rr is a heterozygote who is affected. There is a $\frac{2}{3}$ chance of being a heterozygote, and a $\frac{1}{3}$ chance of being fully affected. Since fully affected carries a bias of 1, and a heterozygote carries a bias of 1, if an individual is affected, their bias will be the composite of these biases, multiplied by their probability. Bias = $\frac{1}{3}$ * 2 + $\frac{1}{3}$ * 1 + $\frac{1}{3}$ * 1 = +1.33.