Biol3120 Problem set 5

1. A microdeletion on 15q13.3 is associated with increased risk of intellectual disability, seizures, autism spectrum disorders, and schizophrenia. A recent study showed that penetrance for having at least one of these symptoms, assuming an average life span, is 30%.

A 5 year old girl has recently been experiencing seizures, this deletion was detected in her, as well as her mother, and concluded to be the cause. **What are the chances that her younger brother will experience one of the above symptoms in his life, assuming he lives to an old age?**

2.

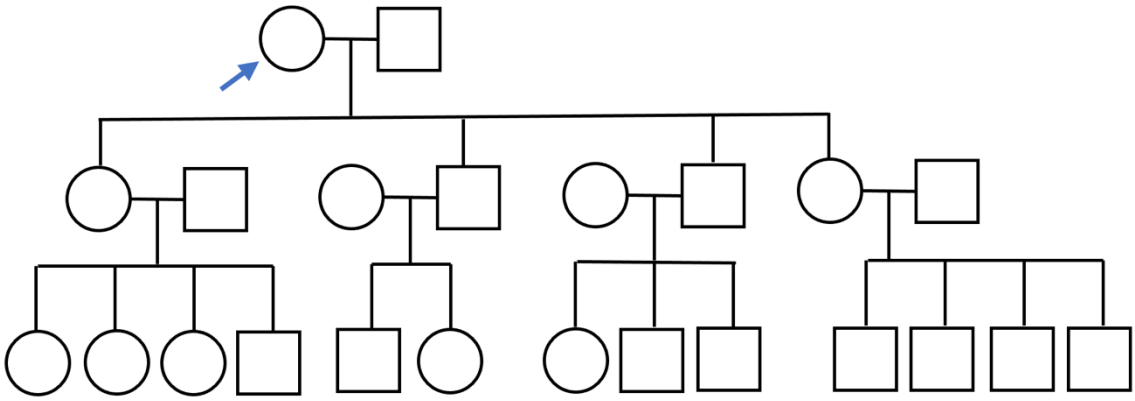
Cumulative Probability of Onset at Different Ages, for a Given CAG Repeat Size

Age of Subject (years)	Cumulative Probability (95% CI) for CAG Repeat Size of			
	39 (n = 21)	40 (n = 111)	41 (n = 98)	42 (n = 129)
30				.02 (.05–.00)
35		.02 (.05–.00)	.02 (.05–.00)	.05[a] (.09–.01)[a]
40	.07[a] (.20–.00)[a]	.08 (.13–.02)	.12 (.18–.05)	.14 (.20–.07)
45		.13 (.19–.05)	.21 (.30–.12)	.32 (.41–.23)
50	.16 (.33–.00)	.21 (.30–.12)	.38 (.48–.26)	.58 (.66–.47)
55		.36 (.46–.25)	.55 (.64–.42)	.81 (.87–.71)
60		.61 (.70–47)	.77 (.85–.65)	.99 (1.00–.91)
65	.36 (.59–.00)	.80 (.88–.67)	.88[a] (.94–.78)[a]	1.00 (NA)

The table above, from Brinkman et al, 1997, shows penetrance of Huntington's disease, by CAG repeat size and age.

A man's mother had HD with a CAG repeat size of 42. He is now 55 years old, and has not experienced any HD symptoms. **Based off the above data, what are the chances that he will start showing symptoms by the age of 65?**

3.



The grandmother in this family (marked with an arrow) has recently been found to be a carrier for an X-linked recessive condition, which has onset in the 50s. The second generation are all in their 30s. Assuming those marrying into the family do not have or carry this disease, **what is the maximum number of people in this family who could develop (ie be affected by) the condition when they reach their 50s?**

4. Familial Mediterranean fever is an autosomal recessive condition, with high carrier frequencies known for multiple ethnicities:

Armenian 1 in 8

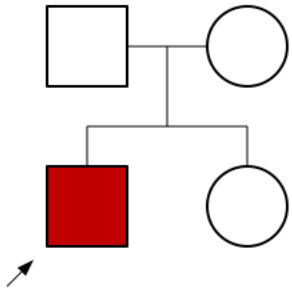
Ashkenazi Jewish 1 in 13

Sephardic Jewish 1 in 14

Turkish 1 in 8

What are the chances of an Armenian man and a Sephardic Jewish woman having a baby who is affected with this condition?

5.

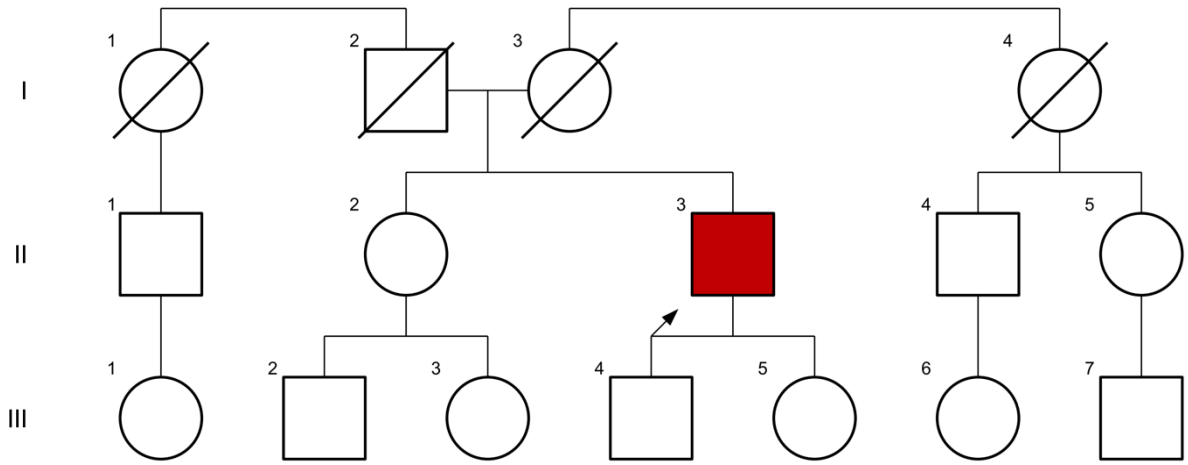


The condition shown in this family has multiple possible modes of inheritance: X-linked recessive, autosomal dominant, and autosomal recessive. It is always one mode of inheritance for each family (ie it doesn't change between people within the same family). Assume full penetrance and onset from birth.

You are trying to determine the mode of inheritance for the condition in this family. **Regardless of the gene it's on, finding a single pathogenic mutation in who in this family (other than the affected person) would allow you to determine the mode of inheritance?**

a) The mother
b) The father
c) The sister
d) Finding a pathogenic mutation in no one individual will give that information

6.



One person in this family has recently been diagnosed with a late-onset condition which has an X-linked recessive pattern of inheritance (note that this pedigree is drawn in a slightly different style than you have previously seen - only blood relatives are shown, partners are not shown. This is often how pedigrees are drawn in clinical settings).

Assume no de novo mutation, assume all partners coming into this family are not affected with or carriers of this condition. Everyone in the oldest and second oldest generation are at an age where they would be affected if they had inherited the appropriate variant.

For each person, indicate whether they:

- May be a carrier
- May be affected when they reach the appropriate age
- Are definitely a carrier
- Can't be affected or a carrier

7. Alpha thalassemia is a blood condition resulting from abnormal hemoglobin production, due to loss of function of copies of either HBA1 or HBA2 genes. These genes are very similar, and for simplicity's sake we talk about having four copies of the HBA gene (two copies of each).

HBA1 and HBA2 genes are located next to each other, and therefore are described within the same allele. For example, αα indicates that both HBA1 and HBA2 copies on an allele are functioning, α- indicates an allele with one of the two genes functioning, and -- indicates an allele with neither gene functioning.

There are multiple versions of alpha thalassemia, which depend on how many of the four HBA copies are functioning. This is outlined in the table below, in order of severity (most severe -> least severe):

Phenotype	**Genotype**
α-thalassemia major	Loss of all 4 α-globin genes
Hemoglobin H (HbH) disease	Loss of 3 α-globin genes
α-thalassemia trait	Loss of 2 α-globin genes *in cis* (--/αα) or *trans* (-α/-α)
α-thalassemia silent carrier	Loss of 1 α-globin gene (-α/αα)

A man who is a silent carrier has a child with a woman who has α-thalassemia trait.

a) Assuming the woman has mutations in **cis**, what are the possible offspring phenotypes for this child? Give the probability for each possible phenotype.

b) Assuming the woman has mutations in **trans**, what are the possible offspring phenotypes for this child? Give the probability for each possible phenotype.