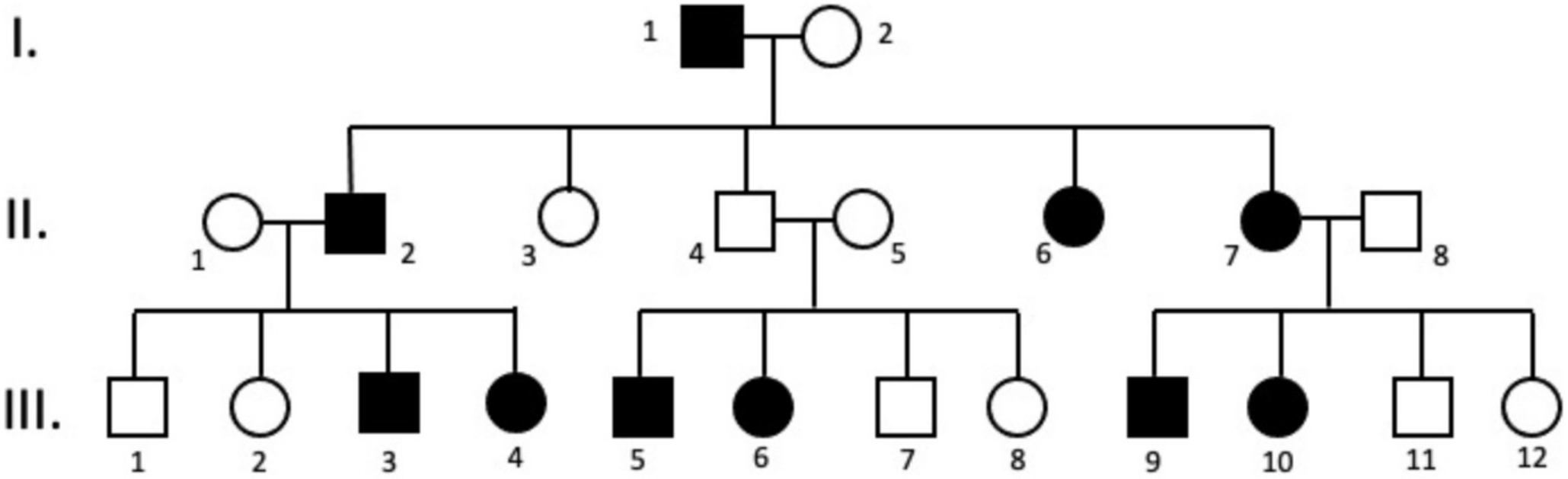
How is it possible?



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can an autosomal dominant disorder skip one generation?

Yes, it is possible for an autosomal dominant disorder to skip a generation.

In autosomal dominant inheritance, the gene mutation responsible for the disorder is located on one of the non-sex chromosomes, and only one copy of the mutated gene is needed to cause the disorder. When an affected person has children, each child has a 50% chance of inheriting the mutated gene and developing the disorder.

However, in some cases, an affected person may not pass on the mutated gene to their children. This could be due to several reasons, such as the affected person having a new mutation in the gene that is not present in their parents, or the mutated gene being located on a chromosome that is not passed on to their children.

In such cases, the disorder may appear to skip a generation, as the affected person's children do not have the disorder, but their grandchildren may inherit the mutated gene and develop the disorder.

There are several possible explanations for this pattern of inheritance in a pedigree:

1. New mutation: It's possible that the man in the second generation did not inherit the autosomal dominant disorder from his affected father. Instead, he may have acquired a new mutation in the gene responsible for the disorder that was not present in his father. This would explain why he does not show any symptoms of the disorder.
2. Reduced penetrance: Autosomal dominant disorders can exhibit reduced penetrance, which means that not everyone who inherits the mutated gene will develop the disorder. In this case, the man in the second generation may have inherited the mutated gene from his affected father but did not develop the disorder, while his daughter inherited the same gene and did develop the disorder.
3. Germline mosaicism: Another possibility is that the affected grandfather in the first generation had germline mosaicism, which means that the mutation is only present in some of his sperm cells. If the mutation is not present in the rest of his body, he may not have any symptoms of the disorder, and it would not be detected clinically. However, if a sperm cell with the mutation fertilizes an egg, the child may inherit the mutated gene and develop the disorder. In this case, the man in the second generation may not have inherited the mutated gene from his father but could still be a carrier due to germline mosaicism.

It's important to note that these scenarios are not exclusive, and other possibilities could exist as well. However, in any case, it is recommended to speak with a healthcare professional or a genetic counselor to discuss the inheritance pattern and any potential risks to future generations.

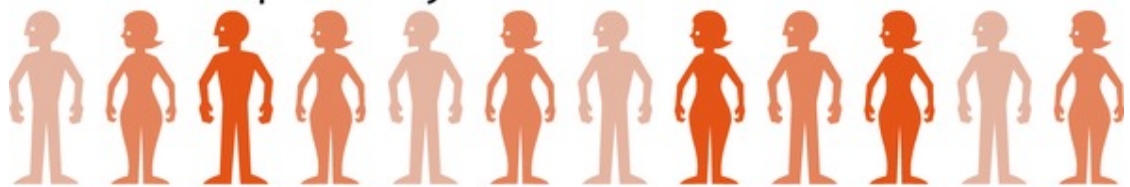
Penetrance: percentage of cases with a given allele who exhibit the phenotype associated with that allele.

Expressivity: the degree to which a given allele is expressed at the phenotypic level.

Complete penetrance and expressivity

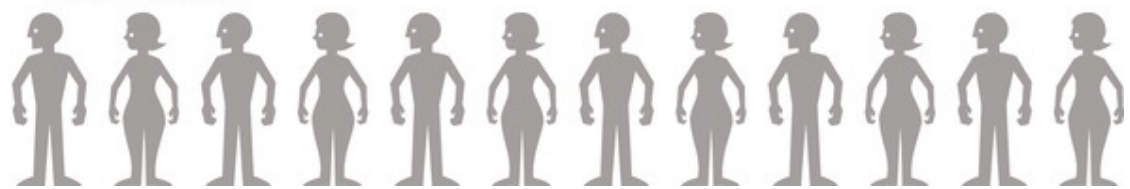
Variable penetrance

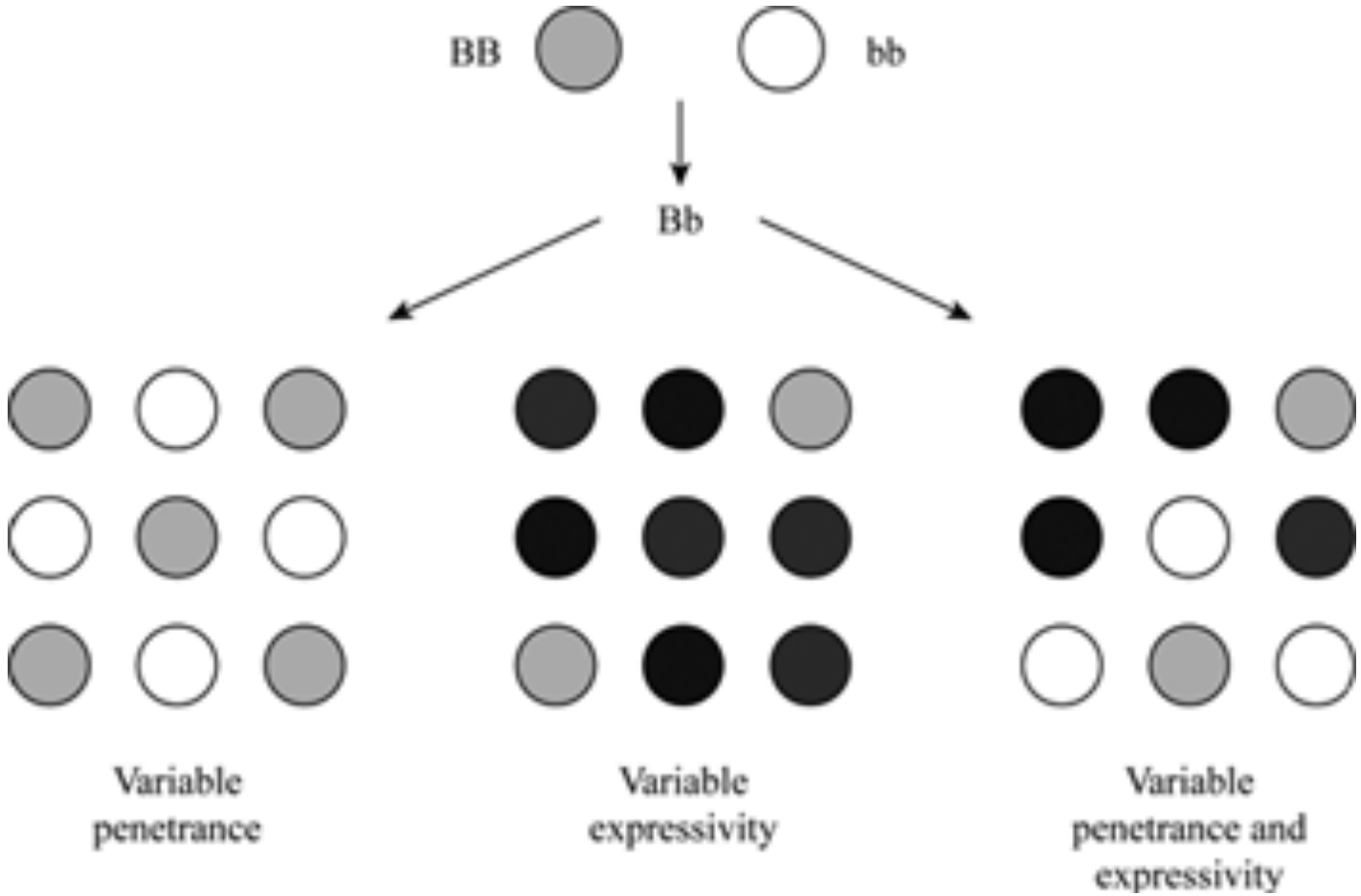
Variable expressivity



Variable penetrance and expressivity

Unaffected

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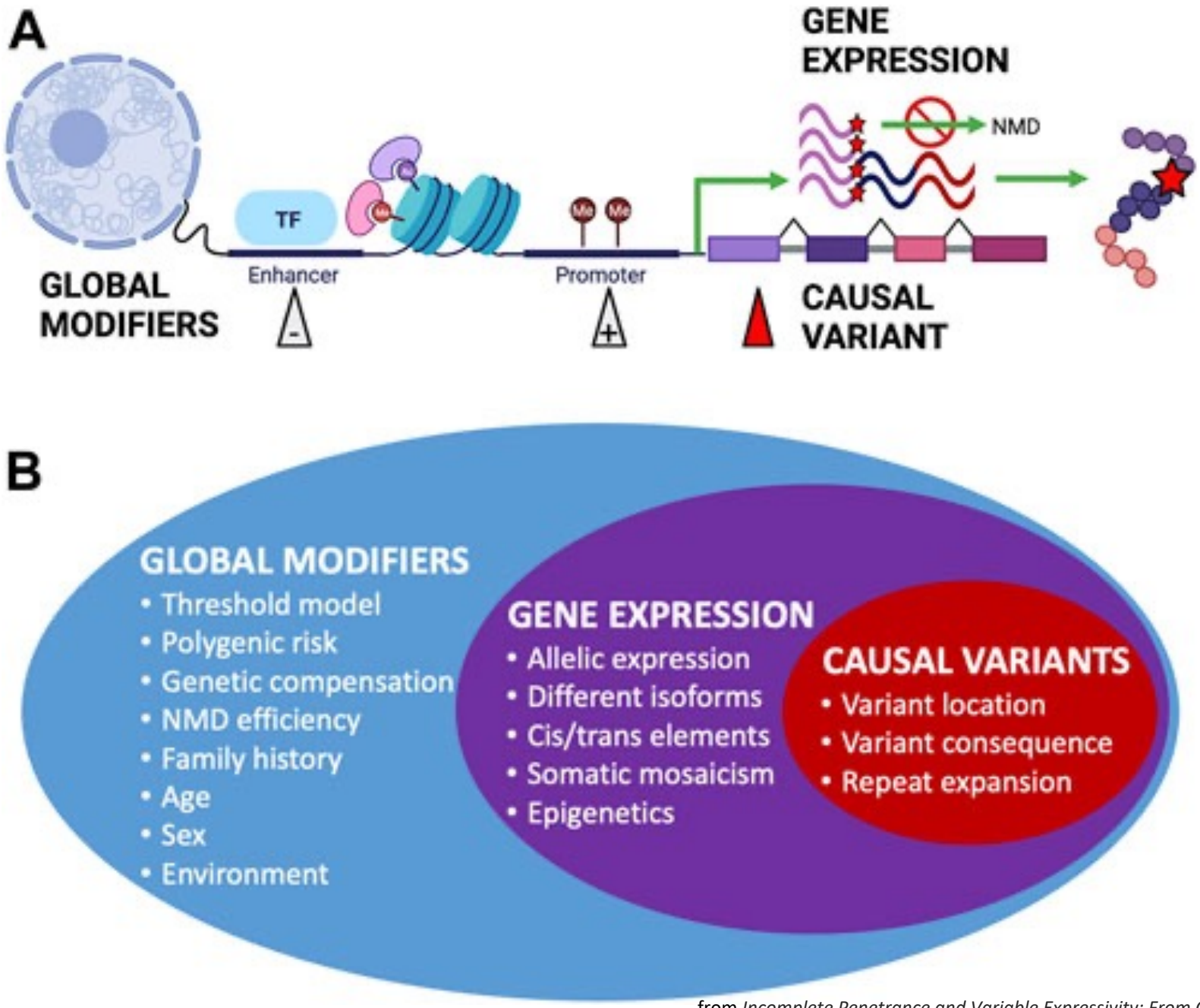
Variable penetrance
Variable expressivity
Variable penetrance and expressivity

Penetrance: percentage of cases with a given allele who exhibit the phenotype associated with that allele.

Expressivity: the degree to which a given allele is expressed at the phenotypic level.

Ok…but, again…..How is it possible?



from *Incomplete Penetrance and Variable Expressivity: From Clinical Studies to Population Cohorts*
Frontiers in Genetics 2022

Disease	Gene	STR	Non-penetrant	Intermediate penetrance	Full penetrance
Spinocerebellar ataxia 8	*ATXN8OS/ATXN8* (Perez et al., 2021)	CTG/CAG	<91	92–106	>107
Spinal muscular atrophy	*SNM1* (Laskaratos et al., 2021)	CAG	<34	35–46	>47
Fragile X	*FMR1* (Hagerman et al., 2017)	CGG	<44	45–200	>200
Huntington's	*HTT* (Kay et al., 2016)	CAG	<36	37–39	>40
ALS	*C9orf72* (DeJesus-Hernandez et al., 2011)	GGGGCC	<23	24+	>700
Friedrich's Ataxia	*FXN* (Kim et al., 2011)	GAA	<34	35–99	>100

FIGURE 4. Threshold model of disease. Some deleterious monogenic variants are sufficient to cause the disease alone and do not need any genetic modifiers to cause the disease phenotype. Other monogenic variants may be incompletely penetrant and only display a disease phenotype when accompanied by other genetic or non-genetic factors that raise them above the clinical threshold for disease presentation. In the latter scenario, individuals may have the same underlying causal variant but have very different phenotypic presentations depending upon their modifying factors.