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Genetic literacy series

Primer part 1- the building blocks of epilepsy genetics

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Abstract

This is the first of a two-part primer on the genetics of the epilepsies within the Genetic Literacy Series of the Genetics Commission of the International League Against Epilepsy. In Part 1, we cover the foundations of epilepsy genetics including genetic epidemiology and the range of genetic variants that can affect the risk for developing epilepsy. We discuss various epidemiological study designs that have been applied to the genetics of the epilepsies including population studies, which provide compelling evidence for a strong genetic contribution in many epilepsies. We discuss genetic risk factors varying in size, frequency, inheritance pattern, effect size, and phenotypic specificity and provide examples how genetic risk factors within the various categories increase the risk for epilepsy. We end by highlighting trends in epilepsy genetics including the increasing use of massive parallel sequencing technologies.

A 28 year old woman with temporal lobe epilepsy asks you for advice regarding a possible genetic contribution to her epilepsy and the role of genetics for family planning. Her epilepsy is relatively well controlled ever since starting on one of the newly available antiepileptic medications, but her complex partial seizures and generalized tonic-clonic seizures were difficult to treat during adolescence. She is thinking about starting a family, but became concerned when a person with epilepsy who she knows from her local support group had a child with a severe epilepsy. She had never even thought about her epilepsy being genetic because her parents have never had a seizure, but after hearing this story and that her friend's parents do not have epilepsy either, she was worried. When she learned that one of her cousins had a febrile seizure at the age of two, she became even more concerned and brought this topic up during the consultation. What can we tell our patient about the genetic contribution to her epilepsy? What is the risk to her future children? And is there any genetic test that would help us to understand the risk to her offspring better?

Over the past decade, the field of human genetics and genomics has experienced major advances in technology that allow us to quickly screen the entire human genome for genetic variation. At the same time, we have gained expanding knowledge about the types of variation that can increase the risk for or cause human disease. Together, these advances have led to an explosion of gene discovery for many human disorders, including epilepsy.

In Part I of this two-part primer, we will provide an overview of the history of epilepsy genetics, introduce the terminology required to understand genetic studies, and demystify some of the common misunderstandings surrounding epilepsies and genes. Rather than discuss the role of particular epilepsy genes, Part I will provide an overview of the general principles that are necessary to answer the types of questions raised in the case vignette above.

In Part II, we will delve deeper into the paradigm shift from genetics to present-day molecular genetics and provide the reader with a brief overview of the key concepts in the field of genetics in the era of exome and genome sequencing. The discussion of the individual genes predisposing to genetic epilepsies will be the topic of further articles in the Genetic Literacy series. Because every specialty seems to have its own terminology and jargon, we include a glossary of terms (Box 1).

A brief history of epilepsy genetics

Historically, our understanding of the genetic contribution to seizure disorders is derived from epidemiological studies and from genetic studies. Despite the tremendous advances of molecular genetic discoveries in recent years, our basic knowledge of the epilepsies as disorders with a genetic component stems from epidemiological studies, most of which predate the genomic era [1-4]. These studies discovered a strong genetic contribution to many epilepsy syndromes and provided us with risk estimates that are still used in genetic counseling today [5].

Traditionally, epidemiological studies assessing the genetic contribution to seizures disorders have been performed at different levels of scientific rigor, ranging from small case series reporting the frequency of patients with a positive family history to well-designed population-based studies that provide us with accurate risk estimates. While the number of population-based studies adhering to stringent epidemiological criteria is low [3], earlier case series already made the observation that some epilepsy syndromes seem to have a higher frequency than others. For example, a familial clustering of idiopathic/genetic generalized epilepsies was already postulated in case-based series.

The systematic twin studies performed by William G. Lennox in the 1940s and 50s deserve a mention for several reasons. Most importantly, these studies provided strong evidence for a predominantly genetic contribution for Childhood Absence Epilepsy and related generalized epilepsies. The clarity of the twin data analyzed by Lennox and others since is still unsurpassed by other epidemiological studies, which, by design, often only provide population risk estimates rather than impressive, albeit epidemiologically less stringent, observations of identical epilepsies in individual twin pairs.

The first epilepsy gene to be discovered was *CHRNA4* in 1994, one of the genes for Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE). In a very simplified manner, the history of gene discovery in epilepsy that followed this initial discovery can roughly be divided in three distinct eras [6]– (i) the pioneer era of gene discovery in monogenic familial epilepsy syndromes; (ii) a relatively dormant period characterized by largely negative candidate gene studies; and finally (iii) the genome-wide era in which large-scale molecular genetic studies have led to the identification of a number of novel epilepsy genes, particularly in severe sporadic forms of epilepsy (Figure 1). The current primer of the Genetic Literacy series aims to provide the building blocks that are required to put the role of these future studies into context.

What patients and populations tell us - the genetic epidemiology

Genetic epidemiological studies aim to quantify the genetic contribution for epilepsies through population-based studies. Historically, there is an abundance of epidemiological studies analyzing the genetic contribution to seizure disorders, though phenotype definitions, phenotypic detail and overall study size have differed enormously in these studies. There are only a few studies that combine a clear and modern phenotype definition, population-based ascertainment and sufficient size to arrive at accurate estimates of the population genetic risk for seizure disorders.

For example, a recent analysis of the Rochester Epidemiology Project arrived at robust estimates for the frequency of epilepsy in relatives of individuals with epilepsy [3]. By the age of 40, the overall risk was increased 3.3-fold, with a higher increase in risk for idiopathic/genetic generalized epilepsies compared to focal epilepsies (Table 1). In 2015, this increase in risk for first-degree relatives is the most reliable and repeatedly confirmed epidemiological parameter that can be used for patient counseling.

Returning to our patient in our case vignette, the role of the clinician is to assess which risk category our patient would fall into. Assuming that she has a non-lesional focal epilepsy, the best estimate for the risk of her children to develop epilepsy is a cumulative risk of 2% by the age of 40. This means that her children have a 2% risk of developing epilepsy, which is roughly 3 times higher than in the general population. There is no solid epidemiological data to suggest that the cousin with febrile seizures raises her offspring's risk further. Several genes for familial temporal lobe epilepsies have been identified (LGI1, DEPDC5, RELN, VPS13A). However, mutations in these genes have mainly been found in patients with familial focal epilepsies, often with rare and atypical features. There is little evidence to suggest that these known genes play a major role in sporadic, non-familial cases. We assume that many genes for focal epilepsies remain to be discovered, which may play a role in our patient. It is unknown how many patients with non-lesional epilepsies have epilepsy due to causal strong candidate genes as opposed to complex inheritance.

The concept of heritability is often used in epidemiological studies and has recently gained some popularity through the concept of "missing heritability" [7], which stipulates that current molecular genetic studies only capture a small proportion of the overall genetic risk for disease. Heritability is a population genetic concept that is frequently misunderstood as it refers to **the** contribution of genetic factors on a population level rather than **the** relative contribution of genetics in a single individual. By definition, heritability refers to the fraction of the variability **of** a phenotype **within a population** that can be attributed to genetic variation compared to non-genetic factors.

To make this concept applicable to epilepsy, epidemiologists have traditionally hypothesized a liability to epilepsy in the population, a hidden continuous trait that results in epilepsy once a certain threshold has been crossed ("liability-threshold model") [8]. This trait is hypothesized to have a certain variability within the population, influenced by both genetic and non-genetic factors. Heritability refers to the relative contribution of genetic factors to this variability.

While the concept of heritability has been important on a population level, heritability cannot be broken down into the contribution of genetic and non-genetic factors in a single individual. Despite this fact, epidemiological studies and heritability estimates do provide convincing evidence that epilepsy has a genetic component and would strongly encourage physicians to pursue genetic testing in groups of patients whose disease cannot be explained by environmental or apparently "acquired" causes.

Returning to our patient in the case vignette, twin studies suggest a contribution of genetic factors to non-lesional epilepsies, but do not provide a risk estimate that can be used in clinical practice. Heritability estimates for this type of epilepsy would probably range between 30% and 50%, but these estimates are irrelevant for genetic counseling and add little to the ~2% offspring risk that was already communicated to the patient.

What genes tell us - the range of variants predisposing to human epilepsy

The past two decades of research have made it painfully clear that the genetics of epilepsy is complicated, and the discovery of genetic variants contributing to the disorder is not as straightforward as we might have predicted [7]. Other than the classical single base pair mutation resulting in monogenic disease, various types of genetic variants have been discovered to contribute to the risk for human epilepsy.

In order to provide an overview of the genetic variants contributing to human epilepsies, we will review five independent~~s~~ dimensions, which characterize genetic variants contributing to human disease. These dimensions include (1) size, (2) frequency, (3) inheritance pattern, (4) magnitude of effect and (5) phenotypic specificity. To acquaint the reader with the different classes of genetic risk factors, we will address these dimensions separately.

Size

Genetic risk factors predisposing to human epilepsies may vary in size, ranging from changes in single base pairs to entire chromosomes (Figure 4). Between both extremes are copy number variants, smaller gains and losses of genomic material. If the structural variants are larger than 1kb (1000 base pairs), they are referred to as copy number variants (CNV). Smaller deletions or insertions **can vary in size**~~, which only span a few base pairs,~~.

Traditionally, CNVs were assumed to be rare occurrences in both health and disease and the variation in single base pairs was thought to be the main contributor to human genetic variation. However, with the availability of high-throughput genotyping platforms, structural variants were found to be frequent in the genome of healthy individuals[9]. Some of these variations are also implicated in human disease. For example, the genetic architecture of the human genome predisposes certain regions to recurrent losses and gains of small genomic regions. These regions are referred to as genomic hotspots [10]. Many of the microdeletions identified in neurodevelopmental disorders, including epilepsy, are due to hotspot rearrangements. In summary, genetic risk factors for epilepsy can range in size from a single base pair to greater than one million, though the degree of risk is not necessarily proportionate to the size of the genetic variant.

Frequency

Genetic risk factors can be common or rare in the overall population. Common variants are present in more than 1% of the population. Variants present in less than 1% of the population are rare variants. A sequence change that is present in the population is called a single nucleotide polymorphism (SNP) while a copy number change is a CNV or copy number polymorphism (CNP).

In general, there is an inverse relationship between the frequency of a genetic risk factor in the population and the magnitude or “effect size”. A common genetic risk factor is likely to be weak and rare risk factors are usually strong, creating a "corridor" of possible genetic risk factors (Figure 2). This corridor is limited through the prevalence of epilepsy on the upper end; a common and strong risk factor would make epilepsy more common. On the lower end, the corridor is limited by the overall ability to detect these risk factors; a weak and rare risk factor requires very large sample sizes to detect.

Inheritance pattern

Genetic risk factors for human epilepsies can either be inherited or arise *de novo* in the affected individual (Figure 3). Familial epilepsies include those in which transmission occurs in a dominant or a

recessive fashion. However, many familial epilepsies are characterized by multiple affected family members but without a clear inheritance pattern and may not easily be grouped into one of these categories.

For dominant transmission, a mutation in one of the two alleles is sufficient to cause disease. This is the case in many of the known familial epilepsy syndromes such as Genetic/Generalized Epilepsy with Febrile Seizures Plus (GEFS+) due to mutations in *SCN1A* or *SCN1B*, Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) due to mutations in *CHRNA4*, *CHRNB2* or *CHRNA2* or the benign familial neonatal and infantile epilepsies due to mutations in *KCNQ2*, *KCNQ3*, *SCN2A* or *PRRT2* (see [6, 8] for review).

Recessive epilepsies are due to mutations in both alleles of a gene. These alleles can be affected through homozygous mutations (where the ~~same exact~~ **identical** mutation is inherited from each parent) or through compound heterozygous mutations (where the specific mutation inherited from the father is different than that inherited from the mother, but affects the same gene). Recessive epilepsies are usually severe disorders and two prominent examples are the progressive myoclonus epilepsies such as Unverricht-Lundborg disease or Lafora disease and many neurometabolic disorders. In many cases, the epilepsy in recessive disorders is secondary to a primary storage or metabolic defect.

The above examples affect the autosomes, the human chromosomes 1 to 22. However, disease-causing mutations can also be transmitted through the X-chromosome. Epilepsies due to mutations on the X-chromosome can either be X-chromosomal dominant, which affect mainly girls (e.g. *CDKL5),* or X-chromosomal recessive, which affect boys (e.g. *ARX* gene).

Mutations in the mitochondrial genome are found in a subset of patients with mitochondrial disorders, which may present as myoclonus epilepsies. The mitochondrial genome is entirely independent of the nuclear genome and mitochondrial mutations are transmitted maternally.

An increasing number of epilepsies are found to be due to *de novo* mutations. In these cases, the mutation is found in the affected proband, but is absent in both parents. These mutations usually arise in the parental germ-line, but can also occur in early stages during embryonic development, as shown for mutations in *SCN1A* [11]. These mutations can be conceptualized as dominant mutations. However, in most cases, there is no transmission in families as the patients are severely affected and do not have children.

In the severe epileptic encephalopathies, there is an increasing focus on *de novo* mutations as recent studies suggest that this mechanism explains a significant number of cases.

Most patients with non-acquired epilepsy either do not have a positive family history, or they have a family history but without a clear inheritance pattern. These cases are due to complex inheritance. Complex inheritance, in contrast to Mendelian inheritance with a strong influence of a major gene, stipulates an interaction of many genetic factors and possibly environmental factors. Complex inheritance, albeit intuitive at first glance, is poorly understood in depth. The number of variants in a particular individual required to result in a phenotype is not known. Moreover, why two individuals such as siblings or even twins who carry the same risk-raising variants may be discordant for the phenotype remains an unsolved problem.

Magnitude of effect

Genetic risk factors may contribute to disease with different magnitude of effect, referred to as effect size. On the one hand, there are genetic risk factors for Mendelian epilepsies that have a very high effect size, i.e. having such a variant makes it very likely to be affected. An example would be a mutation in *SCN1A* that leads to Dravet syndrome.

On the other end of the spectrum are variants that cause only a small increase in risk. For example, the SNP rs2947349 was recently confirmed to be a genetic risk factor for genetic generalized epilepsy [12, 13]. The relative risk associated with this variant is 1.15, meaning that there is a 1.15 fold increase in risk of developing genetic generalized epilepsy compared to the general population. If we assume the risk of genetic generalized epilepsy is ~1% of the population, or 100/10,000, then individuals with the C allele at this locus would have only a slightly elevated risk estimated to be 1.15%, or 115/10,000.

The effect size **of disease-associated variants** is usually described using the odds ratio (OR), which roughly corresponds to the increase in risk [14]. **While this concept is used in associated studies, studies assessing monogenic variants often report the penetrance of a variant**, ~~This is highly related to the concept of penetrance~~, or the likelihood that an individual carrying a particular variant will have disease. A variant that exhibits 100% penetrance will always result in disease in individuals carrying that variant; so the variant has a high effect size. For a variant with 20% penetrance, only 20% of individuals carrying the variant will be affected; such a variant has a lower effect size, and additional genetic, environmental or other influences may be required to manifest disease. In this case, the variant in an affected individual

may be inherited from an unaffected parent. Microdeletions of 15q13.3 provide an example of this, where the variant is inherited in the majority of cases [15-17], but the parent is often unaffected. **These studies provide insight into how odds ratio of a variant and penetrance are related: even variants with a high odds ratio may still have a relatively low penetrance.**

Phenotypic specificity

Genetic risk factors predisposing to epilepsies may be different in how they associate with a given phenotype. For some genes, the connection is very strong. For example, a disruptive mutation in the *SCN1A* gene has a very high likelihood of causing Dravet Syndrome, a condition in which the phenotype is well-defined and the clinical course is relatively consistent among patients. For other genes, the connection to particular phenotypes may not be as tight. For example, mutations in *STXBP1* were first identified in patients with Ohtahara syndrome [18], another classic epileptic encephalopathy. We now know that mutations in the same gene can cause a wider range of phenotypes, including intellectual disability without seizures [19].

Epilepsy-associated microdeletions also have a wide phenotypic spectrum that includes autism spectrum disorder, intellectual disability, and schizophrenia [10]. In many cases, however, the phenotypic range of particular genes is not fully established; to do this requires sequencing the gene in large numbers of patients with varied phenotypes. Notably, the phenotypes associated with specific genes may be specific for mutations in particular domains or even single base pairs. This is the case, for example, for the *ARX* gene, where infantile spasms without brain malformations are associated with a triplet repeat expansion, but other mutations may result in brain malformations or X-linked intellectual disability without seizures [20]. Also, for the *SCN2A* gene, truncation mutations appear to result in intellectual disability, while epileptic encephalopathies appear to be exclusively correlated with missense mutations [21, 22].

Current trends in epilepsy genetics

In order prepare the reader for the remainder of this series, we would like to highlight several trends that are relevant to the field. First and most prominently, novel technologies have entered the field and are increasingly applied, including next generation sequencing technologies including gene panels and exome sequencing. These tools are becoming clinically standard technologies that make it possible to assess genetic variation in hundreds, if not thousands of genes simultaneously. The trend to use these

technologies in a diagnostic setting will become more prominent, although this data needs to be interpreted with great caution given the complexities outlined above.

Second, new syndromes will emerge. Genetic findings will be the common denominator for patients, which will make us have a closer look at what the shared phenotypic features may be. It can be assumed that in some cases, the shared findings may cross traditional epilepsy syndrome boundaries. Third, genetic findings will be integrated into treatment decisions, a trend referred to as "personalized medicine". We will see this field move from individual case reports to developing standards, guidelines and eventually new treatment options.

Returning to our patient in the case vignette, these emerging trends may affect management of patients with sporadic, non-lesional epilepsies. Some providers may consider discussing the utility of gene panel testing to assess for variants in known genes for focal epilepsies that may add to better exploring the genetic contribution to the patient's epilepsy. However, most clinicians and counselors would probably not considered genetic testing given that the diagnostic yield is expected to be very low. ***However, the field of epilepsy genetics is in its infancy and the patient and her offspring can look forward to an era of individualized medicine built on the foundations of current discovery.*** *In Part II of this primer, we will review the role of novel genetic technologies and explore how these diagnostic tools are used in the diagnostic work-up of epilepsy patients.*

Statement on ethical publishing

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors has any conflict of interest to disclose.

Box 1: Terminology

Heritability	The fraction of phenotype variability **in a population**

	that can be attributed to genetic variation
Exome	The protein-coding region of the genome, where most currently known variation relating to disease occurs.
Allele	**One of two or more alternative versions of a gene;** At each site in the genome, a person inherits two alleles, one from mother and one from the father. If the allele is the same the person is a homozygote at that site, and if the allele is different the person is a heterozygote at that site.
Variant, **polymorphism**	Any variation in an individual that **is different from the reference genome** is considered a variant. A polymorphism in found in multiple individuals in a population, and typically is not associated with severe disease that would influence whether or not a person is able to reproduce.
Mutation	A variant that typically leads to a detrimental phenotype **is very rare in the population**
Copy number variant (CNV)	A genetic variant that changes the number of copies of a particular gene or DNA sequence, and can include gain (duplication) and loss (deletion) of genetic material.
Homozygous/**heterozygous**/compound heterozygous/**hemizygous**	Homozygous, heterozygous, **compound heterozygous,** and hemizygous describe the genotype **for a single gene**. Homozygous refers to two identical alleles at a given position. Heterozygous describes a genotype with two different alleles at a given position. Compound heterozygous refers **to** a recessive disease caused by **two different mutant alleles in the same gene (i.e. each copy has a different mutation). Hemizygous refers to the state of having only one allele for a gene with no counterpart, typically for X chromosome genes in males.**

Next-generation sequencing (massive parallel sequencing)	Next-generation sequencing is new technology that allows rapid sequencing of entire genomes or selected portions of the genome by fragmenting DNA in small pieces and sequencing each fragment in parallel.

Box 2: Key Points

1. There is a genetic component to epilepsy; however teasing out the genetic contribution can be complex
2. Heritability is a population-based concept that is difficult to apply to a single patient or family in the clinic
3. The genetic variants influencing epilepsy vary in terms of size, frequency, inheritance pattern, magnitude of effect and phenotypic specificity
4. New trends are emerging in epilepsy genetics, including next generation sequencing, novel epilepsy syndromes, and a greater integration of genetics into clinical decision-making for individual patients.

Figure 1. The history of epilepsy genetics

Figure 2. The ~~"Manolio corridor"~~ **"corridor" of possible genetic variants for human epilepsies**

Figure 3. The various inheritance patterns in human epilepsies

Figure 4. Ranges of sizes for variants related to epilepsy: from single base pairs to chromosomes

Table 1. Odds ratios for particular epilepsies

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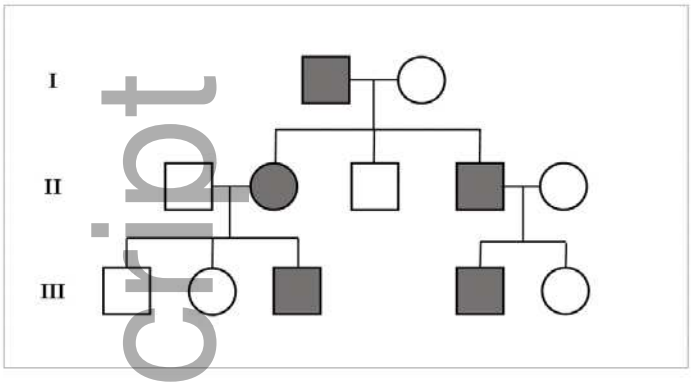
Table 1. Odds ratios for particular epilepsy syndromes[1]

Epilepsy Syndrome	**Cummulative incidence by age 40 (%)**	**Risk for first-degree relatives as Standardized Incidence Ratio (95% CI)**
All epilepsy	4.7	3.3 (2.45–4.32)
Idiopathic, all	7.3	5.5 (3.52–7.93)
Postnatal cause, all	2.7	1.8 (0.66–3.14)
Generalized	2.7	5.0 (3.18–7.45)
Generalized, Idiopathic	7.3	6.0 (3.75–8.93)
Focal	2.9	2.1 (1.27–3.10)
Focal, idiopathic	2.0	2.7 (0.00–6.81)

[1] as listed by Peljto et al., 2014

MCQ test

Q1. A pedigree is shown, where affected members are shaded. Males are represented by squares and females by circles.



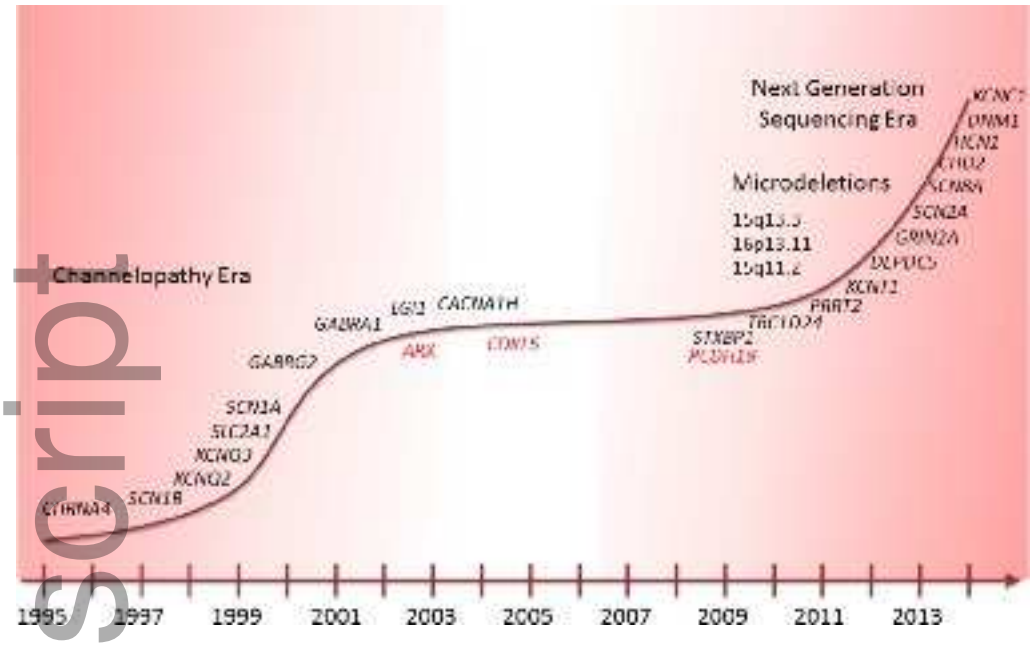
The most likely mode of inheritance is:

A. Autosomal Dominant
B. Autosomal Recessive
C. X-linked Recessive
D. Mitochondrial

Q2. Which of the following statements is FALSE?

A. Microdeletions can increase the risk of epilepsy
B. Genetic risk factors for Mendelian epilepsies have large effect sizes
C. Rare variants are defined as variants seen in <10% of the population
D. Mutations in the same gene can cause a wide range of phenotypes

Test yourself on what you've just read. Try our online MCQs at http://www.geneticliteracy.info/gl-test2a ; answers are provided immediately online.



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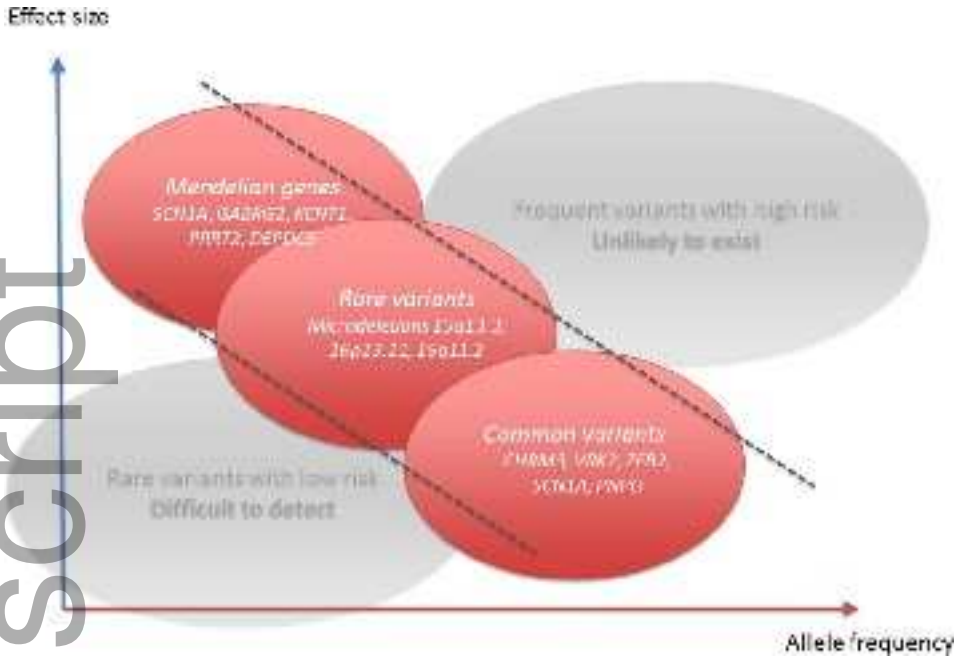

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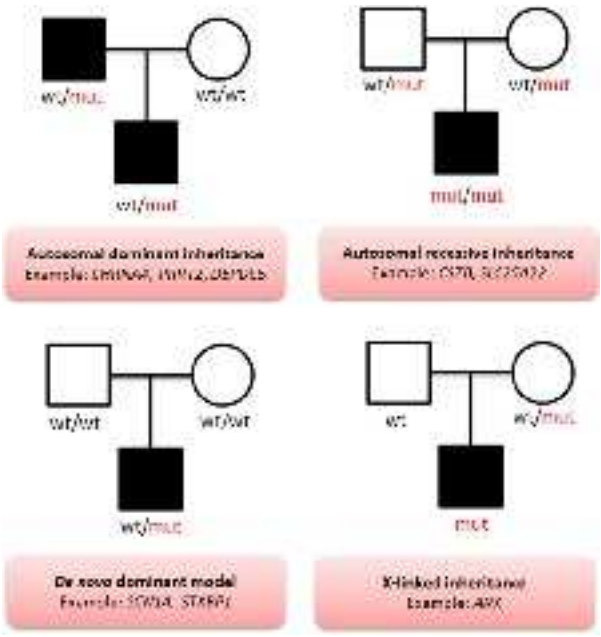

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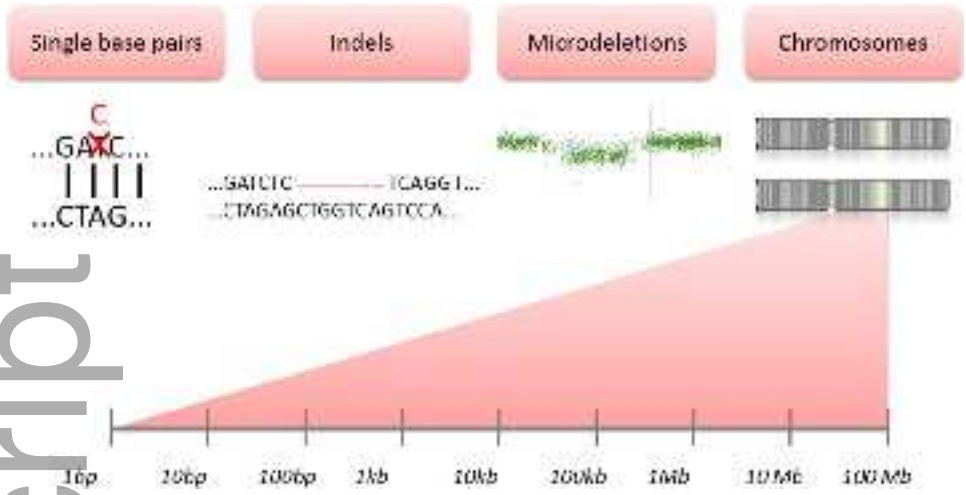

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