Seminars in Pediatric Neurology 51 (2024) 101150

Contents lists available at ScienceDirect

Seminars in Pediatric Neurology

journal homepage: www.elsevier.com/locate/spen

Genetic principles related to neurocutaneous disorders

Leah Ferrante [a,b,*], Chelsey Ortman [a,b]

[a] The University of Texas at Austin, Dell Medical School, Department of Neurology, 1601 Trinity Street, Building B, Austin, TX 78712, USA
[b] Dell Children's Medical Center, 4910 Mueller Blvd. Suite 300 Austin, TX 78723, USA

ARTICLE INFO

Keywords:
Genetics
Neurocutaneous
Pedigree
Mosaicism
DNA
Chromosome
Inheritance

ABSTRACT

A detailed understanding of genetics is critical to the diagnosis, management, and prognostication of neurocutaneous disorders. Inheritance patterns can provide a key to the identification of different neurocutaneous disorders. Autosomal dominant disorders, like neurofibromatosis type 1 and tuberous sclerosis complex, affect males and females equally and are typically seen in every generation of a pedigree due to pathogenic changes to one copy of a gene on a somatic chromosome. Autosomal recessive disorders, such as ataxia-telangiectasia, affect males and females equally but typically skip generations on pedigrees as there needs to be a pathogenic variant of the gene on each of the pair of somatic chromosomes. X-linked disorders such as incontinentia pigmenti and Fabry disease primarily affect males or affect them more severely, but in the case of incontinentia pigmenti, the condition is lethal in males and only females are noted to be affected. The pathogenic variant that is disease causing is on the X sex chromosome, of which females have two and males have one. Somatic mosaic disorders like Sturge Weber syndrome are due to pathogenic variants only in a subset of cells post-fertilization and are not present in gametes, and so are not passed on to the next generation. Conditions that are a result of germline mosaicism are usually identified as autosomal dominant conditions that have not been present in the family prior to a single child being affected, with suspicion strengthening if siblings are diagnosed with the same condition. Regardless of the suspected inheritance pattern, it is essential to consider the ethical implications of genetic testing, including family planning, discovery of consanguinity, disclosure to other potentially affected family members, and diagnostic uncertainty.

Introduction to genetics and neurocutaneous disorders

It is difficult to practice child neurology today without an intimate knowledge of genetics. While neurocutaneous disorders were originally diagnosed clinically with distinct clinical features, with the emergence of genetic testing, single gene variants that account for many of these disorders have been discovered. Neurocutaneous conditions often affect multiple organ systems in addition to the brain and skin, including the kidneys, lungs, spinal cord, retina, and others. The specific disease manifestations may dynamically evolve throughout a person's lifetime, so that at various stages of life, one organ system may be more involved than others. It is essential to understand basic genetics and patterns of inheritance to provide accurate clinical information to patients with neurocutaneous disorders and their families to address multi-system involvement and ensure health throughout the lifespan.

The human genome consists of 20,000-25,000 genes which code for proteins for the human body's functions. Genes are constructed by sequences of deoxyribonucleic acid (DNA) and are compactly stored within structures called chromosomes in the nuclei of cells. Humans typically have 22 pairs of somatic chromosomes and 2 sex chromosomes, totaling 46 total chromosomes. One chromosome of every pair comes from each parent. Each pair of chromosomes have genes arranged in the same order, though each gene may be slightly different among the population and is called a variant.[1,2,3]

There is a myriad of different variant types. The smallest variant includes a change in a single nucleotide and is called a single nucleotide polymorphism (SNP). Insertions and deletions are short nucleotide sequences either added or missing from a gene sequence. Copy number variants (CNV) are insertions and deletions that involve larger sequences of DNA (>50 nucleotides). Tandem repeats involve a few nucleotides in a sequence that repeat multiple times in a row. This category would include trinucleotide repeat disorders, in which a sequence of three nucleotides is repeated multiple times.[4]

Variants can alter the function of the final protein encoded by a gene. Variants that account for the diversity of the human genome are called alleles. Pathogenic variants (historically referred to as "mutations") are

* Corresponding author at: Dell Children's Medical Center, 4910 Mueller Blvd. Suite 300, Austin, TX 78723, USA.
E-mail addresses: leah.ferrante@austin.utexas.edu (L. Ferrante), chelsey.ortman@austin.utexas.edu (C. Ortman).

https://doi.org/10.1016/j.spen.2024.101150
Received 9 August 2024; Received in revised form 2 September 2024; Accepted 3 September 2024
Available online 4 September 2024

alterations in genes that cause disease or increase risk for developing disease. While genetic variants are commonly thought to be inherited from either or both parents, *de novo,* or new, variants may spontaneously arise from the egg or sperm, during early embryogenesis, or in a particular cell population further into embryo development. *De novo* variants explain genetic conditions arising in an offspring without previous family members being affected.

With the inheritance of genetic material, one can create a diagram of a family to determine where a genetic change may have arisen, who is affected by a disease, who may be a carrier of the genetic variant, who may yet be affected by a disease, and the likelihood of a specific gene being the cause of the disease. This diagram, called a pedigree, is drawn using standardized symbols and nomenclature as set by the National Society of Genetic Counselors.[5] Herein, we will discuss the basics of genetic testing and inheritance patterns when there is a suspicion of a neurocutaneous disorder.

Genetic testing

Depending on the differential diagnosis and symptoms of concern, there are multiple genetic testing options to consider. If the clinician has a high suspicion for a specific disorder, single gene testing can be sent which tests for sequence variants and copy number variants (insertions, deletions or duplications of portions of genetic material) in that single gene. Limited gene panels exist which test a few genes that may have very similar phenotypes, essentially testing for a differential diagnosis list of possible disorders. These panels also test for copy number variants or sequence variants. Broader genetic testing can be done including a chromosomal microarray (CMA), which analyzes the entire genome for copy number variants, but importantly, does not sequence the genome.[6] Whole exome sequencing (WES) involves identifying sequence variants of exons, or coding regions of DNA, throughout the whole genome, but not copy number variants. Whole genome sequencing (WGS) can identify pathogenic sequence variants throughout the genome and copy number variants in not just the exon regions of DNA, but also in the non-coding regions of DNA, called introns.

Autosomal Dominant

An autosomal dominant inheritance pattern occurs when a pathogenic variant involving only one of the genes on one of the 22 pairs of somatic chromosomes is sufficient to cause disease, also known as a heterozygous condition. This inheritance pattern is strongly suspected when at least one family member per generation is affected, often with equal distribution among males and females (Fig. 1). Regardless of whether the variant was inherited from a parent or acquired *de novo*, a parent with an autosomal dominant condition would have a 50% chance of their child experiencing the same condition. Anticipation of the inheritance of these conditions may be guided by prenatal genetic testing including cell-free DNA testing, amniocentesis, and chorionic villus sampling, in addition to pre-implantation genetic testing.

There are numerous neurocutaneous syndromes inherited in an autosomal dominant manner. These include Von Hippel-Lindau syndrome, tuberous sclerosis complex, and neurofibromatosis types 1 and 2.

Neurofibromatosis type 1 is associated with germline variants in the *NF1* gene, a gene with one of the highest variation rates in the human genome. An estimated 50% of neurofibromatosis type 1 cases is associated with non-inherited, *de novo* variants.[7] The *NF1* gene encodes the protein neurofibromin, a tumor suppressor that downregulates the RAS/MAPK and mTOR signaling pathways. With pathogenic variants in *NF1* there is non-functional or poorly functioning neurofibromin, dysregulated cell proliferation begins. When a patient with a pathogenic variant in *NF1* accumulates a "second hit" somatic (non-germline) pathogenic variant in another tumor suppressor gene, unchecked cell growth increases the chance of tumorigenesis and atypical cell growth. In neurofibromatosis type 1, while all cells have pathogenic variants in *NF1*, "second hit" variants in specific cell types may explain why only a fraction of patients experience certain manifestations of the syndrome. For instance, those with variants in optic nerve glial cells may develop optic nerve gliomas while those with variants in intracranial glial cells may develop gliomas of the cerebral hemispheres[8]

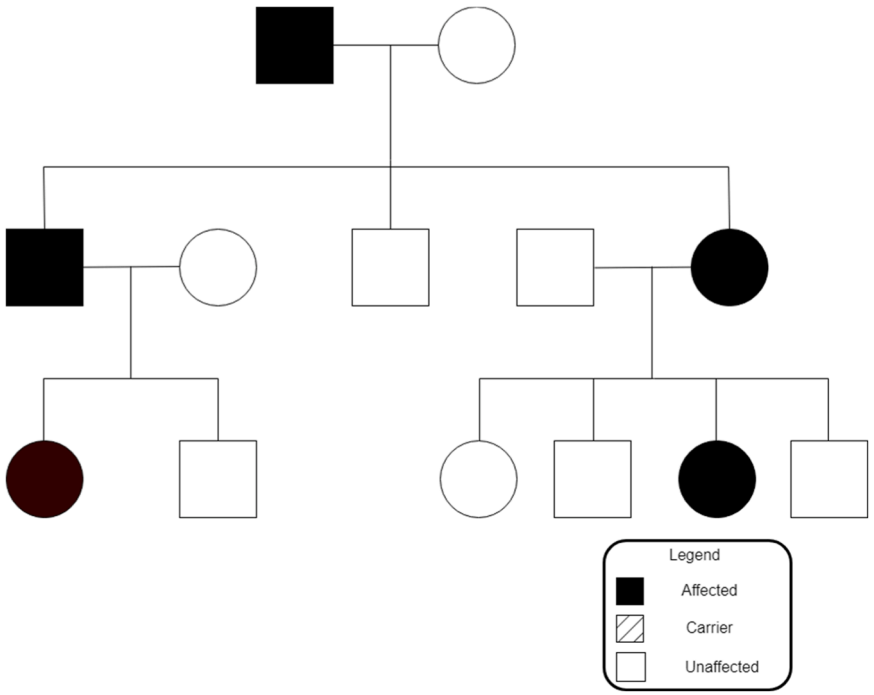

Fig. 1. Autosomal dominant inheritance—Multiple people throughout the 3-generation pedigree are affected. There is a similar ratio of males to females and about half of the family members are affected.

Autosomal Recessive

Autosomal recessive conditions occur when both variants of a gene are pathogenic. These variants can be homozygous, when there are identical variants in each gene, or compound heterozygous, with non-identical variants affecting each of the paired chromosomes. Classically, autosomal recessive conditions occur when one pathogenic variant is inherited from each parent. One or two non-inherited *de novo* variants may also contribute to disease. Individuals with one copy of the variant are known as carriers, and these individuals are unaffected by the disease. There is a 25% chance per offspring to be affected by disease with two carrier parents. Autosomal recessive inherited conditions equally affect males and females (Fig. 2). In some populations throughout the world, a *founder effect* may be seen, where there is less genetic variation within a group of individuals, contributing to a higher frequency of certain autosomal recessive conditions. A founder effect can be seen in the Romani population for the autosomal recessive condition ataxia telangiectasia.[9] Autosomal recessive conditions are much more common in offspring of consanguineous parents due to less genetic variation in the common gene pool between the parents.[10]

Ataxia telangiectasia (A-T) is an autosomal recessive condition involving biallelic pathogenic variants in the *ATM* gene. The *ATM* gene encodes the ATM protein, which performs essential functions involving double-stranded DNA repair and response to oxidative stress. There is a variable spectrum of phenotypes of this condition. The classic or severe form of A-T is associated with cerebellar and extrapyramidal progressive degeneration with ataxia as a prominent early feature, sensorimotor neuropathy, an elevated risk of cancer, immunodeficiency, and multifactorial pulmonary disease. A mild form of A-T is associated with dystonia, tremor, and neuropathy in addition to heightened cancer risk, typically without pulmonary or immunologic deficiencies. Patients with A-T may have cutaneous and ocular telangiectasias, but these are inconsistently present. While A-T does not occur in individuals with only one pathogenic allele in the *ATM* gene, these patients are still at greater risk of developing many types of cancer when compared to the general population. Women with a heterozygous variant in the *ATM* gene are more vulnerable to the development of breast cancer. Testing of at-risk family members and pre-implantation genetic testing are commonly considered in this patient population.[11,12,13]

X-linked

While autosomal dominant and recessive conditions are inherited on the 22 somatic chromosomes, X-linked dominant conditions are inherited through the X sex chromosome. In general, these conditions are much more likely to affect males than females, because males have only one copy of the X chromosome, whereas females have two.

Females may be unaffected carriers of X-linked conditions or may experience a modest degree of disease. This is due to variable patterns of X chromosome inactivation in females. While females have two X chromosomes, the expression of half of all X chromosomal genetic information in females is silenced through a process known as X chromosome inactivation or lyonization. In some females, the X-inactivation pattern may prevent expression of the disease-associated variant entirely. In other females the X-inactivation pattern may not silence the expression of a disease-associated variant at all, resulting in disease. Regardless of the X-inactivation pattern of a mother with an X-linked dominant genetic variant, the male offspring of a female with an X-linked dominant genetic variant have a 50% chance of inheriting the disease (Fig. 3). The female offspring of mothers with an X-linked dominant genetic variant have a 50% chance of inheriting the genetic variant but based on their pattern of X-inactivation they may be asymptomatic carriers or experience some degree of disease.[14]

Incontinentia Pigmenti is a condition characterized by rash-like lesions at birth that evolve over time, seizures, neurovascular abnormalities and eye, hair and nail defects. It is inherited via an X-linked dominant pattern. It is almost exclusively seen in females—it is lethal to XY males in utero. It has been reported in males with a XXY sex chromosome configuration (Klinefelter syndrome) and in a few XY males with mosaicism or with hypomorphic pathogenic variants—variants that do not result in full loss of function of a protein. Mosaicism will be further explained in the next section.

Fabry disease is a disease that is a lipid storage disorder and is inherited in an X-linked recessive manner.[15] Theoretically, X-linked

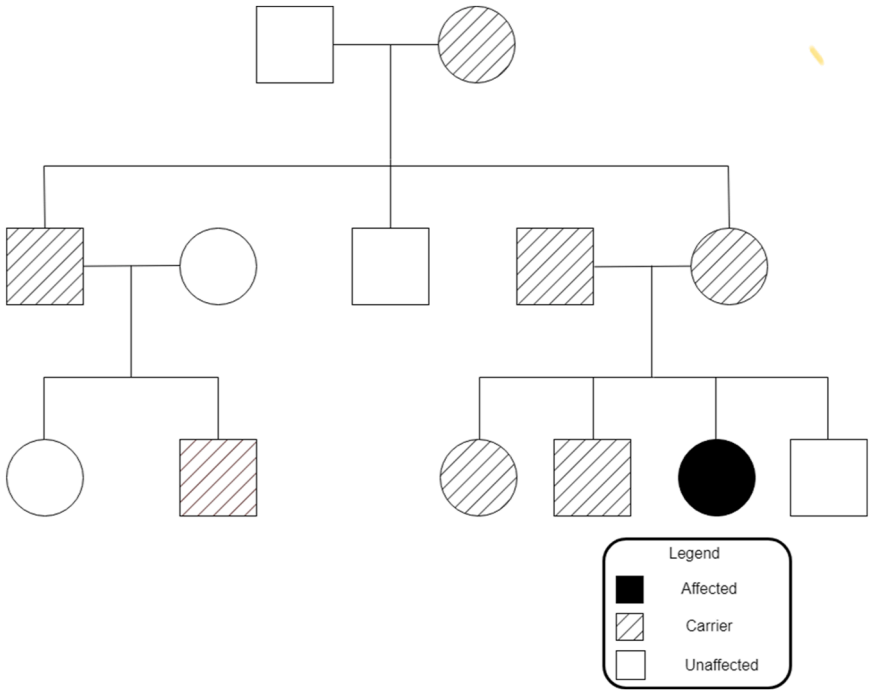

Fig. 2. Autosomal recessive inheritance—Fewer family members are overall affected by the autosomal recessive condition, but more family members carry a pathogenic variant and may pass it on to future prodigy.

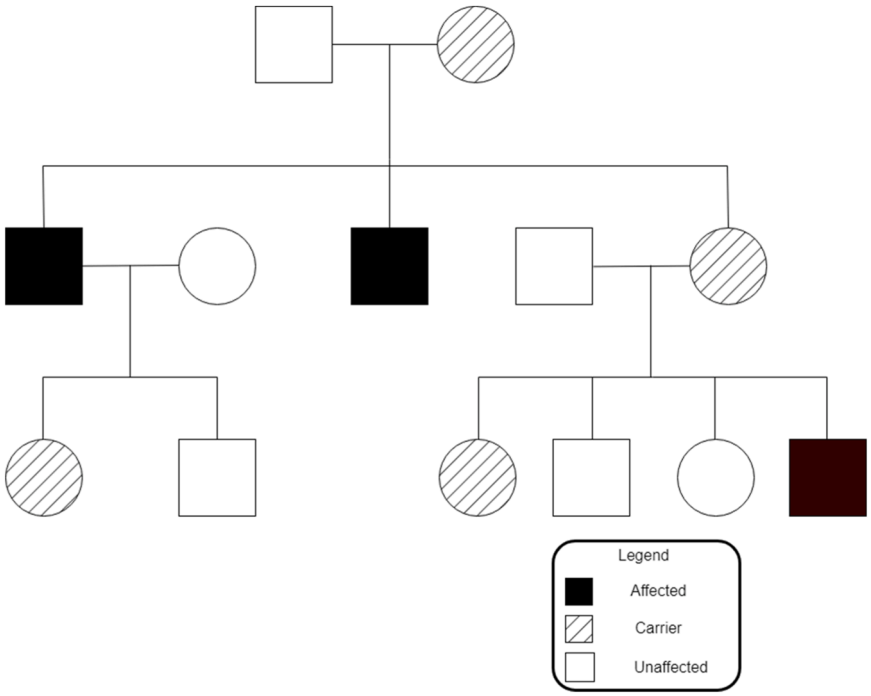

Fig. 3. X-linked inheritance—Only males are affected by X-linked conditions in this pedigree while females can be carriers of X-linked conditions.

recessive disorders primarily affect males, as they only have one copy of the pathogenic variant on their only X chromosome. Fabry disease, which can cause early strokes, renal disease, and skin lesions called angiokeratomas, has high penetrance. Penetrance measures the proportion of patients with a certain genotype that expresses a phenotype associated with disease. Therefore, in Fabry disease, females with a single pathogenic variant can still demonstrate signs and symptoms of disease, though usually to a lesser degree. This differs from expressivity, which examines how individual patients are phenotypically affected by the same genotype.[16]

Somatic Mosaicism

When a variant occurs in the ectodermal layer at the beginning of embryogenesis in a subset of cells, a somatic mosaic neurocutaneous condition may occur. In these conditions, a fraction of the cells in the nervous system and skin harbor a pathogenic variant and is sufficient to cause disease. Genetic testing that utilizes blood samples is insufficient to identify disease-causing variants in somatic mosaic neurocutaneous conditions, although biopsy of affected tissue may yield a genetic etiology. Somatic variants are not passed down from generation to generation, appearing *de novo* in affected patients.

Sturge Weber syndrome (SWS) is an example of a somatic mosaic condition. Individuals with Sturge Weber syndrome typically have a somatic pathogenic variant in the *GNAQ* gene. The most common dermatologic manifestation of SWS is a port-wine stain over the unilateral upper face. Glaucoma may be seen, especially if the port wine stain extends over the eye. Neurologically, SWS affects a portion of the blood vessels and cortex of the brain. There is abnormal growth of leptomeningeal vessels known as leptomeningeal angiomatosis. The cortex associated with the region of leptomeningeal angiomatosis often has a dysplastic appearance with epileptogenic potential. Patients with SWS may experience multiple seizure types arising from the affected tissue, including infantile spasms and focal seizures.[17]

Germline Mosaicism

Germline mosaicism is a condition in which pathogenic variants are present only in egg or sperm cells in an otherwise unaffected person. Since the disease-causing variant is not present in cells in the rest of the body, the individual will not have the disease but may have offspring that develop the condition. The offspring that have the condition would not be mosaic, and both somatic and germline cells would be affected. This may appear to be a *de novo* variant in the offspring. Inheritance is a key difference between germline and somatic mosaicism. Germline mosaicism is usually suspected when a child has a variant or variants, but neither parent is affected. That suspicion increases if there are multiple offspring or affected siblings with the variant and no other family history of its presence. However, the only way to confirm germline mosaicism is to do genetic testing on both parents' gametes.

Ethical and economic considerations

The ethical and economic challenges of genetic testing are also essential to discuss with families as part of the informed consent process. WGS and WES may be cost-prohibitive in some cases, despite the higher diagnostic yield. WES and WGS are more likely to discover variants unrelated to the condition of concern at the time of testing. Some variants found on WES or WGS may be associated with adult-onset disease, including life-limiting conditions that would only manifest in adulthood.[18] Consanguinity can also be incidentally discovered with CMA, WES, WGS, and gene panel testing. Most forms of genetic testing may reveal findings of uncertain significance, which may lead to more diagnostic uncertainty and stress for families. Genetic testing may also reveal findings relevant to a patient's relatives and future offspring. Considering when to disclose a variant of concern to other family members may pose a difficult dilemma. It is important to thoroughly consider the potential implications of any testing ordered and to be prepared to address unexpected results with families when they arise.

Conclusion

Genetics is an integral part of neurocutaneous disorder identification and management, as it can help elaborate a list of possible diagnoses, lead to more precise investigations, and assist with counseling families about likelihood of additional members being affected by a condition. In

this rapidly evolving medical landscape where new genes are regularly discovered, professionals who interact with patients with suspected neurocutaneous disorders should have a working understanding of these basic principles to provide the best care.

CRediT authorship contribution statement

Leah Ferrante: Writing – review & editing, Writing – original draft, Data curation. **Chelsey Ortman:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors are Guest Editors for Seminars in Pediatric Neurology and were not involved in the editorial review or the decision to publish this article.

References

1. Dies KA, Sahin M. *Genetics of Neurocutaneous disorders: basic principles of inheritance as they apply to neurocutaneous syndromes*. Islam MP, Roach ES. *Handbook of Clinical Neurology: Neurocutaneous Syndromes*. Elsevier; 2015:3–8.
2. Jentarra G, Snyder SL, Narayanan V. Genetic Aspects of Neurocutaneous Disorders. *Semin Pediatr Neurol*. 2006;13:43–47. https://doi.org/10.1016/j.spen.2006.01.010.
3. Legius E. Genetics of neurocutaneous syndromes. In: Panteliadis CP, Benjamin R, Hagel C, eds. *Neurocutaneous Disorders: A Clinical, Diagnostic and Therapeutic Approach Third Edition*. Springer; 2022:3–16.
4. National Human Genome Research Institute. Human genomic variation fact sheet, https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genomic-variation; 2023 [accessed 2 September 2024].
5. Bennett RL, Steinhaus French K, Resta RG, et al. Standardized Human Pedigree Nomenclature: Update and Assessment of the Recommendations of the National Society of Genetic Counselors. *J Genet Counsel*. 2008;17:424–433. https://doi.org/10.1007/s10897-008-9169-9.
6. Miller DT, Adam MP, Aradhya S, et al. Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies. *Am J Hum Genet*. 2010;86(5):749–764. https://doi.org/10.1016/j.ajhg.2010.04.006.
7. Wilson BN, John AM, Handler MZ, et al. Neurofibromatosis type 1: New developments in genetics and treatment. *J Am Acad Dermatol*. 2021 Jun;84(6):1667–1676.
8. Friedman JM. *Neurofibromatosis*. 1998 Oct 2;1 [Updated 2022 Apr 21]In: Adam MP, Feldman J, et al. editors. GeneReviews® [Internet]. Seattle (WA).
9. Wallace SE. *Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Romani Population*. Seattle (WA): University of Washington, Seattle; 1993-2024; 2022 Aug 11. In: Adam MP, Feldman J, et al. editors. GeneReviews® [Internet].
10. Olubunmi O, Neves K, Badreldeen A, et al. A review of the reproductive consequences of consanguinity. *Eur J Obstet Gynecol Reprod Biol*. 2018 Oct; 232:87–96. https://doi.org/10.1016/j.ejogrb.2018.10.042.
11. Crawford TO. Ataxia telangiectasia. *Semin Pediatr Neurol*. 1998 Dec;5(4):287–294.
12. Veenhuis S, van Os N, Weemaes C, et al. Ataxia-Telangiectasia. 1999 Mar 19 [Updated 2023 Oct 5]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
13. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, et al. Ataxia telangiectasia: a review. *Orphanet J Rare Dis*. 2016 Nov 25;11(1):159.
14. Dobyns W. The pattern of inheritance of X-linked traits is not dominant or recessive, just X-linked. *Acta Paediatr Suppl*. 2006;95(451):11–15. https://doi.org/10.1080/08035320600618759.
15. *Handbook of Clinical Neurology: Neurocutaneous Syndromes*. Schiffmann, R. Fabry Disease. In: Islam MP, Roach ES, editors. Elsevier; 2015:231–248.
16. Lobo I. Same Genetic Mutation, Different Genetic Disease Phenotype. *Nat Educ*. 2008;1(1):64.
17. Comi A, Sturge-Weber Syndrome. *Handbook of Clinical Neurology: Neurocutaneous Syndromes*. Islam MP, Roach ES, editors. Elsevier; 2015:157–168.
18. Stavropoulos DJ, Merico D, Jobling R, et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. *NPJ Genom Med*. 2016:15012. https://doi.org/10.1038/npjgenmed.2015.12.