COURSE 14: THE GENETICS OF VASCULAR ANOMALIES

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Introduction: The genetics of vascular anomalies

The module starts with a review of genetic terminology and principles as they relate to vascular abnormalities. With the guidance of the recent classification of vascular abnormalities and their entries in the Online Mendelian Inheritance in Man, the module defines the phenotypes that are associated with known genotypes or are hereditary due to unknown genes.
Vascular abnormalities can be isolated or part of a presentation of a syndrome.
Most isolated abnormalities are sporadic due to somatic mosaic mutation to a single gene. Usually, these mutations do not have a germline phenotype. PTEN is an examble of a gene associated with both isolated vascular malformations and with syndromes both hereditary and sporadic. Because of the absence of germline phenotype of the genes associated with isolated vascular malformations (VM), isolated VMs are sporadic and non-hereditary. However, syndromes with vascular malformation can be either sporadic or hereditary.
The photo of the twins reminds us that even sporadic vascular malformations can be hereditary due to either monozygosity or germline mosaicism.

Objectives

Upon successful completion of this activity, participants should be able to:

- Recognize common genetic syndromes with vascular anomalies
- Identify genetic etiologies of isolated vascular abnormalities
- Describe known genotype-phenotype correlations
- Define properties of genetic disorders (i.e. variability of expression, genetic heterogeneity) as they relate to vascular anomalies
- List vascular anomalies that are usually hereditary versus sporadic
- Classify vascular anomalies by genotype and phenotype

Mutation

Mutation is a documented pathogenic variation of the DNA sequence. Many variants reported by genetic tests are of unknown clinical significance.

De novo (new) mutations can happen:

- In the germline: the sperm (more frequently) or the ovum
- In a somatic cell

Germline mutations exist in every cell of the patient, while somatic mutations exist only in the vascular anomaly. Vascular anomalies due to a germline mutation usually harbor a somatic mutation (second hit) in the opposite allele of the germline mutation.

Inheritance

Isolated (non-syndromic) vascular anomalies are usually sporadic (non-hereditary) due to a somatic mutation. Syndromic vascular anomalies can be:

- Sporadic, due to a de novo germline mutation or
- Hereditary, due to inherited mutation or mutations from the parents

Most vascular anomalies are isolated.
Predisposition to isolated vascular anomalies can be due to inherited mutations or genetic variants. Most syndromes with vascular anomalies have known genetic etiology.

Do not expect Mendelian inheritance

The patterns of Mendelian inheritance are very rarely seen in families with vascular anomalies because:

- Somatic mutations are common
- *De novo* germline mutations are common
- Predisposition genetic variants are common; these variants (or high-risk alleles) increase risk for vascular anomaly but do not directly cause it

Mendelian inheritance can be seen in syndromes with vascular anomalies. These syndromes are rare. The association of a single gene with a vascular anomaly does not mean that the anomaly is hereditary.

The notation of a gene is capital letters and numbers in italics: i.e. *RASA1*. If no italics are used, the notation refers to a protein.

Why do we analyze the genetics of vascular anomalies?

Reassure the families of sporadic occurrence in the majority of cases with isolated vascular anomalies; recurrence risk only slightly above the general population because of:

- Presence of predisposing genetic variants in the family
- Possible germline mosaicism (i.e. presence of the mutation in a percentage of sperm)

Genetic counseling regarding inherited syndromes should be made available to patients and their families.

Identification of the gene points to pathogenesis (altered developmental pathways) and emerging clinical trials of specific medications.

Sporadic vascular anomalies : Vascular tumors

Hemangioma

- Rapid, aberrant, and localized proliferation of capillary endothelium with subsequent involution
- Benign tumor of infancy
- Predisposition: susceptibility conferred by germline mutations in the *TEM8* or the *VEGFR2* gene
- Somatic mutations: *VEGFR2*, *VEGFR3*, and *DUSP5* genes
- A few families with autosomal dominant inheritance were described in the medical literature

Sporadic vascular anomalies: Vascular tumors

- Kaposi sarcoma: invasive angioproliferative inflammatory condition that occurs commonly in men infected with human immunodeficiency virus (HIV).
- Locally aggressive tumor due to HHV-8 infection.
- Polymorphic locus in chromosome 3p22 confers predisposition to HHV-8 infection.
- Rarely seen in children with inherited immunodeficiency.
- It is an example of multifactorial disease: Polymorphism in 3p22 + immunodeficiency+ HHV-8 infection.

Sporadic vascular anomalies

Capillary malformations

- Port-wine stain
- Sturge–Weber Syndrome
- Macrocephaly-Capillary Malformation Syndrome

Venous malformations

- Isolated venous malformation
- Blue rubber bleb nevus syndrome

Arteriovenous malformations

- Isolated arteriovenous malformation (AVM)

Sporadic vascular malformations

Port Wine Stain

- Present from birth
- Grows with the individual
- Does not regress spontaneously
- Shows normal rates of endothelial cell turnover
- Somatic gain of function mutations in *GNAQ*
- Van der Horst et al. (1999): 280 new patients with port-wine stains; 55 (19.6%) had relatives with the same anomaly
- Likely autosomal dominant inheritance with reduced penetrance in a few families

Sturge–Weber Syndrome

- Macrocephaly, facial vascular malformations (vms, port wine stain), choroidal vms, glaucoma, buphthalmos, vms in at least first branch (ophthalmic) of trigeminal nerve distribution, unilateral, occasionally bilateral, arachnoid vms, cerebral cortical atrophy, mental retardation, seizures, “double contour” convolutional calcification on CT scan
- Caused by somatic mosaic mutation in the guanine nucleotide-binding protein q gene (*GNAQ*)

More sporadic vascular malformations

Macrocephaly-Capillary Malformation Syndrome

- Somatic overgrowth, hemihyperplasia
- Megalencephaly, macrocephaly progressive in infancy
- Thick, loose, doughy skin
- Cutaneous capillary malformations
- Patchy reticular stains, cutis marmorata
- Intellectual disability, hypotonia, seizures
- MRI shows brain asymmetry, ventriculomegaly, cerebellar tonsil herniation, polymicrogyria, thickened corpus callosum, and cortical and white matter abnormalities
- Caused by somatic mosaic mutation in the phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (*PIK3CA*)

Isolated venous malformation

- The endothelial cell-specific receptor tyrosine kinase *TIE2* or *TEK* causes isolated venous malformation by somatic mosaic mutation
- Frequently the L914F substitution (leu914 to phe) is found in sporadic isolated venous malformations
- L914F is a gain of function mutation resulting in ligand-independent *TIE2* hyperphosphorylation In Vitro

Even more sporadic vascular malformations

Blue rubber bleb nevus syndrome

- Rare venous malformation disorder; cutaneous and visceral blue-colored and easily compressible macules frequently associated with serious, potentially fatal bleeding and anemia
- Skin, CNS, lung, liver and gastrointestinal tract are affected with risk of bleeding, anemia, and chronic consumption coagulopathy
- Bone involvement with coarsened trabeculae, cortical remodeling, limb hyper- or hypotrophy, and risk for pathological fractures
- *TIE2* or *TEK* also cause blue rubber bleb nevus syndrome by somatic mosaic gain of function mutation

Isolated arteriovenous malformation (AVM)

- AVMs occur when arteries connect directly to veins bypassing the capillary bed, and can be cutaneous and visceral
- Spontaneous bleeding can occur
- Increased risk for intracranial hemorrhage of a brain arteriovenous malformation (BAVM) is associated with a promoter polymorphism in the IL6 gene [Pawlikowska et al. (2004)].
- AVMs are likely due to somatic mutations in unknown genes

Hereditary syndromes presenting with different types of vascular anomalies

- CLOVES: congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies
- Klippel–Trenaunay Syndrome
- Proteus Syndrome
- *PTEN* hamartoma tumor syndrome (PHTS)

CLOVES

- Prenatal overgrowth, hemihypertrophy
- Vascular (arteriovenous) malformation, progressive, with cutaneous involvement, capillary malformation, lymphatic malformation usually low-flow, low-flow venous malformation, high-flow perispinal vascular malformations
- Splenomegaly, renal agenesis, or hypoplasia, cysts in spleen, testes
- Hyperostosis of the skull, megaspondylodysplasia, scoliosis
- Large and wide hands and feet with palmar and plantar overgrowth and furrowed soles
- Lipomas with occasional regional lipohypoplasia
- Sporadic, due to somatic mosaic mutation in the phosphatidylinositol 3-kinase, catalytic, alpha polypeptide gene (*PIK3CA*)

Klippel–Trenaunay Syndrome

- Asymmetric limb hypertrophy, macrodactyly, syndactyly, polydactyly, oligodactyly
- Large cutaneous hemangiomata, capillary and cavernous , arteriovenous fistula , lymphedema, lymphangioma, hyperpigmented nevi and streak
- Occasional: glaucoma, mental retardation, seizures, Kasabach-Merritt Syndrome
- Sporadic, unknown gene or genes

PTEN hamartoma tumor Syndrome

Associated phenotypes:

- Cowden Syndrome (CS)
- Bannayan-Riley-Ruvalcaba Syndrome (BRRS)
- PTEN-related Proteus Syndrome (PS)
- Similar to Proteus due to *AKT1* discussed in the previous slides

Proteus-like syndrome:

- Significant clinical features of PS that do not meet the diagnostic criteria for Proteus Syndrome

Cowden Syndrome (CS)

- High risk for benign and malignant tumors of the thyroid (usually follicular, rarely papillary, but never medullary thyroid cancer), breast (85% lifetime risk), and endometrium
- Macrocephaly, dolichocephaly, occassinal mild-to-moderate intellectual disability, autism
- Trichilemmomas, papillomatous papules, acral and plantar keratoses, all appearing in the second and third decade of life
- Autosomal dominant due to mostly sequence variants but also deletions in *PTEN* and its promoter

Bannayan-Riley-Ruvalcaba Syndrome

- Macrocephaly, frontal bossing
- Hamartomatous intestinal polyposis, lipomas, and pigmented macules of the glans penis
- High birth weight
- Hypotonia, gross motor delay, speech delay, mild-to-severe intellectual disability, autism, seizures, thick corpus callosum
- Thyroid follicular cell tumor, meningioma
- Mostly sequence variants but also deletions in *PTEN*.

Proteus Syndrome

- Onset in infancy with variable and progressive worsening of hemihypertrophy with generalized, unilateral, or localized disproportionate overgrowth of any tissue
- Cerebriform connective tissue nevus, lymphangioma, lipoma, lipohypoplasia, epidermal nevi , hypertrophy of skin of soles, skin depigmentation/hyperpigmentation, vascular malformations especially on thorax and upper abdomen
- Macrocephaly, hyperostoses of calvaria, facial bones, and mandible, dolichocephaly, long face, downslanting palpebral fissures, ptosis, epibulbar dermoids, low nasal bridge, wide or anteverted nostrils, open mouth appearance
- Capillary malformations, venous malformations, lymphatic malformations, deep vein thrombosis
- Overgrown long bones, thin cortices, megaspondylodysplasia, kyphoscoliosis, spinal stenosis from angular kyphoscoliosis
- Brain malformations, spinal cord compression by tumor infiltration; some patients with mild or moderate intellectual disability
- Lung cysts, splenomegaly, ovarian cystadenoma, parotid monomorphic adenoma
- Sporadic, caused by somatic mutation in the V-AKT murine thymoma viral oncogene homolog 1 gene (*AKT1*)

Proteus Syndrome clinical diagnostic criteria

All the following general criteria:

- Mosaic distribution of lesions
- Sporadic occurrence
- Progressive course
- Specific criteria from categories A-C:
  (either one from category A or two from category B or three from category C)

Category A

- Cerebriform connective tissue nevus (skin lesions characterized by deep grooves and gyrations as seen on the surface of the brain)

Category B

- Linear epidermal nevus
- Asymmetric, disproportionate overgrowth (should be carefully distinguished from asymmetric, proportionate, or ballooning overgrowth) of at least one of the following:
  - Limbs
  - Hyperostosis of the skull
  - Hyperostosis of the external auditory canal
  - Megaspondylodysplasia
  - Viscera: spleen/thymus

Specific tumors before second decade:

- Bilateral ovarian cystadenoma
- Parotid monomorphic adenoma

Category C

Dysregulated adipose tissue (either of the following):

- Lipomatous overgrowth
- Regional lipohypoplasia
- Vascular malformations (capillary, venous, lymphatic)
- Lung bullae

Facial phenotype (all of the following):

- Dolichocephaly
- Long face
- Down-slanting palpebral fissures and/or minor ptosis

Hereditary vascular anomalies

Vascular malformations

Hereditary capillary malformations:

- Capillary malformation–arteriovenous malformation (CM-AVM)
- Parkes Weber Syndrome
- Macrocephaly-Capillary Malformation Syndrome

Hereditary venous malformations:

- Cutaneomucosal venous malformation (VMCM)
- Glomuvenous malformation (GVM)

Hereditary arteriovenous malformations:

- Hereditary hemorrhagic telangiectasia (HHT)
- Hereditary lymphatic malformations

Syndromes with lymphatic malformations

- Primary congenital lymphedema 1A (Nonne–Milroy disease)
- Nonne–Milroy-like disease (hereditary lymphedema 1D)
- Hereditary lymphedema II (Meige disease)
- Primary lymphedema-myelodysplasia (Emberger Syndrome)
- Choanal atresia-lymphedema
- Lymphedema–Distichiasis Syndrome
- Hypotrichosis–Lymphedema–Telangiectasia (HLT) Syndrome
- Hennekam Syndrome

Syndromes with lymphatic malformations not as a cardinal feature

Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR)

- Autosomal dominant caused by heterozygous mutation in the *KIF11* gene

X-linked syndrome anhydrotic ectodermal dysplasia with immunodeficiency, osteopetrosis, and lymphedema (OLEDAID)

- X-linked male only phenotype allelic to incontinentia pigmenti in females caused by heterozygous mutation in the *NEMO* gene

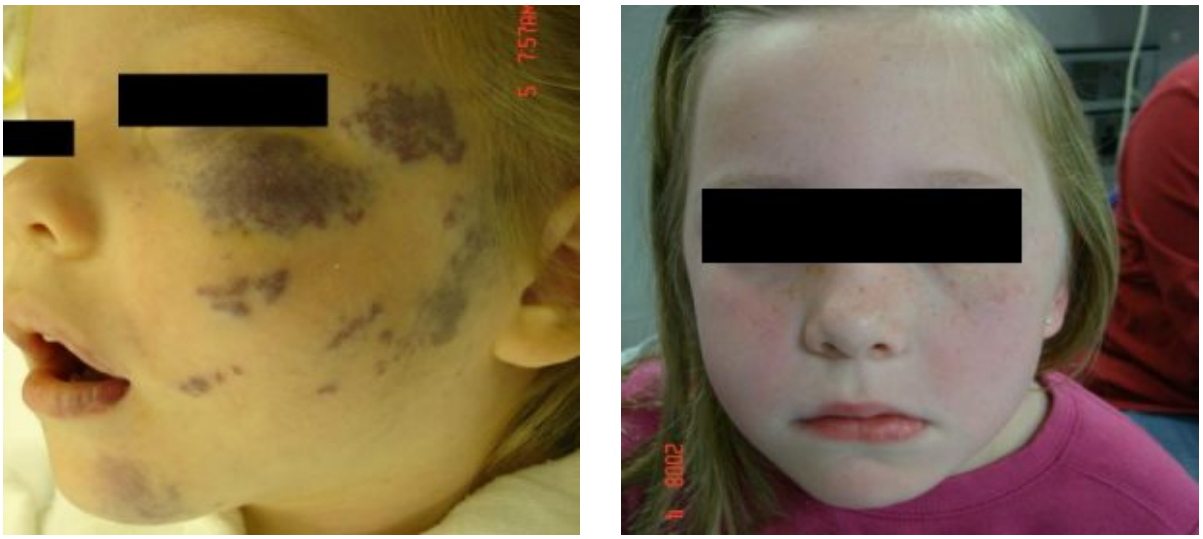
Oculo-dento-digital dysplasia-lymphedema

- Autosomal dominant caused by heterozygous mutation in the connexin-43 gene (*GJA1*)

Hereditary syndromes with many types of vascular anomalies

- CLOVES – congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies
- Klippel–Trenaunay Syndrome
- Proteus Syndrome
- PTEN hamartoma tumor syndromes (PHTS):
  - Bannayan Riley Ruvalcaba
  - Syndrome Cowden Syndrome

Glomuvenous malformation



Glomuvenous malformation before and after Nd:YAG laser treatment

Hereditary vascular anomalies and related syndromes

Capillary malformation–arteriovenous malformation

- Multiple nevi flammei
- Port-wine stain
- Arteriovenus malformation
- Loss of function mutation in the *RASA1* gene in some families
- Autosomal dominant inheritance in some families
- Most commonly sporadic

Parkes Weber Syndrome

- Cutaneous flush with underlying multiple micro-arteriovenous fistulas in association with soft tissue and skeletal hypertrophy of the affected limb
- Loss of function mutation in the *RASA1* gene with a second loss of function hit in the tissue
- Autosomal dominant inheritance has been reported in the medical litarature

Cutaneomucosal venous malformation

- Cutaneous and mucosal multifocal and small venous malformations
- Grossly dilated vascular spaces lined by a single continuous layer of endothelial cells with areas of relative lack of surrounding mural cells
- Mucosal bleeding, gastrointestinal bleeding
- Maxillary and mandibular deformity and other internal organ abnormalities including cardiac
- Autosomal dominant due to mutation in the *TEK* (*TIE2*) gene which encodes the epithelial-specific tyrosine kinase receptor

Hereditary lymphatic anomalies and related syndromes

Nonne–Milroy disease (hereditary lymphedema 1A)

- Lymphedema, predominantly in the lower limbs; lymphography shows hypoplasia of lymphatic vessels
- Hyperkeratosis and papillomatosis over edematous areas
- Upturned toenails
- Other vascular malformations
- Onset usually at birth
- Autosomal dominant caused by mutation in the FMS-like tyrosine kinase-4 gene (*FLT4*)

Hereditary lymphedema 1D

- Lymphedema, prominent veins lower limb
- Lymphoscintigraphy shows impaired lymphatic uptake and drainage
- Tortuous lymphatic tracts with evidence of lymphatic re-routing
- Hyperkeratosis, papillomatosis, fibrosis, cellulitis over affected area
- Deep skin creases in toes with upslanting, dysplastic toenails
- Onset usually at birth
- Autosomal dominant caused by mutation in the vascular endothelial growth factor C gene (*VEGFC*)

Hereditary lymphedema type 2 (Meige Syndrome)

- Lymphedema, severe and predominantly in the lower limbs with onset around puberty
- Paucity or absence of lymph nodes in the axillae and above the inguinal ligaments seen on scintilymphangiography
- Not constant features: facial swelling, cleft palate, yellow nails
- Autosomal dominant, unknown gene

Primary lymphedema with myelodysplasia (Emberger Syndrome)

- Lymphedema of the lower extremities and genitalia
- Recurrent cellulitis and warts
- Pancytopenia, myelodysplasia, bone marrow monosomy 7
- Congenital sensorineural deafness
- Hypotelorism, epicanthic folds, and webbed neck
- Long, tapering fingers
- Autosomal dominant caused by mutation in the GATA-binding protein-2 gene (*GATA2*)

Choanal atresia and lymphedema

- Lymphedema, lower extremities
- Pericardial effusion
- High-arched palate
- Choanal atresia
- Onset of lymphedema in childhood
- Autosomal recessive caused by mutation in the protein-tyrosine phosphatase, nonreceptor-type, 14 gene (*PTPN14*) in one family in the medical literature

Lymphedema-Distichiasis Syndrome

- Accessory eyelashes, districhiasis, corneal irritation/ulceration, conjunctivitis, styes, ptosis
- Lymphedema, predominantly in the lower limbs with onset in puberty and earlier in males
- Congenital heart defects
- Cleft lip/palate
- Renal disease and type II diabetes mellitus in some families
- Autosomal dominant caused by mutation in the forkhead box C2 gene (*FOXC2*)
- Allelic disorders with overlapping phenotypes include hereditary lymphedema type II, lymphedema and ptosis, and yellow nail and lymphedema syndrome

Hypotrichosis-Lymphedema-Telangiectasia Syndrome

- Absent eyebrows and eyelashes
- Eyelid edema at birth
- Hypotrichosis
- Telangiectases (palms, soles, scalp, scrotum, legs)
- Thin, transparent skin (hands and feet)
- Lower limb lymphedema occurs in childhood
- Autosomal recessive caused by mutation in the SRY-box 18 gene (*SOX18*)

Hennekam Syndrome type 1 and 2

- Lymphedematous facies , flat face, retrognathia, broad forehead, smooth philtrum
- Hearing loss, low-set ears
- Periorbital edema, hypertelorism, epicanthal folds, glaucoma
- Gingival hypertrophy, oligodontia, peg-shaped incisors, delayed eruption
- Atrial, ventricular septal defect
- Pericardial lymphangiectasia and effusions
- Pleural lymphangiectasia and effusions
- Lower extremity lymphedema

COURSE 14 QUIZ

1. Why do we study the genetics of non-syndromic (isolated) vascular anomalies?

   A. We can infer prognosis from the results of the genetic tests.
   B. Identification of genes associated with vascular anomalies may lead to novel pharmacologic treatments.
   C. Genetic testing should be accessible to patients because of autosomal dominant inheritance and good genotype-phenotype"correlation.
   D. Diagnosis is based on the genotype.

2. What is the next step in the evaluation of a baby with a facial port wine stain and glaucoma?

   A. Imaging studies of the brain
   B. Evaluation for congenital heart defects by echocardiography
   C. Abdominal ultrasound for hepatic vascular tumors
   D. Genetic testing for mutations in GNAQ in blood

3. The patient has many blue-colored and easily compressible skin macules. What is the next step in the evaluation?

   A. PTEN sequencing in blood
   B. Genetic testing for gain or loss of function mutations in TIE in blood
   C. Detailed clinical examination with measurement of the circumference of extremities and imaging studies of the brain and"abdomen
   D. Evaluation for congenital heart defects by echocardiography

4. A 10-year-old boy with autism, macrocephaly, and multiple lipomas is referred for genetic evaluation. What is the first step?

   A. Detailed clinical examination with measurement of the circumference of extremities and imaging studies of the brain and"abdomen
   B. PTEN sequencing and deletion/duplication test in blood
   C. Penile freckling establishes the diagnosis
   D. Evaluation for congenital heart defects by echocardiography

5. A 10-year-old boy with autism, macrocephaly, and multiple lipomas was referred for genetic evaluation and you have established the diagnosis. What is the next step?

   A. PTEN sequencing and deletion/duplication test in skin of the affected in the family will provide prognosis
   B. Establish surveillance for your patient and examine and test the parents
   C. Detailed clinical examination with measurement of the circumference of extremities and imaging studies of the brain and abdomen for all affected
   D. Total thyroidectomy for the patient and the affected parent

6. Your patient, a 22-year-old male with Proteus diagnosis that fulfills the clinical criteria, wants to father a child. The genetic counseling should include the following:

A. The patient is infertile.
B. Finding of an AKT1 mutation will establish autosomal dominant inheritance.
C. Detailed clinical examination with measurement of the circumference of extremities and imaging studies of the brain and abdomen will determine the genetic diagnosis.
D. Proteus can be due to mosaicism for an AKT1 or a PTEN mutation. The patient can transmit a PTEN mutation which will be germline in the offspring and associated with a syndrome.

7. A female infant is referred for evaluation of a hemagioma of 1 cm diameter on right shoulder. Which of the following statements is true?

A. An immediate excision is necessary because the hemangioma is malignant.
B. The patient and her parents have higher than the population risk for offspring with hemangioma.
C. Detailed clinical examination with measurement of the circumference of extremities will provide prognosis.
D. The patient should be tested for mutations in VEGFR2, VEGFR3, and DUSP5.

8. A 10 year old boy with autism, macrocephaly, and multiple lipomas was referred for genetic evaluation and you have established the diagnosis. One of the parents is also affected. What is the next step?

A. Total thyroidectomy for the patient and the affected parent.
B. Establishing surveillance for your patient and the affected parent and suggest that the affected parent contacts his first degree relatives for genetic evaluation and testing.
C. PTEN sequencing and deletion/duplication test in skin of the affected in the family will provide prognosis
D. Detailed clinical examination with measurement of the circumference of extremities and imaging studies of the brain and abdomen for all affected

9. Your patient reports a history of frequent nosebleeds and the same in many of his relatives, as well as the unexplained sudden death of his 12-year-old brother.

A. You order genetic test and imaging of lungs and abdomen.
B. You refer to a different ENT for another opinion when nosebleed recurs.
C. You counsel your patient that he likely has a sporadic (new mutation) condition.
D. You counsel your patient that he likely has a multifactorial condition.

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Dr. John G. Pappas, is a graduate of the University of Athens Medical School, Greece. He was trained in Pediatrics at Beth Israel Medical Center, NY and in Clinical Genetics at Mt. Sinai Hospital, NY. Post-training, Dr. Pappas was a clinical genetics consultant at Beth Israel Medical Center, NY. Dr. Pappas is currently (since 2001) the Director of NYU Clinical Genetic Services in the Department of Pediatrics , NYU Langone Medical Center.

Dr. Pappas teaches clinical genetics to the first- and third-year medical students in the NYU School of Medicine. He is an active clinician with daily outpatient and inpatient consultations. His academic interests include unusual presentations of genetic syndromes, genomic microdeletions and microduplications, overgrowth syndromes, and vascular abnormalities.

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COURSE 14 QUIZ ANSWER KEY

1. B
2. A
3. C
4. B
5. B
6. D
7. B
8. B
9. A