Medical Genetics for the GP

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Sandy's Concern

Sandy, 25, is worried about her family history of cancer. The initial pedigree indicates that her mother had onset of breast cancer at 33 and a maternal great aunt died of breast cancer at 40. Upon further inquiry, it is discovered that a maternal cousin has breast cancer and a paternal uncle is being treated for prostate cancer.

What should the family physician do?

Rick's Visit

Rick, 55, comes to see you because he read that Alzheimer's disease can be inherited. He is worried because his older sister, 60, and mother, 82, were both diagnosed with the disorder after presenting with dementia. You agree that both the early age of onset and two first-degree relatives are of concern and request a consultation with a neurogeneticist.

What will the neurogeneticist do?

The elucidation of the human genome provides information regarding the "organ" of concern for medical geneticists. The identification of types and interactions of genes allow medical geneticists to advance their understanding of single genes and complex diseases. Clinicians must recognize the wealth of information available in a patient's family history and its vital importance in providing anticipatory care.

Taking a family history

Maximizing the information available in a patient's family history, in terms of genome sharing, requires a minimum of a three-generation pedigree. Using the key features listed below, the family physician can decide whether a referral to a medical geneticist is required (Table 1).

Determining possible links

The pedigree may suggest a particular pattern of inheritance such as autosomal dominant, autosomal recessive, X-linked, and mitochondrial.

It is always important to remember that a single affected individual in a family may represent an autosomal recessive condition or a new mutation for an autosomal dominant condition. Many autosomal dominant conditions have variable expressivity, or non-penetrance may cause the condition to skip a generation (Table 2).

Table 1

When should a referral be made to a medical geneticist?

Preconception

- Maternal medication
- Maternal illness, e.g., PKU
- Family history
  - Mental retardation
  - Recurrent pregnancy loss
  - Recurrent sudden infant death
  - Multiple malformations
  - Ethnic background
  - Known family history of a genetic disorder e.g., cystic fibrosis
  - Multifactorial condition e.g. spina bifida
  - Multiple individuals with same problem

The fetus

- Malformations
- Abnormal joint position
- Short limbs
- Soft markers
- Teratogen exposure
- Abnormal karyotype on chorionic villus or amniocyte karyotyping

The newborn

- Malformations
- Short limbs
- Abnormal head size
- Ambiguous genitalia
- Dysmorphic appearance
- Unexplained hypotonia

The child

- Malformations
- Minor dysmorphic features plus
  - A malformation
  - Short stature
  - Learning disability
  - Atypical behavior
- Areas of skin pigmentation or depigmentation
- Unexplained constellation e.g., diabetes, optic atrophy and deafness
- Early onset of
  - Deafness
  - Cataracts

The adolescent

- Primary amenorrhea
- Male with gynecomastia +/- hypogonadism

The adult

- Common disorder plus
  - Dysmorphic features
  - Learning disability
  - Skeletal abnormality
- Unexplained early death in family members
- Known adult onset inherited disorder in the family

PKU: Phenylketonuria

Multifactorial or complex traits (such as spina bifida or osteoarthritis) can only involve single family members or multiple members without an obvious pattern of inheritance. Beware that some autosomal genes only confer susceptibility for a disorder (*e.g.*, hemochromatosis) and/or produce a spectrum of seemingly unrelated problems.

Key features of increased risk from a family history are:

1. The number of individuals with the same or related condition.
2. The seriousness of the condition.
3. Early onset of the disorder.
4. Closeness of the relation to relatives with the disorder.
5. Any unusual conditions.

Table 1
Clues to the possible inheritance pattern

	Autosomal dominant	Autosomal recessive	X-linked recessive	mitochondrial
Males=Females	Yes	Yes	No	Yes
Multiple generations	Yes	No	Yes	Yes
Males ≥ Females	No	No	Yes	No
Male-to-male transmission	Yes	No	No	No
Recurrence in brothers & sisters	Yes	Yes	No	Yes
All offspring of affected mother are affected	No	No	No	Yes
Consanguinity	No	Yes	No	No

Pedigree I: About Sandy

What steps should be taken after referral?

1. Family history is reviewed with the patient. Consent for access to family members' medical records is obtained to confirm the diagnosis.
2. The pedigree is constructed using the information available.
3. The patient is informed of her for breast cancer. In this case, Sandy's family history suggests there may be a gene for breast cancer in the family.
4. The benefits and risks of gene testing family members are reviewed, as well as any other options, such as increased surveillance.
5. Sandy decides on pursuing gene testing, which is best done on a relative with breast cancer, such as her mother.
6. She contacts her mother, who is also seen, to explain the testing for the Breast Cancer (BRCA)1 and BRCA2 genes, and consent is obtained for testing.
7. Results show Sandy's mother has a BRCA1 mutation. The patient and her mother are seen either together or individually to review the results. The

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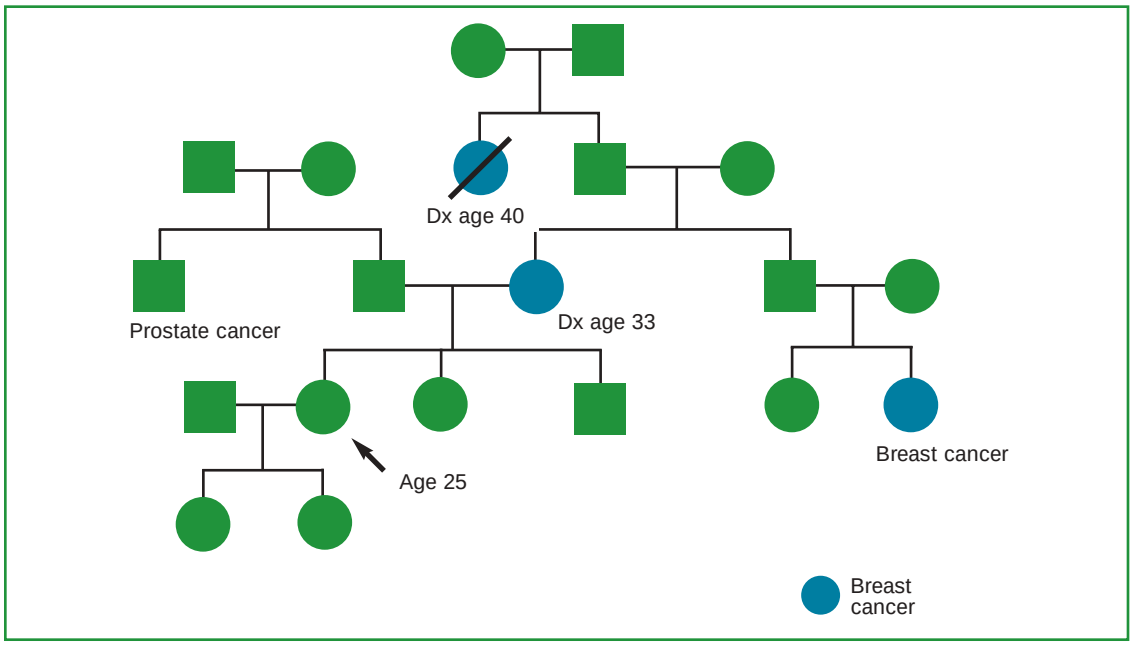

Figure 1. Pedigree I: Sandy.

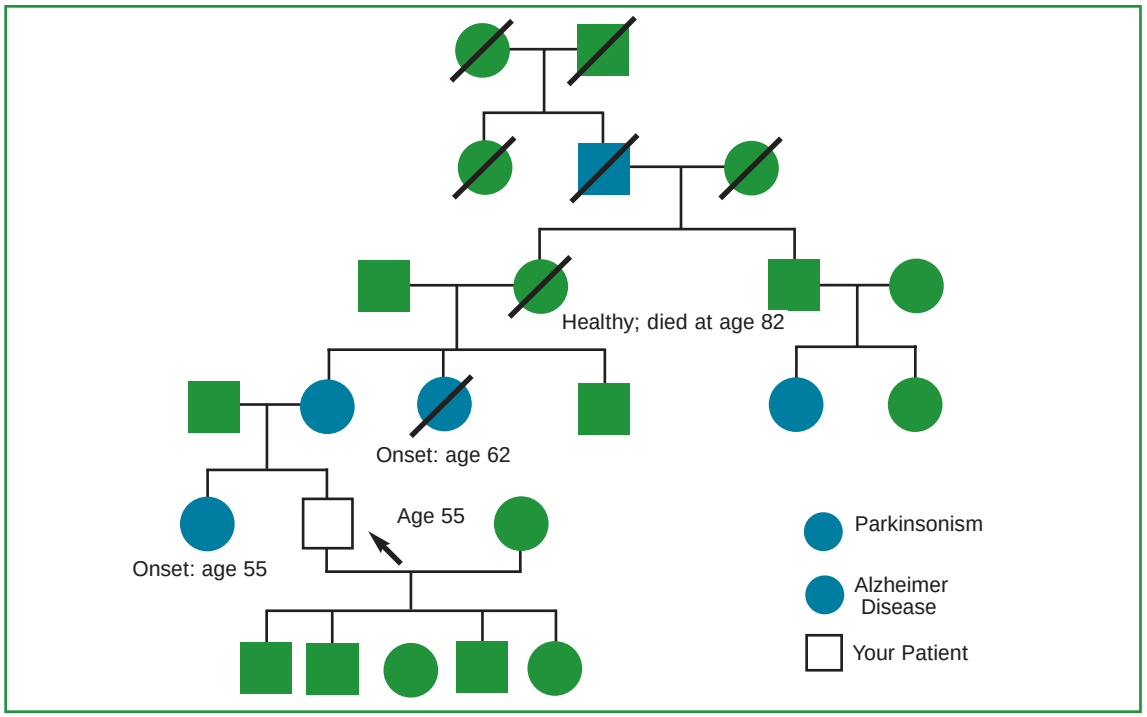

Figure 2. Pedigree II: Rick.

importance of providing information to other family members is outlined. Testing and other options are reviewed. The patient is given the option to proceed.

8. The BRCA1 testing on Sandy shows the mutation. Sandy is provided with options, including increased screening for breast and ovarian cancer, prophylactic surgery, and chemotherapy prophylactic therapy.
9. The medical geneticist provides the patient with a letter to distribute to family members explaining the potential risk of other family members having the BRCA1 gene and suggestions on contacting a medical geneticist.

Pedigree II: About Rick

What happens at the neurogeneticist's office?

1. Additional information indicates two individuals with Parkinsonism. An exam does not indicate any evidence for cognitive dysfunction or a movement disorder.
2. Since the occurrence of multiple neurodegenerative disorders are unusual in a family, the neurogeneticist requests Rick speak with his father about obtaining medical records on his mother, brother-in-law, and sister for review.
3. The subsequent review of the records were consistent with frontotemporal dementia, which can be an autosomal dominant condition presenting with either Parkinsonism or dementia.
4. Further review of brain pathology supports the familial form of the disease and, with consent of his sister's husband, DNA was sent to a specialized laboratory which later confirmed a mutation in the tau protein on chromosome 17.
5. An autosomal dominant condition in the family was found. Rick has a 50% chance of possessing that gene. However, on looking at the pedigree, many individuals who probably inherited the gene did not have symptoms or features of Parkinsonism.
6. Your patient is given the option of predictive testing and assessment of the risks and benefits involved. Because no

Take-home message

- Clinicians must recognize the wealth of information available in a patient's family history and its vital importance in providing anticipatory care.
- The goal of a referral to a medical geneticist is to provide the patient and/or family information on the natural history, anticipatory care, chance of recurrence, options for additional testing, reproductive options and possible adjustments to having the condition in the family.

treatment is available for the condition and the chance someone with the gene would not display symptoms, Rick decided to forgo testing. He had his DNA banked as a potential source of information for his offspring. He died at age 62 from a myocardial infarction.

7. The children subsequently decided they wanted to know if they might inherit the gene. DNA testing showed Rick had not inherited the gene from his mother. Thus, none of his children are at risk. CME

Suggested Readings
1. Bennett RL: The Practical Guide to the Genetic Family History. New York, Wiley-Liss 1999.
2. Harper PS: Practical Genetic Counselling. London, Arnold 2001.
3. Offit K: Clinical Cancer Genetics. New York, Wiley-Liss 1998.

Net Reading

GeneTests
www.geneclinics.org

www.stacommunications.com

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