Genetics and Common Disorders in Pediatrics

Overview
The role of genetics in the diagnosis, treatment, and prevention of many disorders, from the prenatal period to well into adulthood, has long been recognized. However, the scope of that role has usually been restricted to disorders commonly referred to as “genetic.” The common complex disorders that make up the bulk of modern medicine (hypertension, cancer, obesity, asthma, mental illness, and diabetes, to name a few) have usually not been discussed in the context of “genetic disease,” yet they in fact have significant genetic or genomic components that are relevant to their clinical management. Of equal importance, these disorders demand consideration as familial disorders that can affect multiple individuals in addition to the patient. The importance of a family history as a tool in the process of providing anticipatory guidance cannot be overemphasized.

Learning Objectives
Upon completion of Genetics and Common Disorders in Pediatrics, residents should be able to

- obtain and collate family history information relevant to the common disorders in pediatrics,
- “think genetically” in the management of patients with these common disorders, and
- use the family history information for the benefit of the patient and his or her family.

Case Presentation
Initial Presentation
Allison presents at 6 years of age with a prolonged episode of coughing; she has been coughing over the last week, especially after exercise. The month is October, and the beautiful fall colors are everywhere. She has not been febrile, and her cough is nonproductive. She has been able to attend
school but has a difficult time in gym class. She wakes at night to cough. There has not been any post-tussive emesis.

**Question 1.** Given this presentation, which of the following do you suspect?

(A) Asthma-like problems
(B) Allergy to peanuts
(C) Lingering upper respiratory infection, perhaps viral
(D) Developing ear infection

The presentation during peak leaf-changing season and Allison’s symptomatology (cough after exercise, nighttime cough, afebrile) strongly suggest asthma-like symptoms or reversible airway disease. The other possibilities are less likely but might be contributing factors and should be included on the differential diagnosis.

**Question 2.** Because asthma is not a typical Mendelian disorder (that is, characterized by an autosomal recessive, autosomal dominant, or X-linked mode of inheritance), which of the following is true about taking a targeted family history (that is, asking about immediate relatives and others as indicated)?

(A) It will not be helpful, because it will not provide any actionable information.
(B) It will not be helpful and will take too much time.
(C) It will be helpful only if there are no significant environmental triggers in the house (such as mold, dust, or smoking exposure).
(D) It might help guide diagnostic and therapeutic decisions.

A family history is important in evaluation of Allison because it allows for the gathering of appropriate historical information. Actionable information might indeed be collected through the family history, and the time spent to do so need not be excessive. Information about environmental exposures is also vital to the evaluation but not to the exclusion of the family history information.

**Past Medical History**

Allison’s past medical history appears to be normal. Your review of her chart reveals that she was the 3.5-kg product of a term gestation to a G4P4 28-year-old mother. The pregnancy was uncomplicated, as was the neonatal period. She was breastfed (the other children were not). She has not had any hospitalizations, operations, or major illnesses. She is up-to-date on her immunizations and is not on any medications. Her development has been typical. She is active and doing well in 1st grade. Allison’s mother, who is a 10th-grade math teacher, feels that Allison is the healthiest of all of her children.

**Question 3.** Which of the following from the past medical history is most suggestive of a family history factor that needs further definition?

(A) Allison was breastfed and her siblings were not.
(B) **Allison is the healthiest of all of her siblings.**
(C) Allison was born at term to a 28-year-old mother.
(D) Allison’s development has been typical.

Allison’s mother’s statement that Allison is the healthiest of all of her children provides you with a remarkable clue and opens a window onto the health of the family. Finding out more family history information (see next section) may guide your evaluation and management of Allison’s problem. The other factors are not specifically pertinent to the family history.
**Family History**

Allison’s mother provides the following family history information:

- There is a strong family history of allergies on the maternal side of the family:
  - As a child, Allison's mother had asthma and multiple “allergies.”
  - Her sister and brother had multiple allergies and bad eczema as children. The sister had to move to Arizona as an adult to alleviate her allergies.
  - Her mother has bad “hay fever.”
- There is no history of allergies on the Allison’s father’s side of the family.
- Allison’s siblings have the following problems:
  - Jacob, age 10, has ongoing asthma problems and has been hospitalized 3–4 times for asthma, which is managed by a pulmonologist.
  - Sara, age 9, also has allergy problems—periodic wheezing and chronic nasal congestion.
  - Like Jacob, Ethan, age 7, has had several hospitalizations for asthma. His primary care provider is able to manage his asthma with inhalers.

You construct the pedigree below.

**Pedigree**

![Pedigree Diagram]

**Question 4.** On the basis of the family history obtained so far, which of the following statements is true?

(A) There appears to be a significant familial component to the asthma in Allison’s family.
(B) The severity of the asthma in Allison’s siblings suggests the need for aggressive management of her problem (if asthma is diagnosed).
(C) The fact that the father's side of the family is “allergy-free” will not affect your management of Allison’s care.
(D) Obtaining more information about the allergy problems in the affected individuals might be useful because the genetic component seems even more severe than you anticipated.
(E) All of the above are true.
You have discovered a significant family history of atopic disease (asthma, eczema, allergic rhinitis) in Allison’s family. This history informs you that the affected aunt still has problems in adulthood, and the affected siblings have ongoing issues requiring management. This information should guide your choice of appropriate diagnostic measures and aggressive management modalities. Note that this family history information has been targeted—that is, once a positive history was found in the patient, more-complete information on other family members was obtained. This information is pertinent to the patient and to your further treatment of this set of siblings. Targeted family history information can be quite useful for problems that present acutely and are known to have a familial component.

This type of familial inheritance is called multifactorial inheritance (that is, it involves multiple factors, both environmental and genetic) and is the hallmark of common complex diseases. Atopy, obesity, hypertension, diabetes, and heart disease are just a few of the disorders that are multifactorial. Although these disorders are often not considered “genetic,” they should be. As more and more genetic factors (such as susceptibility genes) are discovered, such factors will increasingly become part of the everyday management of these disorders.

It should also be emphasized that collection of the family history might uncover other information that might be important, now or in the future, and should not be neglected.

**Physical Examination**
Allison’s vital signs are stable, and she is afebrile. Her respiratory rate is 20, but she does appear to be spending more time in the expiratory phase than the inspiratory phase. She is not using her accessory muscles for inspiration. Auscultation reveals some scattered wheezes posteriorly and bilateral. No rales or rhonchi are heard. There is no liver or spleen enlargement.

You diagnose Allison with wheezing, and because of the family history, you want to treat her to stay ahead of her bronchospasm.

**Question 5.** Which of the following actions is the most reasonable to take?

(A) Give her a prescription for an metered dose inhaler of albuterol and ask her mother to give you a report in the morning.
(B) Put her on a 5-day course of oral steroids (2 mg/kg) and see her again next week.
(C) **Get pulse oximetry if available and treat her with albuterol in the office.**
(D) Give no treatment now and ask her mother to call in the morning because you worry about side effects of medications that Allison has not taken previously.

Even though Allison is not in respiratory distress, it is appropriate to check her oxygen saturation level (if possible and considered clinically indicated) and treat her in the office. You will be able to assess the efficacy of the treatment and decide on further treatment. Her presentation is certainly milder than that of her siblings, but things can change quickly (especially if this season is a trigger for her). You are using the family history information to help guide your management of Allison’s care.

**Diagnostic Testing**
You decide that no diagnostic tests are needed other than pulse oximetry and auscultation before and after nebulization. You hear no wheezing after her albuterol treatment and decide that a chest radiograph is not needed. You write a prescription for albuterol by metered dose inhaler to be used as needed over the next week, and you schedule a follow-up appointment. A more-complete asthma
evaluation might be necessary (including pulmonary function tests), along with consideration of additional therapies, such as inhaled corticosteroids.

**Question 6.** Given the family history and Allison's acute presentation, you come to which of the following decisions?

(A) That genetic testing might be worthwhile, and you order a microarray test
(B) That direct-to-consumer (DTC) genetic testing will help the family, and you ask them to collect buccal swabs and send the specimens to a DTC lab
(C) **That no genetic testing is indicated at this time, but you will consider it in the future if it will be relevant to management**
(D) That genetic referral is indicated on the basis of the family history

Genetic testing for this family is not indicated at this time. The circumstances suggest that microarray testing will not provide relevant information. DTC testing might reveal a susceptibility “score,” but it will not change the management for Allison or any of her siblings. DTC testing is also subject to variance between companies and might reveal a result that is inconclusive for this family. The American College of Medical Genetics and Genomics has established guidelines to consider when ordering DTC testing. Genetic referral is not contraindicated for this family, but it is not likely to provide much actionable information or to be useful for recurrence risk counseling. The family history indicates that the recurrence risk is empirically high.

Although genetic testing is not indicated at this time, the situation might change dramatically. In the not-too-distant future, genetic markers (detectable by direct gene testing, genome-wide association studies, or whole-exome sequencing) might provide information about pharmacogenetic factors or environmental factors that will directly affect the management of the allergic problems experienced by Allison, her siblings, and her extended family. These tests are not available at this time but might evolve quickly as additional genetic, genomic, and epigenetic information becomes available.

**Management**

Family history information has provided a valuable window onto the allergy problems in Allison’s family. You have known all along that Allison’s siblings have multiple allergy problems, but you did not realize the breadth of the problem until you looked at the pedigree. You have instructed your office staff to label the electronic health records of Allison and her siblings with a special alert, so that these children can be seen in a timely manner when the family calls. Timely interventions are necessary to avoid problems that can rapidly deteriorate. At the same time, you are reassured that genetic testing is not indicated. As a matter of fact, you have already performed the most expedient genetic testing yourself—obtaining a family history!

This case has demonstrated that family history information is important in the diagnosis, treatment, and prevention of common complex diseases.

**Question 7.** Which of the following can be said for disorders similar to asthma?

(A) Obesity tends to run in families. If young adults have weight problems, counseling about recurrence risks for their potential offspring might be helpful.
(B) The diagnosis of hypertension in a family indicates the need to obtain more family history information and to consider how that information is pertinent to the child seen in the clinic.
(C) Family history information in a family with cancer predisposition might help with the monitoring and anticipatory guidance that primary care providers give patients and their families.
(D) Family history information is important for children because it can guide their care and the care of their parents.
(E) All of the above.

Although the answer to this question may be intuitively obvious, the question emphasizes the need to obtain family history information for more than just rare genetic diseases. The diseases that have the greatest impact on our lives and on our society are common complex diseases. These multifactorial diseases have a significant genetic component and potentially modifiable environment factors. Our ability to recognize these genetic components and environmental factors can be enhanced by the simple yet incredibly important tool—the family history.

Summary
Family history information is critical for the diagnosis, treatment and prevention of common complex diseases. A comprehensive 3-generation pedigree may seem time-consuming and perhaps less-than-helpful in the primary care setting. Nevertheless, family history information in the pediatric primary care setting should be collected at well-child visits so that updated information potentially relevant to the patient and family is obtained on an ongoing basis. The information collected at these visits can be tailored for the chronological age or developmental stage of the child.

Targeted information is also important to obtain at acute visits. The case above shows how additional information from the family history assisted you in managing the care of Allison and her siblings. As family history information is collated over the years, the pedigree should be adjusted to reflect any information that becomes relevant as the child approaches the transition to adulthood. Common complex diseases affect both the pediatric and the adult populations, and family history information is pertinent to both.

As stated above, targeted family history information can be quite useful for any problems that present acutely and are known to have a familial component. Multifactorial inheritance is the hallmark of common complex diseases, including atopy, obesity, hypertension, developmental delay, diabetes, and heart disease. Although these disorders are usually not considered genetic by the public, and even by some PCPs, they should be. As more genetic factors (susceptibility genes, pharmacogenetic factors, and the like) are discovered, these factors will be more integrated into the everyday management of common complex diseases. “Thinking genetically” will be even more important in the future training of pediatric residents and the continuing education of general and specialty pediatric providers. Genetic information will be not simply a curiosity of interest only to academic pediatricians but a necessary part of the armamentarium of the practicing pediatrician.

References


**Resources for Parents and Caregivers**

Genetics in Primary Care Institute Web site. www.geneticsinprimarycare.org.