Review

Basic Genetics for GPs

A Crash Course

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Jen & Harry's case

Jen, 38, is of Chinese descent. Her husband, Harry, is 40 and of the same descent.

The couple's first pregnancy resulted in a healthy daughter; the girl is now 10.

Subsequently, Jen has had four miscarriages.The couple is now on their sixth pregnancy and it is complicated by multiple fetal abnormalities detected on ultrasound, including:

- hyperextended neck,
- abnormal brain structure,
- narrow thorax and
- abnormal left hand, among other abnormalities.

Jen miscarries once again.

Fetal autopsy shows dysmorphic facial features and confirms the abnormalities detected prenatally.

The couple meets with their physician to review the autopsy results and the implications the results may have on their future reproductive plans.

For more on Jen and Harry, go to page 82.

The increased knowledge in clinical and molecular genetics and the development of new methods for prenatal and postnatal diagnosis has improved our ability to delineate different genetic conditions. Thus, physicians are able to provide couples with more precise information regarding etiology, prognosis, treatment, followup, recurrence risk and prenatal diagnosis options for future pregnancies.

The most important diagnostic aids include:

- excellent computer programs, which help in listing the differential diagnosis and identifying the best labs involved in research of a specific condition;
- the recent identification of genes and gene mutations associated with different conditions;
- the new methods to identify gene mutations and
- the new cytogenetic techniques, including fluorescence in situ hybridization (FISH) and spectral karyotyping (SKY), as well as the microarray system for the detection of submicroscopic chromosome deletions/duplications and single-gene disorders.

However, the most important component of this process is the clinician who assesses the patient, puts together the differential diagnosis and orders the indicated diagnostic tests.

A genetics review

The most obvious structure within the cells that make up our tissues is the nucleus. Within each nucleus, there are 23 pair of chromosomes. The first 22 pair are the same in both men and women and are called autosomes. The 23rd pair are called the sex chromosomes.

A deletion or addition of a whole chromosome or a chromosome segment results, in most cases, in a fetus/newborn with multiple abnormalities or a miscarriage.

A chromosome abnormality can be a *de novo* event, which means the parental karyotypes are normal. In this case, the recurrence risk is close to the general population risk.

However, sometimes an abnormality can be derived from a parental chromosome abnormality or rearrangement, in which case, the recurrence risk depends on the parent who carries the abnormality/rearrangement and the way it was ascertained.

- If the ascertainment was made through recurrent miscarriages, the recurrence risk for a healthy mother who is a carrier of a rearrangement to have a liveborn with an unbalanced chromosome rearrangement is 3%.
- The risk is 1.5% when the father is the carrier.
- If the ascertainment is through an abnormal liveborn with an unbalanced chromosome rearrangement, the recurrence risk for having a liveborn with an unbalanced chromosome rearrangement, regardless of which individual is the carrier, is 20% to 50%.

Our chromosomes contain approximately 30,000 genes. A change in a specific gene results in a single-gene disorder. Genes on the autosomal chromosomes are called autosomal genes and a mutation in these genes can result in an autosomal condition (can affect both males and females). If the condition is autosomal, it can be either dominant or recessive (Table 1).

A change in a gene on the X or, less frequently, Y chromosome, results in a sex-linked condition.

Table 1

Recessive vs. dominant autosomal conditions

Dominant

- Affected individual has only one altered gene of a pair
- The chance for an affected individual to transmit the abnormal gene is 50% with each conception
- Severity of the condition cannot be predicted
- Examples: Adult-onset polycystic kidney disease, neurofibromatosis type 1 and 2, tuberous sclerosis
- Association exists between advanced paternal age and an increased incidence of a new dominant mutation in the sperm; noted in Marfan syndrome, achondroplasia and thanatophoric dysplasia

Recessive

- Affected person inherits a mutated gene from each of the parents and is a homozygote
- Once a homozygote is identified, recurrence risk for future pregnancies of the same parents is 25%
- Common in metabolic disorders
- Examples: Cystic fibrosis, sickle cell anemia, phenylketonuria, autosomal recessive polycystic kidney disease
- Many autosomal-recessive conditions have a higher incidence in individuals of specific ethnic background and screening tests are being offered to these populations to identify carriers
- In the lack of consanguineous mating in the family, a couple who has affected children will be the only couple with such a problem in the family; the condition will, thus, affect only one generation. (May not be true for conditions with high carrier rates, such as cystic fibrosis in Caucasians, sickle cell anemia in Africans and Tay-Sachs disease in Ashkenazi Jewish populations)

X-linked

- In most cases, females are unaffected or are not affected as severely as males
- Examples: Hemophilia A and B, colour blindness, glucose-6-phosphate dehydrogenase deficiency

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More on Jen & Harry

The recurrent miscarriages and the abnormalities in their last fetus raises the possibility of a chromosome abnormality derived from parental chromosome rearrangement.

Chromosome analysis done on the fetus shows an unbalanced chromosome abnormality. This could have been a *de novo* abnormality; however, chromosome analysis done on the parents shows the mother is a carrier of a balanced chromosome rearrangement.

Regarding the couple's future pregnancies, they are offered prenatal fetal chromosome analysis through:

- Chorionic villus sampling (CVS), done at 10 to 13 weeks gestation and associated with about 1% risk for a miscarriage, or
- amniocentesis, done after 15.5 weeks gestation and associated with about 0.5% risk for a miscarriage.

They are also informed of their non-invasive prenatal options, which they are told will not provide them with accurate information regarding the fetal karyotype. These options include:

- maternal serum screenings, with or without measuring the nuchal translucency, to determine Jen's risk for having a baby with Down syndrome and open spina bifida and
- detailed fetal ultrasound at 18 to 20 weeks gestation.

It is also recommended Jen take folic acid, 1.0 mg/day, in the form of prenatal multivitamins at least a month prior to conception and during the first trimester of pregnancy.

In view of the couple's ethnic background, complete blood count and hemoglobin electrophoresis are performed to screen for thalassemia and hemoglobinopathy.

The couple has normal MCV, which rules out thalassemia carrier state. Hemoglobin electrophoresis is also normal, which rules out hemoglobinopathy carrier state.

Multifactorial conditions

Most congenital abnormalities are not the result of chromosome abnormalities or single-gene disorders, they are multifactorial. Multifactorial conditions result from the interaction of genetic and environmental factors leading to the phenotype. Examples of such conditions are neural tube defects, congenital heart diseases, club feet, hypospadias, *etc*.

There are two models to explain the occurrence of these conditions:

1. **Multiple additive locus model**: Views a phenotype as the sum of the values of many contributing alleles and environmental factors.
2. **Threshold model**: The phenotype is a continuous curve with affected individuals appearing only at one end of the distribution. The point at which a combination of genetic and environmental factors causes the appearance of the trait is considered to be the threshold.

The recurrence risk for multifactorial conditions can only be derived from population studies. Thus, the recurrence risk for a couple who had a child with a neural tube defect in Ontario is 2% to 3% and 10% if the child has hypospadias.

In assessing the recurrence risk for multifactorial conditions, it is important to rule out the possibility of a single-gene disorder, which may result in a higher recurrence risk and a chromosome abnormality, which may have a lower recurrence risk (when not inherited).

What can the GP really do?

The genes associated with any particular condition can't be changed, but the environment can, by decreasing maternal exposure to teratogens and increasing folic acid in the diet. The latter has resulted in a substantial decrease in the occurrence and recurrence of neural tube defects, among other abnormalities. Dx