Neurofibromatosis 2: Genetics and Prenatal Diagnosis

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• Understand the fundamentals of genetics
• Understand the role of genetics in NF2
• Consider the limitations and benefits of prenatal testing for NF2
• Consider the psychosocial implications of prenatal testing for NF2
• **What’s a gene?**
  - A gene is a “blue print” to build a protein.
    - Proteins are the building blocks of every cell, in every living organism.
  - The blue print is written in the chemical language of DNA.
    - DNA is a long string of 4 chemicals. When entwined with a string of complementary chemicals, it forms the double helix.
      - Adenine (A), cytosine (C), thymine (T), guanine (G)
  - Three chemicals in a row on a string make one code.
  - One code makes one amino acid.
    - C-G-A, for example, encodes the amino acid arginine.
  - To create a specific protein, the cell’s machinery connects certain amino acids in a very precise order.
• The Human Genome Project, a collaboration between private and public research labs, was a decade-long, million-dollar project to identify all human genes.

• Humans have about 30,000 genes
  – The long string of chemicals that make up the genetic code is wound up in chromosomes
  – 46 chromosomes all together, organized as 23 pairs.
The gene of interest to us is called *NF2*, located on chromosome 22.

*NF2* was isolated by two research groups in the early 1990s.

- It was then that NF2 and NF1 were confirmed to be distinct conditions.
• *NF2* codes for a protein called *moezin-ezrin-radixin-like protein* -- merlin for short.
• Every protein has a job.
  – Working together, proteins make a cell work properly.

• What does merlin do?
  – It’s not certain.
  – Some thoughts:
    • Merlin is similar to a family of proteins that keep a cell’s membrane (wall) in the right shape.
    • Prevents formation of tumors called schwannomas.
    • Involved with signaling other proteins.
    • Involved with connections between cells.
• Changes in the genetic code are called mutations.

• Mutations happen randomly and commonly.
  – For example, C-G-A accidentally becomes C-G-C as a cell grows and divides.

• A mutation may have no effect upon the blue print……
  – C-G-C also encodes for arginine.

• …Or a mutation may change the coding in a critical way.
• If a mutation changes the way a protein is manufactured, the function of the protein may be altered.

• If a protein begins to work differently, or perhaps stops doing what it’s supposed to do, the cell may be affected.
Just like in life, change can be for the better:
• Mutations create the improvements that bring about evolution.
• Each of us is a unique individual because of random mutations in our genetic codes.

Just like in life, change can be difficult.
• Mutations create the problems that bring about genetic syndromes.
• To date, about 200 mutations have been identified in NF2.

NF2 gene map

• Most mutations have been found to prematurely halt the process of merlin’s production.

• When merlin doesn’t work properly, problems arise.
– NF2 was first described in the early 19th century by John Henry Wishart in a Scottish medical journal.

– The diagnosis is made with specific clinical findings.
– Hallmark symptoms: bilateral vestibular schwannomas
  • Established criteria:
    – Bilateral vestibular schwannomas OR
    – A closely-related family member with NF2

  AND

  – Unilateral vestibular schwannoma or
  – Any two: meningioma, glioma, schwannoma, neurofibroma, posterior subcapsular lenticular opacities
The frequency of NF2 is difficult to estimate, but recent studies approximate 1 person in every 60,000.

- In BC: fewer than 100
- In Canada: about 600
- Worldwide: fewer than 120,000
- There’s no predilection in a certain race or ethnicity.

Symptoms begin, on average, around the age of 20.

- First symptom tends to be hearing loss.
- 25 is the average age when the diagnosis is made.
- The severity and onset of symptoms can sometimes be predicted by the type of mutation.
- Symptoms within a family tend to be similar.
• **NF2 is a “dominant” genetic syndrome.**
  - With dominant inheritance, a condition runs strongly through families.

    Multiple people in a family have the condition.

    It appears generation after generation – it doesn’t skip.

    Both males and females are affected.
• Compared to other dominant conditions, the inheritance of NF2 has complicating qualities: “new” mutations and mosaicism.

  – “New” mutations
  • About 50% of people diagnosed with NF2, the mutation happened randomly and was not inherited by an affected parent.
  • Called a simplex cases
Mosaicism

- In about 30% of people with a new mutation, the mutation happened at some point after conception.
- Mosaicism means there’s a mixture of cells with NF2 and without NF2.
• NF2 is determined by symptoms, not by genetic testing.

• Many different types of mutations can occur in the NF2 gene, some are detectable with current technologies, some are not.

• If a person with NF2 has genetic testing, what’s the chance that a mutation will be found?
  – Familial cases: about 90%
  – Simplex cases: about 75%
• Once a mutation is detected in one person, relatives can be tested.

• Mutations are different from family to family, but everyone in one family will have the same mutation.

• Why have genetic testing?
  – Advantages and disadvantages
  – What value does the information have to the individual?
  – Private and personal decision
• Prenatal Diagnosis

  – Once a mutation is identified in an individual, testing can be offered to determine whether his/her offspring may be affected.

  – There are advantages and disadvantages of prenatal diagnosis.
    • Same quandary as with testing oneself.
      – What value does the information have to the individual couple?
    • Private and personal decision.
• There are two methods of testing during a pregnancy. Couples are given an options between:

– Chorionic Villi Sampling or CVS
  • Chorionic villi are a part of the baby’s placenta.
  • Two methods to collect the sample, depending upon the placental location.
    – Transcervical (thin catheter)
    – Transabdominal (thin needle)
  • Performed in the first trimester, roughly between 10 and 12 weeks.
- Amniocentesis
  - A thin needle is placed into the sac surrounding the baby.
  - Skin cells in the amniotic fluid are collected.
  - Performed in the second trimester, roughly between 15 and 20 weeks.
What are the disadvantages to prenatal diagnosis?

- Procedural risks of complications that may lead to miscarriage.
  - The risk associated with CVS is typically estimated to be around 1%.
  - The risk associated with amniocentesis is typically estimated to be around 0.5%.

- A couple does not want to know the information prior to their baby’s delivery.

- The couple learns about the presence of a condition in the prenatal period that may not cause symptoms until adulthood.
What are the advantages to prenatal diagnosis?

- To determine whether the pregnancy has inherited NF2.
  - What value does this information have to parents?
    » To learn that a pregnancy has NF2.
    » To learn that a pregnancy does not have NF2.

- To test or not to test? Only the couple can decide.
• To make prenatal decision-making a bit more complicated/easier, improvements in genetic diagnosis and treatments for infertility (assisted reproductive technologies) allow us to test embryos for genetic syndromes.

• The technology is called Pre-implantation Genetic Diagnosis or PGD.
• For PGD:
  – Couples go through in-vitro fertilization (IVF) treatments.
    • Eggs are obtained from the woman’s ovary through a surgical procedure; sperm are obtained from the man’s ejaculate.
    • Sperm and egg are brought together artificially in the lab to create fertilization.

Sperm meet egg to create an embryo
• Several days after fertilization, a single cell is removed from the embryo.
  – Genetic testing is performed on the single cell.
  – This result predicts whether the embryo has the genetic condition.
  – Only the embryos without the condition are transferred to the woman’s uterus.

Biopsy of a single cell from an embryo
• What are the disadvantages of PGD?
  – It’s not a perfect technology.
    • Failure rate, false negatives, false positives
  – It reduces the chance of an affected pregnancy, but does not eliminate the chance.
  – The expense of IVF and PGD are considerable.
    • A single cycle may cost about $20,000.
  – Same considerations of decision-making as prenatal testing.

• What are the advantages of PGD?
  – Decision-making occurs prior to the time a pregnancy is created.
• Ethical considerations abound
  – Who decides the quality of one’s life?
  – Who decides which illnesses are worth testing for?
  – Individual right to privacy
    • What do you want to know?
    • When do you want to know it?
• Women with NF2

  – There are advantages to seeking a consultation with a medical geneticist and maternal-fetal medicine specialist or obstetrician prior to starting a family.
    • Pregnancy hormones may affect the size of some tumors.

  – Plan for specialty care or a team-approach with an obstetrician during pregnancy.
• Given the rarity of the condition, it’s vital to connect with others to not feel isolated and alone.

BC Neurofibromatosis Foundation – www.bcnf.bc.ca
Children’s Tumor Foundation – www.ctf.org
Neurofibromatosis, Inc. – www.nfinc.org

• Information and reading

Gene Reviews through the University of Washington - www.ncbi.nlm.nih.gov/books/NBK1201
Local resources in the medical community:

BC Children’s and Women’s Hospital, Department of Medical Genetics
www.bcwomens.ca/Services/Medical+Genetics/default.htm

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