

# Mendel might get dizzy

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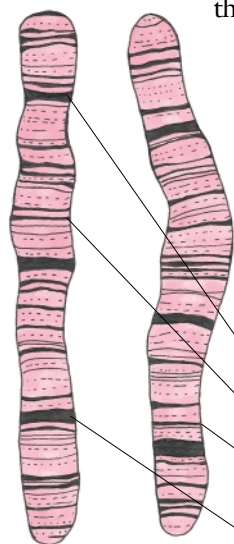


he pace of genetic discovery seems exponential, making it next to impossible for even geneticists to keep up. Yet the news is so exciting, so mind expanding and so applicable to human disease that it has to be shared. Molecular genetic techniques are used by researchers of every persuasion because they are such powerful tools to help answer basic biologic questions.

In 1997 the Human Genome Project made better progress than expected and is ahead of schedule, even though only 2%–3% of the genes in the human DNA sequence have actually been defined. The DNA sequence predicts the protein structure, and most of the newly defined genes are so unique that they are predicting protein types that have not been described previously. Another surprise is how much we humans are like other animals, plants and even bacteria. Genome projects defining the nucleotide sequences of the genetic information of several viruses and bacteria are now complete. The findings will enable the development of unique diagnostic probes to recognize specific strains and to identify specific antibiotic resistance rapidly.

The informatics systems required to keep track of all the information about the DNA sequences of different organisms in a manner that allows for comparison are definitely mind boggling. But rather

than be boggled, computer experts have been stretched to invent new complex-systems systems, even using DNA molecules as models for information storage because they are nondigital. Once the human DNA se-



## It's in the genes to . . .

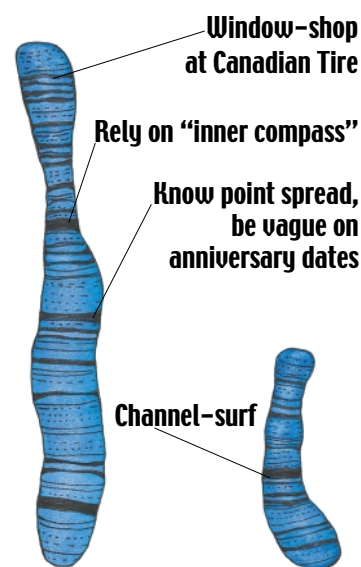
- Ask for directions
- Remember all special occasions
- Understand "like-colour" laundry concept
- Not value a good tool collection

quence is completely defined (by about 2005) the next challenge will be to determine what controls the turning on and off of a genetic blueprint, the orchestration of genes and building blocks. If there is a God, it looks as if she will probably be in control.

A mutation is definitely not what it used to be. Only a few years ago it was comfortably understood to be a change in the DNA sequence that could be inherited and that could

lead to a protein either not functioning or not getting made. Now we find that a mutation can lead to the production of a tenacious receptor or ligand that gets stuck turning things on or off (as in McCune–Albright syndrome, in which the G protein is constitutively turned on). A mutation can also lead to a protein that "sludges" things up or folds the wrong way, precipitating into plaques or crystals (as prions do in Creutzfeldt–Jakob disease), or a mutation can splice the wrong exons together, resulting in wild and weird new combinations (as happens to collagen in osteogenesis imperfecta). If that were not bad enough, more and more examples of "expanding" mutations (triple repeats that add so many nucleotide triplets that the protein-producing apparatus cannot function) are being described and, interestingly, all seem to have their worst effects in the brain (as in Huntington disease, myotonic dystrophy and Fragile X mental retardation). There seem to be strange "hot spots." For instance, achondroplasia, a common type of disproportional short stature, is caused by a mutation in the gene encoding fibroblast growth factor receptor 3 (FGFR3) — for practical purposes always exactly in the same spot — giving a mutation rate 1000 times more fre-

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quent than any other known spot. Last, but not least, among the types of mutations are “jumping genes” — particular sequences of DNA that can move about between generations (as have been described between generations in hemophilia), first causing a mutation in one gene in one generation and then skipping over to another gene in the next generation. Interestingly, plants seem to have a way of silencing these pesky “parasites” that may not have evolved in mammals yet.

Developmental genetics using flies, worms and zebra fish, as well as our surprisingly close relative, the mouse, has made amazing progress during 1997 in defining the sequence of genes involved in “marking” specific tissues so they “know” what they are. There is a hierarchical cascade of gene expression exquisitely timed and positioned in the developing embryo during early embryogenesis. Molecular techniques have allowed the recognition of differential expression even for the briefest periods. The use of knockout animals (animals in whom a particular gene has been deleted) has led to an understanding of the impact and interaction of genes. Comparisons between knockouts and particular mutations confuse even geneticists. For instance, an achondroplasia mutation created at the same spot in the *FGFR3* gene as in humans is sort of what would be expected for achondroplasia in mice; however, the knockout of the same gene leads to an overgrown mouse.

Developmental genetics is very important for understanding how embryogenesis occurs in humans. Unexpectedly, our development parallels that of most lower animals, and the genes involved in early development are “used” and “reused” at different times in development, in a different order, in different tissues — each tissue having its own combination. Growth factors and their receptors are crucial in these processes — the same growth factors and receptors that later in the organism’s development can be involved in cancer. With a better understanding of how tissues and organs are developed and grow, it is expected that interest will turn to how the fetus functions. In humans this would be during the second and third trimester, after organs have formed and when growth and maturation are occurring. It will be important to determine whether fetal function is also controlled by genes, or whether it happens as a chain reaction determined by the physical structures of the fetus itself.

In 1997 a great deal of interest was focused on Dolly, the cloned sheep — not the first or the last, but definitely the most famous mammalian clone. Many critics wagged their tongues about human clones (and surely there are important ethical issues to consider). However, the practi-

cal application of cloning may mean that, together with the emerging knowledge of developmental genetics, personal replacements could be developed for failing tissues or organs, which would solve the current transplantation problems of immune suppression and rejection. With the number of motor vehicle accidents and violent deaths decreasing, organ harvesting may take on a new connotation.

In 1997 we saw the isolation of some of the genes involved in genomic imprinting (the normal process in which a gene is only expressed where it is inherited from a specific parent). Even though we normally inherit 2 sets of genes, 1 from each parent (biparental inheritance), in some cases only a gene from either the mother or father is expressed (uniparental expression). Many genes are now known to fall into this category. This phenomenon of only expressing the maternal or paternal gene is specific to time in development and to tissue. For instance, *UBE3A* (the gene involved in Angelman syndrome) has biparental expression in most tissues but only maternal expression in the brain. *KVLQT1* (one of the genes involved in Beckwith–Wiedemann syndrome) has biparental expression in the heart but only maternal expression in most other tissues; in other words, the paternally inherited gene is turned off. In the past, we tested blood when looking at genes or their expressed product; now we will have to examine each tissue for expression of the gene at different ages and stages to comprehend the remarkable interaction and orchestration of genes and their products.

Over the past year biotech companies have gone crazy developing products and diagnostic tests. It’s scary to see options such as breast cancer screening and pre-implantation diagnosis become commercially available when neither the public nor the medical community really knows how to use them or even whether they should be used. The personal, psychological and social ramifications of using new kinds of tests must be examined. Just because it can be done doesn’t mean it should be done. If there ever was a time for wisdom, restraint and reflection, it is now. As Canadians we can be proud that our participation in the Human Genome Project has made a large contribution to the understanding of the social, legal and ethical aspects of genomic research. However, we need to be sure that this type of work continues in the face of ever-diminishing research funding.

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