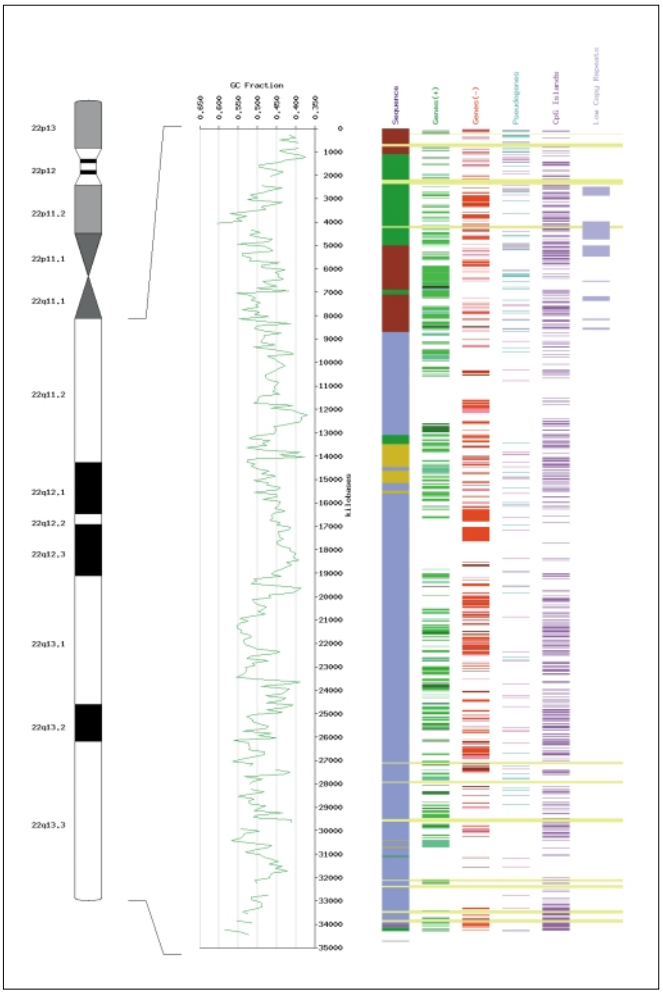
Research update

The unravelling of chromosome 22: start saying goodbye to medicine as you know it

The news that researchers had sequenced the first human chromosome (22) marks the first milestone in the Human Genome Project (HGP), which is now racing to map the entire genome (*Nature* 1999;402:489-95). The announcement, made Dec. 2, may seem esoteric to physicians in everyday clinical practice, but it is a portent of the genetic knowledge that is going to transform medicine. Ultimately, human genome sequencing will allow physicians to concentrate on prevention instead of focusing on treatment.

"The 21st century will be the era of genetic medicine," says Dr. Richard Bruskiewich, a Canadian medical geneticist working at the Sanger Centre in Cambridge, UK, where a third of the international HGP sequencing research is being done. "Sequencing now allows us to 'look under the hood' to identify all the components of the biological system, and hence their interactions with each other and the environment." Bruskiewich, who specializes in bioinformatics, the computational analysis of biological systems, is a coauthor of the *Nature* paper.



The whole chromosome 22 picture (generated dynamically from database)

Chromosome 22, the second smallest human chromosome, is thought to be associated with at least 27 human disorders (see sidebar); causative genes in 8 of them — including schizophrenia — remain to be discovered.

By summer, the draft sequence of about 90% of the entire human genome is slated to be finished; refining the draft sequences into a finished reference sequence and sequencing the remaining 10% — the most difficult — will take another 2 to 3 years. The full sequence will identify the 200 000 to 300 000 proteins that direct the formation of a human being.

The 5-year-old HGP involves hundreds of researchers, mainly in 5 sequencing centres in the US and England but also in smaller centres in Europe, Japan and China. Canada will soon play a larger role with the start-up of the BC Cancer Agency's Vancouver Millennium Genome Sequence Centre.

In the HGP's clone-by-clone sequencing strategy, each DNA fragment is cloned and propagated by inserting it into the genome of a bacterial artificial chromosome (BAC) or a bacteriophage P1 artificial chromosome (PAC). Each BAC or PAC is 40 000 to 400 000 base pairs long, and these base pairs are then sequenced — or rearranged in the order in which they occur on the chromosome. During the mapping of chromosome 22, researchers sifted through 33.4 million base pairs of DNA and identified 545 genes, which contain instructions on creating specific proteins. The sequence is not quite complete; for technical reasons there are 11 gaps.

Although the number and location of the vast majority of genes are the same, sequence variation — for example, single nucleotide polymorphisms (SNPs) — give humans individual characteristics and genetic disorders, including predisposition to various diseases. Once researchers know which genetic variations of the estimated 3 million SNPs are involved in a particular disorder such as diabetes, heart disease or stroke, they can warn people who are at risk to avoid environmental triggers. Prevention, rather than treatment, will become the cornerstone of modern medicine. Information from the human genome sequence may also eventually allow researchers to predict and correct some developmental disorders.

"A complete patient history will eventually include a characterization of the patient's genotype that contributes to disease susceptibility and modulates the patient's response to therapies," says Bruskiewich. "The biggest challenge lying ahead for physicians is how to integrate this overwhelming body of new genetic knowledge effectively into daily practice. I would like to know what physicians think they need to achieve this task."

Geneticist Heather McDermid, who led the only Canadian research team contributing to the *Nature* paper, believes that "this is the start of a big boom in genetic research." McDermid, along with a technician and graduate student at the University of Alberta, mapped the cat-eye syndrome region, associated with a genetic duplication, and the 22q13 deletion syndrome region, associated with a genetic deletion. Cat-eye syndrome can lead to heart, eye, kidney and facial defects, anal atresia and mild mental retardation. The deletion syndrome causes mental retardation and loss of expressive speech.

The HGP is 1 of 2 research groups racing to complete the sequencing of the human genome. Celera Genomics Systems, a private company in Rockville, Md., started sequencing in September using the "whole genome shotgun" method. With this aproach, researchers shatter the entire genome into fragments and read them simultaneously by feeding them into a supercomputer. Aside from methodology, the other major difference between the 2 groups is that Celera sells its information, while the HGP presents all its findings free to the public (**www.ncbi.nlm.nih.gov/genemap99/)**. "The human genome is the common property of all humankind, not just of those who can afford to pay for the information," emphasizes Bruskiewich. "The imposition of any embargo upon that free exchange stifles the progress of scientific understanding." — *Barbara Sibbald*, CMAJ

Chromosome 22 disease list

At least 27 human disorders are known to involve chromosome 22. Other genes may also be associated with some of these disorders.

Amyotrophic lateral schlerosis, susceptibility to
Breast cancer, t(11:22) associated
Cat-eye syndrome
Cataract, cerulean, type 2
Bernard-Soulier syndrome, type B
Breakpoint cluster region (CML)
Colon cancer (deletions)
Deafness, autosomal dominant 17
Dermatofibrosarcoma protuberans
DiGeorge syndrome
Ewing's sarcoma breakpoint region 1
Glioma of brain (deletions)
Glucose-galactose malabsorption
Glutathionuria
Heme oxygenase-1 def.
Hirschsprung disease (dominant megacolon)
Hyperprolinemia type 1
Lysosomal a-N-acetylgalactosaminidase deficiency
Malignant rhabdoid tumour
Meningioma
Mental retardation, chr. 22-associated
Metachromatic leukodystrophy
Myoneurogastrointestinal encephalomyopathy
Neurofibromatosis, type 2
Opitz G/BBB syndrome, autosomal dominant
Ovarian cancer (deletions)
Pheochromocytoma
Pulmonary alveolar proteinosis (rare cases)
Schizophrenia 4
Schwannomatosis
Sorsby's fundus dystrophy
Spinocerebellar ataxia 10
Succinylpurinemic autism
Thrombofilia due to heparin cofactor 2 def.
Transcobalamin 2 deficiency
22q13 deletion syndrome

Socioeconomic status at the heart of health care inequality

A recently published Canadian study suggests that our health care system may not be doing enough to direct cardiac care and promotional strategies to poor patients — the people who generally need these services the most (*N Engl J Med* 1999;341:1359-67).

Researchers with Ontario's Institute for Clinical Evaluative Sciences found that patients living in neighbourhoods with the highest average income received coronary angiography 23% more often and had 45% shorter waiting times for treatment than patients living in the lowest-income neighbourhoods. As well, each $10 000 step up in neighbourhood median income brought with it a 10% drop in the risk that a person would die within 1 year because of acute myocardial infarction (AMI). "Our findings raise the question: Could we as a system be doing a better job in reaching patients of lower socioeconomic status with health care and preventive strategies?" says Dr. David Alter, a cardiologist with Toronto's Sunnybrook and Women's College Health Sciences Centre.

The study followed 51 591 Ontario patients admitted to hospital for an AMI between April 1994 and March 1997. Researchers defined patients' socioeconomic status according to the average incomes of the communities where they lived. All data were adjusted for age, sex, severity of illness, specialty of the attending physician and hospital characteristics.

Alter says the results are evidence of real differences in the health status of patients that appear to be related to socioeconomic status. As such, they lend weight to findings of previous studies that there are disparities between classes in the prevalence of cardiac risk factors. "Why is that? Is it genetic? Or is it related to the way we deliver services and educate the public?" Psychosocial factors such as depression and job stress are also believed to cause worse outcomes for poorer or less educated people with coronary disease, although the precise mechanisms are not fully understood. "What's needed now is a study to address and disentangle all the different factors at play here," says Alter. "I suspect that when we finally do answer the 'why' question, we'll find it's not just diet, or just lifestyle, but rather a whole multitude of factors and how they interplay." — *Greg Basky*, Saskatoon