New method may speed gene searches

To geneticists, the final frontier lies literally at our fingertips – and elsewhere in the body. Each of our cells holds a vast storehouse of genetic information in some 100,000 genes strung out along 46 chromosomes. Collectively this material forms the human genome.

Using DNA probes – snippets of genetic material that home in on specific segments of the genome – geneticists have explored the genes of people in families affected by various inherited illnesses, seeking the defect that causes their disease. These "linkage studies" have scored important successes, but they remain painstakingly slow to carry out.

Now, a new technique, genomic mismatch scanning (GMS), may provide geneticists with a more rapid and precise means of finding genes. The technique uses a series of enzymes to isolate identical stretches of DNA – the thread-like molecule that holds the genetic code – from different individuals. Knowing the regions of DNA shared by two related individuals – possibly inherited from a common ancestor – helps geneticists find the particular locations on chromosomes that carry disease genes.

"GMS makes it appear feasible to go after a lot of genetically complex traits that would be ridiculously expensive and laborious, and maybe impossible, to do by any other means," says Patrick O. Brown of Stanford University Medical Center. Such complex, multi-gene traits include susceptibility to schizophrenia.

Brown and his colleagues describe their use of the technique, which they developed, to study inheritance patterns in yeast in the May issue of NATURE GENETICS. The researchers are now working out the details of how to use GMS on the larger, more complex human genome.

GMS uses a series of enzymes, including several from the DNA-repair machinery of the bacterium *Escherichia coli*. Researchers break up the chromosomes of two individuals into thousands of fragments, unzip their two mirror-image strands of DNA, and then allow the separated strands to regroup, sometimes as a mixture of strands from two individuals. Then, enzymes eliminate all combinations but those that contain identical genetic information from two individuals. Scientists can use these surviving fragments to identify the DNA that two individuals inherited from a common ancestor.

In conventional linkage analysis, researchers use previously mapped reference points on chromosomes, called genetic markers, to narrow the search for a gene to a general region of a chromosome. These markers often pass in identical form from parent to child along with nearby genes. After years of scrutinizing the DNA of related individuals affected by a disease, researchers can find markers that point to the gene's approximate location.

According to Stanley F. Nelson, a postdoctoral fellow in Brown's laboratory, researchers using conventional linkage analysis may have to check scores of markers, one by one, to track down an inherited trait. "The biggest advantage GMS offers is the ability to scan an entire genome all at once," says Nelson.

But a formidable obstacle currently blocks widespread use of GMS on human DNA: The human genome contains a great deal of duplicate information. These repetitious DNA segments interfere with the GMS process, hindering its ability to create useful amounts of perfectly matched DNA fragments. The researchers believe they can solve these problems, however, and the results of preliminary experiments using GMS on human DNA are "encouraging," Brown says.

Dramatic proof of GMS' usefulness may come when scientists use it to track down genes responsible for an inherited disease, comments Jean-Marc Lalouel at the University of Utah in Salt Lake City. Lalouel and his colleagues are working to understand the genetic basis of high blood pressure (SN: 10/10/92, p.230).

"If the [GMS] method could be adapted to the human case, the impact could be very large indeed," says Stanford geneticist David Botstein. *– D. Pendick*

Exxon's *Valdez* studies ignite controversy

Alaska's Prince William Sound "has almost fully recovered from the 1989 *Exxon Valdez* oil spill," assert officials with the Houston-based Exxon Co. USA. That assessment, based on a spate of new papers by company-funded researchers, provoked an immediate flurry of heated charges and countercharges last week.

Exxon scientists say their data indicate that widespread oil contamination has plagued Prince William Sound for more than a century. They interpret these findings to suggest that area aquatic life can coexist with low levels of oil – and even recover from occasional heavy oiling.

Government claims of long-term *Exxon Valdez* damage usually can be traced to a "faulty interpretation" of data, Exxon argues in a statement it released April 26. As a result, the company says, government scientists have mistakenly assumed "that large numbers of biologic and sediment samples from Prince William Sound contained remnants of *Exxon Valdez* crude when, in fact, they did not."

Exxon issued its statement at the opening of a four-day environmental session at an American Society for Testing and Materials (ASTM) meeting in Atlanta. Researchers funded by Exxon presented 25 papers there on the *Valdez* spill.

However, some of those same papers lead chemist Jeffrey W. Short of the National Marine Fisheries Service in Juneau, Alaska, to suspect that there is at least some possibility that Exxon is ascribing to other sources a portion of the oil that actually came from the *Valdez* spill.

His concerns involve studies that attempted to identify the source of an oil from the chemical fingerprints of its polycyclic aromatic hydrocarbons (PAHs). These PAHs offer a relatively stable oil signature – one that persists even after a sample has weathered, or begun to turn tarry.

In one study, chemist David S. Page of Bowdoin College in Brunswick, Maine, and his co-workers assayed PAHs in more than 2,350 seafloor sediments collected in Prince William Sound and the adjacent Gulf of Alaska between 1989 and 1991.

Coauthor A. Edward Bence, a geochemist with Exxon in Houston, recalls how surprised he was to find a consistent background signature of crude oil – one quite different from the *Valdez* oil – going back at least 160 years throughout the supposedly pristine sediments in Prince William Sound. The age of the signature argued for some natural, continuing source of this petroleum.

Realizing that crude-oil seeps had been charted in several places along the eastern Gulf of Alaska, the researchers compared fingerprints of oil from the seeps to those of oil in Prince William Sound sediments. They matched.

Other Exxon studies offered an explanation of how the seeps' oil might have entered Prince William Sound. Clays from glaciers to the east readily combine with oil – especially weathered oil – to form flocculated emulsions (see story, p. 302). These buoyant floc particles would ride west on the Alaska coastal current (see diagram on facing page) until they hit the sound's slow waters and settled.

The Exxon survey of sediment fingerprints revealed large amounts of petroleum PAHs – concentrations sometimes approaching 500 to 1,000 parts per billion. In deep areas, most of the oil appears to have come from seeps. In shallower zones, diesel fuel was often present. And because this diesel oil, perhaps spilled during refueling, bore a signature quite similar to that of the *Exxon Valdez* oil, government chemists often mistook the two, Bence contends.

That's definitely possible and reflects "the bias I entered with," concedes Short, who led some of those analyses. If an oil fingerprint bore the distinctive PAH peaks representing phenanthrenes and dibenzothiophenes – characteristic of North Slope crude oil – "I assumed it was *Exxon Valdez* oil," he says. In fact, North Slope diesel oil contains the same two PAH peaks. Exxon differentiated between the

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