PRENATAL DIAGNOSTICS

Fetal genes in mother's blood

The genome sequence of a fetus can be inferred from the relative numbers of variants of DNA sequences in a pregnant woman's blood. This advance in non-invasive diagnostics comes with some ramifications. SEE ARTICLE P.320

DIANA W. BIANCHI

Until the mid-twentieth century, medical examination of a human fetus was surprisingly crude, consisting principally of uterine palpation to assess fetal growth. Over the past 35 years, however, progress in fetal-imaging techniques, combined with measurement of the chemical composition of maternal blood, has substantially improved the assessment of fetal health[1]. On page 320 of this issue, Fan *et al.*[2] demonstrate that it is now possible to unambiguously determine the whole genome sequence of a fetus from a teaspoon's worth of maternal blood. The potential repercussions of such non-invasive prenatal screening must be carefully considered, particularly as the development comes at a time when many health-care providers are not familiar with the complex concepts of molecular genetics.

Fan and colleagues determined the entire genetic sequence — the order of DNA nucleotides, represented by the letters A, G, T and C — of two unrelated fetuses by sequencing cell-free DNA circulating in the plasma of their mothers' blood. During pregnancy, cells of the placenta undergo programmed cell death, which continuously releases large amounts of nucleic acids into the maternal bloodstream[3], so that a pregnant woman's blood contains a mixture of her own DNA and that of her fetus. Because humans are diploid, meaning they have two copies of each chromosome, there are three haploid (single-copy) genomes in the woman's circulation: her own two (one that she transmits to the fetus and the other that she does not) and the haploid genome contributed by the father of the fetus (Fig. 1).

The advent of rapid and cost-effective techniques for DNA sequencing means that it is now possible to count the number of specific DNA molecules in a sample. Fan *et al.* designed their experiments based on the recent finding[4,5] that parents transmit long stretches of their DNA as blocks, known as haplotypes, to their offspring. The authors paid particular attention to haplotypes containing sequences in which the two copies of the mother's genome differed at just a single DNA base — a single nucleotide polymorphism. They then counted these differing sequences, and applied the premise that those haplotypes that were numerically over-represented in the plasma DNA would correspond to the maternally-inherited part of the fetal genome (Fig. 1). Moreover, they deduced the paternal contribution by identifying sequences that were present in the plasma DNA but absent from the maternal genome.

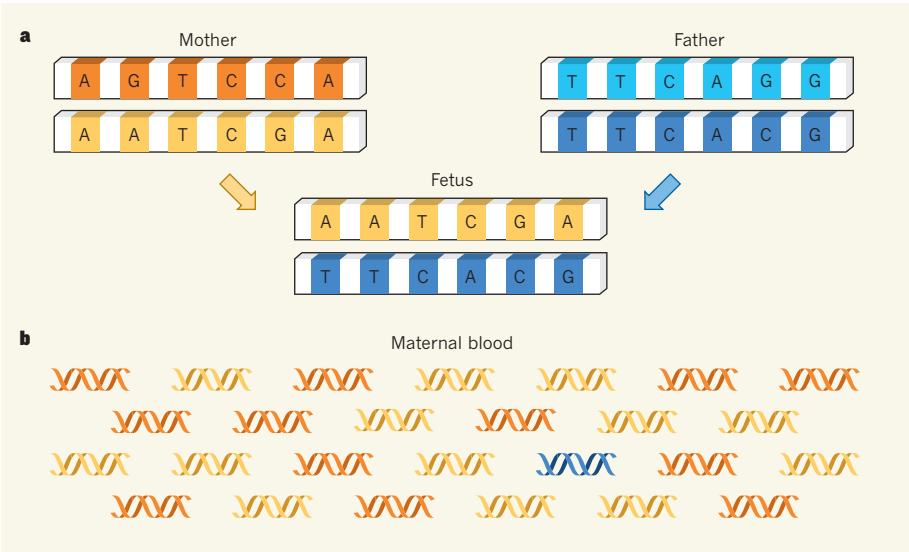

Figure 1 | Deducing a fetal genome. Human cells contain two copies of each chromosome, such that every DNA sequence is represented twice. Egg and sperm cells, however, have only one copy of each chromosome, which comprises a mixture of the sequences from both members of the chromosome pair. Long stretches of DNA sequence, called haplotypes, stay together as a physical unit during the chromosome recombination that occurs during cell replication. When the egg and sperm combine at fertilization, the fetal genome receives one copy of each haplotype from the mother and another from the father. **a**, Small sequence differences between parental chromosomes indicate from which chromosome the haplotype is derived; in this example, the fetal genome at this chromosomal location is derived from the maternal 'yellow' chromosome and the paternal 'dark blue' chromosome. **b**, The blood of a pregnant woman contains both her own DNA and that of her fetus. Therefore, for every haplotype, the blood-derived DNA will contain copies of the paternal sequence inherited by the fetus (blue), copies of the maternal sequence that is not passed to the fetus (orange) and copies of the maternal sequence that was inherited by the fetus (yellow), and which will therefore be present in excess relative to the orange sequence.

In a second set of experiments, Fan *et al.* focused on the more clinically relevant 'exome' portion of the genome — the sequences that encode proteins. The exome is considerably smaller than the entire genome, so the researchers could analyse specific sequences in greater detail and distinguish between sequence variations that were inherited from one of the parents versus those that represented newly occurring mutations.

The authors applied these two approaches to blood samples from two pregnant women. One of the women had a deletion of a large sequence on one of her two copies of chromosome 22, a mutation that is associated with a disorder known as DiGeorge syndrome. By analysing the genes around the deleted region on chromosome 22, the researchers deduced that the haplotype derived from the copy of chromosome 22 containing the deletion was over-represented in the mother's blood, indicating that the fetus shared that section of DNA and was therefore similarly affected by the condition. This finding demonstrates that a non-invasive fetal diagnosis can be made even when the fetus shares the same mutation as its mother.

This advance comes within a month of another report, by Kitzman and colleagues[6], in which fetal genotype was inferred from DNA sequences obtained from blood samples from the mother, father and from umbilical

cord blood. Although having a paternal DNA sample makes such analysis easier, Fan and colleagues' study shows that it is not necessary. Furthermore, comparing the father's DNA sequence with that of the fetus carries the risk of uncovering mistaken paternity, and this is avoided in Fan and colleagues' approach.

How will the ability to non-invasively sequence the fetal genome improve prenatal care? Fan *et al.* posit that it will enable treatment for genetic disorders to begin immediately after delivery. I argue that we could most effectively use the information to begin treatment while the fetus is still in the womb[7]. However, it is striking that before we have even considered all of the ramifications of complete genomic sequencing of a newborn's DNA, we now have three demonstrations of non-invasive sequencing of the fetal genome[2,6,8]. The situation is ethically and clinically more complex with a fetus than with a newborn for two reasons: one, the 'patient' is in the womb and cannot be fully examined, and two, prospective parents have the option of terminating the pregnancy.

These studies therefore raise many ethical and practical questions about how prospective parents and physicians might use this genomic information. For example, Kitzman and colleagues[6] detected 44 spontaneous point mutations in the fetal genome that they sequenced. One of these mutations creates an amino-acid substitution in the protein encoded by the gene *ACMSD*, which is implicated in Parkinson's disease, suggesting that this mutation might have clinical significance later in that unborn child's life. Will expectant couples want to know this sort of information? Now, multiply this point mutation by several hundred — a plausible quantity of 'noteworthy' genetic information that might typically be obtained from a whole-genome sequence — and imagine the time and resources needed to provide parents-to-be with genetic counselling regarding the implications of all of this data.

Although the concept of routine fetal-genome sequencing may still seem futuristic, non-invasive prenatal diagnosis of abnormal chromosome number is already offered to pregnant women in certain high-risk categories in the United States and China[9]. But before the vast amounts of information acquired from fetal-genome sequencing can be applied in a useful manner, the gap between technology and clinical interpretation must be narrowed. For parents to learn their fetal ACGTs, substantial investment is needed in teaching health-care providers about the human genome. ■

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The author declares competing financial interests.
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BIOGEOCHEMISTRY

The great iron dump

The discovery that marine algal blooms deposit organic carbon to the deep ocean answers some — but not all — of the questions about whether fertilizing such blooms is a viable strategy for mitigating climate change. SEE ARTICLE P.313

KEN O. BUESSELER

"Give me half a tanker of iron and I'll give you the next ice age," is perhaps the best-known quote in ocean science. It comes from the late John Martin[1], a leader in the study of iron and its role in sustaining productivity in the ocean. The quip refers to Martin's proposal that the addition of iron to the upper ocean could trigger algal blooms that would ultimately alter climate by sequestering atmospheric carbon dioxide as organic carbon in the deep ocean. Smetacek *et al.*[2] have taken on the challenge of proving Martin's hypothesis experimentally, and on page 313 of this issue they report that carbon formed from iron-fertilized algal blooms does indeed sink to the deep ocean — the first time that this has been convincingly observed.

Productivity in many parts of the global ocean is limited by iron levels, as demonstrated through several studies[3] in which the addition of iron to the upper ocean stimulated phytoplankton blooms and greatly increased CO_2 uptake into surface waters through photosynthesis. But for ocean iron fertilization (OIF) to have an impact on Earth's climate, organic carbon produced by the phytoplankton must be transported to the deep ocean where it cannot readily re-exchange with the atmosphere — this is the key event in Martin's ice-age-inducing scheme. Proving Martin's iron hypothesis therefore requires the fate of blooms to be followed.

This is what Smetacek *et al.* have done as part of the European Iron Fertilization Experiment (EIFEX). By tracking phytoplankton biomass using several methods, the authors demonstrated that at least half of the carbon captured by the algal bloom in their OIF experiment sank to depths well below 1,000 metres, some of which is likely to have reached the sea floor. Their findings help to inform us about how the oceans regulate atmospheric CO_2, and provide further input to the debate into whether the oceans can, or should, be deliberately modified using OIF to mitigate the effects of climate change — an example of a practice known broadly as geoengineering.

OIF experiments are challenging because the waters used in such studies cannot usually

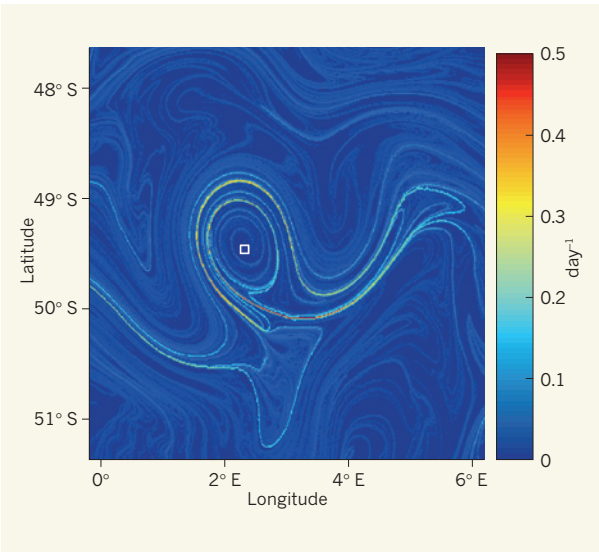

Figure 1 | Ocean eddy. Smetacek *et al.*[2] describe the results of an experiment in which they added iron salts to a patch of ocean within an eddy in the Southern Ocean, near Antarctica. The eddy is depicted here using Lyapunov exponents (reported as day^{-1}). Lines of maxima of Lyapunov exponent represent barriers to the transport of water in the ocean, and can be thought of as fronts between water masses of different origins. The white square corresponds to the centre of the ocean patch to which iron was added. The authors show that algal blooms triggered by the introduction of iron deposit organic carbon to the deep ocean.