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LETTER TO THE EDITOR

Prenatal DNA diagnosis on demand—a possible new approach to DNA service provision

There is a drastic difference between the number of hereditary disorders for which the gene is known or has been localized, and those for which routine DNA analysis is available. Altogether, 280 European laboratories carry out DNA diagnosis for 385 hereditary diseases, although the genes responsible for many more disorders have been localized. In real terms, the number of disorders for which regional DNA laboratories can offer a service is much more limited. This means that many families in Europe cannot get help even where DNA diagnosis is theoretically possible. This paradox could be partially resolved by organizing a collaborative service between different DNA laboratories in the same and other European countries. However, effective cooperation of this nature seems to lie a long way in the future.

The problem of DNA diagnostic service provision is especially acute in Russia, where there are only three laboratories offering DNA diagnosis: in Moscow, St. Petersburg, and Tomsk. Pregnant women with a family history of hereditary disease make up a large proportion of those seeking genetic advice in Russia. We have therefore examined the ways in which we can help such women and their families.

Like many other DNA laboratories, we are experienced in setting up polymerase chain reaction (PCR) markers to establish a new service. This usually includes interrogating databases about the marker in question (for information about polymorphisms, sequence, primers, etc.), choosing primers, and optimizing conditions for amplification and detection (gel composition, ethidium bromide or silver staining, etc.). This procedure usually takes less than a week and we encounter difficulties in fewer than 10 per cent of cases.

In addition, we have a genetic counselling service which provides us with effective and reliable clinical diagnosis. Considering this together with our DNA diagnostic expertise, we have concluded that it is possible to develop a test procedure and carry out prenatal DNA diagnosis on demand, for any genetic disorder which meets the following criteria:

- it must be a monogenic (single-gene) disorder;
- it must be genetically homogeneous (or have a degree of heterogeneity which is less than 5 per cent);
- the clinical diagnosis must be reliable and the diagnostic criteria must be identical to those used by the group which localized the gene in question;
- all necessary informative members of the family must be available and willing to give a blood sample for testing;
- there must be at least three known highly polymorphic markers in the vicinity of the gene (the existence of known major mutations in the disease gene can be even more helpful).

Our centre received a request for prenatal diagnosis from a woman who was 8 weeks pregnant. She had an 8-year-old son with a diagnosis of ataxia teleangiectasia. He was reinvestigated and the diagnosis confirmed by our experts in accordance with commonly accepted criteria (McFarlin *et al.*, 1972; Gatti *et al.*, 1982; Woods and Taylor, 1992). Because of her son's disorder, the mother was advised to undergo prenatal diagnosis.

It took us 2 days to gather appropriate information from OMIM, the Genom Database, and GenBank, and analyse these data. We selected three highly polymorphic markers close to the ataxia teleangiectasia gene (ATM) for DNA testing by linkage analysis: these were D11S384, D11S2179, and D11S1294 (Lange *et al.*, 1995; Savitsky *et al.*, 1995). The ATM gene is localized between D11S384 (upstream) and D11S1294 (downstream), and the third marker, D11S2179, most probably maps to the 3′ part of the gene (Savitsky *et al.*, 1995). Using these markers, we believed that we could make a prenatal diagnosis. The family was informed that this would be the first Russian attempt to do so and that we could not therefore guarantee the success of the laboratory procedure. They elected to make the attempt,

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however, and prenatal diagnosis was successfully carried out. The family proved to be informative for the markers D11S384 and D11S2179, which showed that the fetus had inherited one affected and one unaffected chromosome.

The possibility of genetic heterogeneity complicates genetic risk estimation in ataxia teleangiectasia. However, only two of more than 160 ataxia teleangiectasia families have not shown linkage to the ATM locus (Gatti *et al.*, 1993). We therefore estimated the level of genetic heterogeneity as 2 per cent. This allowed us to reduce the risk that the fetus was affected to below 3 per cent, taking into account the possibility of genetic heterogeneity for the disorder.

We believe that the development of a specific DNA diagnostic procedure 'on demand' may be a useful addition to the range of services provided by DNA laboratories even in countries with a more advanced health-care system, at least for rare genetic disorders.

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