appeared to be a very safe carrier. No tissue damage (including liver and kidney) or monocyte infiltration was observed and the serum enzymes and electrolytes were within normal levels.

Goyenvalle *et al* chose a more complex but also a more efficient and persistent strategy.[2] They explored a previously described antisense-plasmid system – U7SmOPT –,[7] which contains a modifiable gene for U7 small nuclear RNA (U7snRNA). This RNA component of the U7 ribonucleoprotein particle (U7snRNP) is involved in the processing of the 3′ end of histone pre-mRNAs within the nucleus, through an antisense mechanism. In the U7SmOPT plasmid, the original U7 antisense sequence was replaced by two different DMD antisense sequences, which target the 5′splice site of exon 23 and the branch point sequence in intron 22. This modified U7snRNA gene was inserted in a recombinant adeno-associated virus (rAAV). AAV is nonpathogenic and therefore considered as a safe gene therapy vehicle. Importantly, in contrast to other viral vectors, rAAV vectors have been very efficient in transducing mature skeletal muscle.

Following intramuscular injections of this engineered rAAV-U7-AON vector in *mdx* mice, the French group obtained dystrophin-positive fibres in up to 77% of the tibialis anterior muscle. After 3 months, this proportion was still 50%. The dystrophin-rescue restored normal histology of the treated muscle, without any signs of an immune response against either rAAV or the novel dystrophin. When delivered by intra-arterial perfusion of the lower limb, an even higher level (>80%) of dystrophin-rescue was observed. Moreover, this strategy completely restored the dystrophin–glycoprotein complex with which dystrophin is associated. As a result, the contractile and mechanical properties of the treated muscles, and their resistance to exercise induced damage, were improved to normal levels.

These results are obviously very promising. However, the safety concerns inherent to the use of viral vectors in gene therapy cannot be ignored. In particular, further investigation is required for the longer-term effects of this strategy in humans, the potential immunological reaction after repeated treatments, the effect of pre-existing AAV neutralizing antibodies in 10–30% of population, and the risks of integration-related mutagenesis. Although the severity of DMD, and thus the urgent need for an effective treatment, might outweigh some of these risks, they should still be assessed before we consider applying this approach in the clinic.

These studies represent increasing progress in the development of antisense-induced exon skipping for DMD. AONs have also successfully been applied in cultured human muscle cells from DMD patients.[4] The relative simplicity of AONs is for many scientists a relief, and, more importantly, offers the DMD patients and their parents new hope that we finally will be able to alleviate or even stop the progression of this terrible disease. Whereas the term 'antisense' is in accordance with their proven therapeutic applications *against* genes in cancer and viral infections, their capacity to *create* sense in DMD-associated transcripts would deserve a more positive label. Pro-sense...? ■

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Genetic Epidemiology of Cancer

Relatively risky relatives

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Epidemiological studies that demonstrate familial clustering of specific cancers in close (first and second degree) relatives are common,[1] but a new study that draws on a unique combination of databases shows that more distant relatives of those with cancer also have a higher risk of developing the disease.[2]

In principle, clustering of cancers within a nuclear family could be the result of either inherited factors or environmental and lifestyle factors that are shared within those families. If genetic factors are important, more distant relatives, which are less likely to share environmental and lifestyle characteristics, would also be at increased risk. However, few studies have been able to effectively assess familial clustering in more distant relatives. Now data from the Icelandic Cancer Registry (ICR) linked to the deCODE genealogy database have enabled Laufey Amundadottir *et al*[2] to uncover distant familial connections between cases and so estimate cancer risks for more distant relatives.

This new study's finding that relatives outside the nuclear family of a patient with cancer also have increased cancer risks indicates that genetic rather than environmental factors are important. Furthermore,

the authors also show that familial clustering can occur between some cancers at *different* sites: a pattern which indicates that cancer might be considered a broad phenotype with shared genetic factors that are not site-specific.

The study of familial disease risks for relatives outside the nuclear family is difficult because of the difficulties both in identifying distant familial connections and in confirming cancer diagnoses in distant relatives. The ICR contains almost complete records of all cancer cases diagnosed in Iceland since 1955, 95% of which are histologically verified, and the deCODE genealogy database includes information on all 288 000 currently living Icelanders and 400 000 deceased individuals – a large proportion of those who have ever lived on the island. The linkage of these two databases has provided a unique data source for investigating the risks of developing cancer in both close and more distant relatives of cancer cases.

A statistically significantly increased risk to first- and second-degree relatives was seen for 20 of the 27 most prevalent sites. Nonsignificant increases were seen for the other seven sites, but in all seven the risk estimates were based on fewer than 800 cases. The magnitude of the first-degree relative risks are consistently around two-fold for all the common cancers. These results are broadly in line with the results of other large population-based studies.[3,4] Of greater interest, perhaps, was the observation of significantly increased risks in third- to fifth-degree relatives at 14 sites including all of the eight commonest cancers. In most cases, there was a decline in risk from first- to fifth-degree relatives as would be predicted for monogenic disorders or for an additive polygenic model.

In addition to site-specific risks, risks between pairs of sites were estimated. In total, 17 cancer sites were involved in 20 significant pairs. Stomach and prostate cancer appeared most frequently in the pairs followed by colon, ovarian and cervical cancer. However, the power to link rare cancers to other cancer sites might have been lacking. High-risk alleles of genes known to be involved in heritable syndromes might partly explain some of these connections, but clusters were also identified between cancer sites for close and distant relatives that do not correspond to known cancer syndromes. One explanation for this finding would be an interaction between common environmental risk factors such as tobacco smoke or diet and genetic factors, so that the same gene–environment interaction could induce different cancers. One notable risk cluster was that of hormone-related cancers. This pattern indicates that genetic susceptibility factors might directly influence hormonal metabolism to induce several different cancers. Cancers with common developmental origins also tended to occur in risk clusters, which might reflect the presence of risk alleles that regulate embryonic development. A broader interpretation of these data, and one that has more profound implications, is that cancer can be considered a broad phenotype with shared genetic factors across cancer sites. Considering cancer in this way has some important practical implications: in particular, it should be possible to combine different cancer sites to increase the power of linkage and case–control studies■

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Evolutionary Genetics

The human brain – adaptation at many levels

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What makes a human brain bigger and more 'complex' than other primate brains, and how did these changes evolve? Steve Dorus *et al*,[1] in their study recently published in *Cell*, show, by comparing rates of protein evolution between primates and rodents, that there is an accelerated rate of evolution of some nervous system genes in humans. This study reaches some exciting conclusions and highlights some of the promises and pitfalls of comparative genomic analyses that are being used to shed light on the genetic legacy of human evolution.

As the metric of adaptive protein evolution, the authors used the K_a/K_s ratio,[2] which compares the number of nonsynonymous substitutions (K_a; changes that affect the amino-acid sequence) to the number of synonymous substitutions (K_s; changes that do not affect the amino-acid sequence) between two DNA sequences. In a departure from previous studies,[3] the authors chose to calculate K_a/K_s in primates through