that female *BRCA1/2* mutation carriers with at least one allele of 28 repeats or greater had an earlier age of onset of breast cancer than those with shorter alleles[7]. Later studies did not support either of these findings, but most were limited to women with premenopausal breast cancer and did not examine the effect of CAG alleles of less than 20 repeats. A recent study that showed a strong protective effect of these short CAG alleles among postmenopausal women (where 5% of breast cancer cases and 15% of controls had at least one allele of less than 20 repeats) appeared to resolve the earlier paradoxical results: the choice of cutoffs of allele lengths and age at diagnosis have a crucial impact on the results[8]. Alas, the largest study of all, a nested case-control study within the Nurses' Health Study, finds no relationship whatsoever between short or long CAG alleles on breast-cancer risk in pre- or postmenopausal women[9]. Interestingly, we may not have reached the end of the story; the histopathology of the tumors has rarely been considered, and two studies have suggested that poorly differentiated breast cancer may be associated with short repeats[10,11]. Needless to say, larger, better-designed studies will be needed to confirm the result. So we are back to square one.

The mantra of 'larger, better-designed studies' seems to be the only riposte to the question, Where are all the genes? Maybe this will do the trick, but so far, for most candidate-gene studies, the relative risk tends towards 1.0 as sample size increases[12]. Moreover, if alleles interact with each other and with environmental factors, one could envisage a situation where allele A is associated with breast cancer in population 1, but not associated in population 2. This could seriously impede efforts to use genomic information to categorize individuals into meaningful risk groups.

Without some legitimate target candidates, enthusiasm for public health applications of genetic medicine may seem like Pollyanna's view of the world: irrepressible optimism but a certain amount of self-delusion. Only time will tell, but the work of Pharoah *et al*. clearly establishes the rules of the game.

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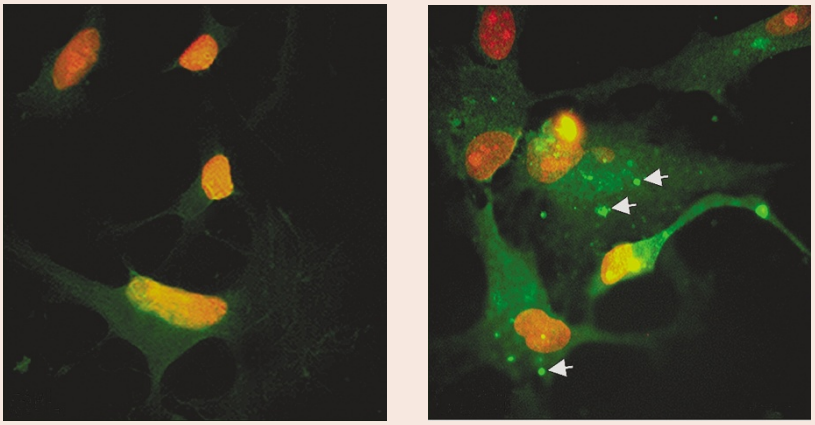
Weak mitochondria permit protein clumps in Down syndrome

A distinct feature of Down syndrome (DS), or trisomy 21, is the onset of Alzheimer disease (AD) by middle age. Previous studies have suggested that increased expression of the gene encoding the amyloid β precursor protein (Aβ-PP) may underlie the development of AD in DS. However, DS individuals also have mitochondrial defects, which have been associated with neurodegeneration in other disorders. In a recent report, Busciglio *et al.* (*Neuron* **33**, 677–688; 2002) draw the link between Aβ-PP metabolism and mitochondrial dysfunction in DS.



Busciglio et al., reprinted with permission from Neuron

Shown here are human astrocytes in cell culture stained with propidium iodide (red) and an antibody that recognizes Aβ-42 (green), a product of AβPP. Intracellular accumulation of Aβ-42 has been associated with AD in previous studies. The authors found that astrocytes treated with a mitochondrial inhibitor, m-chlorophynhydrazone (CCCP) also accumulated Aβ-42 (arrows; right). Untreated astrocytes did not accumulate Aβ-42 (left). The accumulation is similar to that seen in astrocytes derived from the brains of DS individuals, indicating that mitochondrial impairment may underlie the Aβ-42 defect *in vivo*.

Busciglio *et al.* went on to demonstrate that mitochondrial inhibition mimicked other alterations in Aβ-PP processing that occur in DS. Secreted AβPP, for example, was found to be reduced in both DS neurons and mitochondria-inhibited neurons. As secreted Aβ-PP promoted survival of DS neurons *in vitro*, its reduction could lead to neurodegeneration. The authors propose that impaired energy metabolism in DS neurons leads to alterations in the processing of Aβ-PP. Chronic Aβ-PP overexpression due to increased gene dosage could in turn impair mitochondrial function, they speculate, through direct toxicity or because of the metabolic costs of clearing aggregated proteins.

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