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50 & 100 YEARS AGO

50 YEARS AGO

Considerable data are now available on the radiosensitivity of cultivated plants, but very little is known about the tolerance of wild species. We have investigated the doses of γ-radiation needed to prevent weed seeds from growing ... The results obtained indicate that arable soils need treatment with at least 100,000 rads of γ-radiation to inhibit weed growth effectively. This treatment would sterilize any insects, or nematodes present in the soil, and would probably destroy a high percentage of the bacteria and fungi.

From *Nature* 28 March 1959.

100 YEARS AGO

Much interest has been aroused in Sussex by the discovery of the greater part of a skeleton of a mammoth (*Elephas primigenius*) on the shore of Selsey Bill. The remains were found below high-water mark in the estuarine or fresh-water deposit of black clay, which underlies the raised beach and coombe rock on that part of the Sussex coast. The thick mass of shingle, which usually covers this deposit, was temporarily removed during the recent stormy weather, and the teeth and broken bones were found projecting from the clay. Probably the whole skeleton was originally present, but when found the bones were already much eroded, and they were scattered over an area about 30 feet square. Both upper and lower molar teeth were recovered, and their condition shows that the animal was immature and of small size. Fragmentary remains, both of the mammoth and of *Elephas antiquus*, have been found at various times in the same deposit in Bracklesham Bay, some of these specimens being now in the British Museum. Indications of complete skeletons are rare. They seem to have been recorded only twice in England, the first in the brick-earth of Ilford, Essex, the second in a corresponding deposit at Ealing, Middlesex.

From *Nature* 25 March 1909.

cases[3]. For instance, the *SOD1* gene is mutated in ALS with relatively high frequency[4]; so is the *TARDBP* gene, which encodes the TDP-43 protein, a frequent constituent of the disease-associated cytoplasmic inclusion bodies found in patients' motor neurons[5]. Furthermore, a link between several genomic regions and ALS has been suggested, one such region being on chromosome 16, where *FUS* is located[6,7].

Members of a family originating from a Cape Verde island[1] and a British family[2], with evidence of a genetic cause of the disease on chromosome 16, were instrumental in the identification of *FUS* as an ALS-linked gene. Studying the descendants of first-cousin Cape Verdean grandparents, Kwiatkowski *et al.*[1] identified a 4-megabase-pair region in the ALS-linked locus on chromosome 16 in which both DNA strands were identical by descent in patients but not in healthy siblings. Through subsequent sequencing of the genes in this region, the authors pinpointed a single-nucleotide (missense) mutation in *FUS*. Vance *et al.*[2] independently identified a different missense *FUS* mutation in the British ALS family. What's more, the two teams[1,2] screened other patients with familial ALS and identified 12 additional *FUS* missense mutations in 24 families.

Both teams confirm the pathogenic effect of *FUS* mutations through tissue autopsy of patients who carried the mutation, showing that the motor neurons of these patients contain cytoplasmic inclusions of FUS protein. Further studies in cultured cells expressing FUS mutants confirmed the relocation of this protein from the nucleus to the cytoplasm[1,2]. It is noteworthy that, in the autopsy samples, the typical TDP-43 inclusions were absent[2], indicating that FUS-associated ALS has a neuropathological mechanism distinct from that of the TDP-43-associated disease.

Most of the *FUS* mutations identified involved the substitution of evolutionarily conserved arginine amino-acid residues in the carboxy terminus of FUS with other amino acids, emphasizing the crucial role of the arginine residues in the normal functioning of the protein. The age at onset and disease duration, however, varied between carriers of the same or similar *FUS* mutations. For example, Kwiatkowski *et al.* found that in patients who carried a substitution of arginine at position 521 for a glycine residue, the average age of onset was 37.5 years in one family and 60.7 years in another. This observation raises the possibility that other genetic sequence variants in *FUS*, or in other genes, influence the onset and progression of the disease. Such modifying genetic factors could be instrumental in designing drugs that prevent or delay the development of ALS, as they reveal molecular mechanisms that can accelerate or delay the disease's progress.

The identification of *FUS* mutations in patients with familial ALS ends a long period of intense hunting for the genetic defect on chromosome 16 associated with this condition, and provides an impetus for explorative research into the role of FUS in the pathogenesis of the disease. The question now is how FUS mutations affect motor neurons.

Being predominantly a nuclear protein, FUS is an RNA- and DNA-binding molecule that is involved in many cellular processes, including DNA repair, RNA splicing and transcription, and transport of messenger RNA from the nucleus to other destinations — such as the dendritic processes of neurons — for local protein synthesis at the synaptic junctions between neurons[8]. FUS mutations could lead to a loss of any of its normal functions or gain of toxic functions in the nucleus, resulting in impaired RNA processing. Cytoplasmic aggregates of FUS, for instance, could be toxic to the cell, or lead to sequestration of other proteins in the cytoplasm.

In addition, FUS shows intriguing functional similarities to TDP-43, which is also an RNA- and DNA-binding nuclear protein, and this suggests that the two proteins might have shared RNA targets that affect motor-neuron survival. For both FUS and TDP-43, ALS-causing missense mutations predominantly affect the proteins' carboxy terminus, which contains motifs for RNA processing. The common RNA targets of these proteins could include precursors to motor proteins, cytoskeletal proteins and growth factors crucial for the normal functioning of motor neurons. Intriguingly, TDP-43 pathology is associated with loss of the growth factor progranulin in neurodegeneration[9], whereas one target of FUS is insulin-like growth factor-1 (ref. 10). Furthermore, FUS and TDP-43 are not the only RNA-processing proteins implicated in ALS and other motor-neuron disorders[11], underscoring the fact that abnormal RNA metabolism may represent a central pathway for motor-neuron degeneration. So genetic screening of other genes involved in RNA metabolism — such as *ELP3*, which has recently been associated[11] with ALS — is warranted.

Most of the *FUS* missense mutations reported in the two papers[1,2] fit an autosomal-dominant inheritance pattern — that is, mutation in a single copy of the gene is sufficient to cause disease — and an age-dependent increase in the proportion of individuals developing the disorder. The mutation detected in the Cape Verdean family, however, caused ALS only in those who carried it in both copies of their *FUS* gene (homozygous), and so this conforms to a recessive pattern of inheritance[1].

Cultured cells expressing a single copy of the Cape Verdean mutation did not show the same pattern of cytoplasmic FUS retention as that observed for the dominant mutations; but, compared with normal cells, they did show a slight, albeit significant, alteration in the cellular localization of this protein. This mild *in vitro* effect of the single-copy Cape Verdean mutation might reflect a milder or related clinical expression of ALS in individuals carrying this mutation in a single copy of their *FUS* gene, although this possibility awaits further investigation.