vCJD epidemic could be first of many, experts warn

The 130 or so people who have thus far become afflicted with variant Creutzfeldt-Jakob disease (vCJD) might represent a 'mini-epidemic' that could be followed by several much larger epidemics in years to come, according to new research suggesting current mathematical models of the disease are inherently flawed.

The victims to date are those with the shortest incubation times—those whose symptoms have taken the least time to show after eating infected meat. But there are presumably others with longer incubation times—who are infected but asymptomatic.

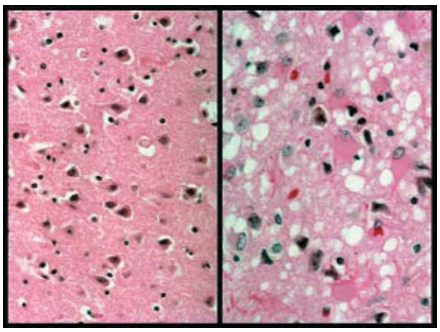
The models used to predict the size of vCJD epidemics do allow for a wide range of incubation times. But they assume that only one gene, the prion gene *PRNP*, controls incubation time. New research, presented in July at the XIX International Genetics Congress in Melbourne, instead suggests that many genes determine when a person begins to show symptoms.

"The predictions that have been done so far are based on a monophasic model—it rises to a single peak and comes down again," says John Collinge of the Medical Research Council (MRC)'s Prion Unit in London. "But if one's dealing with a small number of genes of major effect, then you may not see that," Collinge says. "You may see a polyphasic epidemic with a series of peaks."

No one doubts that *PRNP* is an important determinant of incubation time, because all 130 victims carry two copies of the gene's *M* allele—a relatively rare combination. *PRNP* also determines incubation time in mice, where allele *a* is associated with short incubation times and allele *b* with longer times.

But the gene clearly doesn't work alone, says Sarah Lloyd, also of the MRC Prion Unit. "For a given strain of scrapie, or any of the prions for that matter," Lloyd says, "if you inoculate different strains of mice you see different incubation times, even though the prion protein itself is exactly the same."

Lloyd and colleague Elizabeth Fisher have found that scrapie incubation times for different mouse strains vary between 108 and 188 days. The researchers say incubation time is a quantitative trait—a cumulative effect to which many genes contribute. They have identified regions on mouse chromosomes 2 and 11 that influence that variation, independent of the prion strain with which mice are infected. They are now scrutinizing mouse chromosome 15, which has also been implicated in the timing of disease onset by Ian Jackson's group at the MRC Human Genetics Unit in Edinburgh.



Brain sections from normal (left) and vCJD individuals (right) show sponge-like changes in the infected tissue.

Finding the many genes that contribute to a quantitative trait is not easy because much of the genetic heterogeneity that exists in wild mice is lost in the inbred animals studied in laboratories. To get around that problem, Fisher's group is working with a heterogeneous stock of mice based on eight strains crossed over many generations.

Because they know the ancestry of the mice as well as the degree of genetic recombination, the researchers are able to map regions of interest much more narrowly within closely spaced genetic markers. They have now homed in on a stretch of DNA on chromosome 15 that is only seven megabases wide, and are preparing to study tissue from some of the human vCJD victims to look for polymorphisms in this region.

Meanwhile, at the McLaughlin Research Institute in Great Falls, Montana, institute director George Carlson and his colleagues have engineered mice to carry DNA stretches from chromosomes 9 and 11, also thought to modify incubation time. Genes in the region might affect the rate of prion replication within a neuron or the site in the brain where they replicate, Carlson says. "A similar rate of replication in two different regions of the brain could produce disease at different times," he says.

Given the high degree of conservation between the mouse and human genomes, genetic modifiers are likely to have a similar mode of action in humans. If so, says Collinge, the current human toll could represent a highly susceptible subpopulation with unlucky combinations of alleles—and the major epidemic, or epidemics, could be yet to come.

Laura Spinney, Melbourne

Spain approves human embryo research

The Spanish government in July approved a measure that explicitly authorizes the use of frozen embryos to derive new stem cell lines, making it the first Catholic country to allow work on human embryos. The reform, which updates a 15-year-old assisted reproduction law, is intended to decrease the number of spare embryos stored at *in vitro* fertilization (IVF) clinics in the country.

The move, regarded as a maneuver to keep content both the progressive and conservative sectors and the Catholic church, came a few weeks after the European Commission approved guidelines to regulate and fund embryo research.

Under the new law, embryos currently stored at IVF facilities can be used for research, with the parents' consent. Once the law takes effect, spare embryos are to be frozen "throughout the full fertility period of the woman" rather than for the current allowance of five years. The measure also limits the number of embryos transferred to three per cycle.

A new national center will be launched to establish a centralized registry of IVF facilities, oversee embryo research and grants and manage a reference bank of stem cell lines. The new law is expected to take effect by the end of the year.

Xavier Bosch, Barcelona