QUESTION 39

In patients with familial Creutzfeldt-Jakob disease, which of the following types of mutation is most likely to be identified in the prion protein gene?

A. Promoter methylation  
B. Deletion with frameshift  
C. Splice-junction mutation  
D. **Missense mutation**  
E. Nonsense mutation

Prion Disease
- Neurodegenerative  
- Long incubation periods  
- Progress inexorably once clinical symptoms appear  
- 5 human prion diseases:
  - Kuru  
  - Creutzfeld-Jakob disease (sporadic is most common prion disease)  
  - Variant CJD  
  - Gerstmann-Staussler-Scheiker syndrome (GSS)  
  - Fatal familial insomnia (FFI)
- Prion diseases are disorders of protein conformation  
- Prions reproduce by binding to the normal cellular isoform of the prion protein (PrPc) and stimulate conversion into the disease causing isoform (PrPSc)
- Role of PrPc unknown  
- Normally exists primarily in alpha helical conformation  
- PrPSc is beta helical  
- PrPSc is transported to the nervous system via axons  
- Leads to apoptosis and cell death  
- Prions are only known infectious pathogens that are devoid of nucleic acid  
- Can be infectious, genetic or sporadic  
- fCJD results from mutation of PRNP gene which codes for PrPc  
- GSS, FFI and fCJD are all caused by dominantly inherited PRNP gene mutations  
- Kuru has occurred in the Fore people of New Guinea after ritualistic canabalism – now almost disappeared  
- vCJD results from exposure to tainted beef from cattle with BSE  
- Scrapie in sheep is another form of animal prion disease  
- sCJD results from sporadic mutation or spontaneous conversion of PrPc to PrPSc

CJD
- Sporadic (85-95%)  
- Familial (5-15%)  
- Iatrogenic (<1%)  
- Variant

Neuropathology
- Often some atrophy of brain but frequently normal on gross examination  
- Spongiform changes (neuronal vacuoles – see picture below)
- Astrocyte gliosis (constant but non-specific finding)
- Neuronal loss without inflammation
- Accumulation of the abnormal prion protein
- In vCJD there is the characteristic feature of “florid plaques” – amyloid plaques surrounded by vacuoles give appearance of a flower

http://www.utdol.com/utd/content/image.do?imageKey=neuropix/classi70.htm

Clinical Features

sCJD

- Rapidly progressive mental deterioration and myoclonus are cardinal features of sCJD
- Mean age of onset is ~60yrs
- Mood changes, sleep disturbance are also common
- Death usually within 1 year
- Extrapyramidal signs (such as hypokinesia, nystagmus, ataxia) occur in ~2/3 patients
- Corticospinal tract signs occur in 40 to 80% - hyperreflexia, extensor plantar responses, spasticity
- fCJD has slightly earlier onset than sCJD but similar features (?)

iCJD

- Accidental transmission has occurred with corneal transplantation, contaminated EEG electrode implantation and surgical procedures including dural grafts
- Also may be associated with human growth hormone and pituitary gonadotropin therapy
- Largely cerebellar signs early in disease
- Earlier onset than sCJD

vCJD

- >140 cases have occurred, >90% in Britain
- Thought to be from beef tainted with BSE
- Younger age of onset than sCJD (mean 29yrs)
- Less rapid progression than sCJD
- Psychiatric symptoms predominate early
- Ataxia commonly first neurological sign (average onset 4-6 months)
- Cognitive decline common with advancement of disease
- Sensory symptoms also common
Diagnosis

- Brain biopsy is gold standard
- MRI
- EEG: can support diagnosis but no definitive – characteristic pattern of periodic synchronous bi- or triphasic sharp wave complexes (very specific for sCJD, occasionally seen in fCJD, not in vCJD)
- Protein 1433 common in sCJD
- Genetic testing for PRNP in fCJD and sCJD

Figure 13. Serial EEGs of a 62-year-old patient with Creutzfeldt-Jakob disease. The first EEG (A), obtained 2 months after the onset of dementia and progressive right hemiparesis, shows left-sided delta activity. EEG 2 weeks later (B) shows periodic lateralized epileptiform discharges over the left hemisphere, and an EEG taken 5 months after the onset of illness (C) shows typical bisynchronous high-amplitude periodic complexes superimposed on “flat” background. Myoclonic jerks monitored on the last channel are synchronous to the periodic complexes. (Reprinted from Markand,[10] with permission from Lippincott Williams & Wilkins.)
http://www.medscape.com/content/2003/00/45/85/458594/458594_fig.html

WHO Diagnostic Criteria (probable sCJD)

- Progressive dementia
- At least 2 out of the following 4 clinical features: myoclonus, visual or cerebellar disturbance, pyramidal/extrapyramidal dysfunction, akinetic mutism
- Typical EEG and/or positive 1433 CSF assay with clinical duration to death less than 2 years
- Routine investigations should not suggest an alternative diagnosis
- Definitive diagnosis requires brain tissue with typical features or gene mutation for fCJD/sCJD

Treatment and Prognosis

- No treatment
- Always fatal

Genetics

- Gene encoding PrP (PRNP) is located on short arm of chromosome 20
- In familial CJD a missense mutation involving the substitution of lysine for glutamine in codon 200 is the most common PRNP gene mutation
- Over 50 mutations of the PRNP gene have been identified

A Bit on Genetics Generally

- Missense mutations are types of point mutations where a single nucleotide is changed to cause substitution of a different amino acid
- Eg: in sickle cell disease, the 17th nucleotide of the gene for the beta chain of Hb is changed from codon CAG (for glutamic acid) CTG (for valine)
- A nonsense mutation is also a point mutation that results in a premature stop codon
- A promoter is a regulatory region of DNA located upstream of the gene, providing a control point for regulated gene transcription – I suppose methylation could potentially cause the failure of protein production by this gene
- Splicing is a modification of genetic information after transcription – introns are removed and exons are joined
- Mutations of a splice site result in loss of function of that site → premature stop codon, loss of an exon or inclusion of an intron

From Wikipedia (the absolute basics):

Deoxyribonucleic acid, or DNA is a nucleic acid molecule that contains the genetic instructions used in the development and functioning of all living organisms. The main role of DNA is the long-term storage of information and it is often compared to a set of blueprints, since DNA contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.

Chemically, DNA is a long polymer of simple units called nucleotides, with a backbone made of sugars and phosphate atoms joined by ester bonds. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This
information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription. Most of these RNA molecules are used to synthesize proteins, but others are used directly in structures such as ribosomes and spliceosomes.

Within cells, DNA is organized into structures called chromosomes and the set of chromosomes within a cell make up a genome. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms such as animals, plants, and fungi store their DNA inside the cell nucleus, while in prokaryotes such as bacteria it is found in the cell's cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA, which helps control its interactions with other proteins and thereby control which genes are transcribed.