693 - MboII

717 +Bcl2

Normal +MboII; -BlC2

4. Alzheimer disease

Background: Alzheimer disease is by far the most common cause of dementia in aging persons. The disease symptoms are identical to other forms of senile dementia, and diagnosis had been possible only at autopsy by the detection of protein clusters called amyloid plaques in the cerebrum. The disease is multifactorial and inheritance patterns are complex. Some forms of familial Alzheimer disease appear to be inherited as autosomal dominant traits, while others are recessive. Spontaneous Alzheimer disease also can occur in the absence of inherited factors.

Mutations in at least four genes have been linked to Alzheimer disease. One of these is the amyloid precursor protein (APP) gene, which encodes the b-amyloid peptide found in the cerebral plaques of Alzheimer patients. The function of APP is not yet known, but certain APP point mutations are associated with inheritance of late-onset Alzheimer disease in some families. Two examples which can be detected by RFLP analysis are the codon 693 Glutamic acid to Glycine mutation and the codon 717 Valine to Isoleucine mutation. The 693 mutation results in the loss of a MboII site, while the 717 mutation results in the gain of a BclI site.

Case A: Martha, age 71, has been exhibiting increasingly severe symptoms of senile dementia and has been hospitalized for testing. She is in good health otherwise. Her three children - Sam (age 43), Joan (age 41) and Robert (age 38) - want to find out the cause of the dementia and determine the prognosis for Martha's future condition. They are also concerned that Martha may have a form of familial Alzheimer disease and want to know if they are at risk. The physician decides initially to test Martha for two mutations, 693 Gly and 717 Ile, in the amyloid precursor protein (APP) gene which are associated with inherited Alzheimer disease.

DNA samples: Martha (mother)
Sam (son)
Joan (daughter)
Robert (son)
Control normal APP gene
Control with 693 mutation
Control with 717 mutation

To test for the 693 Gly mutation, digest the DNA with MboII and perform a Southern blot using the APP probe. To test for the 717 Ile mutation, digest the DNA with BclI and then use the APP probe. Compare the test samples to the control samples, and use the results to determine the genotype of each individual. [Note: Small fragments are generated with the MboII digestion - use 1.2% agarose and short run times.]

1. Does Martha have either of these two APP mutations?
2. Did any of Martha's children inherit an APP mutation?
3. What conclusions can you draw regarding Martha's diagnosis?
4. What can you tell Martha's children about their risk for Alzheimer disease
5. What issues are raised by this type of testing?

Case B: Lisa, age 17, and her cousin Jen age 18, were half-listening to music in the den and half-listening to their mothers discuss Grandma Eloise and her older sister Florence. Lisa and Jen loved Eli and Flo dearly but even they could tell something wasn't quite right about their increasingly odd

behavior. The teens moved into the kitchen to join the conversation. "Is Grandma's erratic behavior and forgetfulness Alzheimer's or just senile dementia commonly associated with old age?" They decide to talk to Eloise and Florence about DNA testing. The mothers also wonder about their risk for Alzheimer disease and decide to be tested.

DNA samples:
Eloise (grandmother)
Florence (Eloise's older sister)
Lisa's mother
Jen's mother
Control with 693 mutation
Control with 717 mutation
Control normal APP gene

To test for the 693 Gly mutation, digest the DNA with MboII and perform a Southern blot using the APP probe. To test for the 717 Ile mutation, digest the DNA with BclI and then use the APP probe. Compare the test samples to the control samples, and use the results to determine the genotype of each individual. [Note: Small fragments are generated with the MboII digestion - use 1.2% agarose and short run times.]

1. What conclusions can you draw from the results?
2. What is the molecular basis of this disease, and why does this result in the observed gel patterns?
3. What options are available to the family?
4. What issues are raised by this type of testing