Case-Based Questions (please see page 3 for answers)

1. An infant is born with several craniofacial anomalies including microcephaly and cyclopia. Autopsy examination reveals alobar holoprosencephaly. What is the most likely etiology?
   a. Mutation in DHCR7
   b. Mutation in SHH
   c. Mutation in ZIC2
   d. Trisomy 13
   e. Trisomy 18

2. A 22-year-old female presents with new onset seizures. MRI reveals subcortical band heterotopia. Mutations in which of the following genes are associated with both band heterotopia and lissencephaly type I?
   a. ARFGEF2
   b. Doublecortin (DCX)
   c. Filamin 1 (FLNA)
   d. POMT1/2
   e. RELN

3. A 6-year-old male with a history of intractable epilepsy undergoes surgical resection of a seizure focus within the right frontal lobe. Histologic evaluation reveals the presence of dysmorphic neurons as well as cells with abundant, glassy, eosinophilic cytoplasm and eccentrically located nuclei. What is the diagnosis based on the International League Against Epilepsy (ILAE) classification system of focal cortical dysplasias (FCD)?
   a. FCD type Ia
   b. FCD type Ib
   c. FCD type Ic
   d. FCD type IIa
   e. FCD type IIb
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Question 1: Correct answer and rationale: D. While all of the above etiologies are associated with holoprosencephaly, cytogenetic abnormalities are seen in 50% of holoprosencephaly cases; Trisomy 13 is the most frequent. 25% of cases of holoprosencephaly are syndromic (such as Smith-Lemli-Opitz syndrome which is associated with mutations in DHCR7). Mutations in other genes including SHH and ZIC2 are seen in a small percentage of cases.

Question 2: Correct answer and rationale: B. Mutations in Doublecortin (DCX) are associated with both lissencephaly type I (4 layer cortex with anterior predominance) and band heterotopia. DCX is important for microtubule function and neuronal migration. RELN mutations are associated with autosomal recessive lissencephaly type I but not band heterotopia. POMT1/2 mutations are seen in Walker-Warburg syndrome. Alterations in ARFGEF2 and FLNA have been described in patients with nodular heterotopias.

Question 3: Correct answer and rationale: E. The pathology described is a FCD consisting of dysmorphic neurons and balloon cells, consistent with a diagnosis of ILAE FCD type IIb. FCD type IIa contains dysmorphic neurons and no balloon cells. All FCD type I are characterized by abnormalities in cortical lamination.