## eTable 1. Encephalitis diagnostic criteria from selected published studies

| Ref | Clinical manifestations | | CSF | Neuroimaging | EEG | Definition |
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| | Mandatory neurologic finding | Other | | | | |
| 1 | Encephalopathy: altered consciousness for ≥24 hours (including lethargy, irritability, change in personality or behavior) | 1. Temperature ≥ 38.0° C during presenting illness<br>2. Seizures<br>3. Focal neurologic findings | WBC ≥ 5/ $mm^3$ | Abnormality consistent with encephalitis | Abnormality consistent with encephalitis | Presence of mandatory neurologic finding plus ≥ 2 other criteria |
| 2 | Encephalopathy: depressed or altered level of consciousness for ≥24 hours (including lethargy, irritability, change in personality or behavior) | 1. Temperature ≥ 38.0° C<br>2. Seizures<br>3. Focal neurologic findings | WBC ≥ 5/ $mm^3$ | Abnormality consistent with encephalitis | Abnormality consistent with encephalitis | Presence of mandatory neurologic finding plus ≥ 2 other criteria |
| 3 | Encephalopathy (definite-presence of both a and b; possible presence of b only)<br>a. Significant change in mental status persisting ≥24 hours independent of a seizure, syncope, or medication effect<br>b. One of the following:<br>i. Decreased or absent response to environment<br>ii. Decreased or absent eye contact<br>iii. Inconsistent or absent response to external stimuli<br>iv. Seizure associated with loss of consciousness<br><br>OR<br><br>Focal neurologic findings | Not specified | Pleocytosis (adjusted for age) | Abnormality consistent with inflammation | Not specified | Definite encephalitis - definite encephalopathy or focal neurological findings plus pleocytosis or neuroimaging abnormality<br><br>Probable encephalitis - possible encephalopathy or focal neurological findings plus pleocytosis or neuroimaging abnormality<br><br>Possible encephalitis - definite or possible encephalopathy or pleocytosis or neuroimaging abnormality |
| 4 | Encephalopathy: depressed or altered level of consciousness for ≥24 hours, lethargy or personality change | 1. Fever<br>2. Seizures<br>3. Focal neurologic findings | Pleocytosis | Abnormality consistent with encephalitis | Abnormality consistent with encephalitis | Presence of mandatory neurologic finding plus 1 or more additional criteria |
| 5 | Encephalopathy (presence of a and b):<br>a. Depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours<br>b. One or more of the following<br>i. Decreased or absent response to | Fever | Pleocytosis (WBC> 5/$mm^3$ if ≥ 2 months of age or WBC >15 cells/$mm^3$ if | Abnormality consistent with encephalitis | Abnormality consistent with encephalitis | Diagnostic certainty: |

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| | environment<br>ii. Decreased or absent eye contact<br>iii. Inconsistent or absent response to external stimuli<br>iv. Decreased arousability<br>v. Seizure associated with loss of consciousness<br><br>OR<br><br>Focal or multifocal neurologic findings, including one or more of the following<br>a. Focal cortical signs<br>b. Cranial nerve abnormality<br>c. Visual field defect<br>d. Presence of primitive reflexes<br>e. Motor weakness<br>f. Sensory abnormality<br>g. Altered deep tendon reflexes<br>h. Cerebellar dysfunction | | < 2 months of age) | | | Level 1: Demonstration of acute inflammation of CNS parenchyma by histopathology<br><br>Level 2: Mandatory neurologic finding and ≥2 additional criteria<br><br>Level 3: Mandatory neurologic finding and 1 additional criteria |
| 6 | Acute onset of:<br>Decreased consciousness OR<br>Seizures OR<br>Altered mental status OR<br>Focal neurologic signs | Temperature ≥ 38.0$^{o}$ C | WBC ≥ 4/mm$^{3}$ or protein ≥ 40 mg/dL | Not specified | Not specified | Presence of mandatory neurologic finding plus fever and CSF abnormality |

**References:** 1 Granerod et al. Lancet Infect Dis 2010 10:835-44; 2 Kolski et al., Clin Infect Dis 1998 26:398-409; 3 Ball et al., J Clin Epidemiol 2002 55:819-824; 4 Glaser et al., Clin Infect Dis 2006 43:1565-1577; 5 Sejvar et al., Vaccine 2007 25:5771-5792; 6 Mailles et al. Clin Infect Dis 2009 49:1838-1847

**eTable 2. Strategies for identification of genotypic determinants of disease**

| Approach | Description | Advantages | Disadvantages |
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| Genomewide linkage scan | Genotypes are determined for a set of markers in cases and related controls within a given pedigree. Exploits expected Mendelian inheritance, associating transmission of linked alleles with disease status. | Adequate power obtainable with small study. Is effective with as few as 3,000 to 5,000 genome-wide single nucleotide polymorphism markers. Can efficiently localize genetic lesions of large effect, although typically to a large genomic interval. | Difficult to identify and enroll intact pedigrees for many infectious diseases. Must rigorously verify exposure and clinical history in unaffected family members. Poorly suited to complex phenotypes (e.g. multiple genes involved). |
| Candidate gene association study | Genotypes (often single nucleotide polymorphisms) are determined in cases and controls for a set of genes of biological interest or plausibility. | Reduction in multiple hypothesis testing increases power to detect alleles of modest effect. Allows for fine mapping of genetic lesions, and, ideally, the direct identification of causative polymorphisms. | Requires a larger study population relative to linkage studies, but fewer than for GWAS (see below). Unidentified differences in genetic ancestry among cases and controls (e.g. stratification) can lead to false positive signals. Limited by prior biological hypotheses. |
| Genomewide association study (GWAS) | Genotypes are determined in cases and controls for a large (often $>10^6$) number of markers across the entire genome. | Well powered to detect multiple genes of potentially modest effect, which contribute to a given trait, without limitations of prior biological hypotheses. Robust methods are available to control for population stratification and other sources of confounding. | Often require very large sample sizes (often > 1000 cases and controls), which can be difficult to obtain for many infectious diseases. Can be very expensive. |
| Genomewide resequencing of extreme phenotypes | DNA sequence is analyzed across either the protein coding exome or the entire genome for individuals who have a rare and extreme phenotype. Rare variants shared | Can be an efficient approach to identify rare, “pseudo-Mendelian” genes with a large effect on a given phenotype. Possible to simultaneously identify gene and | Difficult to identify lesions in complex or multifactorial traits. Lack of statistical inference makes this a hypothesis-generating approach. Still too expensive for larger study |

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| | among unrelated individuals suggest a candidate gene worthy of further study. | generate hypotheses based on the impact of the mutation(s) on the gene product. Also can be applied to family-based designs with improved power. | designs. |
| Functional studies | Candidate genes are identified using cellular or molecular phenotypes, often in biospecimens derived from cases. Causative alleles identified by sequencing these genes or others in the same biological pathway. | Can be used to identify a candidate gene and verify its biological role. The ultimate proof for genes/variants identified through all of above approaches. | Time and resource intensive. |