CH10: Identifying the genetic basis for human disease

In this type of gene mapping, one looks for the inheritance of a particular segment of the genome in conjunction with the trait of interest.

Association study

Linkage analysis

Family-based association test

Radiation hybrid mapping

Haplotype mapping

In order to assess recombination events between two markers, which two of the following must be known?

Dominance/ recessiveness of alleles

Position of markers on chromosome

Phase of marker alleles

Allele frequencies

Parents are heterozygous at both markers

Deviation from independent assortment of alleles is known as:

Linkage

Association

Haplotype

Recombination

Meiotic segregation

What property is associated with the co-inheritance of marker alleles at frequencies that deviate from that expected based on the allele frequencies?

Marker association

Linkage disequilibrium

Recombination

Marker phasing

Marker coupling

How are the linkage scores from multiple families combined?

Added

Subtracted

Multiplied

Averaged

Cannot be combined

What is the likely explanation for the smaller size of the linkage disequilibrium (LD) blocks in African populations compared to non-African populations?

Increased selection in Africa

Increased genetic drift in Africa

More generations since the African population was founded

Population bottleneck when humans moved out of Africa

Increased recombination in African populations

Which of the following does a logarithm of odds (LOD) score allow you to estimate?

The recombination frequency between a marker and a trait locus

The recurrence risk of a trait in a family

The population attributable risk of a mutation

The heritability of a trait

The amount of selection on a trait

Which of the following is a nonparametric linkage method?

Linkage analysis in phase-unknown pedigrees

Linkage analysis in phase-known pedigrees

Affected sib-pair analysis

Case-control study

A or B

Using the following groups, compose a formula for the odds ratio for a disease-marker association.

a. Affecters who have marker allele of interest

b. affecters who lack the marker allele of interest

c. Controls who have the marker allele of interest

d. Controls who lack the marker allele of interest

ab/cd

ac/bd

ad/bc

cd/ab

cb/ad

A false positive association that results from the use of a mixed population in an association study is caused by which of the following?

Linkage disequilibrium

Population stratification

Genetic diversity

Genetic drift

Gene flow

Which of the following are possibly explanations for a positive result in an association study?

Population stratification

You have found the allele that confers risk of your trait of interest

The allele you have found is in LD with the risk-conferring allele

It is a false positive caused by the number of markers examined in the study

All of the above

What do tagSNPs define?

Genes

Exons

All variation

Chromosomes

Haplotypes

Which of the following is an assumption that must hold for large-scale association studies to be successful?

The risk allele is in a coding region

Only one gene is involved in the trait

The mutation giving rise to the risk allele occurred only once

The risk allele must not occur in the control group

All of the above

Which of the following is true ONLY for association studies, as compared to linkage studies?

Can use thousands of markers in the analysis

Can identify the functional risk allele for the trait of interest

Families can be used in the analysis

Makes use of the correlation between recombination and genetic distance

Requires model specification

Which of the following is true ONLY for linkage analysis, as compared to association studies?

Families can be used in the analysis

Makes use of the correlation between recombination and genetic distance

Recombination events within families can be highly informative in this analysis

Model-free methods are available

Can use thousands of markers in the analysis

Which of the following situations would support use of positional cloning for disease gene identification?

Disease pathogenesis is poorly understood

Candidate genes are not apparent

Chromosomal rearrangements highlight regions of interest

Many disease alleles can be present in the disease gene

All of the above

Which of the following methods would be used to find the disease gene for a Mendelian trait, as opposed to a complex trait?

Parametric linkage analysis

Association studies

Examining chromosomal rearrangements

A and B

A and C

CH11: Hemoglobinopathies

Which of the following is the most common effect of a disease-causing mutation on a protein?

Loss of function

Gain of function

Heterochronic expression

Ectopic expression

Dominant negative

Which of the following types of mutations can cause a loss of function to the protein?

Missense

Nonsense

Frameshift

Splice site

Any of the above

At which stage can a mutation disrupt the normal production of a protein?

Translation of polypeptide

Protein folding

Posttranslational modification

Subcellular localization

Any of the above

A transition between which two hemoglobin molecules occurs around the time of birth?

α to β

α to γ

β to γ

γ to β

ε to γ

What is the effect of deletion of the locus control region for the β-globin gene cluster?

Loss of fetal hemoglobin expression

Reduced expression of hemoglobin

Absent expression of all of the hemoglobin genes in the cluster

Overexpression of all of the hemoglobin genes in the cluster

Inappropriate expression of fetal and embryonic hemoglobin after birth

Four sites associated with what type of DNA conformation are important for the regulatory control of β globin expression by the locus control region (LCR)?

Open chromatin conformation

Closed chromatin conformation

DNA hairpin

DNA break

DNA loop

Why can α-globin mutations have an effect earlier in life than β-globin mutations?

There are fewer α-globin genes

The β-like globin hemoglobin F (HbF) is produced during fetal development and β globin predominates only after birth

Fewer α globin's are in each hemoglobin molecule

More α globin's are in each hemoglobin molecule

Mutations in the α-globin genes prevent proper developmental expression of other globin genes

Which clinical phenotype is associated with an imbalance in the production of the α- and β-globin chains?

Hemophilia

Hemolytic anemia

Sickle cell anemia

Thalassemia

Polycythemia

Which clinical phenotype is associated with a β-chain mutation that locks the hemoglobin into the relaxed state, which has a high affinity for oxygen?

Hemophilia

Hemolytic anemia

Sickle cell anemia

Thalassemia

Polycythemia

Why is hydrops fetalis largely restricted to Southeast Asia?

Dietary differences between populations affect expressivity of the phenotype

The type of malaria present in this area

Two α-globin alleles are commonly deleted in cis in this population

α-Thalassemia carrier status is most common in this population

A compensating hemoglobinopathy is less common in this population

In addition to mutations in α globin, α thalassemia can result from mutations in which of the following genes?

β globin

γ globin

(XIST) C and D are gene names and don't need to be spelled out

(ATRX)

A or B

The hemoglobin E (HbE) allele of β globin, which is associated with reduced production of the β-globin chain, occurs at a very high frequency in which region?

Europe

South America

Sub-Saharan Africa

The Middle East

Southeast Asia

CH:12 Genetic diseases

If an infant is found to have hyperphenylalaninemia based on a newborn screen, but this defect doesn't respond to a low phenylalanine diet, what type of molecular defect would be suspected?

Null mutation for phenylalanine hydroxylase

Dominant negative mutation for phenylalanine hydroxylase

A defect in tetrahydrobiopterin (BH4) metabolism

A mutation in tyrosine hydroxylase

A mutation in tryptophan hydroxylase

Which patients with mutations in phenylalanine hydroxylase are most likely to respond to BH4 supplementation?

Those with null mutations

Those who have only one phenylalanine hydroxylase (PAH) mutation

Those who are compound heterozygotes for PAH mutations

Those with residual PAH activity

Those with a defect in BH4-PAH binding

A mother with phenylketonuria (PKU) has a child with microcephaly, growth impairment, and mental retardation. She is concerned with the recurrence risk for her current pregnancy. What is the risk likely to be?

Very low because of carrier mutation rate

25%

50%

Almost 100%

Not enough information given

What observation has facilitated genetic testing for Tay-Sachs's disease in the Ashkenazi Jewish population?

Three mutations account for the vast majority of disease alleles

The causative gene is small

There are no pseudo-disease alleles

Only missense mutations cause disease

Only nonsense mutations cause disease

Where are GM2 ganglioside and mucopolysaccharides digested?

Proteasome

Endosome

Lysosome

Extracellularly

Cytoplasm

The finding that fibroblasts from a patient with X-linked Hurler syndrome could correct the defect in fibroblasts from a patient with autosomal recessive Hurler syndrome (and vice versa) demonstrated what about the two disorders?

There is a mild phenotype in either case

One form of Hurler is more severe than the other

Different proteins were deficient in the two disorders

The same protein was deficient in the two disorders

One was caused by a missense mutation and the other by a nonsense mutation

Which of the following properties allows enzyme replacement therapy to work for some lysosomal storage disorders?

Excess enzyme causes formation of new lysosomes

The enzymes can be dried into a pill

The enzymatic defect is generally mild

Cells can take up the enzymes from extracellular fluid

The therapy triggers upregulation of the deficient enzyme

Why can vitamins be used to treat some enzymatic defects?

They are water-soluble

They can increase the activity of the defective enzyme

They often serve as enzyme cofactors

They can sometimes stabilize the defective enzyme

All of the above

Genetic defects that impair the activity of methionine synthase are mimicked by a dietary deficiency of which vitamin?

Vitamin C

Vitamin A

Vitamin B12

Vitamin D

Vitamin K

What inheritance pattern is most common for metabolic disorders?

Autosomal dominant

Autosomal recessive

X-linked dominant

X-linked recessive

None of the patterns predominates

How can a single gene defect lead to multiple enzyme deficiencies?

The enzymes share a cofactor

The enzymes are modified by the same processing pathway

The enzymes are transported in similar ways

The organelle in which the enzymes work is defective

Any of the above

α1-antitrypsin deficiency leads to excess activity of which enzyme?

Elastase

Tyrosinase

A glycosylase

Cystathionine synthase

α-l-iduronates

What environmental exposure greatly influences the life expectancy of individuals with the ZZ genotype for α1-antitrypsin deficiency?

Low folic acid intake

Cigarette smoking

Excess sunlight exposure

Low fiber intake

Alcohol intake

The genes associated with familial hypercholesterolemia all have an effect on which protein?

Apolipoprotein E (ApoE)

Amyloid precursor protein

Apolipoprotein C-I

Low-density lipoprotein (LDL) receptor

Sterol regulatory element-binding protein

What is the inheritance pattern for familial hypercholesterolemia caused by a defect in the gene for the LDL receptor?

Autosomal dominant

Autosomal recessive

X-linked dominant

Complex trait

None of the above

Variation in which familial hypercholesterolemia-causing gene has also been associated with protection from coronary artery disease and high cholesterol levels in general populations?

LDL receptor (LDLR)

PCSK9 protease

Apoprotein B-100 (ApoB100)

ARH adaptor protein (ARH)

All of the above

Which of the following phenotypes is found in people with mutations in cystic fibrosis transmembrane conductance regulator (CFTR)?

Cystic fibrosis

Congenital bilateral absence of the vas deferens

Idiopathic chronic pancreatitis

Meconium ileus

Any or all of the above

Which of the following is the major cause of chronic pulmonary infection in individuals with cystic fibrosis?

Pseudomonas aeruginosa

Influenza

Common cold

Clostridium difficile

Francisella tularensis

Which of the following is the most common CFTR mutation in white populations?

Arg117His

Gln1412X

IVS10 G>A -1

ΔF508

2 BP Ins, 1154TC

Mutations in the dystrophin gene cause which phenotype?

Duchenne muscular dystrophy

Becker muscular dystrophy

Congenital bilateral absence of the vas deferens

Both A and B

Both A and C

What phenomenon has a large effect on the phenotype of female carriers of dystrophin mutations?

Imprinting

X-inactivation

Expression of sex-specific modifier genes

The lower muscle mass in females

All of the above

In contrast to mutations associated with Duchenne muscular dystrophy, what is a feature of the mutations associated with Becker muscular dystrophy?

They are found mostly in the 5’ region of the gene

They are found mostly in the 3’ region of the gene

They are unlikely to be deletions

They are associated with some production of the dystrophin protein

They are always point mutations

Which of the following leads to the higher frequency of inherited Becker muscular dystrophy compared to Duchenne muscular dystrophy?

Higher fitness of mutations in males affected with Becker than Duchenne muscular dystrophy

Higher mutation rate for Duchenne-associated disease

Increased frequency of prenatal termination for Duchenne cases

Lower penetrance in female carriers for Becker versus Duchenne mutations

None of the above

Mutations in the genes for which major structural protein of bone and other fibrous tissues is mutated in osteogenesis imperfecta?

Fibrin

Actin

Type I collagen

Myosin

Dystrophin

Which of the following is the only residue that can fit into certain portions of the triple helical segment of collagen because of its small size?

Alanine

Glycine

Proline

Aspartic acid

Lysine

Which type of mutation is likely to be associated with a milder osteogenesis imperfecta phenotype?

Missense mutation for glycine in proα1(1) chain

Missense mutation for glycine in proα2(1) chain

Missense mutation in either chain disrupting rate of α helix formation

Mutation affecting posttranslational modification of collagen

Null mutation for proα1(1) chain

What is the likely cause when a family has two children affected with osteogenesis imperfecta type II?

Autosomal dominant mutation in family

Germline mosaicism in parent

Recurrent mutation

Increased penetrance in family

Skewed X-inactivation

What common effect do mutations that are associated with monogenic forms of Alzheimer disease typically have?

Increased production of Tau

Increased production of amyloid precursor protein

Decreased production of amyloid precursor protein

Increased production of Aβ42 peptide

Decreased production of Aβ42 peptide

Which of the following is true for the association of ApoE and Alzheimer disease?

ε4 is over-represented in samples of affected individuals

ε4 is associated with an earlier age of onset

Genetic screening for the ε4 allele is performed to identify those at risk of Alzheimer disease

A and B

All of the above

Why is maternal inheritance observed with mitochondrial DNA?

The sperm mitochondria are eliminated from the embryo

Sperm lack mitochondria

Female cells have more mitochondria than male cells

No mitochondrial genes are encoded on the paternal genome

There is imprinting of the mtDNA

What feature of oogenesis can greatly influence the level of mtDNA mutation in the offspring of a women carrying a mtDNA mutation?

The small number of mitotic divisions

The long time that elapses between the beginning and end of meiosis in females

The mitochondrial genetic bottleneck

Energy requirements in the egg mean natural selection has a strong effect on mitochondrial (mtDNA) mutations

mtDNA deletions have low fitness in the egg

The tissues that are most affected by mtDNA mutations have high requirements for which of the following?

Free radicals

Protein

Macromolecular transport

Metabolic energy

Blood flow

What is the histopathologic phenotype associated with mitochondrial myopathy?

Ragged red fibers

Excess mitochondria in muscle cells

Pseudohypertrophy

Protein inclusions

Myelin sheath hypertrophy

What is the mechanism thought to be responsible for the expansion of trinucleotide repeats?

Nonhomologous recombination

Segmental duplication

Slipped mispairing during DNA replication

Resolution of tangled secondary structure

Polymerase stuttering

CGG expansions in the 5′ untranslated region 5′UTR of FMR1 cause which of the following?

Expression of polyglutamine sequences

Repeat methylation and transcriptional silencing

Gain of function toxicity of the FMR1 mRNA

A or B

B or C

What is the likely mechanism by which repeat expansions cause myotonic dystrophy?

Expression of polyglutamine sequences

Repeat methylation and transcriptional silencing

Translational silencing by the repeat

Expanded repeats sequester excessive amounts of RNA-binding proteins

C and D

CH14: DEVELOPMENTAL

In dysmorphology, a disruption is a type of variation that is characterized by which of the following?

Destruction or interruption of intrinsically normal tissue

An underlying genetic mechanism

An abnormal developmental process

High recurrence risk

Somatic mutation during development

To which of the following categories does polydactyly belong?

Malformation

Disruption

Deformation

Skeletal dysplasia

Sequence

What term is used for a collection of abnormalities that are caused by a single causative agent in parallel?

Deformation

Disruption

Cluster

Syndrome

Sequence

What term is used for a collection of abnormalities in which the causative agent affected a single organ system at one point in development, and this had subsequent pleiotropic secondary effects?

Deformation

Disruption

Cluster

Syndrome

Sequence

What do we call an environmental agent that causes abnormal development in a fetus or embryo?

Mutagen

Teratogen

Carcinogen

Fetotoxic agent

Morphogen

Which of the following is a totipotent cell?

Bone marrow stem cell

Nerve in central nervous system

Epithelial cell

Embryonic stem cell

All of the above

What is the downstream effect of exposure to a morphogen?

Abnormal development

Cellular mutations

Cancer

Cellular differentiation

Cellular arrest

What cell type is the exception to the rule that the gene expression profile in a particular type of differentiated cell does not involve permanent changes to the DNA sequence?

Neuron

Erythrocyte

Lymphocyte precursors

Epithelial cell

Germ cell

Given the fact that the genome in an individual is the same in every cell in the body, what determines the gene expression pattern for any type of differentiated cell?

Genomic rearrangements

Epigenetic changes

Mitochondrial genome

Teratogens

All of the above

Which of the following is a natural example that proves there is early regulative development in humans?

Monozygotic twinning

There are a predictable number of cells at various time points in early development

Exposure to teratogens can lead to defects that are obvious in the fetus

The vast majority of humans are symmetrical in overall body structure

Amniotic bands can lead to fetal disruptions

During which stage in development is preimplantation diagnosis possible?

Prior to fertilization

Regulative development

Mosaic development

Specification

Differentiation

What is the mechanism by which developmental morphogens such as Sonic hedgehog control body patterning?

By directly inducing gene expression

By directly suppressing gene expression

Through concentration gradients

The order of expression of hedgehog genes relates to their position in the genome and determines body patterning

By degrading proteins that suppress transcription

Which of the following occurs as a result of defects in migration of cortical neurons during development?

Holoprosencephaly

Anencephaly

Microcephaly

Lissencephaly

Spina bifida

Which of the following results from defects in migration of neural crest cells?

Lissencephaly

Hirschsprung disease

Crohn disease

Miller-Dieker syndrome

Achondroplasia

Which of the following is the major form of programmed cell death during development?

Necrosis

Apoptosis

Cytolysis

Complete transcriptional shutdown

Autophagy

Which morphogen is primarily responsible for setting the anterior-posterior axis in the developing limb?

Tbx4

Hedgehog

Sonic hedgehog

Wnt7

GLI3

Which of the following is a possible consequence of a defect in anterior-posterior patterning in the limb?

Shortened limb

Synpolydactyly

Waardenburg syndrome

Congenital segmental overgrowth

Arthrogryposis