Medical Genetics for the MRCOG and Beyond

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Contents

Abbreviations

A	adenine
aCGH	array comparative genomic hybridisation
α-FP	alphafetoprotein
ARMS	amplification refractory mutation system
bp	base pair
BRCA1	breast cancer type 1 gene
C	cytosine (or consultand in a pedigree diagram)
cffDNA	cell-free fetal DNA
CFTR	cystic fibrosis transmembrane conductance regulator gene
CPK	creatine phosphokinase
CVS	chorionic villus sampling
DMD	Duchenne muscular dystrophy
DMPK	dystrophia myotonica-protein kinase gene
DNA	deoxyribonucleic acid
EDTA	ethylenediamine tetra-acetic acid
FβhCG	free beta human chorionic gonadotrophin
FISH	fluorescence *in situ* hybridisation
FMR1	fragile site mental retardation 1 gene
FXTAS	fragile X tremor/ataxia syndrome
G	guanine
Gy	gray
hCG	human chorionic gonadotrophin
HNPCC	hereditary nonpolyposis colorectal cancer
HPRT	hypoxanthine phosphoribosyltransferase gene
IDUA	alpha-L-iduronidase gene
IRT	immunoreactive trypsinogen
kb	kilobase

L1CAM	L1 cell adhesion molecule gene
Mb	megabase
MLPA	multiplex ligation-dependent probe amplification
M/M	mutant/mutant
MOM	multiples of the median
MSAFP	maternal serum alphafetoprotein
N/M	normal/mutant
NGS	next-generation sequencing
NIPD	noninvasive prenatal diagnosis
PAPP-A	pregnancy-associated plasma protein A
PCR	polymerase chain reaction
PGD	preimplantation genetic diagnosis
QF-PCR	quantitative fluorescent polymerase chain reaction
rads	radiation absorbed doses
T	thymine
TP63	tumour protein p63

Glossary

allele	alternative forms of a gene at the same locus
array comparative genomic hybridisation (aCGH)	detection method for DNA duplications or deletions by competitive hybridisation, using a microarray of known mapped sequences and fluorescently labelled control and test DNA
autosomal dominant inheritance	mutation in one member of an autosomal gene pair results in disease
autosomal recessive inheritance	mutation in both members of an autosomal gene pair is necessary for disease to occur
autosome	chromosomes numbers 1 to 22 inclusive
balanced translocation	transfer of chromosomal material between chromosomes with no overall gain or loss and hence no clinical effect
base pair	unit of length of DNA of one set of paired bases (AT or GC)
carrier	a person with one mutation in an autosomal or X chromosomal gene pair who shows recessive inheritance (i.e. no clinical effect unless both members of the gene pair are mutated)
centromere	a constricted area of the chromosome that divides it into short and long arms
chromosome disorder	any abnormality of chromosome number or structure visible under the light microscope
codon	three consecutive bases in DNA (or RNA) that specify an amino acid

concordance	likelihood that both (e.g. twins) will be affected or unaffected
congenital	present at birth
consanguineous	mating between individuals who share at least one common ancestor
consultand	a person requesting genetic counselling
deletion	loss of chromosomal material
diagnostic test	a test that confirms or refutes a diagnosis
dizygotic twins	twins which arise from the fertilisation of two separate eggs
dominant	a trait expressed in the heterozygote
empiric risk	recurrence risk based on experience rather than calculation
false negative rate	proportion of affected cases missed by a screening test
first-degree relatives	immediate relatives who have one half of their genes in common (e.g. parent and child or brother and sister)
fluorescence *in situ* hybridisation	the use of a fluorescently labelled DNA probe to bind to specific chromosomal region of interest
gene	a segment of DNA that codes for a functional product (e.g. a protein)
gene probe	a labelled segment of DNA that can be used to find its matching segment among a mixture of DNA fragments
genetic counselling	communication of information and advice about inherited disorders
genetic heterogeneity	genetic mimicry where mutations in different genes can produce a similar clinical picture
genomic imprinting	parent-specific expression or repression of genes in offspring
genotype	the genetic make-up of an individual
gonadal mosaic	a person with a mixture of cells in their gonad, some with a mutation and some without

heterozygous	a person with a gene pair who has one mutant and one normal gene
homozygous	a person with a gene pair in which both copies of the gene are mutant or normal
independent risks	risks where the outcome of one event has no influence on the outcome of the other (e.g. if two coins are tossed heads or tails may occur for either and the result for one does not influence the other)
karyotype	the chromosomal make-up of an individual
kilobase	a unit of length of DNA of 1000 base pairs
length mutation	a type of DNA change where the DNA sequence is increased or decreased in size
locus	the location of a gene on a chromosome
megabase	a unit of length of DNA of 1 000 000 base pairs
meiosis	reduction cell division that occurs in the gonads in the production of eggs and sperm
microdeletion	a chromosomal deletion that is at or below the limit of resolution using a light microscope
mitosis	normal cell division that results in daughter cells with an identical genetic complement
monozygotic twins	twins which result from the early division of a single fertilised egg into two embryos
mosaic	an individual with cells with two or more genetic constitutions
multifactorial inheritance	conditions arising from the interaction of multiple genes and environmental factors
mutation	alteration of genetic material

mutational heterogeneity	different mutations in a particular gene may cause the same disease
mutually exclusive risks	risks where one outcome of an event precludes another outcome (e.g. a single tossed coin can result in heads or tails but not both)
nonpenetrance	no signs or symptoms in an individual who has inherited an autosomal dominant trait
phenotype	the clinical features of an individual
point mutation	a type of DNA change where a single base is replaced with another base
polymerase chain reaction	a technique for amplification of a target segment of DNA
polymorphism	a common DNA or chromosomal variant (present in at least 1% of the population)
proband	the individual who draws medical attention to the family
recessive	a trait that is expressed only in homozygotes
satellite stalks	the short arms of chromosomes 13, 14, 15, 21 and 22
screening test	a test that divides a population according to risk for a condition; those at high risk are then offered a diagnostic test
second-degree relatives	close relatives with one-quarter of their genes in common (e.g. grandparent and grandchild or nephew/niece and aunt/uncle)
sensitivity	the proportion of cases detected by a screening test
sibship	a family group of brothers and/or sisters
somatic cell disorders	genetic conditions that arise after conception from accumulation of genetic mutations in a cell or group of cells
somatic mosaic	a person with a mixture of cells, some with a mutation and some without

specificity	the proportion of the unaffected population included by a screening test in the high-risk group (also called the false positive rate)
syndrome	a nonrandom combination of clinical features
telomere	the ends of the short and long arms of the chromosomes
third-degree relatives	more distant relatives who share one-eighth of their genes (e.g. first cousins)
trait	any gene-determined characteristic
translocation	the transfer of chromosomal material between chromosomes
triploidy	an extra half set of chromosomes resulting in 69 in total
trisomy	an extra copy of a chromosome resulting in 47 in total
variable expressivity or expression	variation in clinical effects of an autosomal dominant trait
X-linked recessive inheritance	disease due to mutations in genes on the X-chromosome; males with only one X are affected if that copy is mutant whereas females with two X chromosomes are usually unaffected if only one copy is mutant

Preface

There is a long history of successful interaction between obstetrics and gynaecology and medical genetics. Initially, most applications related to obstetrics, especially with the use of prenatal diagnosis and screening but, more recently, the growth has been in applications related to gynaecology, especially in relation to gynaecological malignancies.

However, despite this long history, there is a widespread misconception that genetics is a difficult subject to understand. This book thus aims to dispel this misconception as well as providing a revision aid for the MRCOG candidate. The first section covers basic principles. The second section outlines the more common situations where obstetrics and gynaecology and medical genetics interact and the third section contains real-life clinical case scenarios. These scenarios have been selected to represent typical problems and to highlight areas that, if mismanaged, could (and did, in many of these cases) lead to medico-legal consequences.

The book discusses the uses of the latest techniques, such as 'next-generation sequencing', quantitative fluorescent polymerase chain reaction (QF-PCR), array comparative genomic hybridisation (aCGH), preimplantation genetic diagnosis (PGD) and the recently introduced analysis of free fetal DNA in the maternal circulation for noninvasive prenatal diagnosis (NIPD). In addition, the increasing importance of online databases is reflected in the greatly expanded section (Appendix 1) that outlines the online medical genetic resources, which are most useful and appropriate for different purposes and provides their web addresses. An accompanying online guide (www.essentialmedgen.com) provides the reader with links to these databases from a single website in addition to news of the latest developments in the field.

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