Medical Genetics for the MRCOG and Beyond

Second edition
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Edward S. Tobias and J. Michael Connor
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## Abbreviations

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<tr>
<td>A</td>
<td>adenine</td>
</tr>
<tr>
<td>aCGH</td>
<td>array comparative genomic hybridisation</td>
</tr>
<tr>
<td>α-FP</td>
<td>alphafetoprotein</td>
</tr>
<tr>
<td>ARMS</td>
<td>amplification refractory mutation system</td>
</tr>
<tr>
<td>bp</td>
<td>base pair</td>
</tr>
<tr>
<td>BRCA1</td>
<td>breast cancer type 1 gene</td>
</tr>
<tr>
<td>C</td>
<td>cytosine (or consultand in a pedigree diagram)</td>
</tr>
<tr>
<td>cfDNA</td>
<td>cell-free fetal DNA</td>
</tr>
<tr>
<td>CFTR</td>
<td>cystic fibrosis transmembrane conductance regulator gene</td>
</tr>
<tr>
<td>CPK</td>
<td>creatine phosphokinase</td>
</tr>
<tr>
<td>CVS</td>
<td>chorionic villus sampling</td>
</tr>
<tr>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>DMPK</td>
<td>dystrophia myotonica-protein kinase gene</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediamine tetra-acetic acid</td>
</tr>
<tr>
<td>FβhCG</td>
<td>free beta human chorionic gonadotrophin</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridisation</td>
</tr>
<tr>
<td>FMR1</td>
<td>fragile site mental retardation 1 gene</td>
</tr>
<tr>
<td>FXTAS</td>
<td>fragile X tremor/ataxia syndrome</td>
</tr>
<tr>
<td>G</td>
<td>guanine</td>
</tr>
<tr>
<td>Gy</td>
<td>gray</td>
</tr>
<tr>
<td>hCG</td>
<td>human chorionic gonadotrophin</td>
</tr>
<tr>
<td>HNPCC</td>
<td>hereditary nonpolyposis colorectal cancer</td>
</tr>
<tr>
<td>HPRT</td>
<td>hypoxanthine phosphoribosyltransferase gene</td>
</tr>
<tr>
<td>IDUA</td>
<td>alpha-L-iduronidase gene</td>
</tr>
<tr>
<td>IRT</td>
<td>immunoreactive trypsinogen</td>
</tr>
<tr>
<td>kb</td>
<td>kilobase</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>LICAM</td>
<td>L1 cell adhesion molecule gene</td>
</tr>
<tr>
<td>Mb</td>
<td>megabase</td>
</tr>
<tr>
<td>MLPA</td>
<td>multiplex ligation-dependent probe amplification</td>
</tr>
<tr>
<td>M/M</td>
<td>mutant/mutant</td>
</tr>
<tr>
<td>MOM</td>
<td>multiples of the median</td>
</tr>
<tr>
<td>MSAFP</td>
<td>maternal serum alphafetoprotein</td>
</tr>
<tr>
<td>N/M</td>
<td>normal/mutant</td>
</tr>
<tr>
<td>NGS</td>
<td>next-generation sequencing</td>
</tr>
<tr>
<td>NIPD</td>
<td>noninvasive prenatal diagnosis</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>pregnancy-associated plasma protein A</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PGD</td>
<td>preimplantation genetic diagnosis</td>
</tr>
<tr>
<td>QF-PCR</td>
<td>quantitative fluorescent polymerase chain reaction</td>
</tr>
<tr>
<td>rads</td>
<td>radiation absorbed doses</td>
</tr>
<tr>
<td>T</td>
<td>thymine</td>
</tr>
<tr>
<td>TP63</td>
<td>tumour protein p63</td>
</tr>
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</table>
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
autosomal 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 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
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>mutational heterogeneity</td>
<td>different mutations in a particular gene may cause the same disease</td>
</tr>
<tr>
<td>mutually exclusive risks</td>
<td>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)</td>
</tr>
<tr>
<td>nonpenetrance</td>
<td>no signs or symptoms in an individual who has inherited an autosomal dominant trait</td>
</tr>
<tr>
<td>phenotype</td>
<td>the clinical features of an individual</td>
</tr>
<tr>
<td>point mutation</td>
<td>a type of DNA change where a single base is replaced with another base</td>
</tr>
<tr>
<td>polymerase chain reaction</td>
<td>a technique for amplification of a target segment of DNA</td>
</tr>
<tr>
<td>polymorphism</td>
<td>a common DNA or chromosomal variant (present in at least 1% of the population)</td>
</tr>
<tr>
<td>proband</td>
<td>the individual who draws medical attention to the family</td>
</tr>
<tr>
<td>recessive</td>
<td>a trait that is expressed only in homozygotes</td>
</tr>
<tr>
<td>satellite stalks</td>
<td>the short arms of chromosomes 13, 14, 15, 21 and 22</td>
</tr>
<tr>
<td>screening test</td>
<td>a test that divides a population according to risk for a condition; those at high risk are then offered a diagnostic test</td>
</tr>
<tr>
<td>second-degree relatives</td>
<td>close relatives with one-quarter of their genes in common (e.g. grandparent and grandchild or nephew/niece and aunt/uncle)</td>
</tr>
<tr>
<td>sensitivity</td>
<td>the proportion of cases detected by a screening test</td>
</tr>
<tr>
<td>sibship</td>
<td>a family group of brothers and/or sisters</td>
</tr>
<tr>
<td>somatic cell disorders</td>
<td>genetic conditions that arise after conception from accumulation of genetic mutations in a cell or group of cells</td>
</tr>
<tr>
<td>somatic mosaic</td>
<td>a person with a mixture of cells, some with a mutation and some without</td>
</tr>
</tbody>
</table>
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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J. Michael Connor
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Fig. 1.31: Nicola Williams
Fig. 3.20: Margo Whiteford

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