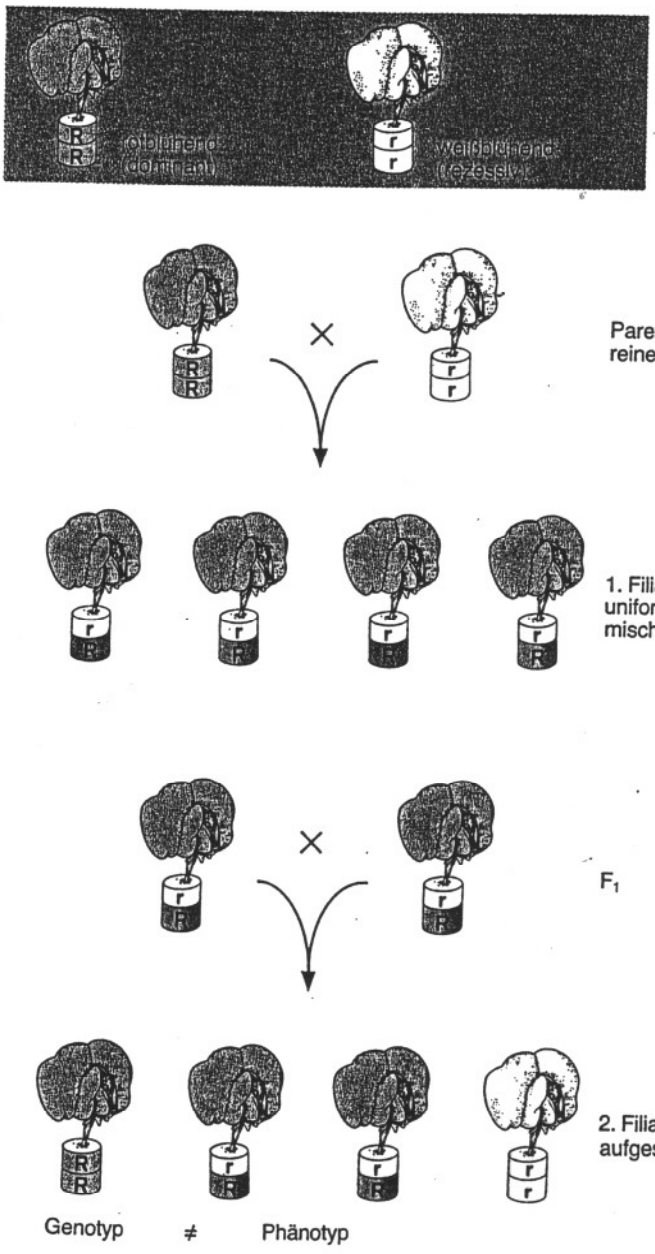



**Abb. 3.3 Kreuzungsexperimente von Mendel**
Reinerbige Elternrassen (P), die sich in nur einem Merkmal unterscheiden, werden gekreuzt. Die $F_1$-Generation ist uniform, sie prägt im Phänotyp das dominante Merkmal aus, ist im Genotyp heterozygot. Kreuzung von $F_1$-Nachkommen untereinander führt in der $F_2$-Generation zur Segregation (Aufspaltung) der Merkmale. Es resultieren reinerbige und heterozygote Nachkommen

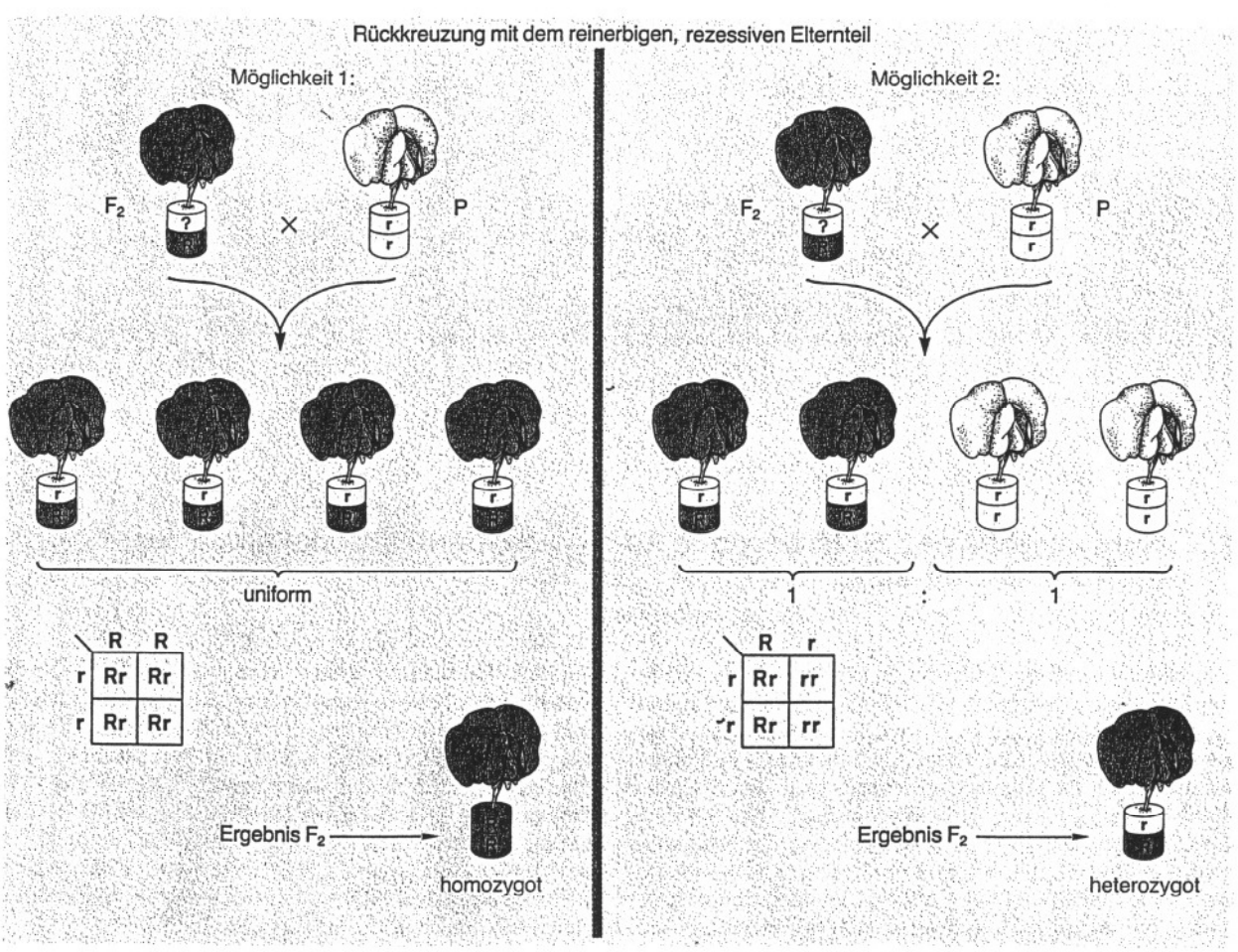



**Abb. 3.4 Mendels Testkreuz: ein Weg zur Ermittlung des Genotyps**
Phänotypisch gleiche Individuen können durch Rückkreuzung mit dem für das rezessive Merkmal reinerbigen Elternteil auf ihren Genotyp hin analysiert werden

- Alleles are the variants of a given gene

- Gene: defined region of chromosomal DNA carrying the information that determines a character

- Wild-type / variant alleles (e.g.mutation)

- Organism carries a maximum of two alleles
One paternal allele and one maternal allele

- Within a species, the same gene is localized at he same position (gene locus) on the two homologous chromosomes

- Alleles: dominant, recessive, co-dominant, semi-dominant
in fact, properties of of characters, not genes

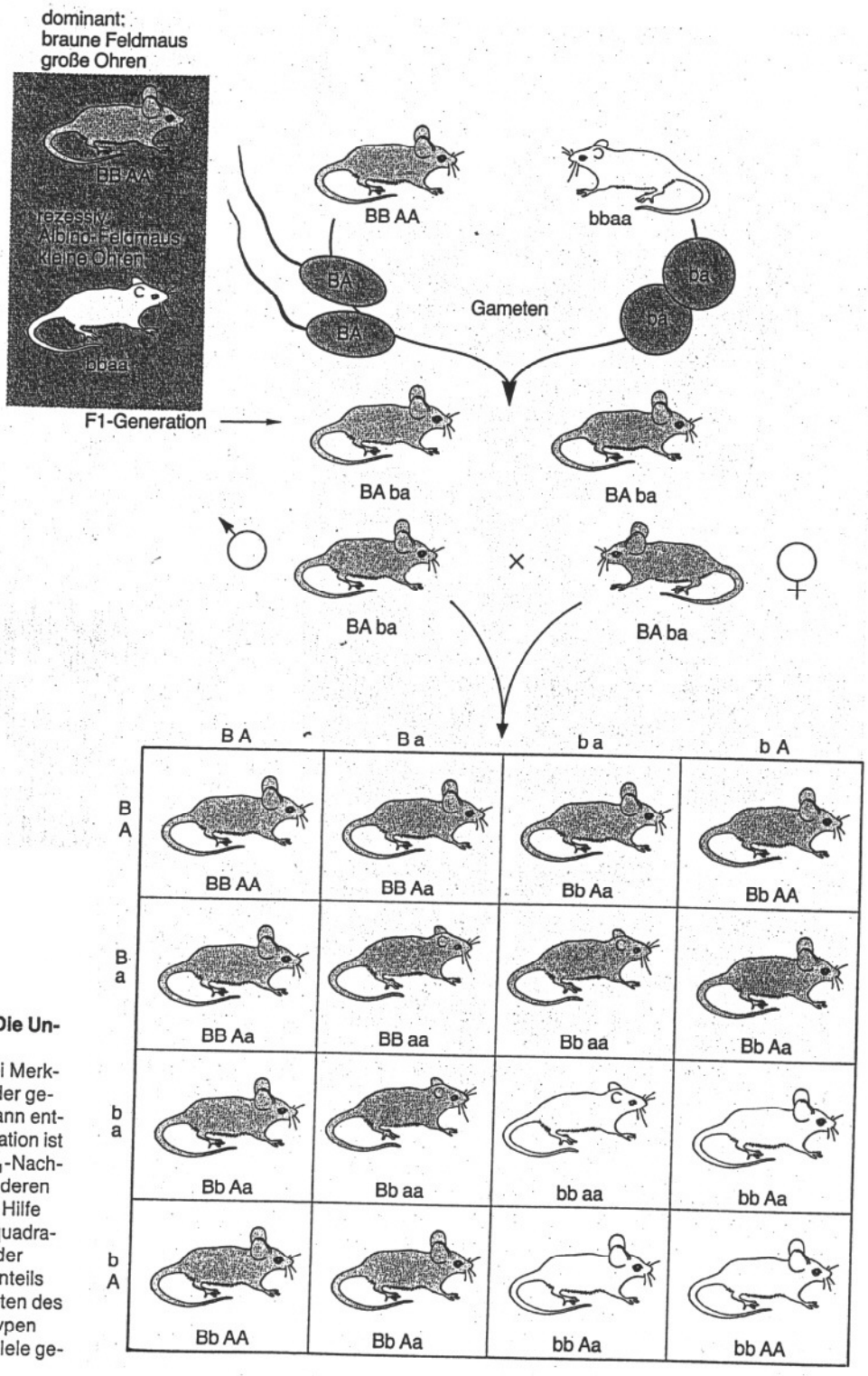
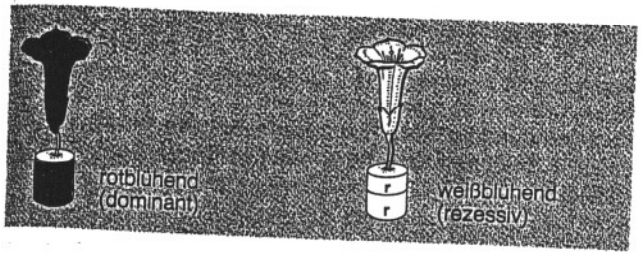
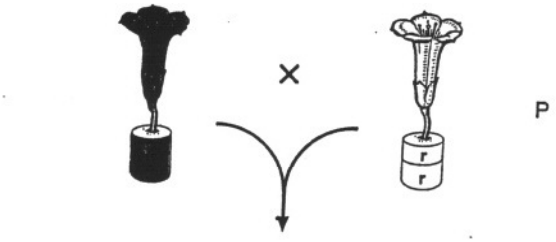
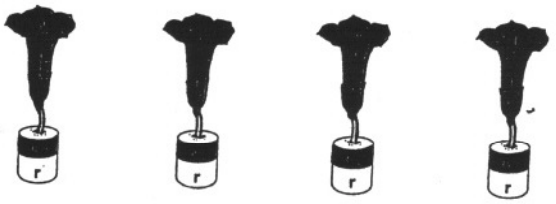


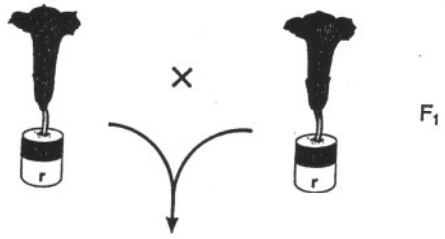

**Abb. 3.5 Mendels Genetik: Die Unabhängigkeitsregel**
Werden Rassen, die sich in zwei Merkmalen unterscheiden, miteinander gekreuzt (Mehrfaktorkreuzung), dann entstehen Dihybride. Die $F_1$-Generation ist wieder uniform. Kreuzung der $F_1$-Nachkommen führt zu $F_2$-Individuen, deren Genotypen und Phänotypen mit Hilfe des genetischen Kombinationsquadrates ermittelt werden können. Jeder mögliche Gamet des einen Elternteils wird mit jedem möglichen Gameten des anderen kombiniert. Die Phänotypen werden durch die dominanten Allele geprägt

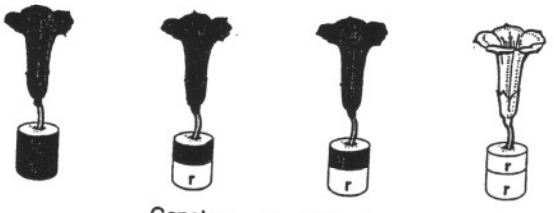



heterozygot: rosablühend = intermediär




Genotyp ≠ Phänotyp

**Abb. 3.6 Intermediärer Erbgang bei der Wunderblume *(Mirabilis jalapas)***
Kreuzung rot- und weißblühender Pflanzen führt zu einer intermediären Farbe (rosa) in der $F_1$-Generation. In der $F_2$-Generation entspricht in diesem Falle die Zahl der Phänotypen der der Genotypen, da keines der Farballele dominant ist und somit sich die Heterozygoten von den Homozygoten phänotypisch unterscheiden. Beide Farballele tragen zum Phänotyp bei, es herrscht Semidominanz

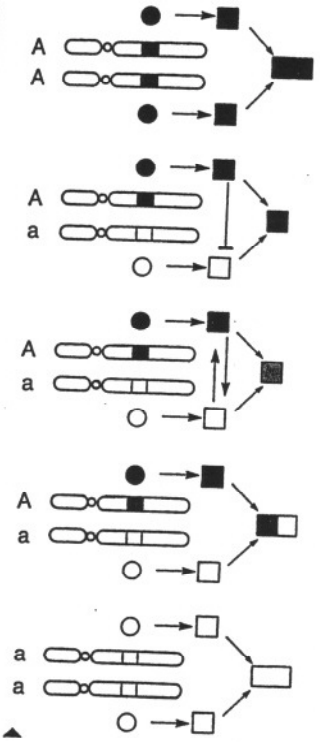



**Abb. 3.7 Dominante, rezessive, codominante und intermediäre (semidominante) Ausprägung der Allele eines Gens**
Symbolische Darstellung eines Gens im diploiden Zustand, dessen Genprodukt (Enzym) entsprechend den jeweiligen Zustandsformen des Gens (Allels) gebildet wird. Das vorliegende Enzym führt seinerseits zur Ausbildung eines Merkmals, das den Phänotyp prägt
● Allel eines Gens
○ Enzym
□ Merkmal

## Applications to Human genetics

- Mendelian character: a genotype at one locus that is both necessary and sufficient for the character to be expressed

- Basic Mendelian pedigree patterns

- OMIM is the standard database of mendelian characters

• Mc Kusik- Online Mendelian Inheritance in Man
• In human, close to 9,000 mendelian characters are known
• Information of mendelian characters, both pathological and non-pathological

Entrez

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Search Morbid Map

Help
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Genetic Alliance
Databases
HGMD
Locus-Specific
Model Organisms
MitoMap
Phenotype
Davis Human/Mouse
Homology Maps
Coriell
The Jackson Laboratory
Human Gene Nomenclature

Human Genome Resources
Genes and Disease
LocusLink
Map Viewer
Sequencing Progress

# OMIM Statistics for April 27, 2002

## Number of Entries

| | Autosomal | X-Linked | Y-Linked | Mitochondrial | **Total** |
|---|---|---|---|---|---|
| Established genes or phenotype loci (*) | 9456 | 521 | 38 | 37 | 10052 |
| Phenotype descriptions (#) | 944 | 81 | 0 | 22 | 1047 |
| Other loci or phenotypes (*no prefix*) | 2294 | 162 | 2 | 0 | 2458 |
| **Total** | 12694 | 764 | 40 | 59 | **13557** |

## Synopsis of the Human Gene Map

| Chr. | Loci | Chr. | Loci | Chr. | Loci |
|---|---|---|---|---|---|
| 1 | 762 | 9 | 287 | 17 | 457 |
| 2 | 491 | 10 | 265 | 18 | 111 |
| 3 | 401 | 11 | 499 | 19 | 512 |
| 4 | 294 | 12 | 408 | 20 | 176 |
| 5 | 398 | 13 | 132 | 21 | 113 |
| 6 | 460 | 14 | 245 | 22 | 178 |
| 7 | 369 | 15 | 218 | X | 481 |
| 8 | 271 | 16 | 293 | Y | 34 |
| Total number of loci: **7855** | | | | | |

NCBI

# OMIM

*Online Mendelian Inheritance in Man*

*Johns Hopkins University*

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM

**The OMIM Morbid Map** presents the cytogenetic map location of disease genes described in OMIM. For a map organized by chromosome, see the OMIM Gene Map. For more refined maps of genes and DNA segments, use NCBI Entrez Map Viewer and the Genome Data Base.

Search for: [ ] Find

- Enter gene symbol, chromosomal location, or disorder keyword to search for, e.g. "recessive", "CYP1","5", "1pter", or "Xq".
- You must capitalize X and Y to search for those chromosomes.

Move Down>>

| Disorder | Symbol(s) | OMIM | Location |
|---|---|---|---|
| 3-Methylcrotonylglycinuria I (3) | MCCC1, MCCA | 210200 | 3q25-q27 |
| 3-Methylcrotonylglycinuria II (3) | MCCC2, MCCB | 210210 | 5q12-q13 |
| 3-beta-hydroxysteroid dehydrogenase, type II, deficiency (3) | HSD3B2 | 201810 | 1p13.1 |
| 3-ketothiolase deficiency (3) | ACAT1 | 203750 | 11q22.3-q23.1 |
| 3-methylglutaconicaciduria, type III, 258501 (3) | OPA3, MGA3 | 606580 | 19q13.2-q13.3 |
| 3q21q26 syndrome (1) | EVI1 | 165215 | 3q26 |
| 5-oxoprolinuria, 266130 (3) | GSS, GSHS | 601002 | 20q11.2 |
| 6-mercaptopurine sensitivity (3) | TPMT | 187680 | 6p22.3 |
| ACAT2 deficiency (1) (?) | ACAT2 | 100678 | 6q25.3-q26 |
| ACTH deficiency (1) | POMC | 176830 | 2p23.3 |
| ACTH deficiency, 201400 (2) | CRH | 122560 | 8q13 |
| ADULT syndrome, 103285 (3) | TP63, KET, EEC3, SHFM4 | 603273 | 3q27 |
| AGAT deficiency (3) | GATM, AGAT | 602360 | 15q15.3 |
| Aarskog-Scott syndrome (3) | FGD1, FGDY, AAS | 305400 | Xp11.21 |
| Abdominal obesity-metabolic syndrome (2) | AOMS1, SYNX | 605552 | 3q27 |
| Abdominal obesity-metabolic syndrome, 605552 (2) | AOMS2 | 605572 | 17p12 |
| Abetalipoproteinemia (3) | APOB, FLDB | 107730 | 2p24 |
| Abetalipoproteinemia, 200100 (3) | MTP | 157147 | 4q22-q24 |
| Acampomelic campolelic dysplasia (3) | SOX9, CMD1, SRA1 | 114290 | 17q24.3-q25.1 |
| Acatalasemia (3) | CAT | 115500 | 11p13 |



Move Down>>

**Box 3.1:** Principal features of mendelian patterns

**Autosomal dominant inheritance (*Figure 3.2A*):**

An affected person usually has at least one affected parent (for exceptions see *Figure 3.4*).

Affects either sex.

Transmitted by either sex.

A child of an affected × unaffected mating has a 50% chance of being affected (this assumes that the affected person is heterozygous, which is usually true for rare conditions).

**Autosomal recessive inheritance (*Figure 3.2B*):**

Affected people are usually born to unaffected parents.

Parents of affected people are usually asymptomatic carriers.

There is an increased incidence of parental consanguinity.

Affects either sex.

After the birth of an affected child, each subsequent child has a 25% chance of being affected.

**X-linked recessive inheritance (*Figure 3.2C*):**

Affects almost exclusively males.

Affected males are usually born to unaffected parents; the mother is normally an asymptomatic carrier and may have affected male relatives.

Females may be affected if the father is affected and the mother is a carrier, or occasionally as a result of nonrandom X-inactivation (page 72).

There is no male-to-male transmission in the pedigree (but matings of an affected male and carrier female can give the appearance of male-to-male transmission, see *Figure 3.4F*).

**X-linked dominant inheritance (*Figure 3.2D*):**

Affects either sex, but more females than males.

Females are often more mildly and more variably affected than males.

The child of an affected female, regardless of its sex, has a 50% chance of being affected.

For an affected male, all his daughters but none of his sons are affected.

**Y-linked inheritance (*Figure 3.2E*):**

Affects only males.

Affected males always have an affected father.

All sons of an affected man are affected.

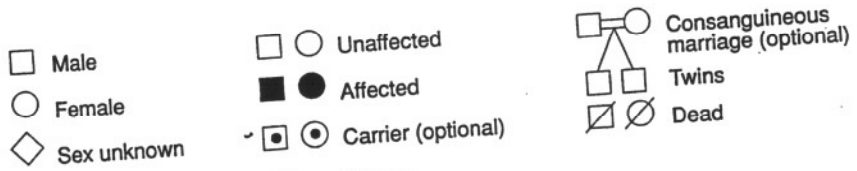



**Figure 3.1:** Main symbols used in pedigrees.

Generations are usually labeled in Roman numerals, and individuals within each generation in Arabic numerals; III-7 or $III_7$ is the seventh person from the left (unless explicitly numbered otherwise) in generation III. An arrow ↗ can be used to indicate the *propositus* (female: *proposita*) through whom the family was ascertained.

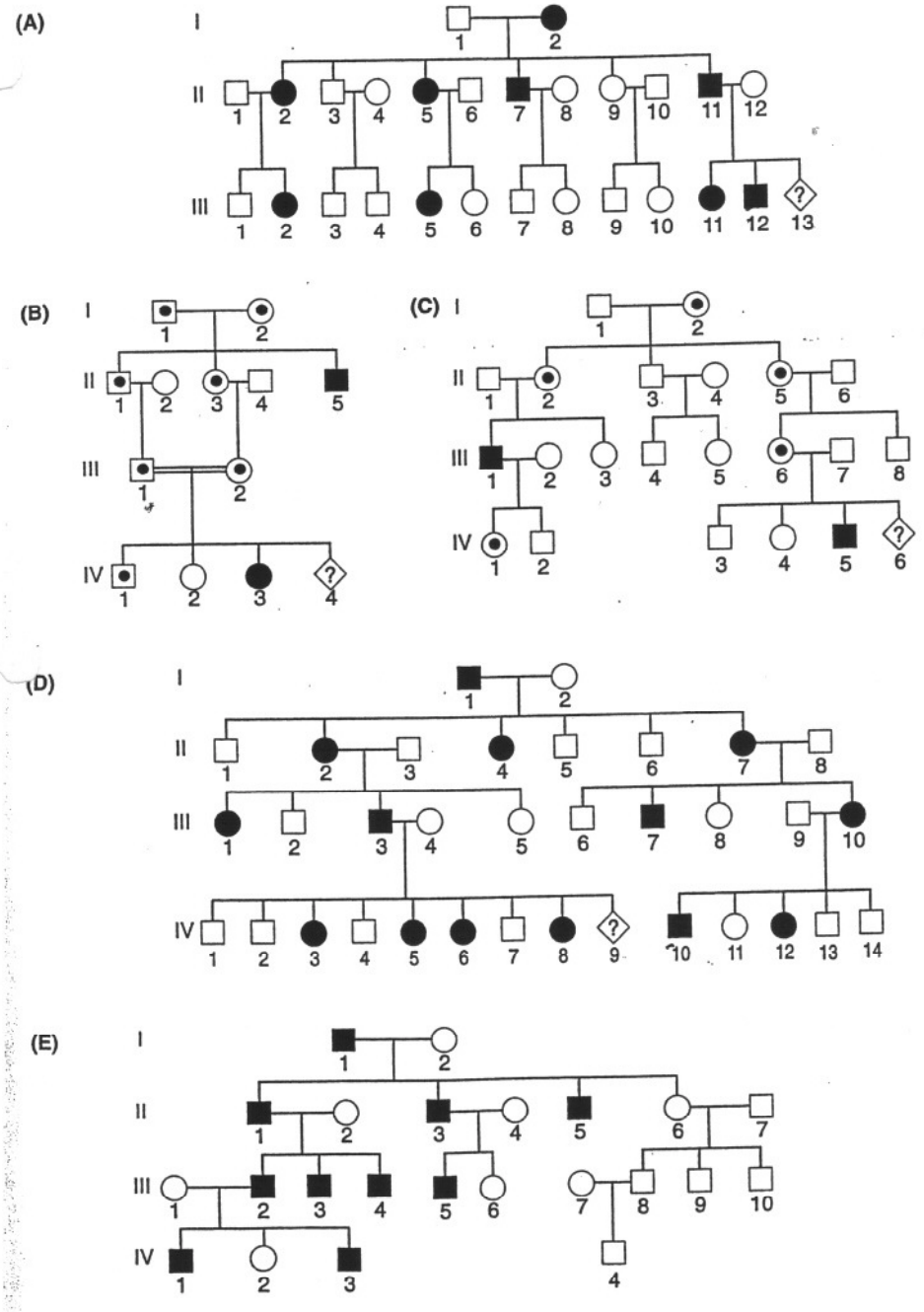



**Figure 3.2:** Basic mendelian pedigree patterns.

**(A)** Autosomal dominant; **(B)** autosomal recessive; **(C)** X-linked recessive; **(D)** X-linked dominant; **(E)** Y-linked. The risk for the individuals marked with a query are **(A)** 1 in 2, **(B)** 1 in 4, **(C)** 1 in 2 males or 1 in 4 of all offspring, **(D)** negligibly low for males, 100% for females. See page 66 and *Figure 3.4* for complications to these basic patterns.

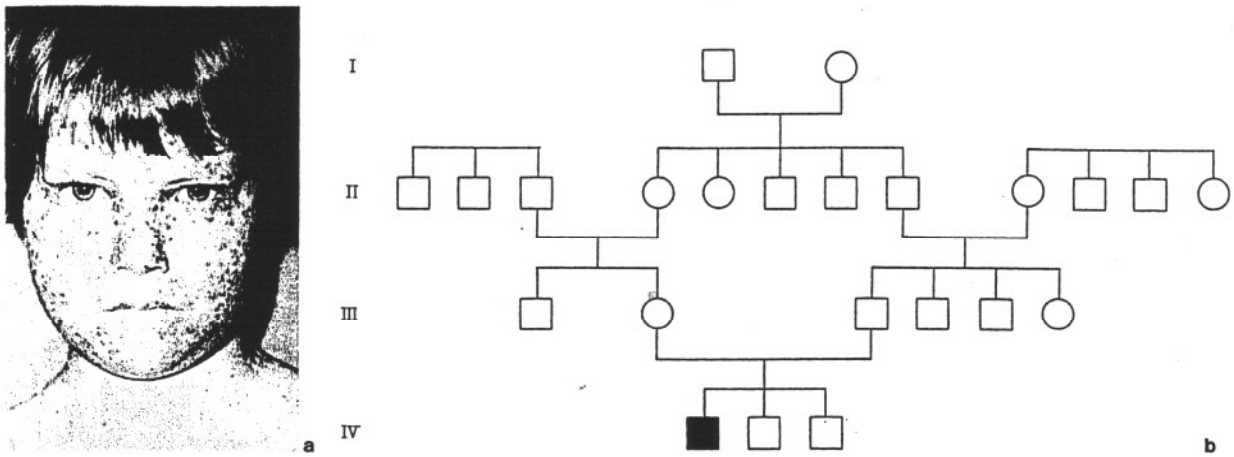



Fig. 4.7 a, b. Xeroderma pigmentosum. a Girl with this condition (Courtesy of Dr. U. W. Schnyder) b Pedigree of single case with first-cousin marriage. (From Dorn 1959 [14]).

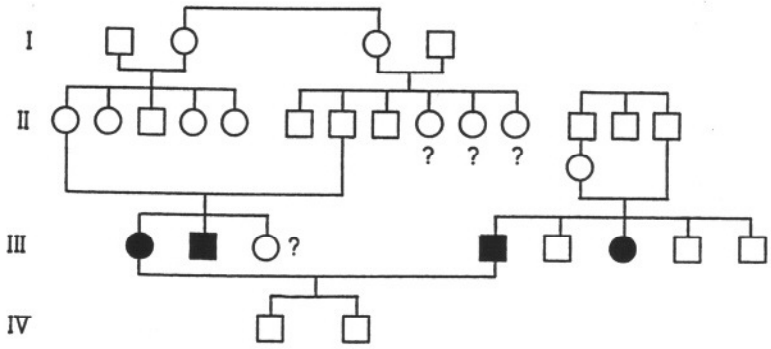



Fig. 4.8. Pedigree of deaf-mutism showing genetic heterogeneity. Both parents are affected with a hereditary type of deaf-mutism; they have affected sibs and come from consanguineous marriages; however, the two sons are not deaf. They are compound heterozygotes for different deaf mutism genes. (From Mühlmann 1930 [44]).

## Three fundamental laws

**1** - Crosses between organisms homozygous for two different alleles at one gene locus leads to genetically identical offspring (F1 generation)

**2** - F1 x F1 (intercross) - Various genotypes segregate
one half heterozygous
one quarter homozygous for each of the parental types
(1:2:1) segregation
This is assuming formation of two types of gametes 1:1 ratio
(law of segregation and law of purity of gametes)

**3** - When organisms differing by more than one gene are crossed every single gene pair segregates independently
(law of free combination of genes)
applies only when there is no linkage

**Mendel enounces the basic principles of genetics**

- Dominant or recessives transmission of the genetic characters

- Pure characters = homozygous

- Mixed characters = heterozygous

- Genetic characters are defined in germ cells (gametes)

- F1 generation is uniform (dominant character)

- Segregation of the genetic characters in the F2 generation

- Different genetic characters can segregate independently

- Genotype does not always determine one distinct phenotype

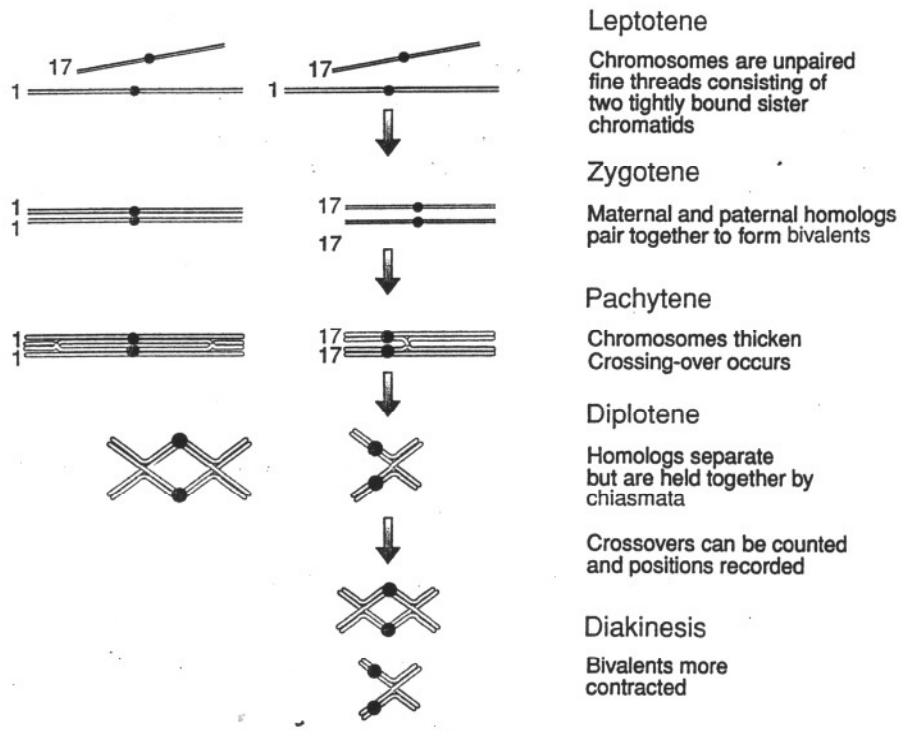



**Figure 2.11:** The five stages of prophase in meiosis I.

Two representative pairs of homologs are shown. Of these, the chromosome 1 pair are envisaged to undergo two crossovers; the chromosome 17 pair are shown to undergo only a single crossover. For the sake of clarity, in each case the crossover is envisaged to involve only a single paternal chromatid and a single maternal chromatid. *Note*, however, that the number of crossovers is likely to be higher in practice and may involve three or even all four chromatids in a bivalent.

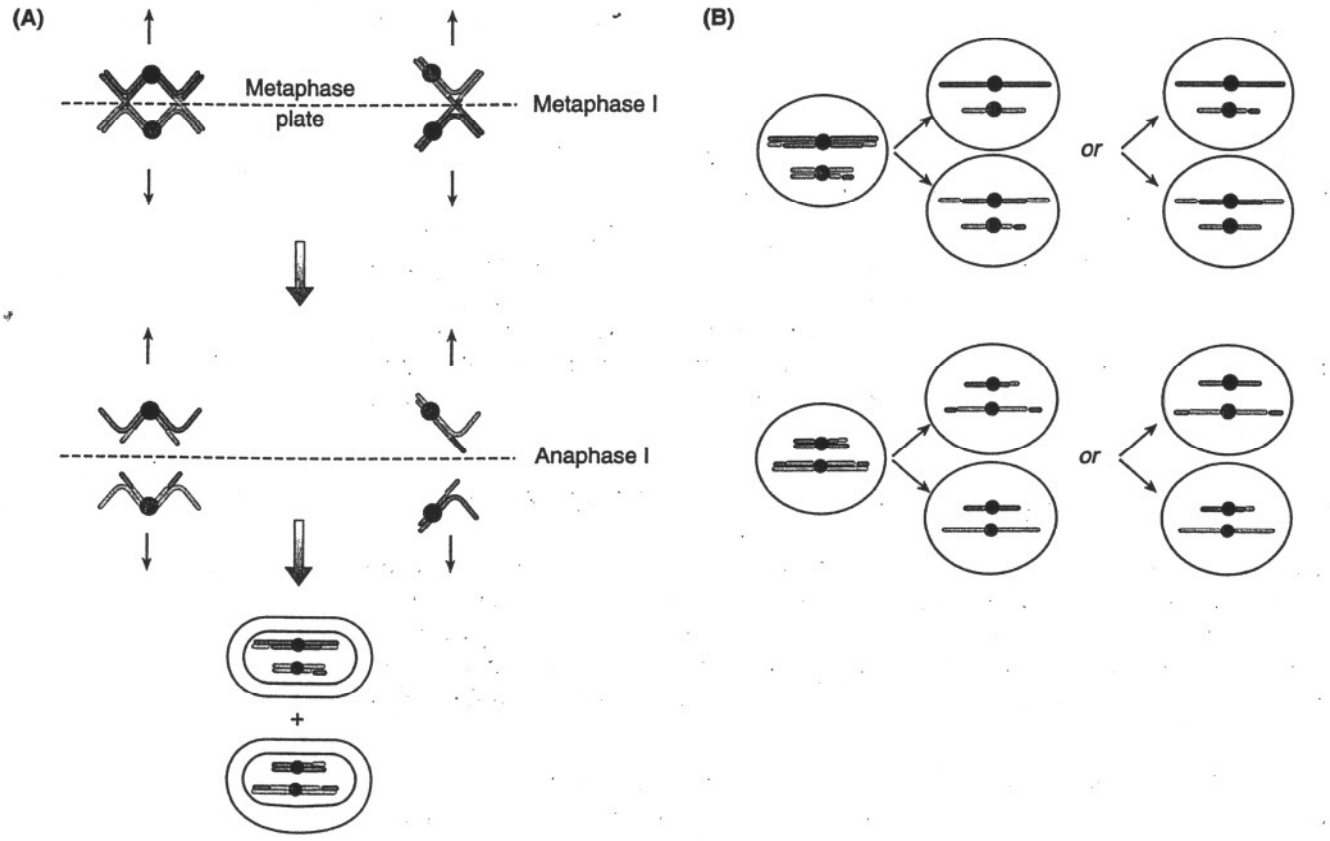



**Figure 2.12:** From metaphase to the products of meiosis II.

**(A)** From metaphase to cell division in meiosis; **(B)** from meiosis I to meiosis II. The figure follows on from *Figure 2.11* to show possible fates of two pairs of homologs that have undergone recombination at metaphase. In the example shown, the maternal chromosome 1 and paternal chromosome 17 segregate to one cell during meiosis I, while the paternal chromosome 1 and maternal chromosome 17 segregate to the other cell. Because the recombination events of *Figure 2.11* are envisaged to involve only two nonsister chromatids in each case, the final meiotic products will contain some nonrecombinant chromosomes as well as recombinant chromosomes. Although the two sister chromatids of each chromosome will segregate to different daughter cells, the different chromosomes behave independently and so different combinations are possible, as shown.

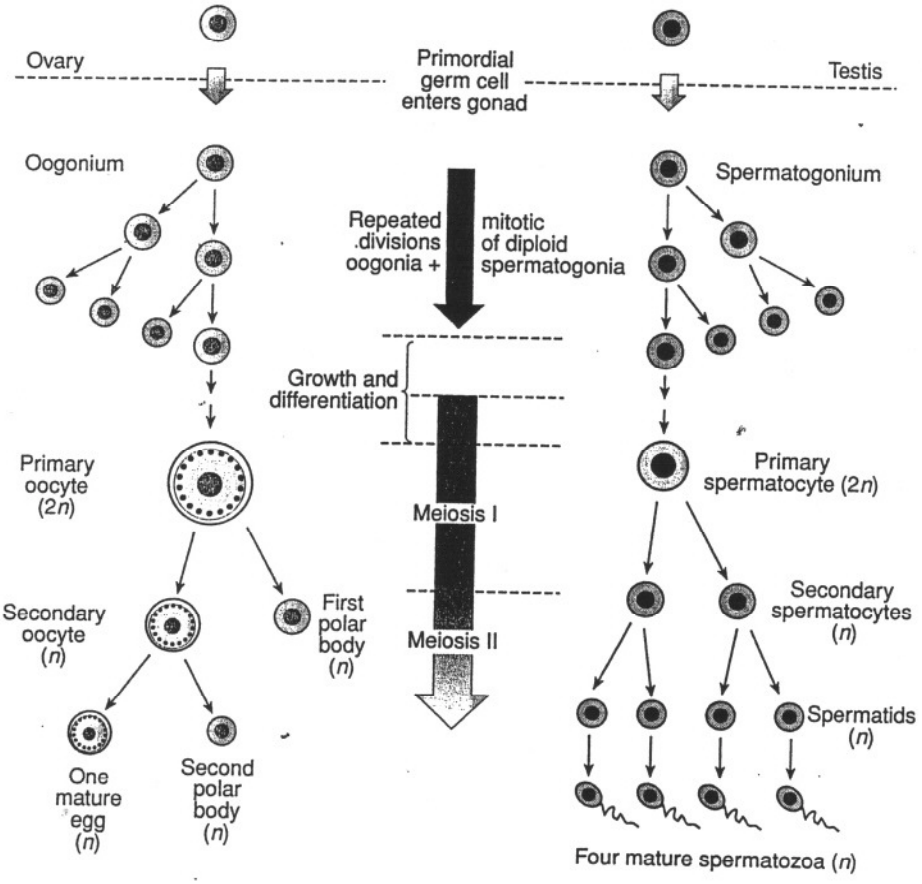


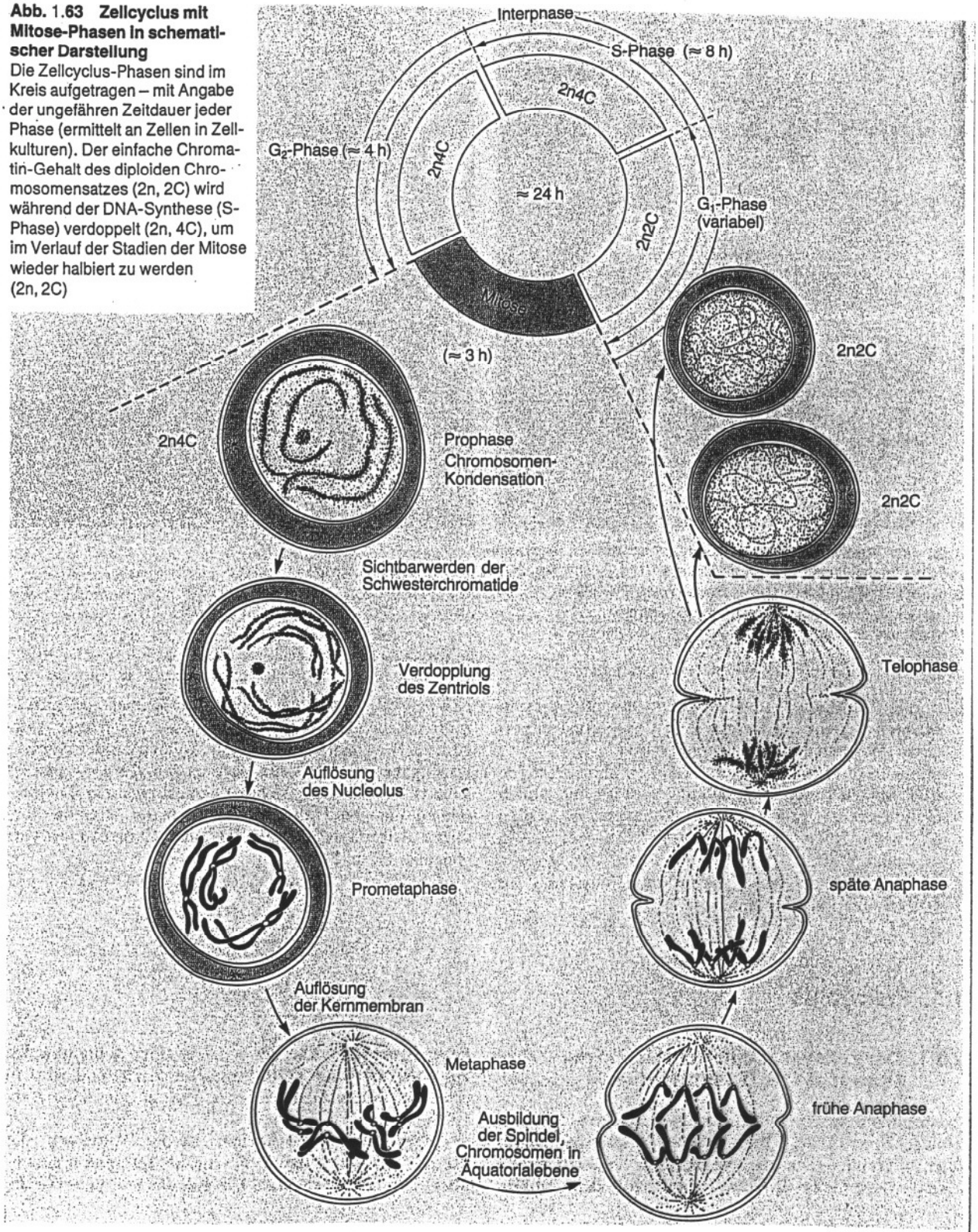

**Figure 2.9**: Eggs and sperm cells are generated by mitotic division of precursor gonadal cells, followed by meiotic division of primary oocytes and spermatocytes.

The first meiotic division (meiosis I) may take up to several years. For example, in human oogenesis, meiosis I is arrested at the prophase stage from the fetal stage right through to puberty. During this time, the primary oocytes complete their growth phase, acquiring an outer jelly coat, cortical granules, ribosomes, mRNA, yolk, etc. At puberty, hormones induce the completion of meiosis I in a small number of primary oocytes, and the resulting secondary oocytes undergo meiosis II. The secondary spermatocytes and oocytes are haploid because meiosis I does not involve a DNA duplication stage, unlike meiosis II.

**Table 2.2**: Differences between meiosis and mitosis

| | Mitosis | Meiosis |
|---|---|---|
| Location | All tissues | Only in testis and ovary |
| Products | Diploid somatic cells | Haploid sperm and egg cells |
| DNA replication and cell division | Normally one round of replication per cell division | Only one round of replication (in meiosis I); but two cell divisions |
| Extent of prophase | Short (~30 min in human cells) | Long and complex in meiosis I; can take years to complete |
| Pairing of homologs | None | Yes (in meiosis I) |
| Recombination | Rare and abnormal | Normally at least once for each pair of homologs |
| Relationship between daughter cells | Genetically identical | Different (recombination and independent assortment of homologs) |

**Abb. 1.63 Zellcyclus mit Mitose-Phasen in schematischer Darstellung**
Die Zellcyclus-Phasen sind im Kreis aufgetragen – mit Angabe der ungefähren Zeitdauer jeder Phase (ermittelt an Zellen in Zellkulturen). Der einfache Chromatin-Gehalt des diploiden Chromosomensatzes (2n, 2C) wird während der DNA-Synthese (S-Phase) verdoppelt (2n, 4C), um im Verlauf der Stadien der Mitose wieder halbiert zu werden (2n, 2C)



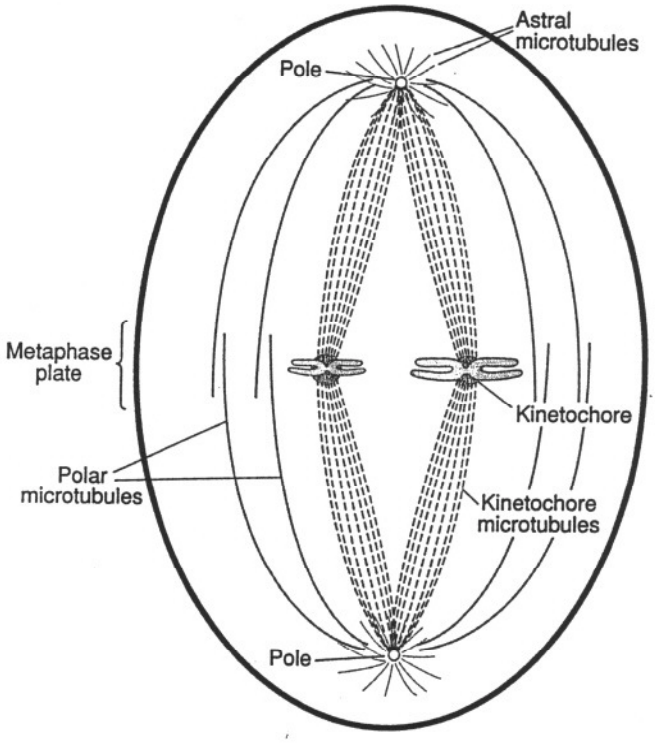



**Figure 2.7:** The mitotic spindle is composed of different classes of microtubule.

Spindle microtubules are of three classes: astral microtubules radiate from each pole; polar microtubules form attachments that link the two poles; and kinetochore microtubules link metaphase chromosomes at the equatorial plane (metaphase plate) to each of the poles, by attaching to the pair of kinetochores of each chromosome. For the sake of clarity, only a small fraction of the microtubules is shown.

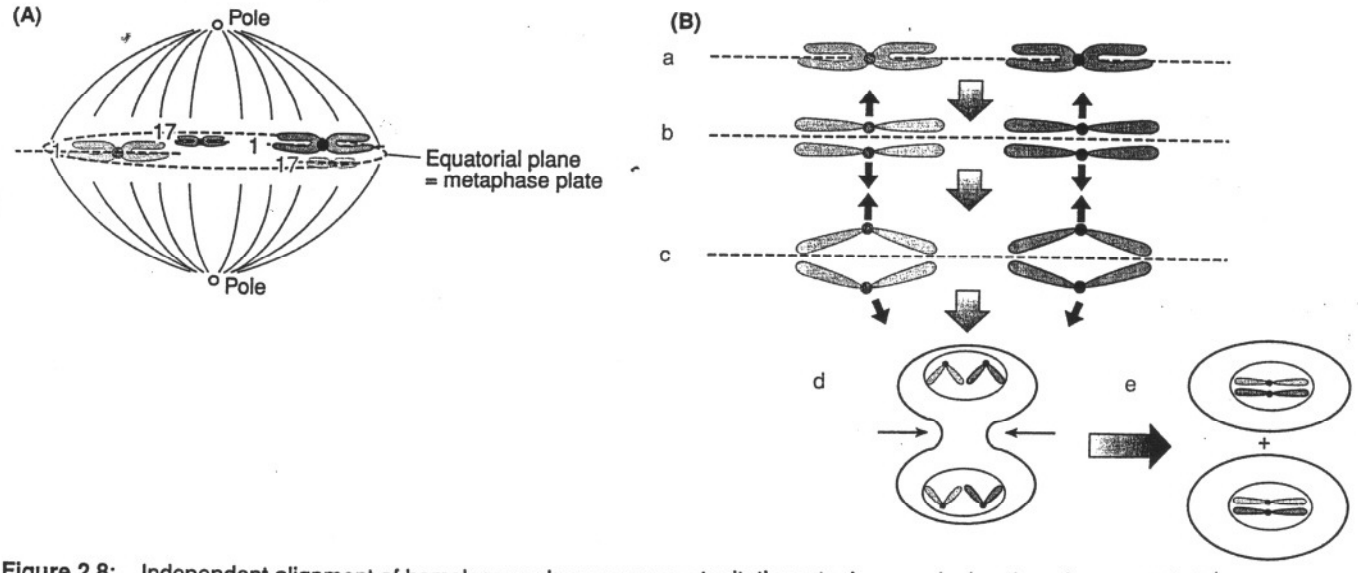



**Figure 2.8:** Independent alignment of homologous chromosomes at mitotic metaphase and migration of separated chromatids to the opposing poles.

**(A)** Physical separation of the paternal (black) and maternal (red) homologs of each chromosome pair (e.g. human chromosome 1 and chromosome 17) is meant to indicate that they are independently aligned at the metaphase plate.
**(B)** Independently aligned maternal and paternal homologs of each chromosome pair (a) subsequently undergo centromeric duplication and separation of chromatids at the anaphase stage (b,c). Solid arrows indicate spindle-derived forces pulling on the kinetochores of the centromeres, eventually driving the sister chromatids of each chromosome to the opposing poles. At this stage (telophase) they become enclosed in a nuclear envelope (d), prior to cytokinesis (e).

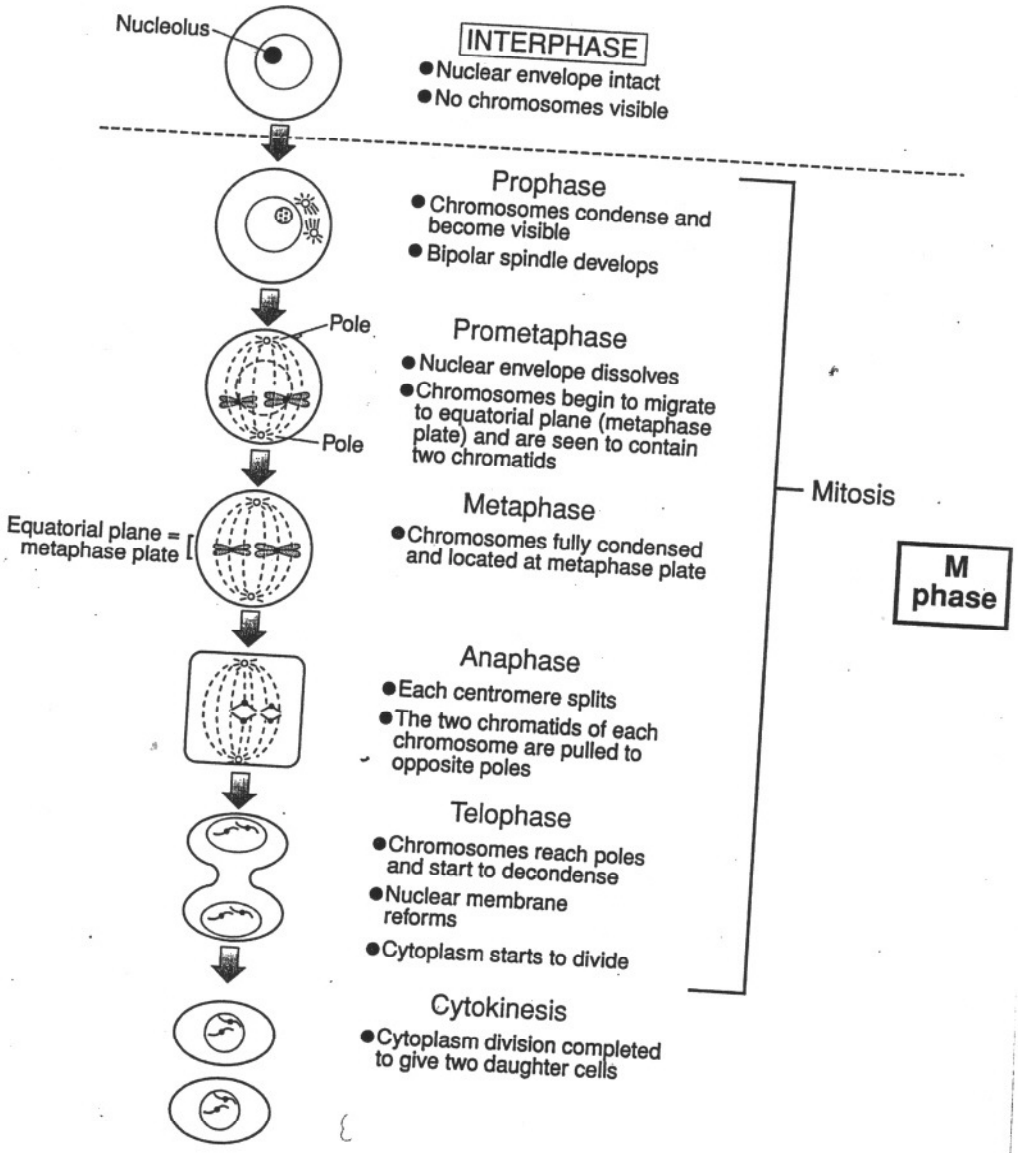



**Figure 2.6:** From interphase through M phase.

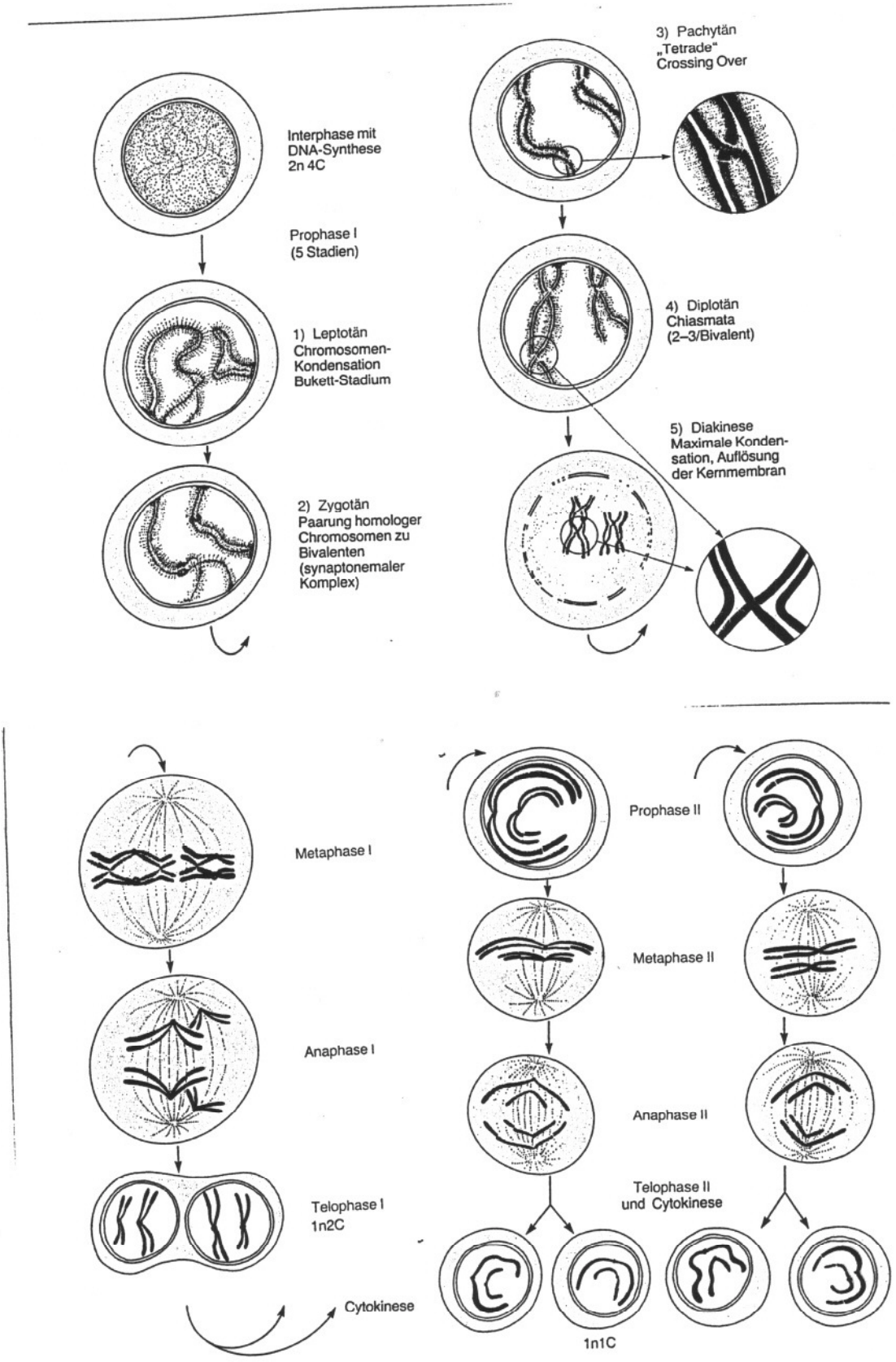



**Abb. 1.67 Stadien der Meiose**
Stellvertretend für den diploiden Chromosomensatz von 23 homologen Paaren beim Menschen werden zwei homologe Chromosomenpaare durch die Stadien der Meiose verfolgt. Vor der Prophase I findet in der S-Phase der Interphase eine Verdopplung des Chromatin-Gehaltes von 2n, 2C zu 2n, 4C statt. Während des Pachytäns der Prophase I findet das Crossing-over mit Stückaustausch statt; der Vorgang ist vergrößert herausgezeichnet, ebenso ein Chiasma. Nach der Metaphase I werden homologe Chromosomen in der Anaphase I getrennt. In der Telophase I besitzen die Zellen einen haploiden Chromosomensatz mit noch verdoppeltem Chromatin-Gehalt 1n, 2C. Trennung der Chromatide in der Anaphase II führt zu Zellen mit haploidem Chromosomensatz und einfachem Chromatin-Gehalt 1n, 1C.

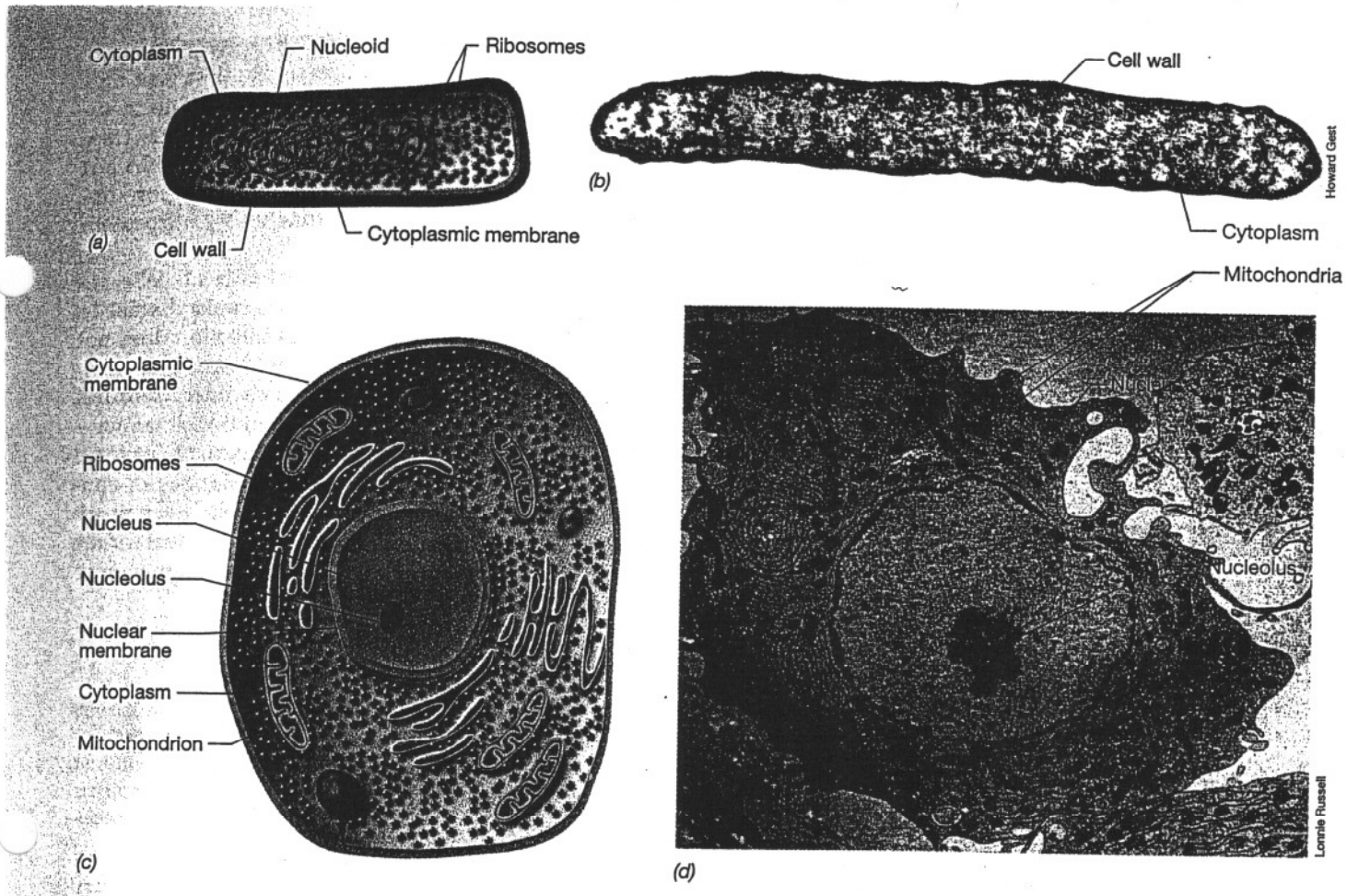



**FIGURE 1.5** Internal structure of microbial cells. (a) Diagram of a prokaryote. (b) Electron micrograph of a prokaryote. The cell is about 1 μm in diameter and the light-colored areas in the cell are DNA (the nucleoid). (c) Diagram of a eukaryote. (d) Electron micrograph of a eukaryote (animal cell). The cell is about 25 μm in diameter.

**TABLE 12.3** Summary of major differentiating features among Bacteria, Archaea, and Eukarya[a]

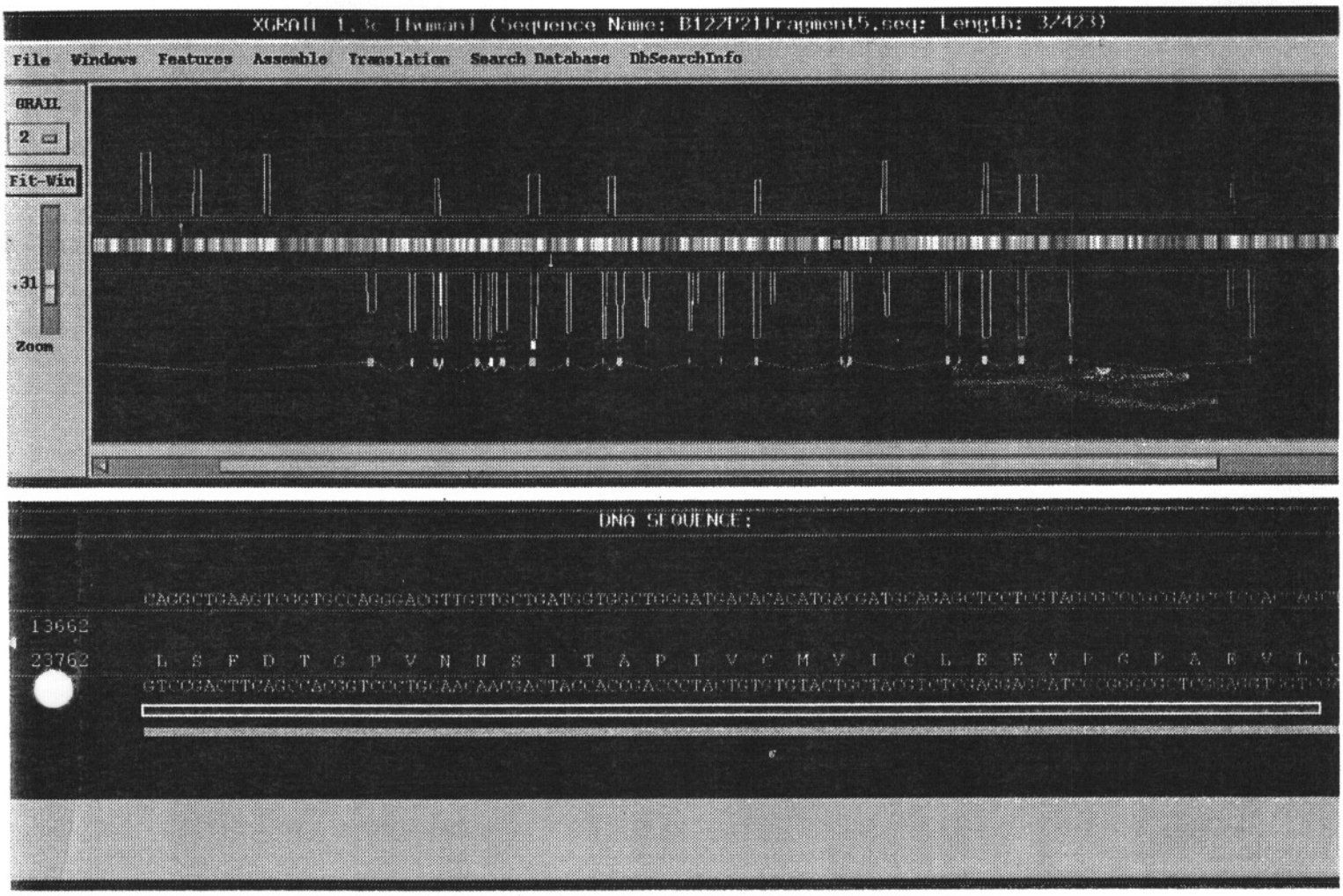
| Characteristic | Bacteria | Archaea | Eukarya |
|---|---|---|---|
| Prokaryotic cell structure | Yes | Yes | No |
| DNA present in covalently closed and circular form | Yes | Yes | No |
| Histone proteins present | No | Yes | Yes |
| Membrane-enclosed nucleus | Absent | Absent | Present |
| Cell wall | Muramic acid present | Muramic acid absent | Muramic acid absent |
| Membrane lipids | Ester-linked | Ether-linked | Ester-linked |
| Ribosomes | 70S | 70S | 80S |
| Initiator tRNA | Formylmethionine | Methionine | Methionine |
| Introns in most genes | No | No | Yes |
| Operons | Yes | Yes | No |
| Capping and poly-A tailing of mRNA | No | No | Yes |
| Plasmids | Yes | Yes | Rare |
| Ribosome sensitivity to diphtheria toxin | No | Yes | Yes |
| RNA polymerases (see Figure 12.16) | One (4 subunits) | Several (8–12 subunits each) | Three (12–14 subunits each) |
| Transcription factors required (Section 6.8) | No | Yes | Yes |
| Promoter structure (Sections 6.7 and 6.8) | −10 and −35 sequences (Pribnow box) | TATA box | TATA box |
| Sensitivity to chloramphenicol, streptomycin, and kanamycin | Yes | No | No |
| Methanogenesis | No | Yes | No |
| Reduction of $S^0$ to $H_2S$ or $Fe^{3+}$ to $Fe^{2+}$ | Yes | Yes | No |
| Nitrification | Yes | No | No |
| Denitrification | Yes | Yes | No |
| Nitrogen fixation | Yes | Yes | No |
| Chlorophyll-based photosynthesis | Yes | No | Yes (in chloroplasts) |
| Chemolithotrophy (Fe, S, $H_2$) | Yes | Yes | No |
| Gas vesicles | Yes | Yes | No |
| Synthesis of carbon storage granules composed of poly-β-hydroxyalkanoates | Yes | Yes | No |
| Growth above 80°C | Yes | Yes | No |

[a] Note that for many features only particular representatives within a domain show the property

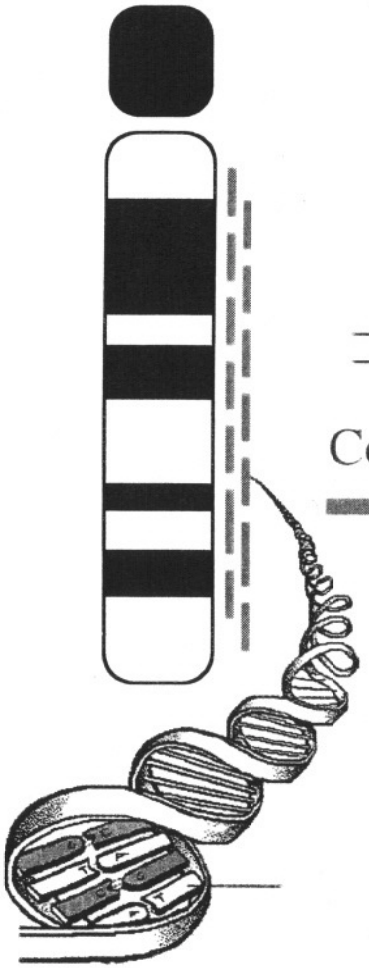
**Table 1.2** Some of the organisms for which complete genome sequences should be available by 2005

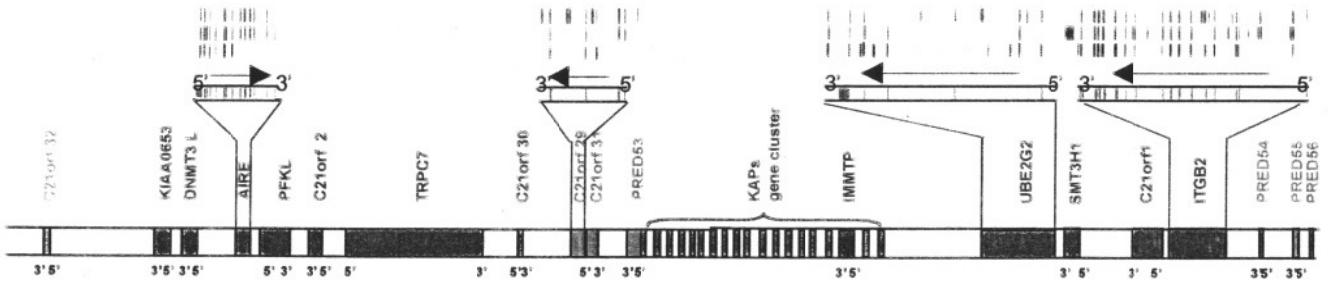
| Organism | Genome size (Mb) | Internet address for latest news |
|---|---|---|
| **Archaea**[†] | | |
| *Methanococcus jannaschii* | 1.66 | http://www.tigr.org/tdb/mdb/mjdb/mjdb.html |
| *Methanobacterium thermoautotrophicum* | 1.75 | http://www.genomecorp.com/htdocs/sequences/methanobacter/abstract.html |
| *Archaeoglobus fulgidus* | 2.18 | ftp://ftp.tigr.org/pub/data/a_fulgidus |
| **Bacteria**[†] | | |
| *Mycoplasma genitalium* | 0.58 | http://www.tigr.org/tdb/mdb/mgdb/mgdb.html |
| *Mycoplasma pneumoniae* | 0.81 | http://www.zmbh.uni-heidelberg.de/M-pneumoniae/MP_Home.html |
| *Treponema pallidum* | 1.14 | http://www.tigr.org/tdb/mdb/tpdb/tp_bg.html |
| *Borrelia burgdorferi* | 1.44 | ftp://ftp.tigr.org/pub/data/b_burgdorferi |
| *Aquifex aeolicus* | 1.55 | |
| *Helicobacter pylori* | 1.66 | http://www.tigr.org/tdb/mdb/hpdb/hpdb.html |
| *Haemophilus influenzae* | 1.83 | http://www.tigr.org/tdb/mdb/mdb.html |
| *Synechocystis* sp. | 3.57 | http://kazusa.or.jp/cyano/cyano.html |
| *Bacillus subtilis* | 4.20 | http://www.pasteur.fr/Bio/SubtiList.html |
| *Mycobacterium tuberculosis* | 4.40 | http://www.sanger.ac.uk/Projects/M_tuberculosis/ |
| *Escherichia coli* | 4.64 | http://www.genetics.wisc.edu:80/index.html |
| **Eukaryotes** | | |
| *Saccharomyces cerevisiae* | 12.1 | http://www.mips.biochem.mpg.de/ |
| *Arabidopsis thaliana* | 100 | http://genome-www.stanford.edu/Arabidopsis/ |
| *Caenorhabditis elegans* | 100 | http://moulon.inra.fr/acedb/acedb.html |
| *Drosophila melanogaster* | 140 | http://flybase.bio.indiana.edu/ |
| *Oryza sativa* | 565 | http://www.staff.or.jp/ |
| *Homo sapiens* | 3000 | http://gdbwww.gdb.org/ |
| *Mus musculus* | 3300 | http://www.informatics.jax.org/ |

[†] Most of these archaeal and bacterial sequences have already been completed. See also Appendix – Keeping Up to Date.


XGRAIL 1.3c [Human] (Sequence Name: B122P21Fragment5.seq; Length: 32423)
File Windows Features Assemble Translation Search Database DbSearchInfo
GRAIL
2
Fit-Win
.31
Zoom
DNA SEQUENCE:
13662
23762

# Sequenzierung und Gen-Identifikation






Computeranalyse zur Gen-Identifikation

**Genkatalog von Chromosom 21**

**mit 225 Genen**

**33,5 Mio. Basenpaare sequenziert**

**Ursachen von genetisch bedingten Krankheiten**

**The DNA sequence of human chromosome 21**
**The chromo-some 21 mapping and sequencing consortium, Nature, 18th May 2000**