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THE EYE IN CHROMOSOME DUPLICATIONS AND DEFICIENCIES

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The Eye in Chromosome Duplications and Deficiencies

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FOREWORD

There has been, in recent years, an explosion of information dealing with genetics and ophthalmology. Much of the information does not appear in the ophthalmologic literature but rather has been concentrated in journals dealing with heredity and genetics. Marcelle Jay has had a long interest in genetics and, because of her particular association with ophthalmology, has coupled her interest so that she has developed an outstanding knowledge of genetic diseases as they affect the eye. In this volume, which is an outgrowth of her thesis, she has compiled all of the extant information on the relationship of chromosomal duplications and deficiencies upon the human eye. She provides outstanding source material for anyone who would desire to pursue the subject in depth. Clinicians in the area of ophthalmology, pediatrics, and otolaryngology will find this to be a handy reference volume. The enormous task in compiling all the material is one that would have caused most researchers to shy away, and we can only admire such an effort, which makes our work easier.

Paul Henkind, M.D., Ph.D.

PREFACE

The study of human cytogenetics has made very rapid advances in the past fifteen years due to improved techniques, and new syndromes of chromosomal abnormalities are still being discovered.

The purpose of this book is to review the literature on ocular abnormalities associated with structurally abnormal chromosomes, deletions, and duplications. These so-called "new chromosomal syndromes" have not been previously discussed in detail, no doubt because it is only recently that technical advances have made their detection possible.

The literature on the Turner syndrome has been included, because although the ocular abnormalities in this syndrome are well known, and it is not a deletion syndrome, it has a relatively high incidence and it would be useful for ophthalmologists to have a recent review for reference.

The greater part of the review of the literature is devoted to deletions rather than to duplications. There are earlier references in the literature to abnormal chromosomes, but these have been omitted wherever the origin of the chromosomal segment in excess was unknown. Most of the references given in the chapters on duplications are relatively recent; this is probably because the newer banding techniques have made possible the accurate identification of a given chromosomal segment. It is inevitable that such a review cannot be exhaustive, but I hope that all the more important publications have been included, and the references are complete (except for human error) to the end of 1974.

It is obviously invidious to isolate the ocular from other congenital abnormalities which occur in deletion and duplication syndromes, and also to isolate any one sign. For this reason, the whole phenotype has been given wherever possible, with particular emphasis on facial abnormalities. The abnormality of the karyotype and case numbers are given as in the original papers.

It is interesting to note that the majority of cases have been reported by physicians and geneticists, and only a few by ophthalmologists, and yet some ocular abnormality has been noted in almost every case. It would

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seem that a closer study of these syndromes by ophthalmologists might prove fruitful, and stricter criteria might be applied for the evaluation of certain signs. For example, hypertelorism is reported in many cases, whereas the more correct term "telecanthus" is very rarely used and then nearly always when an ophthalmologist has examined the case.

A brief introduction to cytogenetics has been given in the hope that this review will thereby be more meaningful when read by those not readily acquainted with the terms and techniques which are now in use, and will enable them to keep up with recent advances.

Anyone writing about ophthalmology and cytogenetics must acknowledge the inspiration given by the work of François, Berger, and Saraux on this topic; their book, "Les Aberrations Chromosomiques en Ophtalmologie," Paris, Masson & Cie, 1972, is widely quoted throughout this review.

I would like to thank my teachers in genetics and in ophthalmology, Professor Cedric Carter, Dr. Rufus Howard, and Mr. Barrie Jay for their patience and their valuable comments. My thanks are also due to the Department of Audio-Visual Communications at the Institute of Ophthalmology, London; in particular to Mr. Terry Tarrant for his line drawings, and to Mr. Roger Fletcher for preparing photographs. Dr. Michael Daker prepared the karyotypes and I am grateful to Professor Paul Polani of the Paediatric Research Unit at Guy's Hospital Medical School, London, for permission to publish Figures 1-7, 1-9, 1-10, 1-11, 1-12, and 1-16 which have appeared in "Handbuch der Urologie," Vol. 15: Urology in Childhood, by Innes Williams, Heidelberg, Springer Verlag, 1974, and also to Dr. Jack Singer of the Paediatric Research Unit for his permission to use Figure 1-8 which is reproduced from "The Fetus: Physiology and Medicine," edited by R. W. Beard and P. W. Nathanielsz, London, W. B. Saunders, Ltd., 1976. I would also like to thank Dr. M.-O. Réthoré of the Hôpital des Enfants Malades, Paris, for permission to use Figure 10-1 which appeared as Figure 2 in the article "Trisomie 9p par t(4;9)(q34;q21)mat" by M.-O. Réthoré, J. Ferrand, B. Dutrillaux, and J. Lejeune, published in Annales de Génétique, 17: 157-161 (1974).

Several authors have been kind enough to let me use previously unpublished photographs for which they own the copyright and I am most grateful to Dr. Renata Lax and Dr. Michael Ridler of the Kennedy Galton Institute, Harperbury Hospital, Radlett, Herts., to Mr. L. J. Butler of Queen Elizabeth Hospital for Children, Hackney Road, London E2 8PS, to Mr. A. J. Bron of the Nuffield Laboratory of Ophthalmology, Walton

Street, Oxford, and to Professor Norman Ashton of the Institute of Ophthalmology, Judd Street, London, WC1H 9QS, for their help and beautiful photographs.

Finally I am most grateful to Miss Audrey Jones who typed the manuscript in its present form.

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KEY TO TABLES

+	Sign present bilaterally
(+)	Sign present unilaterally
0	Sign absent
?	Sign doubtful
L	Left
R	Right
Con	Convergent
Div	Divergent
Alt	Alternating
M	Myopia
A	Astigmatism
D	Deuteranopia
P	Protanopia

Wherever possible, the case numbers used and the chromosomal abnormalities are those given in the original papers.

CONTENTS

CHAPTER 1

INTRODUCTION TO CYTOGENETICS

I. CELL DIVISION

The human cell passes through several stages during its life-span. The first stage is interphase, during which the cell is at rest and the chromosomes appear as single threads. These chromosomes are deeply-staining structures in the nuclei of cells and are composed of deoxyribonucleic acid (DNA) combined with a protein. Towards the end of interphase there is the S period, during which DNA is synthesized and replication occurs. The chromosomes then double and appear as two identical threads or chromatids which are joined by a main constriction, the centromere (Fig. 1-1). The nuclei of all human somatic cells contain 46 chromosomes, consisting of 22 identical pairs of chromosomes or homologues and two sex chromosomes: a pair of X chromosomes in the female and an X and Y chromosome in the male. Somatic cells divide by the process of mitosis, whereby each daughter cell retains the same number of chromosomes as the parent cell.

FIG. 1-1. Diagrammatic representation of a metaphase chromosome.

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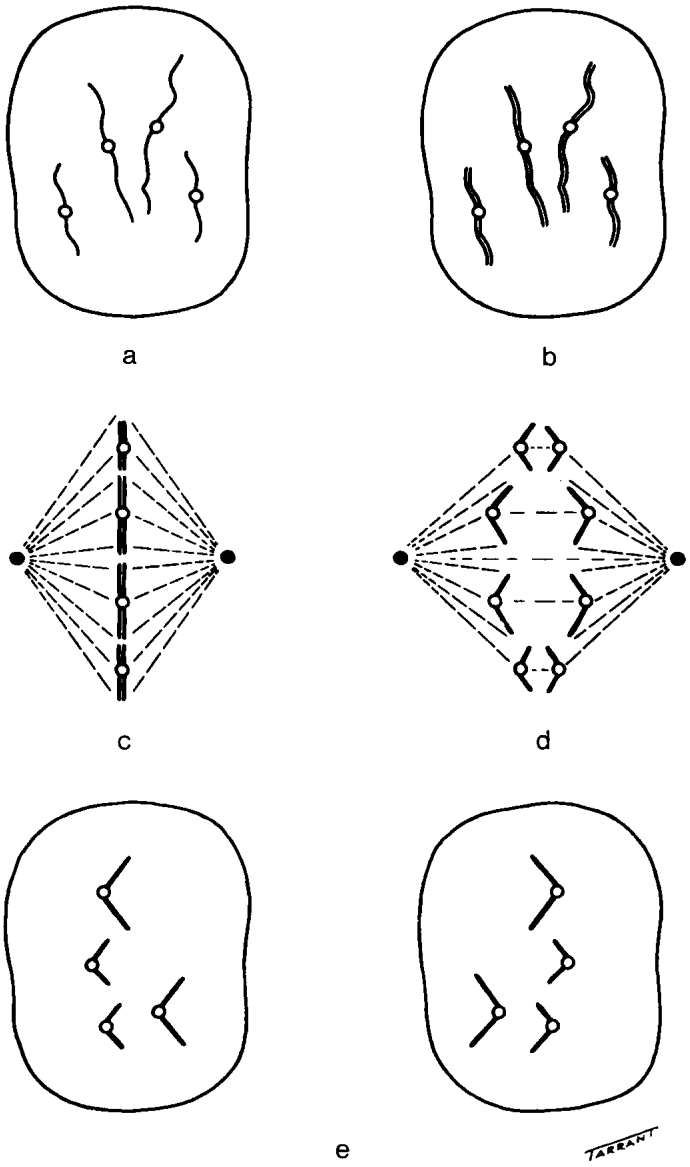

FIG. 1-2. The behaviour of 4 chromosomes at mitosis. (a) Interphase with 4 chromosomes in the parent cell. (b) Prophase during which each chromosome is doubled into identical chromatids. (c) Formation of the spindle at metaphase. (d) Each chromosome splits during anaphase. (e) Telophase and the formation of two daughter cells, each with 4 chromosomes.

A. Mitosis

Mitosis follows interphase and is divided into four stages: prophase, metaphase, anaphase, and telophase (Fig. 1-2). Each stage is defined as follows:

1. Prophase. During this stage the chromosomes contract, each chromatid becomes tightly coiled, and the nuclear membrane disappears.
2. Metaphase. It is at this stage that chromosomes can be observed readily by using various staining techniques, which are described later in this chapter. A spindle is formed by long strands of fibres which pass between the two poles of the cell. The chromosomes then move so as to lie in an equatorial plane equidistant from the two poles of the spindle, where they are distributed evenly.
3. Anaphase. The centromeres split longitudinally and the single chromatids then move to the opposite poles of the spindle.
4. Telophase. In this final stage, the spindle disappears and a new cell membrane is formed. The two daughter cells separate and the chromosomes again become thin and thread-like. The cell now resumes its resting interphase stage.

B. Meiosis

The process whereby gametes (sperm and ova) are formed is called meiosis. This is a form of cell division resulting in the number of chromosomes being halved. Each human gamete contains 23 chromosomes, the haploid (single) number, while each human somatic cell contains 46 chromosomes, the diploid (double) number. When two haploid gametes fuse at fertilization, the resultant cell is the zygote which has a diploid number of chromosomes.

Meiosis consists of two divisions, which are each divided into prophase, metaphase, anaphase, and telophase (Fig. 1-3).

1. Prophase I. During this long stage, the chromosomes, consisting of two chromatids, form pairs which are called bivalents. Each bivalent consists of two homologous chromosomes, one maternal and the other paternal in origin. The exchange of genetic material that may take place at this time (Fig. 1-4) is called crossing-over and the points at which it

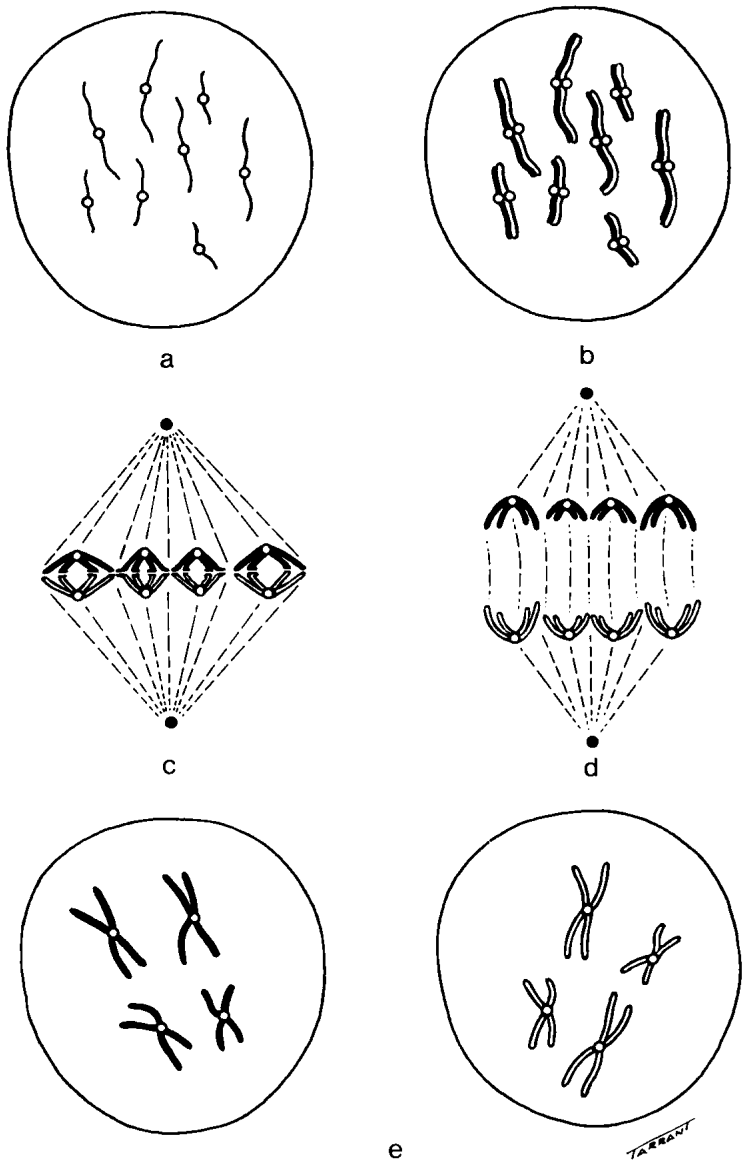

FIG. 1-3. First division of meiosis showing the behaviour of 8 chromosomes. (a) Interphase with 8 chromosomes in the parent cell. (b) Prophase 1 and the formation of bivalents. (c) Metaphase 1 during which the bivalents lie on the equatorial plane. (d) Anaphase 1, the bivalents divide. (e) Telophase 1, two daughter cells are formed, each with 4 chromosomes. These cells then proceed to the second division of meiosis which occurs in the same way as mitosis.

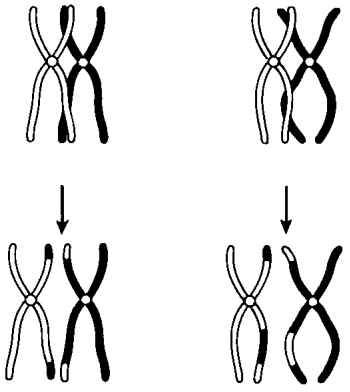

FIG. 1-4. Crossing-over. The exchange of genetic material between chromosomes of maternal and paternal origin.

occurs are called the chiasmata. During prophase I the bivalents contract, and at the end of this stage they reach maximal condensation. The bivalents that are joined only at the chiasmata now tend to fall apart.

2. Metaphase I. The nuclear membrane disappears, the spindle forms, and the bivalents move to the equator of the spindle, with the centromeres of each bivalent lying on either side of the equator.

3. Anaphase I. The bivalents split and then the chromosomes move to opposite poles of the cell so that half their number is at one pole and half at the opposite pole.

4. Telophase I. The haploid groups of chromosomes may uncoil and a new membrane may form, or they may proceed to the second division in meiosis. This consists of prophase II, metaphase II, anaphase II, and telophase II, and occurs exactly as in mitosis, but only the haploid number of chromosomes is involved.

II. EXAMINATION OF CHROMOSOMES

The analysis of chromosomes is made on cells which are dividing, since chromosomes can only be examined in detail during the metaphase stage of mitosis, or during the late prophase and metaphase stages of meiosis. Various tissues are available for culture, but those used are usually the

lymphocytes of peripheral blood and the fibroblasts of skin. The culture of lymphocytes is a relatively simple procedure and has the advantage of requiring only two to three days. The culture of fibroblasts is more elaborate and expensive, requiring 14 days, but it has the advantage that the culture can be prolonged and also that the cells can be deep frozen. This method is used for the culture of cells in the amniotic fluid which is obtained by amniocentesis.

Another method of chromosome analysis is the direct study of bone-marrow cells, as used in the chromosome study of patients with leukemia. Since bone-marrow cells are already dividing in vivo, the time required for analysis is much shorter as compared with previous methods. Using a recent modification of this method, a chromosome count may be obtained in two hours which is of great assistance to physicians faced with problems of differential diagnosis and management. In certain cases, testicular biopsy is performed to obtain cells in meiosis; this procedure is sometimes used in cases of infertility. Chromosomes in meiosis have their own characteristic appearance, but the interpretation of the results obtained requires great skill. Other tissues are also used in experimental work, as for example, the cornea in mammals.

III. CLASSIFICATION AND NOMENCLATURE

The appearance of chromosomes at metaphase shows two identical chromatids joined by the centromere (Fig. 1-1). Various classifications can be made according to size and structure, with one classification depending upon the relative position of the centromere (Fig. 1-5). A chromosome is said to be (a) metacentric when the centromere is at its centre; (b) it is submetacentric when the centromere is to one side of the centre; and (c) it is acrocentric when the centromere is towards one end of the chromosome. The centromere divides the chromosome into unequal arms, the short arm being denoted by the letter "p" and the long arm by the letter "q."

A. Chicago Classification

A standard international system of nomenclature was adopted after the Chicago Conference of 1966, whereby chromosomes were divided into groups according to their size and structure. The 22 pairs of autosomes

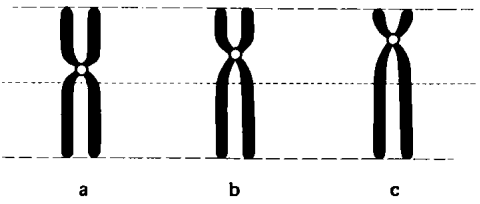

FIG. 1-5. (a) Metacentric chromosome; (b) submetacentric chromosome; and (c) acrocentric chromosome.

were divided in descending order of size into seven groups: A, B, C, D, E, F, and G. The sex chromosomes were X and Y, with the male complement being XY and the female complement XX.

Group A consists of chromosome pairs 1 to 3. These are metacentric and are the largest pairs. Chromosome 3 has arms of equal length.

Group B consists of chromosome pairs 4 and 5 which are submetacentric and long, although shorter than those in group A.

Group C is composed of chromosome pairs 6 to 12 and the X chromosome, and these are all submetacentric.

Group D is formed by the acrocentric chromosome pairs 13 to 15.

Group E consists of chromosome pairs 16 to 18. Of these, pair 16 is metacentric but pairs 17 and 18 are submetacentric.

Group F contains chromosome pairs 19 and 20 which are small and metacentric.

Group G contains chromosome pairs 21 and 22 which are the smallest of the chromosomes and are acrocentric. The Y chromosome also belongs to group G and in most cells it can be distinguished from chromosomes 21 and 22, although its length may vary from one individual to another.

B. Paris Classification

Chromosomes can be further classified by the presence of secondary constrictions and satellites, and by a characteristic linear pattern along the length of the chromosome which can be demonstrated by special techniques. This linear pattern is called banding and the presence of chrom-

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