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Basic concepts of medical genetics: Formal genetics, Part 2

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5. Functional genomic maps

Hypothetical applications of functional human genomic maps in medical genetics can include a wide range of diagnostic techniques and therapeutic approaches. Comparative analysis of **proteome maps** of normal cells and those of malignant cells can, for instance, depict functional deviations of the genome in cancer cells and detect oncogenic proteins synthesized and expressed by the malignant cell and responsible for pathogenesis and development of the malignant phenotype. **Oncoprotein maps** constructed from this information would, certainly, have beneficial impact on research studies aiming at better, and proper, understanding of malignant transformation through targeting pivotal oncoproteins that initiate and promote the malignant phenotype of cancer cells. They would, also, have similar impact on research studies aiming at designing and tailoring specific therapeutic trials for challenging carcinogenesis through e.g. engineering of monoclonal antibodies against relevant oncoproteins inside intracellular compartments as well as on cell membranes and within intercellular spaces. Interruption of signaling pathways involved in the mediation of many selective advantageous functions of malignant cells, e.g. enhanced glycolysis, metastasis and neovascularization, which depend on the synthesis of specific oncoproteins could, probably, represent a promising approach in the treatment of cancer via disassembly of metabolic and regulatory networks actively participating in malignant transformation and development of the malignant phenotype.

On the molecular level, comparative analysis of **transcriptome maps** of messenger RNA and those of different micro RNA species in normal and in diseased subjects could offer remarkable help in the diagnosis of genetic diseases characterized by substantial genomic activities. Malignant cells express large numbers of actively transcribed genes, and detailed cancer-specific transcriptome maps could be constructed for pathologically distinct types of malignancies, thus allowing for better understanding of the aberrant phenomena of differential suppression of certain genes and of mass overexpression of specific gene families, e.g. proto-oncogenes, in malignant cells. They can also offer more information on the genic and intergenic pathogenetic and pathological mechanisms underlying the development of specific types of cancer. Cancer-specific transcriptome maps and oncoprotein maps constructed for pathologically distinct types of malignancies might offer rapid and accurate diagnostic tools of these malignancies when compared with corresponding maps of normal cells. Delineation of the whole spectrum of proto-oncogenes and of oncogenes in the human genome and construction of informative maps detailing relevant databases of this spectrum remains, and represents, a prospective ultimate goal crucial for understanding and designing radical therapies for cancer.

6. Developmental genomic, proteomic and transcriptomic maps

During embryonic and fetal development, and to much lesser extent during early post-natal life, organ and tissue-specific differential suppression of large numbers of certain sets of genes,

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paralleled by selective expression and/or over-transcription of similar numbers of other sets of genes, is indispensable for normal regulation, synchronization and progression of consecutive processes of differentiation, specialization, growth and development. Comparative analysis of genome, transcriptome and proteome functional maps during each of these stages of embryonic and fetal life could disclose the intimate correlations between synchronized activities of these three components, and reveal many obscure aspects of temporal regulation of these activities during this critical period of life. This information might prove helpful in understanding genomic regulation of development stages and revealing genetic disturbances that predispose to the pathogenetic mechanisms and the pathophysiological alterations that mediate and underlie the development of congenital malformations. Comprehensive understanding of these aspects of genetic regulation of development represents a pre-requisite step indispensable for hypothesizing and designing effective prophylactic measures and early therapeutic intervention approaches against teratogenesis.

Additionally, analysis of formal databases of structural and functional genomic and proteomic maps of fetal development can add, significantly, to our current vague and scanty knowledge of many, still, unknown aspects of regulatory genetic mechanisms, particularly those of genetic and genomic imprinting and temporal synchronization of mass suppression and activation of large, sometimes, huge numbers of genes that characterize development and differentiation. The role played by increased transposon activity in causing, seemingly, spontaneous mutagenic events that predispose to developmental malformations during fetal development deserves serious attention if effective prophylactic and therapeutic anti-teratogenic measures are to be hypothesized and designed. Also, the effective opposition of this teratogenic mechanism by the silencing action exerted by piwiRNA on transposon regulatory sequences, represents an important regulatory mechanism responsible for maintaining genomic integrity and genomic stability during this critical period of life. Comparison of malformation-specific transposon maps with their normal counterparts would offer invaluable information which can be used to construct anomaly-specific databases correlated with these particular transposon maps that depict specific overexpressed transposons in specific types of congenital malformations. These data could have both predictive value in delineating malformation-causing transposons, as well as potential therapeutic and/or prophylactic application by choosing and designing proper and specific piwiRNA silencing molecules against these particular anomaly-causing transposons.

7. Limitations of formal genetic analysis

Computational analysis of bioinformatics databases represented by different types of formal genetic maps, whether for comparative or predictive purposes, represents a real challenge. Not only because of lack of many pieces of information necessary to complete these maps, but also due to paucity of our knowledge as regards basic essential genetic mechanisms that regulate the structural integrity and functional specialization of the genome as a whole. For instance, the nature of the real regulatory systems that master the highly conserved species-specific genetic constitutions of all creatures, including the human genome, is extremely vague, without any clues to the possibility of disclosing the design or the components of the genetic material responsible for it, even in the near future. Similarly, the significance of many puzzling and enigmatic phenomena regarding the known detailed structure and actual functions of the genetic material continues to be a matter of debate in spite of the many theories and hypotheses trying to explain them. Examples of such phenomena include genetic imprinting, transposon activity, apoptosis, metabolic adaptations and many others. However, the nature of the mechanisms through which biomolecules, notably nucleic acids and proteins, can conceive, interpret and execute pre-programed biological processes that are embodied within their structural configuration remain on the top of these unsolved phenomena.

8. Formal genetic maps

Formal genetic maps comprise three main categories that are widely used in clinical, diagnostic and experimental genetics. They include: the **family pedigree**, **physical maps** and **induced** or experimentally constructed **maps** (Table 2).

8.1. The family pedigree

The family pedigree is a simple graphic interface figure intended for presentation of information and data of patients with genetic diseases or families with a history of genetic diseases. It summarizes personal and family data of examined or counseled cases and their concerned family members, thus allowing rapid collection and interpretation of presented data, inference of possible patterns of inheritance, deduction of assumptions regarding probable etiologies of recorded findings and identification of family members in need of further diagnostic/prognostic investigations or confirmatory tests to reveal their carrier status, so that proper counseling advice could be offered to them. Additionally, properly constructed pedigree is mandatory for formulation of proper counseling approaches to concerned patients and their related family members. Family pedigree construction utilizes arbitrary symbols agreed upon by most geneticists and used to depict and represent specific data and information of the pedigree. Additional important and informative data of members represented in the

Table 2 Types of genetic maps.

A. The family pedigree
B. Physical maps
1. Genomic maps
2. Sequence maps
3. Gene maps
4. Chromosome maps
5. Transposon maps
6. Pseudogene maps
7. Pyknon maps
8. Linkage maps
C. Induced/experimental maps
1. Hybridization maps
2. Radiation hybrid maps
3. Restriction fragment polymorphism maps
4. Probe-specific maps
5. Disease-association maps

pedigree are added as text and recorded on the pedigree to be analyzed with the rest of the data of the pedigree (Figs. 1 and 2) [1].

8.2. Patterns of inheritance

Genetic diseases manifest distinctive wide variations as regards their ways of occurrence and recurrence, as well as their ways of inheritance, or transmission, from parents to offspring. The specific patterns of inheritance of genetic diseases describe the characteristic features which outline, control and regulate the transmission of genetic traits or diseases from normal, carrier or affected parents to their offspring. These features vary widely according to the actions and interactions of many genetic factors in addition to many other modifying genetic and/or environmental conditions.

The pattern(s) of inheritance of a specific genetic disease depends on many factors including whether the disease is caused by single mutant gene, by more than one gene or by a multifactorial genetic-environmental interaction, the gene locus, the status of the transmitting parent(s), the nature of the gene product(s), the causative pathogenetic mechanism(s) underlying the development of the disease, and whether this transmission happens in a classic traditional manner or within the context of an abnormal genetic framework.

The distinction between genetic diseases due to single mutant genes, referred to as single gene disorders, and other types of genetic diseases is of prime importance because it makes a clear delineation between genetic disorders that follow specific rules of inheritance referred to as classic/traditional or Mendelian patterns of inheritance, and other genetic diseases caused by different genetic mechanisms that do not follow these classic rules. They, rather, follow other rules referred to as non-Mendelian/non-classic or non-traditional patterns of inheritance. Accordingly, two main patterns of inheritance of genetic disorders could be identified: **Mendelian/classic/traditional pattern of inheritance** of single gene disorders and **non-Mendelian/non-classic/non-traditional pattern of inheritance** of other types of genetic disorders (Table 3) [2].

The **locus** of the mutant gene defines the nature of the genetic disorder in two different ways. First, it defines three broad groups of genetic diseases: **nuclear gene diseases** due to mutant genes located on the chromosomes in the nucleus, **mitochondrial disorders** due to mutant genes of the mtDNA and combined **nuclear-mitochondrial genetic diseases** due to affection of both nuclear and mitochondrial genes, e.g. oxidative phosphorylation disorders. Alternatively, it can delineate three different categories of single gene disorders each having its own specific pattern(s) of inheritance: **autosomal diseases** caused by genes located on the autosomes, **sex-linked diseases** caused by genes located on the sex chromosomes and **mitochondrial disorders** caused by mutations of mitochondrial genes. Sex-linked diseases are further classified into **X-linked diseases** caused by mutant genes on the X-chromosome and **Y-linked diseases** caused by mutant genes lying on the Y-chromosome.

An individual having both normal genes, or alleles, transmitted from both parents is termed a normal or a homozygote normal. An individual having both abnormal, defective or mutant genes transmitted from both parents is termed a homozygote diseased or affected individual. An individual having a normal gene transmitted from one parent and an abnormal, defective or mutant gene transmitted from the other parent is termed a carrier or a heterozygote. Males with single X-chromosome are hemizygotes for genes located on the X-chromosome since they have only one copy of these genes.

The status of the transmitting parent, or both parents, determines many different aspects of the pattern(s) of inheritance of the inherited disease. For single gene disorders, one aspect defines the transmission of the gene in a dominant or a recessive way, for both autosomal and sex-linked genes. So, we have five main different patterns of inheritance based on the way of transmission of the single mutant gene relative to the status of the transmitting parent(s). These patterns are: autosomal dominant (AD), autosomal recessive (AR), X-linked dominant, X-linked recessive and Y-linked patterns [3].

8.2.1. Autosomal dominant inheritance

For human traits and diseases, dominance refers to the ability of the gene to confer a specific phenotype on the individual harboring it when present in a single copy or allele. An autosomal dominant (AD) genetic disease entails the presence of one mutated allele of the disease-causing gene on one of the

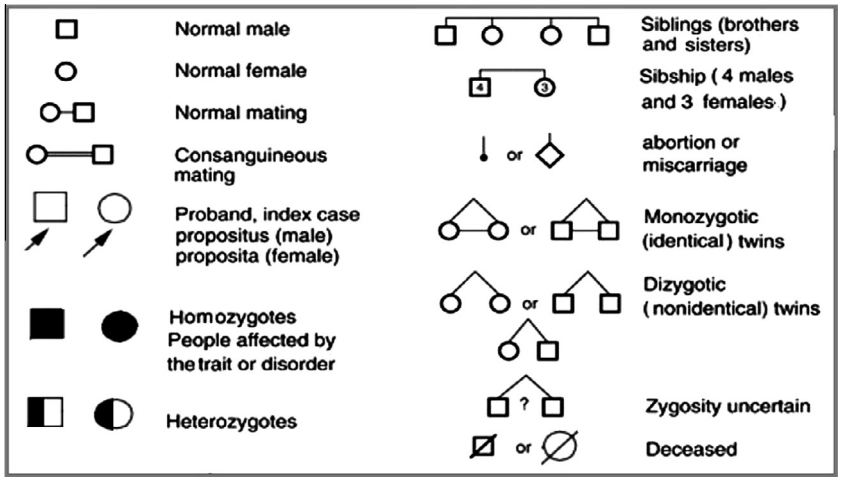

Fig. 1 Different symbols used in construction and description of the family pedigree.

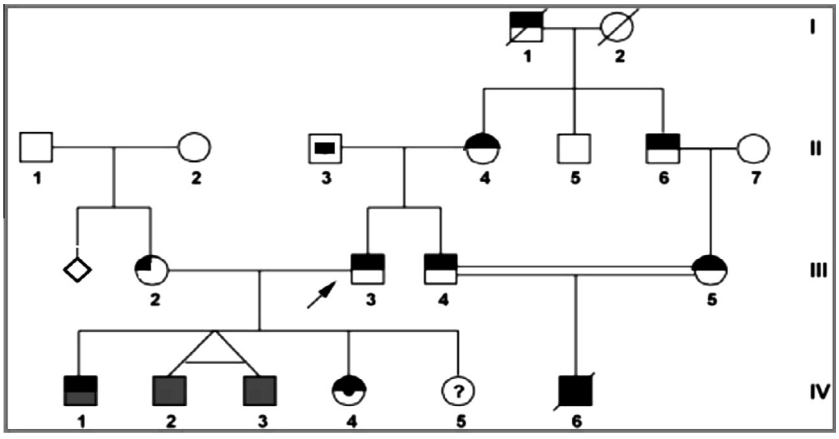

Fig. 2 The family pedigree.

Table 3 Patterns of inheritance of genetic traits/diseases.

Mendelian/classic/traditional patterns	Non-Mendelian/non-classic/non-traditional patterns
1. Autosomal dominant diseases	1. Genetic imprinting: genic–genomic
2. Autosomal recessive diseases	2. Uniparental disomy (UPD): heterodisomy–isodisomy
3. X-linked dominant diseases	3. Trinucleotide, or triplet repeat, expansion
4. X-linked recessive diseases	4. Mitochondrial inheritance
5. Y-linked diseases	5. Microdeletion/microduplication syndromes
	6. Gonadal mosaicism
	7. Multifactorial disorders
	8. Nuclear/mitochondrial disorders

autosomes and a normal allele on the other homologous chromosome, and the pathogenesis of a specific disease phenotype due to defective and/or deficient production of the structural protein encoded by the mutated gene.

Since autosomal dominant genes exist on the autosomes, they can be transmitted to either male or female offspring, and as only half the germ cells of the parent having the disease gene are affected, with the other half having the other normal allele, there is 50% statistical chance in each conception of having an affected offspring and 50% chance of having a normal free offspring.

As autosomal dominant diseases are caused by single mutant genes, there are no carriers of these diseases, rather there are affected diseased heterozygotes and, in some rare exceptional conditions, affected diseased homozygotes if both alleles of the gene are mutated.

Penetrance and expressivity

Penetrance is the probability that a dominant disease will appear in an individual when a disease-allele is present. For example, if all the individuals who have the disease-causing allele for a dominant disorder have the disease, the allele is said to have 100% penetrance. If only a quarter of individuals carrying the disease-causing allele show signs/symptoms of the disease, the penetrance is 25%. Expressivity, on the other hand, refers to the range of signs/symptoms that are possible for a given disease. For example, an inherited disease like the Marfan syndrome can have either severe or mild phenotype and can have either a partial or full range of expression with affection of the skeletal, ocular and cardiovascular systems.

8.2.2. Autosomal recessive inheritance

An autosomal recessive (AR) genetic disease entails the presence of two mutant alleles of the disease-causing gene on both autosomes. The pathogenesis of a specific recessive disease phenotype results from absence, in varying degrees ranging from total absence to mild deficiency, of the gene product or synthesis of defective gene product. Contrary to autosomal dominant diseases, carriers of autosomal recessive genes are typically normal. They might show some disease manifestations only under exceptional conditions, e.g. stressful physiological circumstances or abnormal metabolic derangements. Recessive genes need to exist in two copies, or alleles, in order that a specific recessive disease or trait phenotype can show up. Homozygosity, or similarity, of both alleles (disease causing genes) on both autosomes which results in total absence or severe deficiency of the gene product, is a pre-requisite for pathogenesis and development of the disease phenotype.

This difference between dominant and recessive diseases can be attributed, in part, to the different underlying pathogenetic mechanisms and might be explained in view of the specific pathological characteristics of each type. Dominant diseases result, mostly, due to deficient and/or defective production of structural proteins produced by mutant genes. These structural proteins are vital integral constituents of

nearly all cellular components, e.g. cell membranes, cytoskeleton, cell organelles, spindle apparatus, chromatin material and mitochondrial components. Structural proteins define all anatomical aspects and regulate dynamics of cellular activities like cell division, cell movement and cell migration, signaling pathways, intercellular contact and many others. In AD diseases, 50% reduction of the amount, or functions, of these structural proteins happens which is a drastic burden that cannot be tolerated by the cell, hence the expression of the disease phenotype in heterozygotes of AD genes. Autosomal recessive diseases, on the other hand, comprise genetic diseases resulting mostly from deficient and/or defective production of catalytic proteins that act as enzymes rather than as structural proteins. Enzyme dynamics allow for mediation of prolonged and recurring metabolic reactions by small limited amounts of the enzyme, sometimes as low as 5% of the amount needed under normal conditions. Hence, for an AR disorder to be expressed in an affected patient, mutation of both genes is required thus necessitating a carrier or heterozygous status of both parents, except under exceptional abnormal conditions like parental disomy, for instance.

8.2.3. X-linked inheritance

X-linked inheritance refers to patterns of inheritance of traits and diseases caused by genes located on the X-chromosome. Though a normal female has two X-chromosomes in her somatic cells, only one of these two is active and the other, for most of its genes, is inactive. This phenomenon of inactivation or suppression of one of the two X-chromosomes in any normal female somatic cell is termed **Lyonization** of the X-chromosome. Lyonization, or inactivation of all X-chromosomes but one in somatic cells, happens very early during the first two weeks of embryonic development. Most important is its apparent random occurrence, i.e. it can affect either the paternally or the maternally inherited X-chromosome. Also, once it happens, the inactivation of a particular X-chromosome in a cell continues to affect the same inherited chromosome in all daughter descendent cells of the original cell.

The implications of the process of **Lyonization** include the following aspects:

1. Any normal female has only one active X-chromosome in each of her somatic cells.
2. Any somatic cell has only one active X-chromosome regardless of the number of X-chromosomes in the cell, i.e. all X-chromosomes in excess of one get Lyonized, suppressed or inactivated.
3. Any normal female has a mosaic genotype for her X-linked genes since, on the average, half of her cells has one active chromosome inherited from one parent and the other half has one inactive X-chromosome inherited from the other parent.
4. If a female inherits a mutant X-linked gene from one of her parents, on the average, half of her cells will have the X-chromosome carrying the mutant gene and the other half will have the normal chromosome carrying the normal gene. Accordingly, most females having X-linked recessive diseases do not suffer any effects or complications since they have, on the average, 50% of the gene product produced by the normal allele on the active X-chromosome. However, only under rare exceptional conditions resulting in targeted inactivation of the normal X-chromosome in most cells will a female carrier of an X-linked recessive disease suffer from the disease. A similar situation might be encountered in female patients having the Turner's syndrome with a single X-chromosome. If they inherit mutant genes linked to their only X-chromosome they suffer from the pathogenetic phenotype(s) caused by these genes.

Contrary to the situation in females, males carrying mutant genes on their single X-chromosome are affected with the disease since they do not have any reserve gene to replace for or counteract the pathogenetic defects due to lack of another X-chromosome.

8.2.3.1. X-linked recessive inheritance

These facts impart special inheritance features to X-linked recessive disorders. In statistical terms, carrier mothers transmit their defective gene to half of their male offspring who will be affected, and transmit the normal gene to the other half who will be normal. Female offspring who might inherit the mutant gene will be carriers like their mothers and, usually, would not show any disease manifestations as they concurrently inherit a normal copy of the gene through the paternal X-chromosome they inherit from their father.

As referred to previously, females might be affected with X-linked recessive diseases under exceptional circumstances, for instance in 45,X Turner syndrome if the only X-chromosome they have carries the mutant gene, in abnormal Lyonization states if inactivation targets exclusively the normal X-chromosome, via an affected father in addition to a carrier or affected mother or, quite rarely, if they suffer a fresh mutation of their normal allele in addition to the inherited mutant allele they already have.

8.2.3.2. X-linked dominant inheritance

X-Linked dominant genes, like autosomal dominant genes can induce a disease phenotype when present in a single copy. So, females carrying an X-linked dominant gene will show the disease similar to males carrying the same gene, albeit in a milder form since they have another normal copy of the gene on the other normal X-chromosome. They will also transmit this gene to half of their male offspring thus having a 50% chance of getting a normal male child and 50% chance of having an affected male child.

Similarly, half of her female offspring who inherit the mutant gene will be affected, sometimes in a milder form, and the other half will be quite normal females.

Their affected male children, on the other hand, upon mating will transmit their affected X-linked dominant gene only to all their daughters who will be affected, while none of their male offspring who inherit the Y- chromosome from their fathers will be affected [4].

8.2.4. Y-linked inheritance

Y-linked inheritance, or Holandric inheritance, refers to inheritance of traits or diseases caused by genes carried on the Y-chromosome. Though the prime role of the Y-chromosome resides in sex determination due to the effect of the SRY (sex-

Table 4 Genes located on the Y-chromosome (Y-linked genes).

SRY: Sex-determining region	*RBM2:* RNA binding motif protein 2
TDF: Testis determining factor	*RBM1:* RNA binding motif protein, Y-chromosome, family 1, member A1
TSPY: Testis-specific protein	*CSF2RY:* Alpha subunit of granulocyte–macrophage colony-stimulating factor receptor
AZF1: Azoospermia factor 1	*ANT3Y:* Adenine nucleotide translocator-3
AZF2: Azoospermia factor 2	*IL3RAY:* Interleukin-3 receptor
DAZ: Deleted in azoospermia	*ASMTY:* Acetyl-serotonin methyltransferase
AMELY/AMELX: Amelogenin	*RBM2:* RNA binding motif protein 2
RPS4Y1/RPS4Y2/RPS4X: Ribosomal protein S4	*UTY:* Ubiquitously transcribed TPR gene on Y-chromosome
USP9Y: Ubiquitin specific peptidase 9, Y-linked	*PRKY:* Protein kinase, Y-linked
BPY2: Testis-specific basic protein Y 2	*ZFY:* Zinc finger protein

Table 5 Pseudoautosomal region genes.

ASMT: N-Acetyl-serotonin *O*-methyltransferase	*CSF2RA:* Granulocyte macrophage colony-stimulating factor receptor	*IL3RA:* Interleukin-3 receptor, alpha (low affinity) (CD 123)
ASMTL: N-Acetyl-serotonin *O*-methyltransferase-like protein	*SFRS17A:* Splicing factor, arginine/serine-rich 17A	*P2RY8:* P2Y purinoceptor 8
CD99: CD99 antigen (cluster of differentiation 99)	*DHRSXY:* Dehydrogenase/ reductase (SDR family) X-linked	*PLCXD1:* Phosphatidylinositol-specific phospholipase C, X domain containing 1
CRLF2: Cytokine receptor-like factor 2	*GTPBP6:* GTP binding protein 6	*PPP2R3B:* Serine/threonine–protein phosphatase 2A regulatory subunit beta
SHOX: Short stature homeobox gene	*SLC25A6:* ADP/ATP translocase 3 (solute carrier family 25 member 6)	*XG:* XG antigen
ZBED1: Zinc finger BED domain-containing protein 1	*SPRY3:* Protein sprouty homolog 3	*SYBL1:* Vesicle-associated membrane protein 7 (VAMP-7)
IL9R: Interleukin 9 receptor (IL9R) (CD129 or cluster of differentiation 129)	*PCDH11X:* Protocadherin 11 X-linked	*PCDH11Y:* Protocadherin 11 Y-linked
CXYorf1: WAS protein family homolog 6 pseudogene	*TGIF2LX:* TGFB-induced factor homeobox 2-like, X-linked	*TGIF2LY:* TGFB-induced factor homeobox 2-like, Y-linked

determining region) located on its long arm in driving the destination of the primitive gonad toward differentiation into testes and maleness of the developing embryo, large numbers of Y-linked genes have been defined which have important functions in the regulation of gene expression, of many metabolic pathways as well as the regulation of immune functions (Table 4). Certain Y-linked genes probably exert critical effects on brain functions during development through defining male specific brain phenotypes, and hence male-typical behaviors. An alternative perspective is that, in some cases, Y-linked genes may act to attenuate sex differences, e.g. where the Y homolog of an X-linked escaping inactivation performs a functionally equivalent role [4].

8.2.5. Pseudoautosomal region of the X- and Y-chromosomes

The pseudoautosomal regions (PAR) are short regions of sequence homology shared between the X- and Y-chromosomes, that pair and recombine during meiosis. Two of these regions (PAR1 and PAR2) have been located at both ends of these chromosomes. PAR1 is located at the terminal region of the short arms and PAR2 at the tips of the long arms. Currently, 24 genes have been assigned to the PAR1 region and 4 genes have been defined in the PAR2 region (Table 5). The main function of these pseudoautosomal regions is to allow proper pairing and segregation of both chromosomes during meiosis in males. Of relevant importance in this regard is the finding that deletion of the PAR1 region of the Y-chromosome results in failure of X-Y pairing and male sterility. Also, haploinsufficiency of the SHOX gene (short stature homeobox-containing), located in PAR1 contributes to certain features in Turner syndrome. Both chromosomes, however, share other regions of sequence homology along their lengths.

Genes of the pseudoautosomal regions (PAR1 and PAR2) behave like autosomal genes and recombine during meiosis. Normal males have two copies of these genes: one in the pseudoautosomal region of their Y-chromosome, the other in the corresponding pseudoautosomal portion of their X-chromosome. Normal females also have two copies of each of the pseudoautosomal genes, as each of their two X-chromosomes contains a pseudoautosomal region. During meiosis, crossing over between the X- and Y-chromosomes is restricted only to the pseudoautosomal regions, thus, PAR genes exhibit an autosomal, rather than sex-linked, pattern of inheritance. So, females can inherit an allele originally present on the pseudoautosomal region of the Y-chromosome of their father

and males can, also, inherit an allele originally present on the pseudoautosomal region of the X-chromosome of their father. Since all pseudoautosomal genes escape X-inactivation they are candidates for having gene dosage effects in sex chromosome aneuploidy conditions like the Turner syndrome, Klinefelter syndrome, triple X syndrome and the like [5].

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