

Mendelian and Atypical Patterns of Inheritance

I MONOGENIC MENDELIAN INHERITANCE

[French](#)

I.1 SYNOPSIS

I.2 AUTOSOMAL DOMINANT INHERITANCE

I.3 AUTOSOMAL RECESSIVE INHERITANCE

I.4 X-LINKED RECESSIVE INHERITANCE

I.4.1 MOST FREQUENT CASE / MARRIAGE HEZ
WOMAN / NORMAL MAN

I.4.2 PARTICULAR CASE : MARRIAGE NORMAL
WOMAN / AFFECTED MAN

I.4.3 PARTICULAR CASE : MARRIAGE HEZ WOMAN
/ AFFECTED MAN

I.5 FACTORS AFFECTING THE PHENOTYPE

II MULTIFACTORIAL INHERITANCE

III MITOCHONDIAL INHERITANCE

*

INTRODUCTION

Mendelian inheritance is based on the transmission of a single gene on a dominant, recessive or X-linked pattern. Discoveries on DNA structure, the genetic code, the genome and the observation that some characters and hereditary diseases do not follow classical mendelian inheritance have led researchers to define other patterns of transmission, referring particularly to multifactorial and mitochondrial inheritance. Multifactorial inheritance is based on the synergy of genes and environmental factors. Extra nuclear mitochondrial heredity can only be transmitted by the mother whose cells contain a number of mitochondria. Several factors can modify the expected individual phenotypes. There will undoubtedly be important advances in our knowledge of the pattern of inheritance of characters and diseases given a better understanding of gene structure and role, interaction of genes between them and with the environment.

I MONOGENIC MENDELIAN INHERITANCE

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- X linked chromosome recessive inheritance

I.1 Synopsis

- An eukaryote gene is made of successive coding segments (exons) and not coding (introns) ---> pre-messenger RNA; splicing ---> RNA messenger

- Meiosis (one diploid cell with 46 chromosomes ---> 4 haploid cells with 23 chromosomes) is, with mutations, responsible for diversity and genetic mixing by:
 - random dispersion of chromosomes in the gametes
 - exchange between homologous chromosomes (crossing over).
- Eukaryotes have 2 copies of the hereditary message (by contrast with prokaryotes and viruses), 1 paternal and 1 maternal: 2 alleles are 2 alternates of a gene at the same locus on both copies of the genome; any change of a hereditary character at the level of one of the two copies of the genome (homologous chromosomes) can:
 - either modify the phenotype: this is expressed as a dominant pattern (D)
 - or not modify the phenotype: recessive gene (R)
- If 2 alleles are expressed simultaneously, the genes are co-dominant (ex: ABO blood group).
 - One individual who at the same locus has 2 identical alleles is known as homozygous (HOZ) for this allele.
 - One individual who has 2 different alleles at the same locus is called heterozygous (HEZ)for this allele.
---> a recessive character is phenotypically expressed only in the HOZ state.
- This general picture refers to autosomal inheritance; but sex chromosomes are different in male and female: in the woman, XX, recessivity and dominance of X linked characters will be expressed as an autosomal pattern; the male, XY, is hemizyous for the X, the phenotype will be the expression of the X genotype.

I.2 Autosomal dominant inheritance (AD):

Most frequent instance: Aa x AA (marriage of an affected individual HEZ with a normal individual).

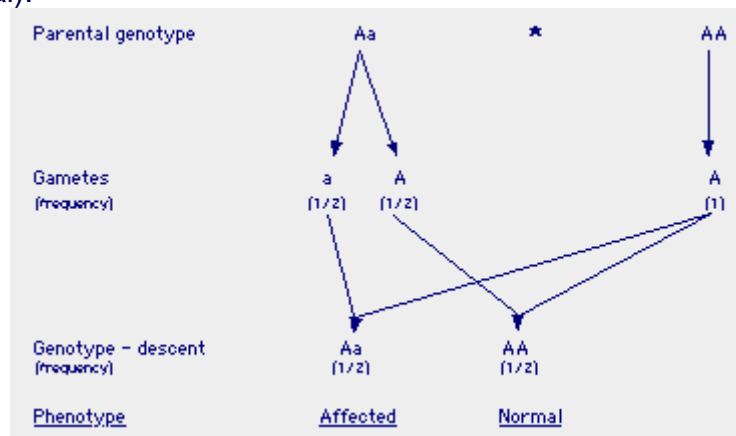


Fig. 1

--> Gamètes (fréquence)	a (1/2)	A (1/2)	
A (1)	Aa (1/2)	AA (1/2)	<-- Genotype - descent (frequency)
	(a) <u>Affected</u>	(A) <u>Normal</u>	<-- <u>Phenotype - descent</u>

Fig. 2

- Affected individuals are always the product of a parent carrier of the same character (except in a mutation).
- The character is apparent in each generation (does not skip a generation, except when the penetrance is reduced).
- There are as many daughters and sons affected.
- In a sibship one finds as many affected as normal individuals.
- Half of descents of an affected individual will be affected.
- All children of a normal individual will be normal.
- Consanguinity is not elevated.
- The character can be expressed if there is a mutation and be transmitted or eliminated if the defect is severe.

Remarks :

- Most of the time one ignores what would be a HOZ individual for a dominant character.
- Some observations suggest that the individual would be affected earlier and more severely or that the disease would progress more rapidly.
- Penetrance and expressivity play a role.
- If a disease is not compatible with reproduction, its frequency equals the mutation rate.

Examples of AD diseases :

- Achondroplasia
- Aniridia
- Marfan syndrome
- Steinert myotonic dystrophy
- Polydactyly
- Adenomatous polyposis of the colon

I.3 Autosomal recessive inheritance

Most frequent case: Aa x Aa (marriage of 2 normal heterozygotes).
 Parental genotype: Aa x Aa

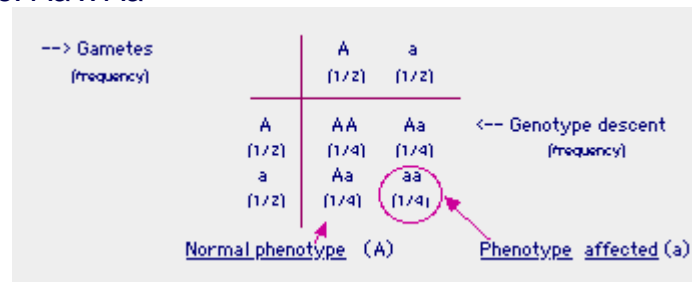


Fig. 3

- In the instance of a rare disease, affected individuals have normal parents.
- There are as many daughters and sons affected.
- In a sibship there are usually one affected and three normal individuals.
- An affected individual who marries a normal, non consanguineous person, usually has normal children.
- However the disease can affect only one individual who has mutant genes: due to the small number of sibs in families this does not mean that this situation is due to a de novo mutation.
- The frequency of consanguineous families is elevated (the risk of matings between 2 individuals, carriers of the same mutation, and with common ancestors is increased) and more so if the disease is rare.
- When a mutation occurs it will not be apparent in the individual carrier

Remarks:

- Mating between HOZ individuals is a common event: individuals with similar handicaps (deafness, vision defect...) often attend the same medical clinics and social functions which may facilitate the establishment of relationships.
- Most enzyme deficiency diseases are autosomal recessive.
- In fact few genes are completely recessive and often we can detect HEZ carriers.
- HEZ is different of the two types of HOZ: intermediary inheritance; the ability to detect HEZ allows for genetic counseling.
- Often affected HOZ die early or do not reproduce.
- Sometimes the affected HOZ will survive and reproduce (ex: albinism) . If this affected individual marries a HEZ individual with a normal phenotype, the pattern of inheritance will appear incorrectly as a dominant transmission.
- Even if the disease is rare, HEZ frequency may be elevated (cystic fibrosis incidence 4/10,000. ---> heterozygotes frequency: 4/100).
- Penetrance and expressivity ought to be considered.

Examples of AR diseases:

- Glycogenosis, VI types.
- Sugar intolerance: galactose, fructose, saccharose, lactose.
- Mucopolysaccharidoses VI types, except Hunter disease MPS II which is RLX.
- Most amino acid disorders : phenylketonuria, tyrosinosis, cystinosis, leucinos. albinism variants (except ocular albinism which is RLX) etc...
- Several lipid metabolism diseases.
- Wilson disease.
- Several disorders of hormono synthesis, mainly thyroid and adrenal.
- Sickle cell anemia, Thalassemia.
- Factor I,II,V,VII,XII,XIII deficiencies
- Cystic fibrosis

I.4 X linked recessive inheritance (RLX)

I.4.1 Most frequent case: heterozygote woman, a normal carrier who marries a normal man.

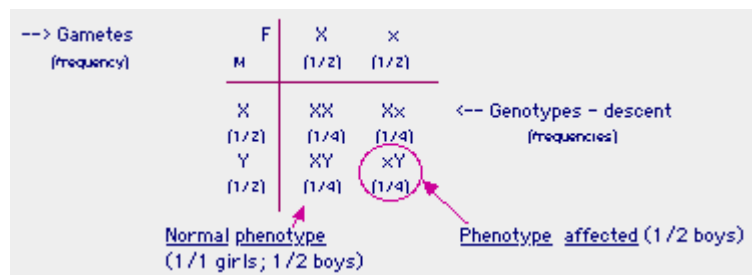


Fig. 4

- Affected individuals are usually born of normal parents.
- In the paternal progeny all individuals are normal.
- In the maternal progeny one often finds affected brothers or male sibs.
- Usually affected individuals are male.
- In the affected sibship , one male out of two is affected, and one female out of two is carrier.

Particular cases:

I.4.2 Mating normal female / affected male

Parental genotype : XX * xY

--> Gametes (frequency)		F	X	
		M	(1/1)	
x	(1/2)	Xx	(1/2)	← Normal phenotype (1/1 girls)
Y	(1/2)	XY	(1/2)	← Normal phenotype (1/1 boys)

Fig. 5

- All boys are normal and carry no mutation.
- All girls are normal but are HEZ carriers.

I.4.3 Marriage HEZ female / affected male

Parental genotype: Xx / xY

--> Gametes (frequency)		F	X	x	
		M	(1/2)	(1/2)	
x	(1/2)	Xx	(1/4)	xx	(1/4)
Y	(1/2)	XY	(1/4)	xY	(1/4)
<u>Phenotype</u>			normal	affected	
			1/2 girls	1/2 girls	
			1/2 boys	1/2 boys	

Fig. 6

Rare situation if the mutation is severe.

- One boy out of two is affected.
- Normal girls are HEZ.
- Girls can be affected.

Situation not likely to happen for a rare gene, but more frequent if the gene frequency is high (ex: colour blindness).

---> The fact that the disease is restricted to males is not an absolute criterion of X linked inheritance. The criterion of n on transmission from father to son is more objective

---> (it allows to differentiate between autosomal dominant diseases with sex limitation).

Remarks: to detect heterozygote carriers for genetic counseling.

Examples of RLX diseases :

- Colour blindness
- Hemophilia A and B
- Angiokeratosis (Fabry disease)

- Duchenne muscular dystrophy
- Incontinentia pigmentosum
- Agammaglobulinemia, Bruton type
- G6PD deficiency

I.5 Factors affecting the phenotype

I.5.1 Penetrance

Some individuals who carry the deleterious gene (for instance in an autosomal dominant disease) do not present the expected phenotype: we then say that the penetrance is incomplete. The number of individuals who carry a mutation is less than the number of individuals who have an abnormal phenotype. This is a quantitative estimate. In the neurofibromatosis type I, penetrance is evaluated at approximately 80 % , but it is often difficult to detect a mild form of the disease. An improved method to evaluate mutations in those families will allow us to better understand this notion of penetrance.

C not to confound an isolate case due to a reduced penetrance with a sporadic case due to a mutation.

1.5.2 Expressivity

The phenotype can be more or less severe among affected individuals. This a variable expressivity of the deleterious gene. It is a qualitative evaluation.

In Marfan syndrome for an identical familial gene mutation, some individuals will have a severe form of the disease affecting the cardiovascular, ocular and skeletal systems while for other individuals only the tall stature and arachnodactyly, without lens dislocation or aortic aneurysm, will be noted.

--->Reduced penetrance and incomplete expressivity are described mainly in autosomal dominant diseases.

I.5.3 Age of onset of the disease / anticipation

Although they are present at birth several diseases manifest only later in life. A normal physical examination of a 20 year old individual, from a family at risk for Huntington disease, does not rule out the possibility that this individual is affected with the disease.

---> If the genetic defect is known in a family, the molecular analysis will allow an early detection of the mutation or rule out this possibility before the expected age of onset of the disease.

---> Anticipation refers to a phenomenon characterizing the earlier onset of a disease in younger generations accompanied by more severe manifestations. The phenomenon is mainly observed in autosomal dominant diseases, when there is an increased elevation of triplet repeats from one generation to the next as for instance in myotonic dystrophy (CTG) and Huntington disease (CAG). In Friedreich ataxia, an autosomal recessive disease, the literature reports several families in which the increased triplet repeats (GAA) from one generation to the next is accompanied by an early onset and a more severe symptomatology. However one also finds in Fragile X syndrome, a X-linked disease, a more severe expressivity in the presence of increased triplet repeats without necessarily considering this an anticipation phenomenon.

1.5.4 Pleiotropy

In a number of genetic diseases the mutation can produce alterations in more than one system. For instance in the < Moon Biedl > syndrome, an autosomal recessive disease, malformations are seen in the nervous, endocrine, skeletal and ocular systems. The mutant gene effects are found at different stages of the development.

1.5.5 Mutation / Heterogeneity

The heterogeneity of mutations will lead to variable manifestations :

- The same mutation can induce different phenotypes.
- Some diseases are due to a mutant gene with a variable structure then susceptible to produce different phenotype effects. In cystic fibrosis there are several mutations at the locus of gene CFTR. More especially in this disease we find patients mainly affected with pulmonary disease, pancreatic insufficiency and / or intestinal disease.

In contrast with genes that code for one disease, the opposite is also noted that is that more than one gene can be responsible for the same disease: in <ectodermal dysplasia> syndrome, finger nail dysplasia, oligodonty and absence of hair can be attributed to 3 different mutant genes, inherited as dominant, X linked or a less frequent recessive patterns, all producing a similar phenotype.

1.5.6 Disomy

Infrequently homologous chromosomes can have an uniparental origin. This is called a maternal or paternal disomy for a pair of homologous chromosomes. For example an individual affected with cystic fibrosis had one parent carrier of a known mutation for which he was

homozygous having received two chromosomes 7 from the same parent carrier of this mutation and none from the other. Disomies are rare and their effect is not well known yet.

1.5.7 Imprinting / parental sex influence

During the course of development maternal and paternal genomes are not equivalent but complementary due to an epigenetic phenomenon that occurred during gametogenesis

Gene function can vary depending upon the maternal or paternal origin of the allele in question.

- A deletion on chromosome 15 (15q11-13) in the paternal chromosomal complement will lead to a Prader Willi syndrome different from the Angelman syndrome observed if the deletion involves the maternal chromosome.

- In some diseases the sex of the affected parent can influence the degree of severity of the disease in the individual to whom the mutant gene has been transmitted.

- In myotonic dystrophy the disease will be more severe, even often congenital, if the mother is the affected parent who transmitted the disease.
- In Huntington disease the age of onset may be earlier and the severity more pronounced if the father transmitted the disease.

In those two examples it has not been demonstrated beyond doubt that the phenomenon is due to parental imprinting, triplet amplification or a mitochondrial mutation.

--->Fertilization of an ovum without a nucleus by a sperm cell that has undergone a duplication of its haploid set or a dispermy could lead to a hydatiform mole.

1.5.8 Gene interaction / Co-factors

Gene action is sometimes regulated by more than one gene acting as regulator. A gene may have a normal structure but other genes in the metabolic chain or the absence of co-factor(s) may be responsible for the inhibition of a protein activity and the production of a genetic disease.

- For some individuals rickets is due to a vitamin D deficiency that will be corrected by the addition of a vitamin supplement in the diet. For others the disease due to the absence of the active form of Vitamin D, an autosomal recessive disease, or several other mutations regulating the vitamin D metabolism.
- Mutations of cancer suppressors, protein regulators (enzymes) or DNA repair genes have been identified. For example those mutations can induce metabolic diseases like mucopolysaccharidoses, ovary and colon cancers and DNA repair defects like Ataxia telangiectasia.

1.5.9 Genes susceptibility to cancer and malformations

A number of genes susceptible to be at the origin of a cancer can simultaneously cause a malformation syndrome.

- If a deletion occurs in gene WT1 located on chromosome 11 in region 11p13, it will lead to a Wilms tumor and a nephropathy. Syndrome WAGR (W:: Wilms; A: aniridia, G: genito-urinary malformations, R: mental retardation) would result from the deletion of this and other contiguous genes located in region 11p13-11p14.
- Another example is Beckwith-Wiedemann syndrome also located on chromosome 11, in region 11p15.5, that would imply several contiguous genes. The syndrome manifests with obesity, macroglossia, nephroblastoma (hepatoblastoma, neuroblastoma) gigantism and omphalocele. Growth factor IGF-2 ('insulin-like growth factor 2') a paternally expressed gene would be responsible for the pathogenesis of macrosomia; mutation of other genes like CDKN1C (p57K1P2) (maternal expression), may be responsible for other aspects of the phenotype.

---> Other case reports and molecular studies are essential to circumvent etiological mechanisms in those malformation syndromes with susceptibility to cancer.

1.5.10 Paternity

A false paternity may sometimes be at the origin of an incomplete or incorrect family history. Doubt may arise about the paternity of an individual if ongoing molecular studies do not find in the suspected father the presence of one or more DNA sequences.

1.5.11 Diagnostic error / classification

Difficulties encountered sometime in the evaluation of a pattern of transmission of a disease may be due to diagnostic or classification errors. Several groups of diseases like glycogenoses and mucopolysaccharidoses often have a similar phenotype but a different enzymatic deficiency confirmed by the identification of a specific mutation for each one of them.

II MUTIFACTORIAL INHERITANCE

Definitions :

- Multiallelic : there are at the same locus several possible alleles; each individual has only 2 and the transmission is done on a monogenic mode.

- Multifactorial:
 - There are for one specific character, a series of genes (and not loci) that form the basis of its identity (synonymous : polygenic system, quantitative inheritance, quantitative heredity, multiple factors).
 - Their study is mathematical and complex.
 - Contributing role of environmental factors. Examples: height of the individual, cardiopathies, epilepsy.

1. Continuous quantitative heredity

Distribution of the population on a Gauss model curve (ex: height).
Threshold model often arbitrary.

2. Discontinued quantitative heredity

- Quite often certain characters have a discontinued binary distribution, meaning that they are present or not in an individual (club foot, cleft palate, pyloric stenosis, diabetes, congenital cardiopathies, etc..) but their inheritance is as if they were multifactorial characters; this is due to a threshold effect that makes them appear as discontinued: multifactorial inheritance with a threshold.
- The individuals related to the population at the right of the threshold have a higher risk of being affected, and this is more so if they are closely related (if p is the frequency of a polygenic character in the population, the risk for first degree related individuals is approximately the square root of p).
- The threshold can be different for men and women for some diseases (pyloric stenosis: boys are 5 times more often affected than girls : congenital dislocation of the hip approximately 7 times more frequent in women than men)
- The risk of recurrence is higher when the first affected newborn is of the least susceptible gender of being affected.
- The disease is more frequent in individuals related to the patient than it is rare in the general population
- The more severe is the expressivity of a disease and the more elevated is the risk of recurrence.
- The risk of recurrence increases with the number of affected individuals in the progeny.
- Consanguinity plays a role: an individual whose spouse is related to him (her) has a higher risk of bringing together exact copies of the deleterious genes that were responsible for a given malformation in the family than if he was to marry to an individual chosen at random in the population. (If a couple has a child affected with an autosomal recessive disease, the risk of the next child of being affected is the same, irrespective of the parents being related or not, that is 1/4. If the

risk is more elevated when the parents are related than when they are not, heredity is said to be polygenic).

Examples of multifactorial diseases

- Cleft palate
- Hare lip and cleft palate
- Cardio-vascular diseases
- Schizophrenia
- Diabetes
- Gout
- Hip dislocation
- Strabismus
- Psoriasis etc...etc...

III MITOCHONDRIAL INHERITANCE

Mitochondrias come from ancestor anaerobic bacteria ;---> they have their own DNA. We then have extranuclear DNA in our cells.

MITOCHONDRIAL DNA :

- Circular DNA of 16 kb for which the sequence is entirely known.
- 37 genes code for 13 proteins, ribosomal RNA and transfer RNA.
- The genetic code is different from the universal code (1): Mito Univ UGA Trp STOP AUA Met Ile AGA/AGG STOP Arg.
- Mitochondria are present in the ovocyte (in large number).
- ---> non mendelian inheritance: strictly maternal inheritance.
- There are hereditary diseases due to mutant mitochondrial genes.
- Mitochondrial cytopathies are often deleterious with a pleiotropic symptomatology (multiple), since the deficit involves several organs: Pearson syndrome: exocrine pancreatic insufficiency, medullar insufficiency/ myelodysplasia, muscular deficit, hepatic, renal and gastro intestinal diseases.

A mitochondrial gene disease is transmitted :

1. solely by women.
2. to all her descents. Often the genetic defect is not present in all-but in a fraction only of mitochondria transmitted to the next generation; then according to the number of gene mutations in mitochondria.
3. variable expressivity.

The term mitochondrial cytopathy may be ambiguous : the mitochondrial cytopathies include not only the pathologies due to mitochondrial gene mutations but also those due to nuclear genes coding for proteins involved in the mitochondrial metabolism (enzymes of the respiratory chain).

Examples of of mitochondrial hereditary diseases :

- Leber optic atrophy
- Mitochondrial myopathies
- Pearson syndrome...

Contributor(s)

Written 12-2002 Louis Dallaire, Jean-Loup Huret

Citation

This paper should be referenced as such :

Dallaire L, Huret JL . Mendelian and Atypical Patterns of Inheritance. Atlas Genet Cytogenet Oncol Haematol. December 2002 .

URL : <http://AtlasGeneticsOncology.org/Educ/GenetFormelEngID30025ES.html>

© *Atlas of Genetics and Cytogenetics in Oncology and Haematology*
