Cardioscreen®

The test that identifies patient at risk of

- ✓ Sudden cardiac arrest
- ✓ Inherited cardiomyopathies

GENOMA®
Molecular Genetics Laboratories Group

Summary

- ✓Genoma Group presentation
- ✓The DNA and its biological role
- ✓Polymorphisms and mutations
- ✓Heredity
- ✓Cardiomyopathies and sudden cardiac arrest
- ✓Cardioscreen genetic tests
- ✓How to interpret the result

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GENOMA® Molecular Genetics Laboratories Group

Cardioscreen®

A total of 5.000 sq. m of laboratory surface area

2 headquarters logistics optimization

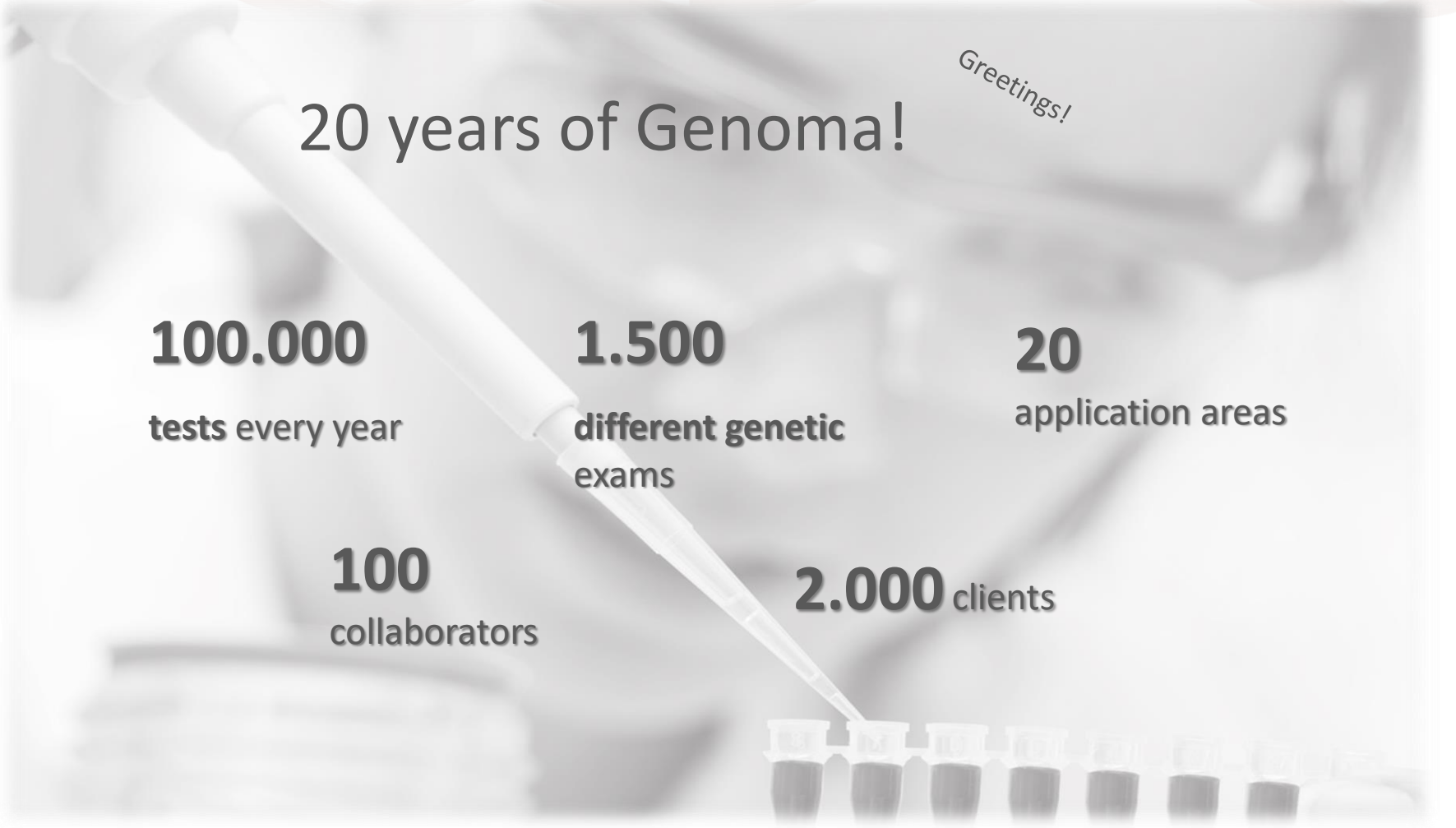
Rome

Milan

GENOMA® Molecular Genetics Laboratories Group

Cardioscreen®

Let's give the numbers!



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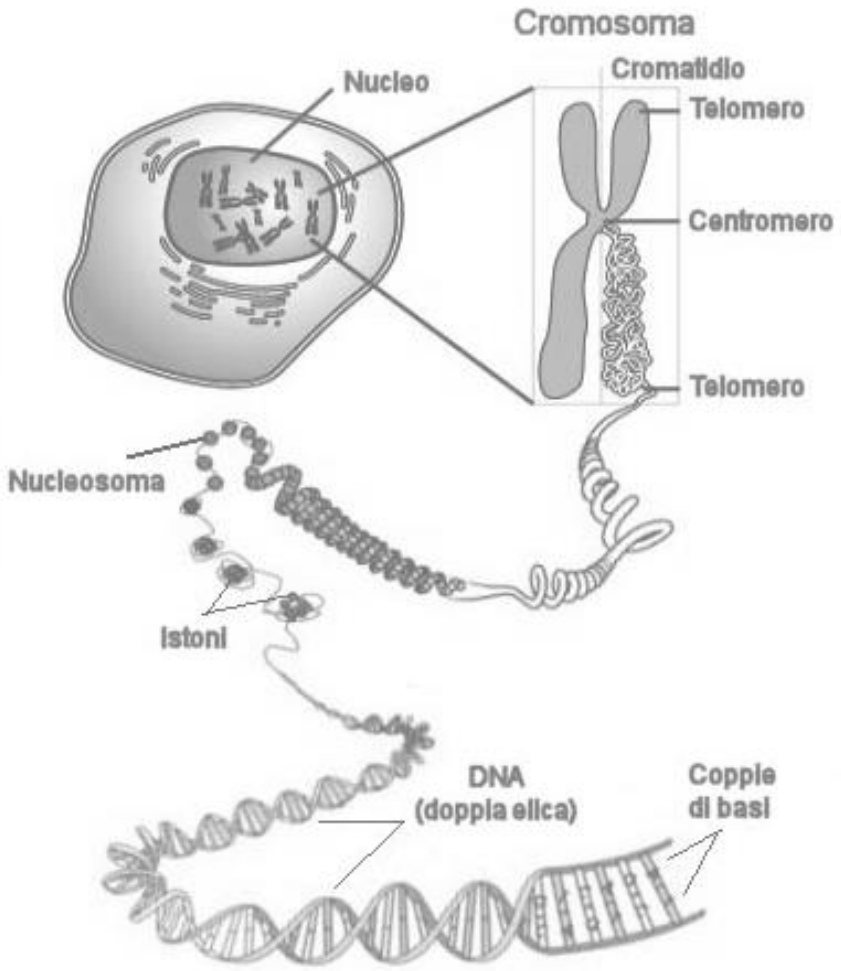
Levels of DNA organization in the nucleus



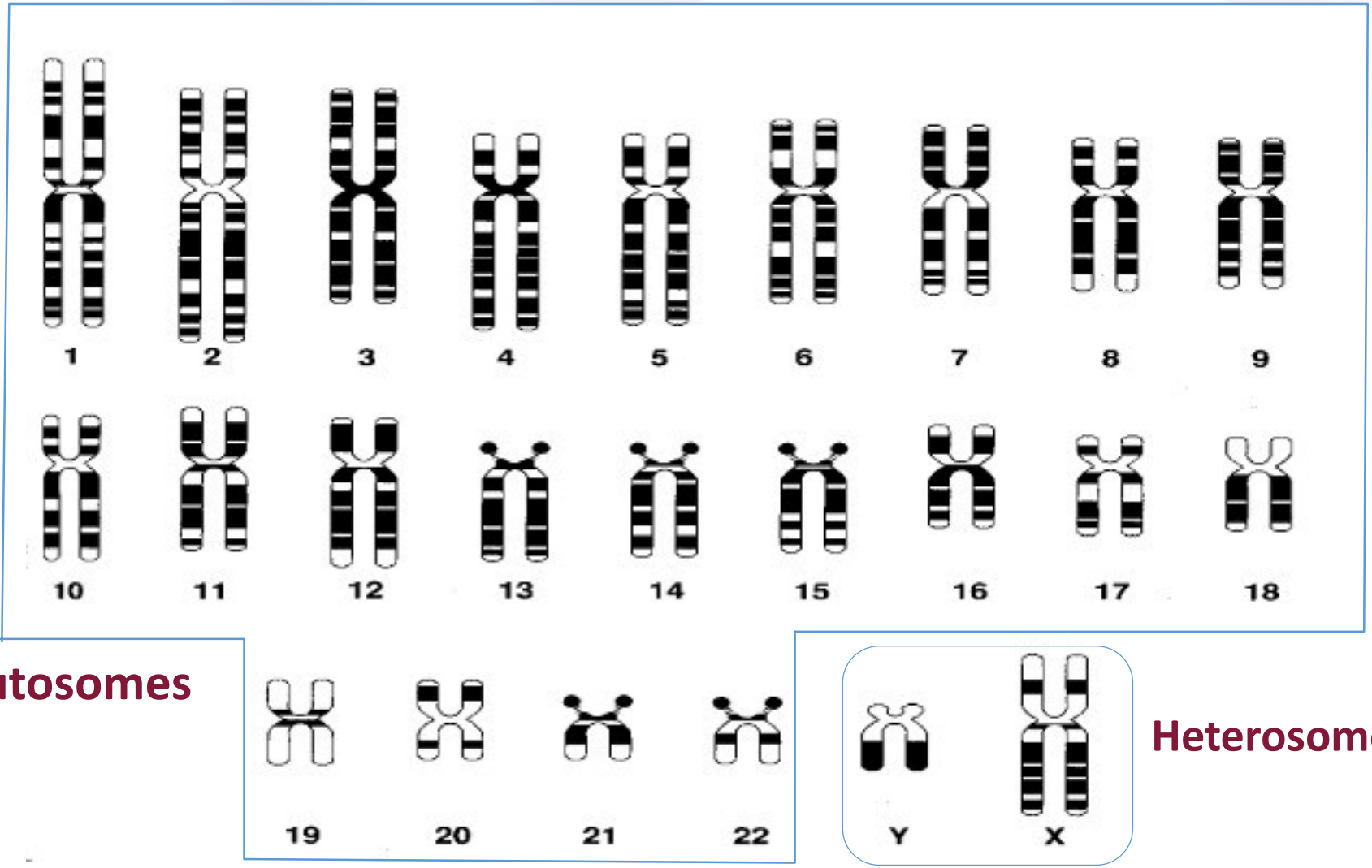
Euploid organism

46 chromosomes

23 maternal copies +

23 paternal copies

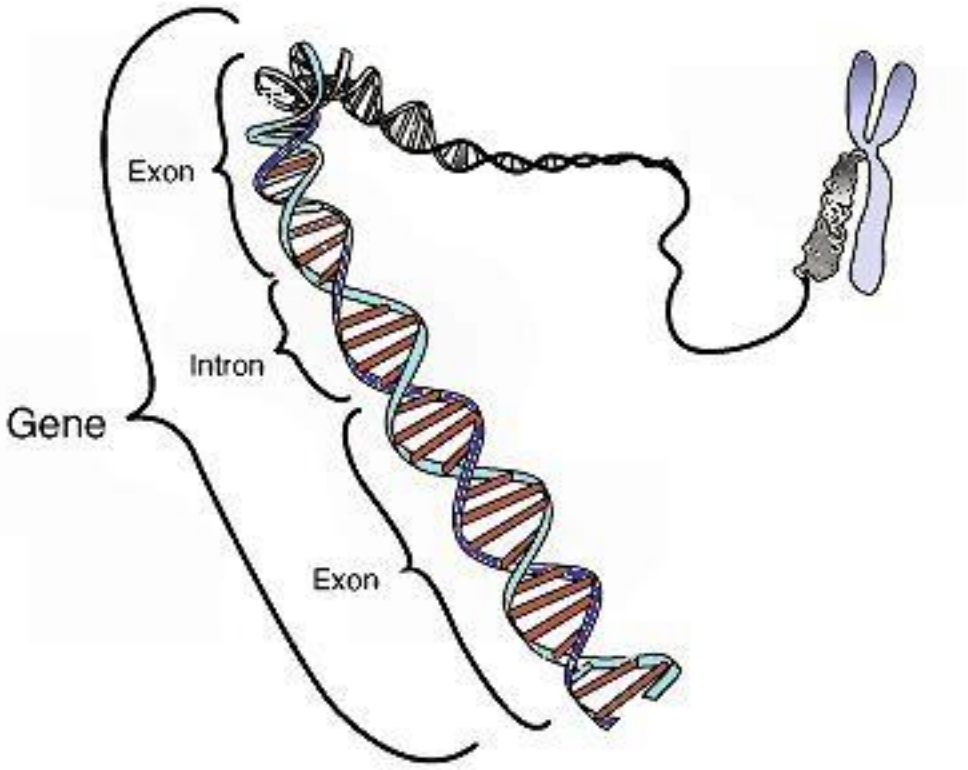
Human karyotype



Autosomes

Heterosomes

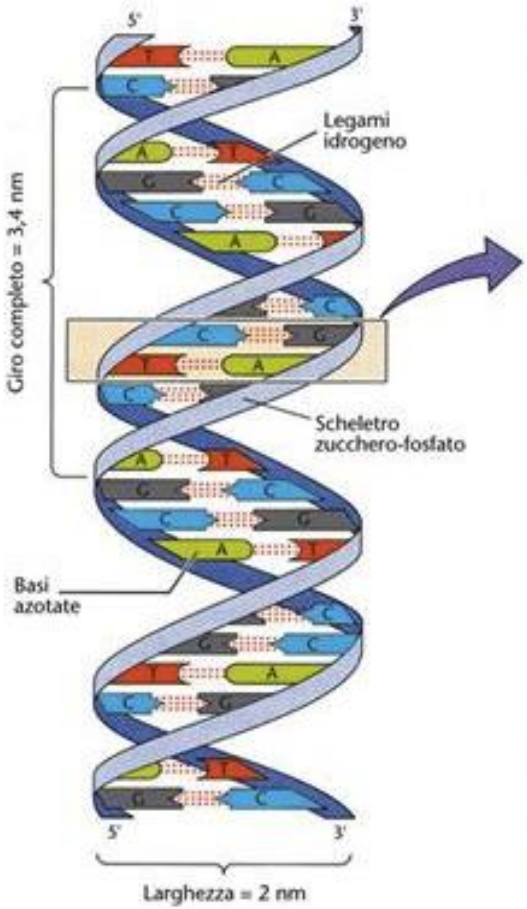
Gene structure

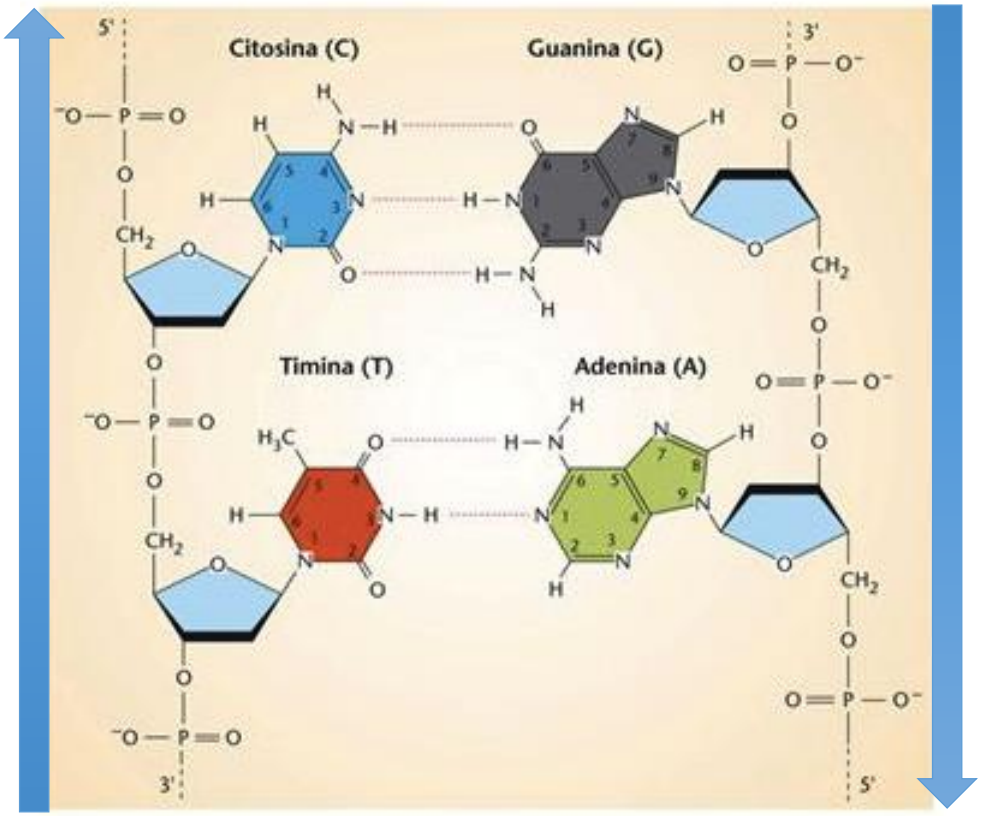


Exon= coding sequence in a gene

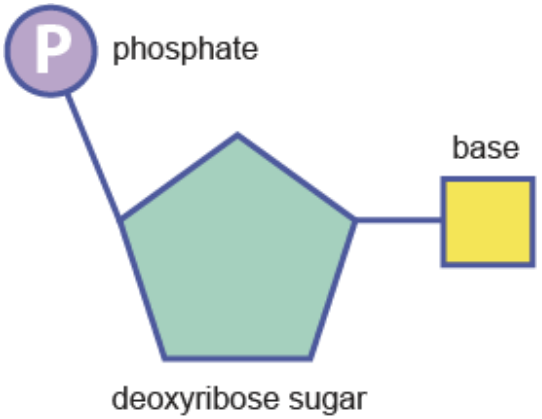
Intron= non-coding sequence in a gene

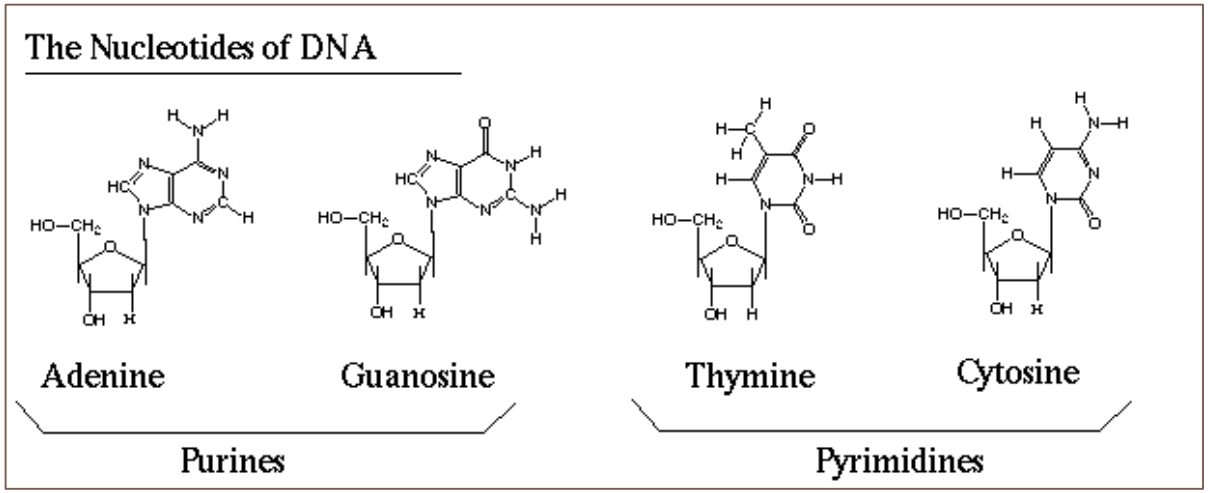
DNA structure



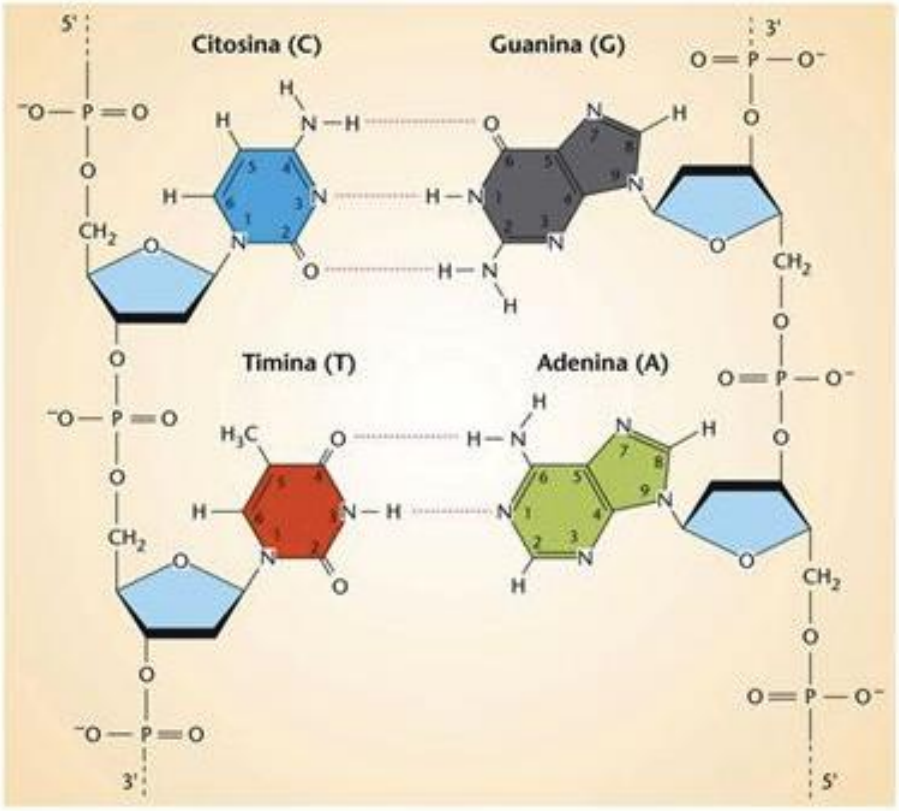


Nucleotide structure





Pairing of nitrogenous bases



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Polymorphisms and mutations

Stable DNA variations

Polymorphisms

Genetic variation with at least 1% frequency in the population

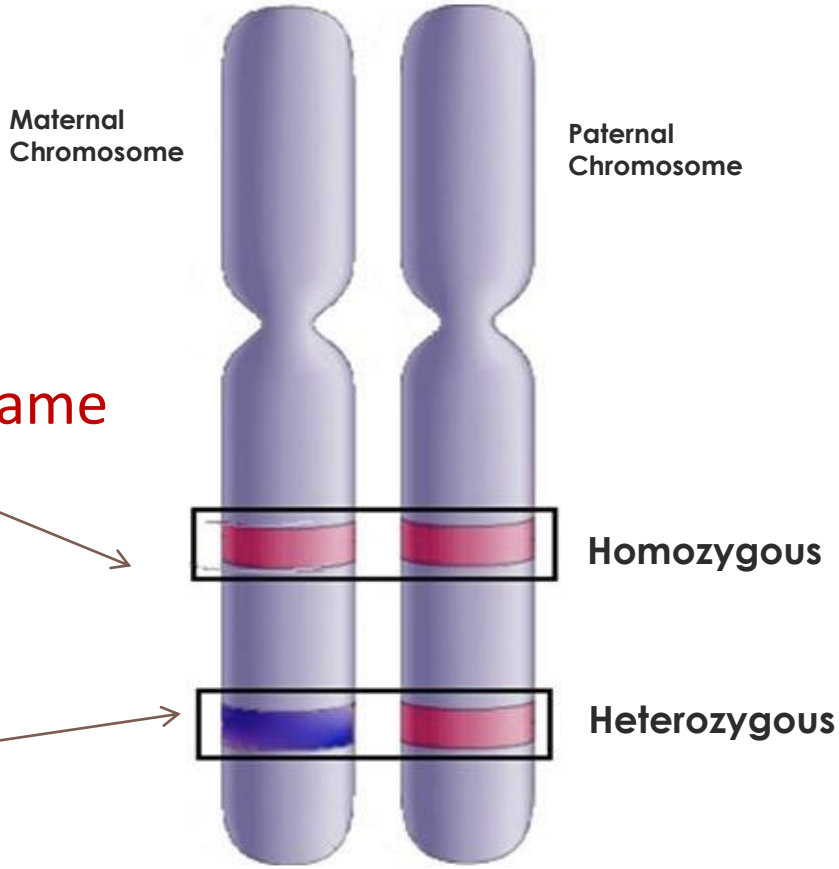
Responsible for **genetic variability**

Mutations

Responsible for **genetic diseases**

There are two alleles for each locus

Alleles: Different forms of the same gene, control the same character, possible different products



Alleles are the same

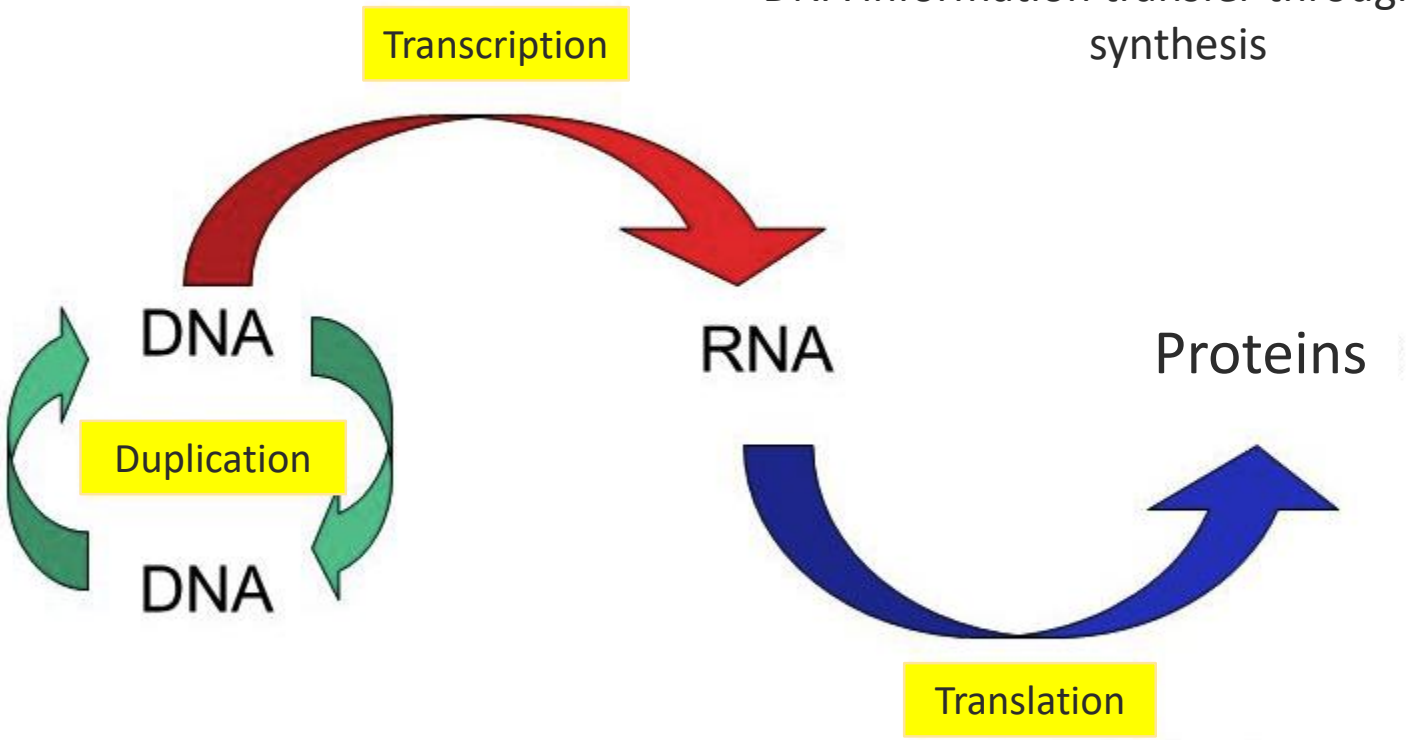
Alleles are different

Homologous chromosomes

Same genes can bring different information

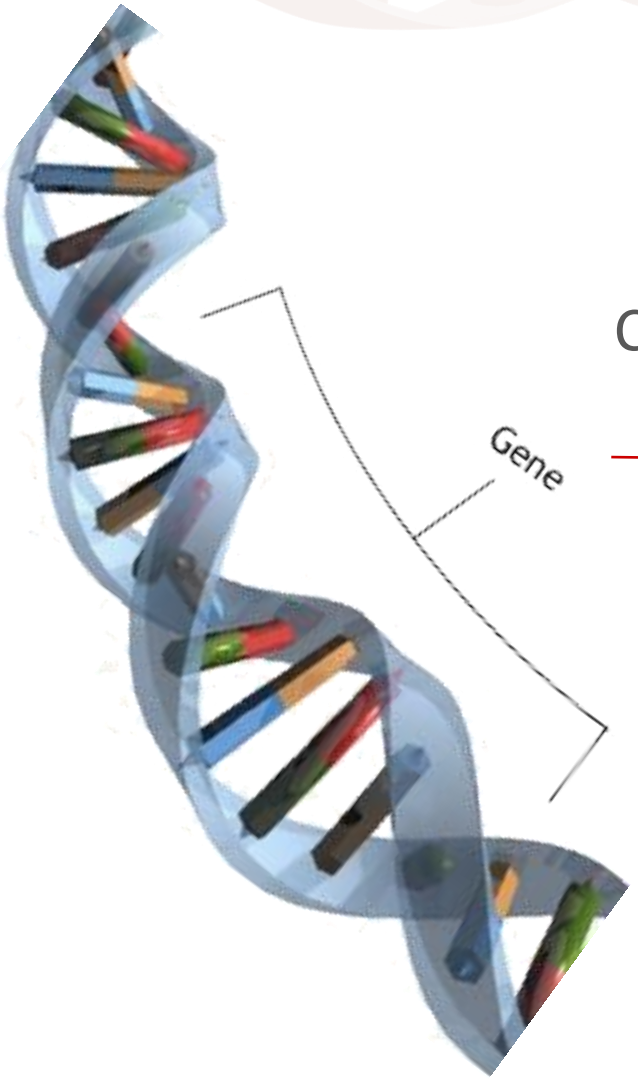
The "central dogma" of biology

DNA information transfer through the RNA synthesis

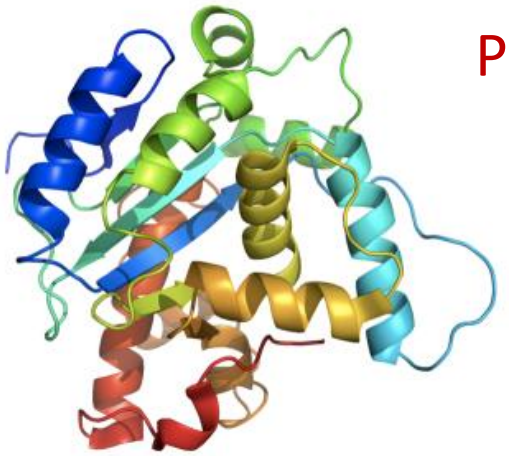


construction of the polypeptide chain

Consequences of a variation



Codification



Protein

Macromolecules with precise biological functions(ex. Metabolism, cell signaling, structural functions)

Qualitative and quantitative variations

- **Qualitative variations:** the protein is produced in the right amount but has a reduced or no biological functional capacity

- **Quantitative variation:** the protein is produced with the right biological functional capacity but in a reduced amount

A practical example

LTC	-13910 T-C	rs4988235	T	C	CC= Intollerante al lattosio
	-22018 A-G	rs182549	A	G	GG= Intollerante al lattosio

LTC coding for lactase, when **both** variations are present **in homozygous, the enzyme is produced in a reduced amount** and is not sufficient to properly digest lactose

Naming the mutations according to the involved cells

Somatic:

- **will manifest themselves if they are dominant**, and they occur during growth in some parts of the body

- They are NOT transmissible to progeny

Germinal:

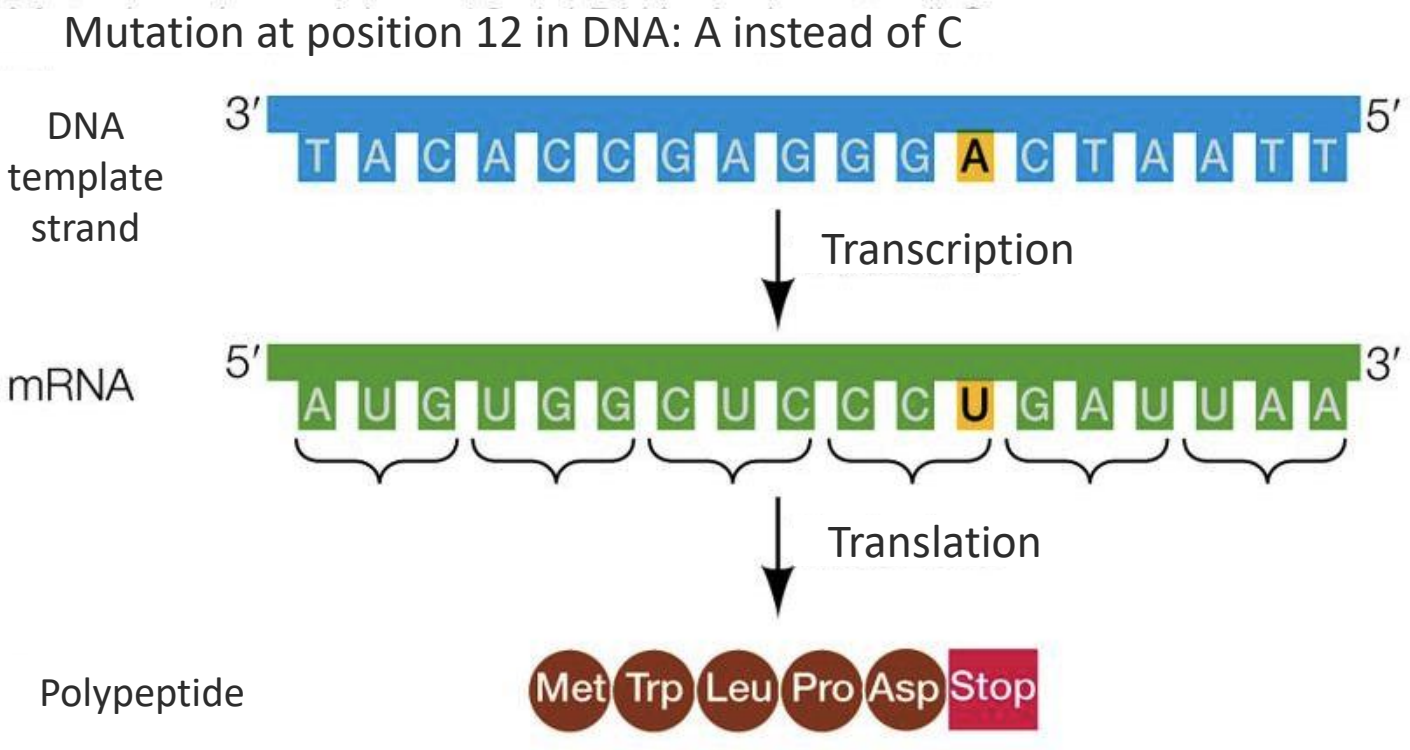
they involve gametes and therefore ARE inheritable

Denomination of genetic alterations according to dimensions

- ✓**Genes (point)**: one or more nucleotides
- ✓**Chromosomic**: one or more chromosomes
- ✓**Genomics**: entire genome

Point mutations

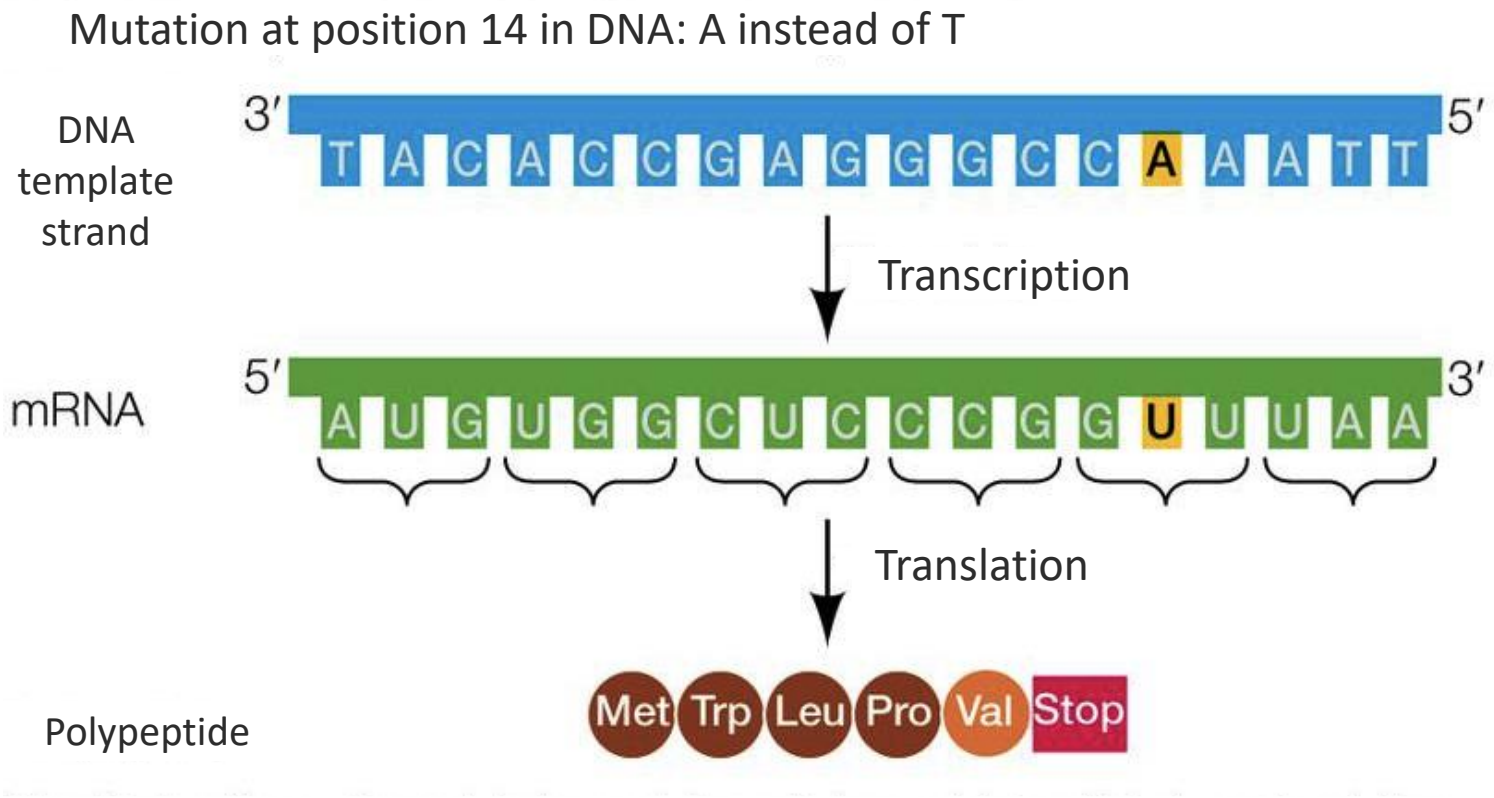
Silent: they do not change the amino acid sequence produced



Result: no change in amino acid sequence

Point mutations

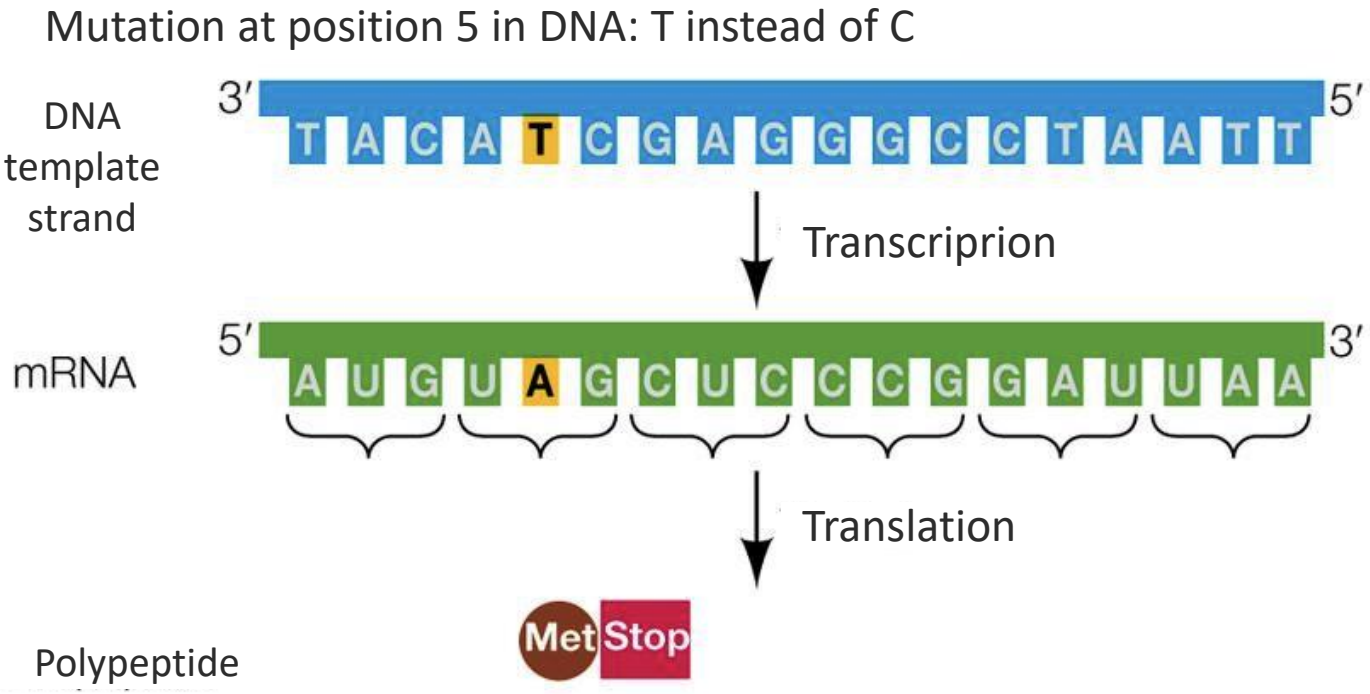
Missense: the change of the base causes the change of an amino acid within the protein (missense)



Result: amino acid change at position 5 : Val instead of Asp

Point mutations

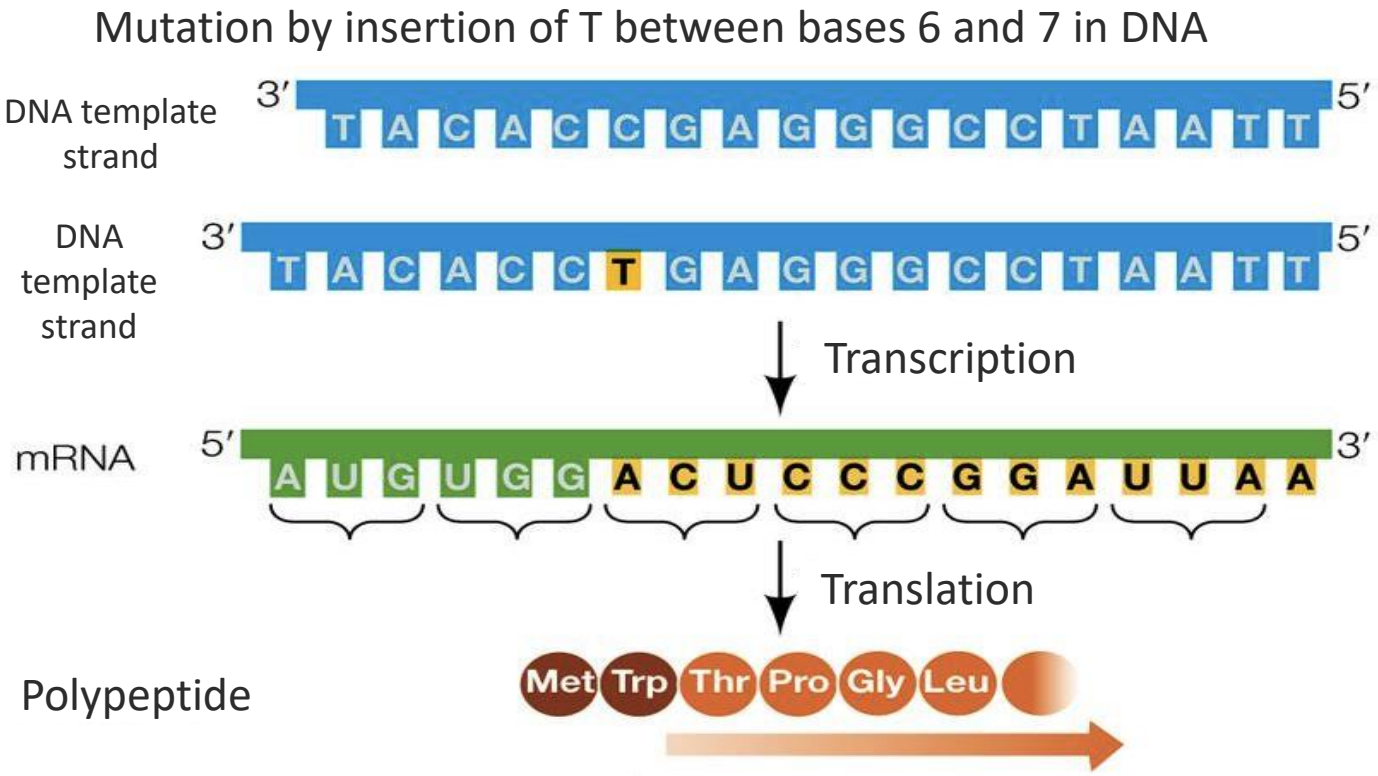
Nonsense: a stop codon is formed on the mRNA and the protein is shorter than normal



Result: only an amino acid is translated; no functional protein is produced

Point mutations

Frameshift (Ins/Del): the insertion of a pair of bases leads to an out of sync reading of the genetic code downstream of the mutation



Result: all amino acids changed beyond the point of insertion

SNP

Single nucleotide polymorphisms

Natural SNPs are associated to:

- Biodiversity
- Genetic variability
- Ability to adapt

Genetic tests and variations on DNA

A genetic test is able to detect whether there is, on one or both alleles, a **known variation** of **a nucleotide**

The genetic test reveals whether the variation is present in **homozygous** or **heterozygous**

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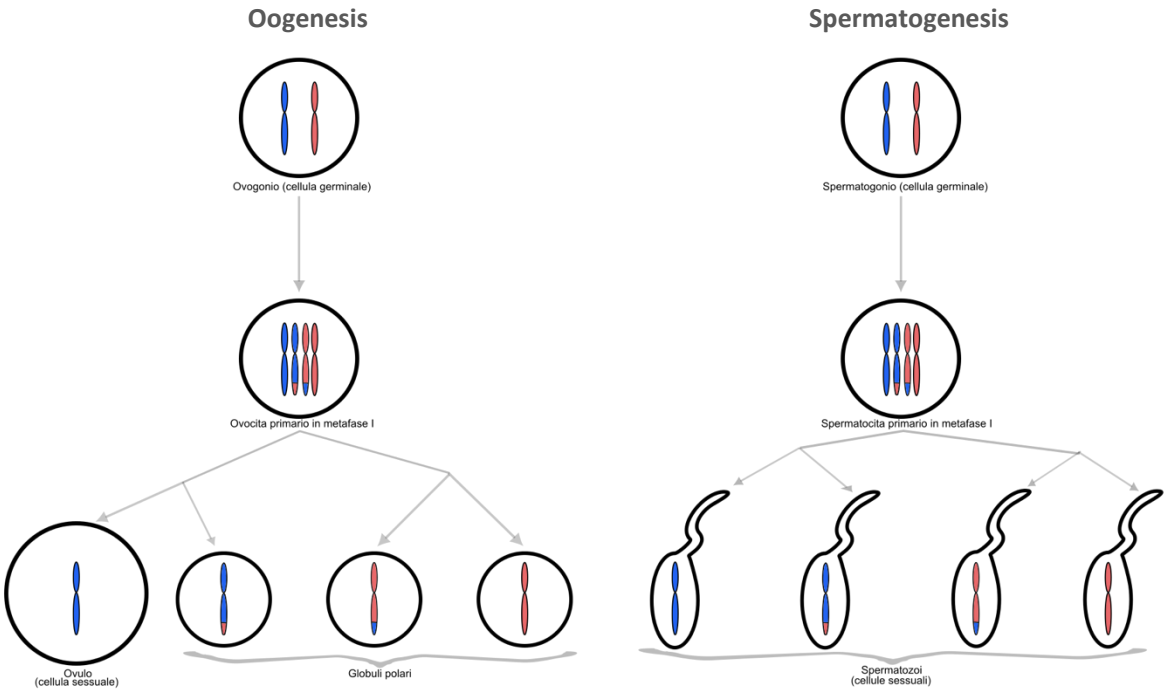
Heredity

The mutations in the germ cells are heritable

Gametogenesis



Example of a test that reveals hereditariness

Dilated cardiomyopathy(DCM)

Characterized by cardiac dilation and reduced systolic function

DCM is the most common form of cardiomyopathy and represents more than half of all transplanted heart disease done in patients between 1 and 10 years . An inherited model is present in 20 to 30% of cases. Autosomal dominant usually presents in the second or third decade of life

European Journal of Human Genetics (2010) 18, 1160–1165; doi:10.1038/ejhg.2010.83; published online 16 June 2010
Familial neonatal isolated cardiomyopathy caused by a mutation in the flavoprotein subunit of succinate dehydrogenase
Aviva Levitas1,2,8, Emad Muhammad1,3,8, Gali Harel1,3,8, Ann Saada4, Vered Chalifa Caspi5, Esther Manor1,6, John C Beck7, Val Sheffield7 and Ruti Parvari1,3,5

Epigenetics

Is the set of factors that are not written in our DNA, but that are able to “give instructions” about which genes express or silence

In summary

Tests about inherited pathologies help in the correct management of the patient and his first and second relatives, whether the test is positive or negative

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Inherited cardiomyopathies

Inherited heart diseases are characterized by a **marked genetic and allelic heterogeneity**; therefore, they require extensive sequencing for their genetic characterization.

The growing knowledge of genetics of cardiomyopathies reduces diagnosis time, improves morbidity and mortality

Inherited cardiomyopathies

Current Heart Failure Reports

December 2015, Volume 12, Issue 6, pp 339–349

Evolving Approaches to Genetic Evaluation of Specific Cardiomyopathies

Authors | Authors and affiliations

Loon Yee Louis Teo, Rocio T. Moran, W. H. Wilson Tang

It summarizes the guidelines and the characteristics of the 5 principal forms of inherited Cardiomyopathies:

- ✓ Dilated cardiomyopathy (DCM)
- ✓ Hypertrophic cardiomyopathy (HCM)
- ✓ Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- ✓ Restrictive cardiomyopathy (RCM)
- ✓ Left ventricular non-compaction (LVNC)

Inherited cardiomyopathies

Current Heart Failure Reports
December 2015, Volume 12, Issue 6, pp 339–349

Evolving Approaches to Genetic Evaluation of Specific Cardiomyopathies

Authors Authors and affiliations

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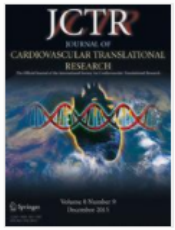
IMPORTANT: genetic test!

BUT there are many other equalization factors that influence the manifestation of the pathology

Genetics and other factors

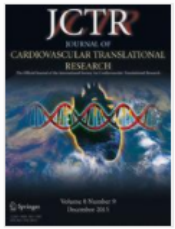


Journal of Cardiovascular Translational Research
December 2015, Volume 8, Issue 9, pp 506–527

Linking Genes to Cardiovascular Diseases: Gene Action and Gene–Environment Interactions

Pathologies like cardiomyopathies are the result of the interaction of several genes, factors that may influence genetic expression and environmental factors. But the understanding of genetics in the first place is essential for better diagnosis and better therapies.

Genetics and other factors



Journal of Cardiovascular Translational Research
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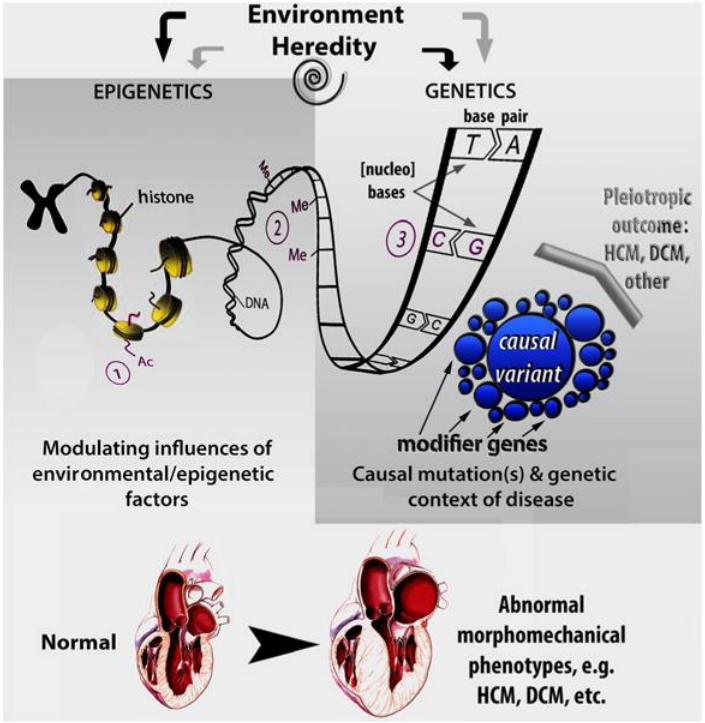
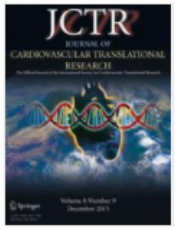


1 / 2- Epigenetic mechanisms: cell with = DNA differentiates (acetylation, methylation)
3 - Genetic Factors: Variations in the DNA sequence

Random variants + modifier genes: act in genetic cardiomyopathies

MYh7 variant for hypertrophic cardiomyopathy (HCM), Mendelian inheritance

Genetics and other factors



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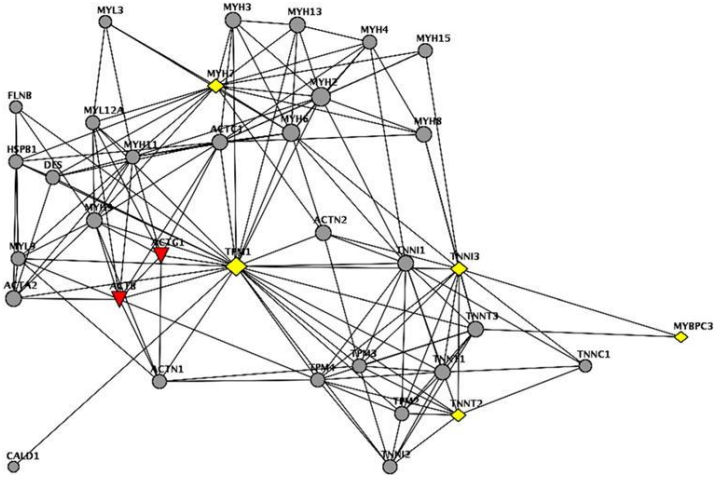

The interaction network between genes around 5 query genes for HCM (MYH7, MYBPC3, TNNT2, TNNI3, TPM1)

Genetics and other factors

Genes commonly implicated in HCM & DCM in descending frequency order

% of HCM associated with the mutation of this gene	Gene	Proteins name	Fetotipo
40%	*MYH7*	Miosina-7	Cardiomyopathy, dilated, 1S
40%	*MYBPC3*	Miosina-binding protein C, tipo cardiaco	Cardiomyopathy, dilated, 1MM
5%	*TNNT2*	Troponina T, muscolo cardiaco	Cardiomyopathy, dilated, 1D
5%	*TNNI3*	Troponina I, del muscolo cardiaco	Cardiomyopathy, dilated, 2A
2%	*TPM1*	Tropomiosina alfa-1 catena	Cardiomyopathy, dilated, 1Y
% of HCM associated with the mutation of this gene	Gene	nome proteine	
20%	*TTN*	titin	Cardiomyopathy, dilated, 1G
6%	*LMNA*	Lamin-A / C	Cardiomyopathy, dilated, 1A
4,2%	*MYH7*	Miosina-7	Cardiomyopathy, dilated, 1
3% -4%	*MYH6*	Miosina-6	Atrial septal defect 3
2% -4%	*MYBPC3*	Miosina-binding protein C, tipo cardiaco	Cardiomyopathy, dilated

Tabella preparata utilizzando i dati di capitoli provenienti *GeneReviews* [Pagon RA, Adam MP, Ardinger HH, et al., Editors.GeneReviews® [Interenet]. Seattle (WA): University of Washington, Seattle; 1993-2015]

Inherited cardiomyopathies

Review

Journal of Human Genetics (2016) **61,** 41–50; doi:10.1038/jhg.2015.83; published online 16 July 2015

Molecular genetics and pathogenesis of cardiomyopathy

Akinori Kimura[1]

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Correspondence: Professor A Kimura, Department of Molecular Pathogenesis, Medical Research Institute, Tokyo Medical and Dental University (TMDU), 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. E-mail: akitis@mri.tmd.ac.jp

Received 11 June 2015; Accepted 15 June 2015
Advance online publication 16 July 2015

Characteristics functional alterations generated by mutations associated with the disease, are strictly related to clinical characteristics: Ca increase/decrease, muscle contraction

Inherited cardiomyopathies

Mutations in Z-disk component detected in HCM and DCM may provoke the sarcomere stiffness increase and decrease

Mutations in other components of cardiac muscle have suggested that the metabolic stress altered response is associated with cardiomyopathy

→ **heterogeneity in etiology and pathogenesis of cardiomyopathy.**

Sudden cardiac death

50 000 people in Italy every year[1]

350 000 people in the USA every year[1]

In the majority of patients who die suddenly, fatal arrhythmias are the first sign of heart disease

1. Data from European Society of Cardiology-ESC_London 2015

Sudden cardiac death

Sudden cardiac death in the young: the molecular autopsy and a practical approach to surviving relatives FREE

Christopher Semsarian ✉, Jodie Ingles, Arthur A.M. Wilde

Eur Heart J (2015) 36 (21): 1290-1296. **DOI:** https://doi.org/10.1093/eurheartj/ehv063
Published: 12 March 2015 **Article history** ▾

Up to 30% of young SCDs, no cause of death is identified in post-mortem (the so-called negative-autopsy death syndrome)

Sudden cardiac death

The most important challenge for cardiology is to identify subjects at risk before the event:

primary prevention
of sudden death

Multiple genetic analysis: Molecular cardiology

The new guidelines of European Society of Cardiology[2] for the prevention of sudden cardiac arrest, have updated diagnosis criteria by promoting the use of genetic analysis

[2.] Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015
ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv316

ESC GUIDELINES

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)

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*Representing the Association for European Paediatric and Congenital Cardiology (AEPC).

†Andrea Mazzanti: Coordinator, affiliation listed in the Appendix.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.

ESC entities having participated in the development of this document:

ESC Associations: Acute Cardiovascular Care Association (ACCA), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

ESC Councils: Council for Cardiology Practice (CCP), Council on Cardiovascular Nursing and Allied Professions (CCNAP), Council on Cardiovascular Primary Care (CCPC), Council on Hypertension.

ESC Working Groups: Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy, Cardiovascular Surgery, Grown-up Congenital Heart Disease, Myocardial and Pericardial Diseases, Pulmonary Circulation and Right Ventricular Function, Thrombosis, Valvular Heart Disease.

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CardioScreen® is a genetic test, developed by GENOMA Group, available in two versions:

CardioScreen-Cardiomyopathies®

CardioScreen-Prevention of sudden cardiac arrest®

Examples of genetically investigated cardiomyopathies:

- ✓ Long QT syndrome (principal cause of sudden death) AKAP9, CALM1, KCNE1, KCNE2, KCNH2, KCNJ5, SNTA1,
- ✓ Brugada syndrome (sudden death) CACNA1C, CACNB2, GPD1L, HCN4, KCND3, KCNE3
- ✓ CPVT (catecholaminergic polymorphic ventricular tachycardia) (sudden death) DSC2, DSG2, DSP, Jup, PKP2, RYR2, TGFB3, TMEM43
- ✓ HCM (hypertrophic cardiomyopathy)

Indications

Both tests are recommended for those who know about a case of sudden cardiac death in their family (included sudden infant death), heart failure or transplant, which suggest inherited cardiac pathological substratum.

Clinical usefulness

Both tests are useful to arrange prevention strategies so that unexpected serious events do not occur and do not affects members of the same family.

Clinical usefulness

Furthermore is particularly useful as a prevention instrument in case of:

- ✓ Professional or amateur agonistic activity, also for individuals with no familiarity
- ✓ Young individuals (younger than 40 years) with idiopathic cardiac symptomatology
- ✓ Children and teenagers with a suspect clinical picture for QT anomalies or cardiac rhythm

Clinical usefulness: the athlete

ATHLETES

versely, in consideration of the higher risk of arrhythmias and the worsening of structural or genetic diseases in individuals exposed to intense physical exercise,[81,82] we do support the existing recommendations for pre-participation screening in athletes. In Europe there is consensus that clinical evaluation, personal or family history taking and a baseline 12-lead ECG should be performed in this population (refer to section 12.7).

3.4.2 Screening family members of sudden death victims

The diagnosis of an inheritable arrhythmogenic disorder is established in up to 50%[83] of families with a SADS victim, especially channelopathies [e.g. LQTS, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT)] and occasionally subtle forms of cardiomyopathy [HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC) in particular] or familial hypercholesterolaemia. As a consequence of these findings, when an autopsy is either not available for the victim (i.e. SUDS or SUDI) and/or when the post-mortem examination fails to detect structural abnormalities and toxicology results are normal (i.e. SADS or SIDS), first-degree relatives of the victim should be informed of the potential risk of similar events to themselves and should undergo cardiac evaluation. A family history of recurrent premature SUDS or inheritable heart disease represents a 'red flag' that makes familial evaluation strongly recommended.

Family screening of first-degree relatives of victims of sudden death is an important intervention to identify individuals at risk, advise on available treatment and adequately prevent sudden death.[14,84] Currently only 40% of family members are screened,[85] partially due to a lack of adequate screening infrastructure, but

members with symptoms suggestive of the presence of a cardiac condition, such as syncope, palpitations or chest pain, should be prioritized for evaluation.

The recommended core evaluation of a first-degree relative of a sudden death victim is illustrated in *Table 4*. In the absence of a diagnosis in the family, very young children should be screened at least with a baseline ECG and an echocardiogram.

As many inheritable arrhythmogenic diseases are characterized by age-related penetrance and incomplete expression, younger individuals should be followed-up at regular intervals. Asymptomatic and fully grown adults can be discharged from care unless symptoms appear or new information from the family becomes available.

When an inheritable arrhythmogenic disease is suspected, DNA samples from the victim are the best source of information when performing a molecular autopsy. If there is a positive result, family members should be offered the opportunity to undergo predictive genetic screening, in a cascade fashion. The 'right not to know' and the possibility to decline molecular screening should be included in any pre-informative communication with the relatives.

In the absence of biological samples from the deceased person, targeted molecular screening in first-degree relatives may be considered when there is the suspicion of the presence of an inheritable disease in family members. Conversely, genetic screening of a large panel of genes should not be performed in SUDS or SADS relatives without clinical clues for a specific disease after clinical evaluation. This is especially true in SIDS cases, where molecular autopsy identifies a lower burden of ion channel disease compared with SADS and sporadic genetic disease as a cause of sudden death may be

A STRONGLY RECOMMENDED TEST FOR ATHLETES because during intense effort is possible a worsening of unknown structural or genetic cardiac pathologies

How is it the test done?

The taking of a haematic sample

By means of a complex laboratory analysis, the DNA is isolated from nucleated cells and amplified by **C-reactive protein (CRP)** technique. Later, thanks to an innovative technological process of **massive parallel sequencing (MPS)**, which employs **Next Generation Sequencing (NGS)** techniques using **ILLUMINA** sequencers

How is the test done?

Sequencing of:

43 genes (exons and adjacent intragenic regions) connected to inherited cardiomyopathies **CardioScreen-Cardiomiopatie®**

157 genes (exons and adjacent intragenic regions) connected to inherited cardiac pathologies correlated to sudden cardiac arrest **CardioScreen-Prevention of sudden cardiac arrest®**.

Advanced bioinformatics analysis

Summary

- ✓ Genoma Group presentation
- ✓ The DNA and its biological role
- ✓ Polymorphisms and mutations
- ✓ Heredity
- ✓ Cardiomyopathies and sudden cardiac arrest
- ✓ Cardioscreen genetic tests
- ✓ How to interpret the result

The report consists of two parts

- Instrument output
- Interpretative technical report

Instrument output: the report

Cardioscreen®

GENOMA® Molecular Genetics Laboratories Group

B65692 SGRUDATO

AZIENDA CON SISTEMA DI GESTIONE QUALITÀ CERTIFICATO DA DNV GL = ISO 9001 =

Referto Analisi : CardioScreen® - Prevenzione arresto cardiaco improvviso - sequenziamento NGS

Data Referto: 26/01/2016 ***Ora:*** 15:15

Anagrafica Laboratorio / Medico

Centro Inviante:	LABOGEN sas
Città:	CATANIA

Anagrafica Paziente

Cognome:	SGRUDATO	***Nome:***	ALFONSO
Data di Nascita:		***Luogo di Nascita:***	
Origine Etnica:	N.A.	***Sesso:***	M
Medico inviante:		***Vs. Codice di riferimento:***	
Indicazione:			
Storia Clinica:			

Dati Campione

Tipo Campione:	DNA	***Ns. Codice campione:***	B65692
Data Accettazione:	24/11/2015 ***Ora Accettazione:*** 16:41	***Data prelievo:***	23/11/2015

Dati Analisi

Analisi effettuata/e:	CardioScreen® - Prevenzione arresto cardiaco improvviso - sequenziamento NGS		
Codice OMIM:		***Ereditarietà:***	
Gene investigato:	***OMIM:***	***Sequenza riferimento:***	
Metodo di analisi:	Next Generation Sequencing (NGS)		
Strategia diagnostica:			
Data inizio analisi:	25/11/2015 ***Data fine analisi:***	26/01/2016	

GENOMA Group S.r.l. Unipersonale

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Laboratori e Studi Medici Milano 20161 Milano - Affori Centre, Via Enrico Cialdini, 16 Tel.: +39 02 3929 7626 - Fax: +39 02 3929 76261 Web: www.genomamilano.it E-mail: info@genomamilano.it

CHIAMATA GRATUITA NUMEROVERDE 800-501651

GENOMA® Molecular Genetics Laboratories Group

B65692 SGRUDATO

AZIENDA CON SISTEMA DI GESTIONE QUALITÀ CERTIFICATO DA DNV GL = ISO 9001 =

Risultati e Conclusioni

Risultato:

- gene ANKRD1 (Cardiomyopathy, hypertrophic):
Presenza della mutazione P52A (c.154 C>G) in eterozigosi.

- gene NKX2-5 (Atrial septal defect):
Presenza della variante aminoacidica R25C (c.73 C>T) in eterozigosi.
[rs28936670]

Interpretazione: Il campione in esame presenta la mutazione:

P52A (c.154 C>G) in ETEROZIGOSI a livello del gene ANKRD1.
Ref: Arimura (2009) J Am Coll Cardiol **54**, 334

La variante aminoacidica R25C riscontrata nel campione in esame a livello del gene NKX2-5, non è mai stata prima descritta in letteratura come mutazione, conseguentemente il suo ruolo patogenetico non è chiaro.

Note tecniche: Relazione tecnica in allegato

Commenti:

Suggerimenti: L'esame effettuato ha prodotto un risultato per il quale è consigliabile un colloquio di approfondimento con uno specialista in genetica medica.

Risultati verificati da: Giuliano Cottone ***Data verifica :*** 21/12/2015

Risultati validati da: Francesco Fiorentino ***Data validazione :*** 26/01/2016

Il presente referto costituisce copia conforme all'originale, il quale è depositato negli archivi del laboratorio Genoma Group Srl.

Il Genetista
Dr.ssa Marina Baldi

Il Direttore del laboratorio
Dr. Francesco Fiorentino

Genoma Group Srl **Genoma Group Srl**

ROMA, 26 gennaio 2016

How to read the report

GENOMA® Molecular Genetics Laboratories Group

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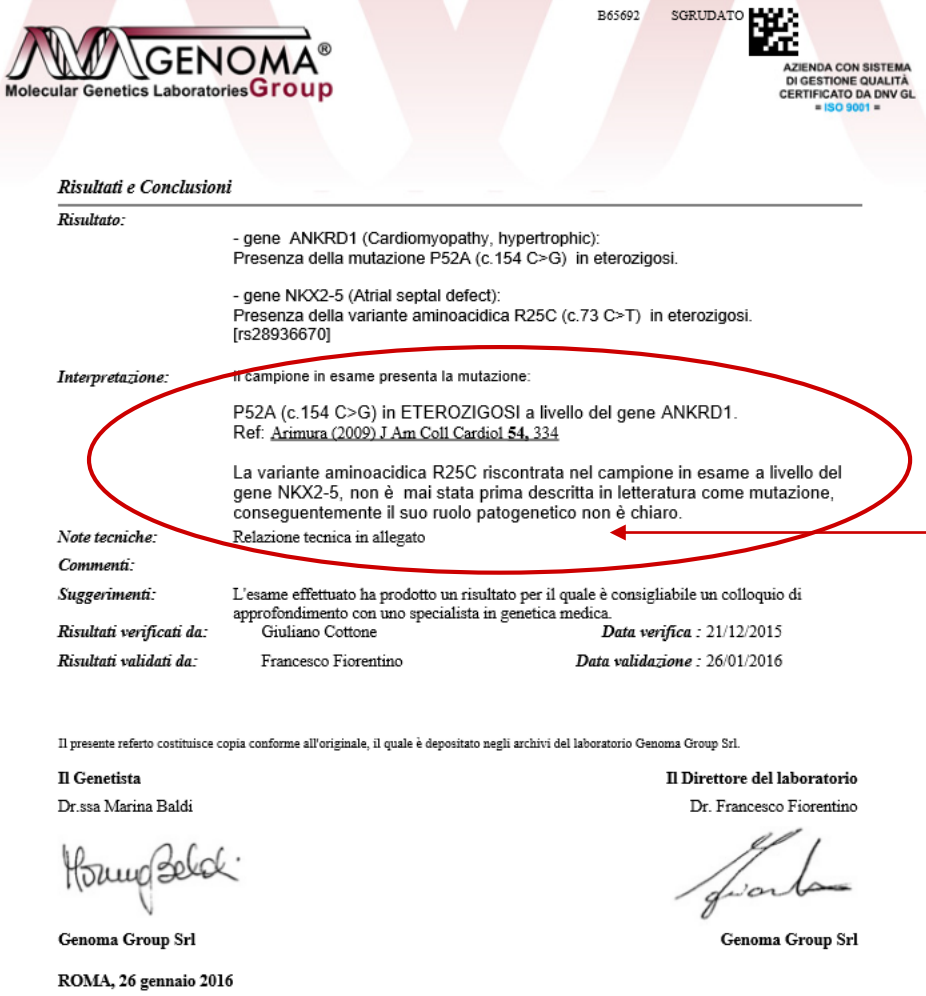
Dr. Francesco Fiorentino

Genoma Group Srl **Genoma Group Srl**

ROMA, 26 gennaio 2016

Result

How to read the report



GENOMA® Molecular Genetics Laboratories Group

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Il Direttore del laboratorio
Dr. Francesco Fiorentino

Genoma Group Srl

Genoma Group Srl

ROMA, 26 gennaio 2016

Constitutional anomalies present in all cells.
They have pathogenetic but unclear role

Cos'è l'arresto cardiaco improvviso?

L'**arresto cardiaco improvviso** (**SCA**) si manifesta con una repentina assenza di "polso" e uno stato di incoscienza causati da una incapacità del cuore di pompare il sangue al cervello, e nel resto del corpo, in maniera efficace. In genere l'arresto cardiaco improvviso è causato da aritmie potenzialmente mortali e da anomalie del sistema elettrico cardiaco. E' definito "**improvviso**" perché, data la sua natura, può colpire qualsiasi individuo, in qualunque luogo senza alcun preavviso, anche soggetti che non hanno mai avuto in precedenza diagnosi di malattie cardiache o condizioni cliniche critiche.

Se l'arresto cardiaco improvviso non viene trattato immediatamente nel giro di pochi secondi la persona perdi i sensi e per ogni minuto che passa, senza ricevere alcun intervento, la percentuale di sopravvivenza si riduce del 10 per cento.

Per salvare la vita di un paziente colpito da arresto cardiaco improvviso è necessario procedere con una rianimazione cardiopolmonare (RCP) e con una defibrillazione che ristabilisca il ritmo cardiaco, prima che il cervello subisca danni irreversibili in seguito al mancato afflusso di sangue e ossigeno, eventi che si verificano tra i 4 e i 6 minuti.

L'arresto cardiaco improvviso ha componenti ereditarie?

Nei paesi sviluppati, la morte cardiaca improvvisa è responsabile di oltre il **5%** delle morti totali e di oltre il 50% della mortalità per malattie cardiovascolari. In Italia, si può stimare con buona approssimazione che l'incidenza di questo fenomeno sia intorno a 0.7/1000 abitanti/anno. La morte improvvisa si verifica nel **20-25%** dei casi in soggetti apparentemente sani, come prima manifestazione di una patologia sottostante misconosciuta. Il 5-10% dei casi di morte improvvisa si verifica in assenza di anomalie cardiache strutturali evidenti in cuori strutturalmente normali (morte improvvisa *sine materia*), in presenza di disordini elettrofisiologici che determinano un'instabilità elettrica responsabile dell'insorgenza di aritmie ventricolari, come nel caso della sindrome del QT lungo (LQTS), della sindrome di Brugada (BS), della tachicardia ventricolare polimorfa catecolaminergica (CPVT). In uno studio condotto dallo Steering Group britannico in 32 casi consecutivi di morte improvvisa aritmica sine materia, non selezionati per età, lo screening cardiologico dei parenti di primo grado ha svelato la presenza di una malattia cardiaca ereditaria nel 22% delle famiglie esaminate e in circa la metà dei casi si trattava di LQTS.

In un'analisi di Tan et al. condotta su 43 famiglie in cui si era verificato almeno un caso di morte improvvisa in età <40 anni, nel 40% dei casi lo screening cardiologico ha permesso di identificare una cardiopatia ereditaria (LQTS, CPVT, BS e cardiomiopatia aritmogena ventricolare destra ARVC). Uno studio più recente condotto in Inghilterra su 262 parenti (di cui il 70% di primo grado) appartenenti a 57 famiglie con almeno un caso di morte improvvisa, ha documentato una cardiopatia ereditaria nel 53% delle famiglie esaminate: nel 17% dei casi si trattava di una cardiopatia strutturale (ARVC, cardiomiopatia ipertrofica HCM, cardiomiopatia dilatativa e ventricolo sinistro non compatto); nel restante 26% la diagnosi è stata di LQTS o di BS.

Interpretative technical report

Introduction
+
For whom is indicated
Test benefits
How it is done
Achievable results
Accuracy and limits

GENOMA®
Molecular Genetics Laboratories Group

Azienda con sistema di qualità certificato
UNI EN ISO 9001:2008

Cardioscreen®

Tabella 1: CardioScreen® - Prevenzione arresto cardiaco improvviso.

Elenco dei geni analizzati e della malattie genetiche investigate

	DISEASE NAME	PhenoMIM	GENE
1	Atrial fibrillation, familial, 12	614050	ABCC9
2	Sitosterolemia	210250	ABCG5
3	Sitosterolemia	210250	ABCG8
4	Myopathy, actin, congenital, with cores	161800	ACTA1
5	Aortic aneurysm, familial thoracic 6	611788	ACTA2
6	Atrial septal defect 5	612794	ACTC1
7	Cardiomyopathy, dilated, 1AA, with or without LVNC	612158	ACTN2
8	Long QT syndrome-11	611820	AKAP9
9	Alstrom syndrome	203800	ALMS1
10	Cardiac arrhythmia, ankyrin-B-related	600919	ANK2
11	Cardiomyopathy, hypertrophic/Cardiomyopathy, dilated	609599	ANKRD1
11	Hyperchylomicronemia, late-onset	144650	APOA5
12	Hypercholesterolemia, due to ligand-defective apo B	144010	APOB
13	Hyperlipoproteinemia, type Ib	207750	APOC2
14	Lipoprotein glomerulopathy	611771	APOE
15	Cardiomyopathy, dilated, 1HH	613881	BAG3
16	Cardiofaciocutaneous syndrome	115150	BRAF
17	Brugada syndrome 3	611875	CACNA1C
18	Brugada syndrome 4	611876	CACNB2
19	Long QT syndrome 14	616247	CALM1
	Ventricular tachycardia, catecholaminergic polymorphic, 4	614916	
20	Cardiomyopathy, hypertrophic, 19	613875	CALR3
21	Ventricular tachycardia, catecholaminergic polymorphic, 2	611938	CASQ2
22	Cardiomyopathy, familial hypertrophic	192600	CAV3
	Long QT syndrome 9	611818	
23	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia	613563	CBL
24	Homocystinuria, B6-responsive and nonresponsive types	236200	CBS
25	Hyperalphalipoproteinemia	143470	CETP
26	Ehlers-Danlos syndrome, type III	130020	COL3A1
27	Ehlers-Danlos syndrome, classic type	130000	COL5A1
28	Ehlers-Danlos syndrome, classic type	130000	COL5A2
29	Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency 2	615119	COX15
30	Atrioventricular septal defect, partial, with heterotaxy syndrome	606217	CRELD1

Summarizing interpretative table

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Bibliography

Results

POSITIVE 

Presence of one or more mutations:

it indicates the test has revealed one or more mutations of one (or more) related genes

Results

Mutations observed through **CardioScreen®** test can have:

- ✓ Known pathological meaning;
- ✓ Benign meaning, since they can be found in normal individuals and they are pathologically meaningless
- ✓ Pathological uncertain meaning, since they aren't known or characterized from the scientific-medical community.

Results

NEGATIVE –

Absence of mutations:

It indicates the test didn’t detect the presence of mutations in the analysed genes.

Doesn’t mean the patient has zero risk.

This because not all forms of cardiomyopathy and sudden cardiac arrest has to be connected to genetic causes.

Cardioscreen®

Thank you!

www.cardioscreen.it

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GENOMA® Molecular Genetics Laboratories Group