Farmaci Innovativi

"Qualità Efficacia Appropriatezza"

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TERAPIE PERSONALIZZATE: UNA PROSPETTIVA CONCRETA?

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Applicazioni biotecnologiche emergenti in medicina

- Terapie cellulari di base
- Cellule staminali
- Terapia Genetica
- Terapie su RNA Antisense e RNA interference (RNA i)
- Vaccini terapeutici
- Farmacogenetica
- Nanomedicina

Conclusioni: genomica in oncologia

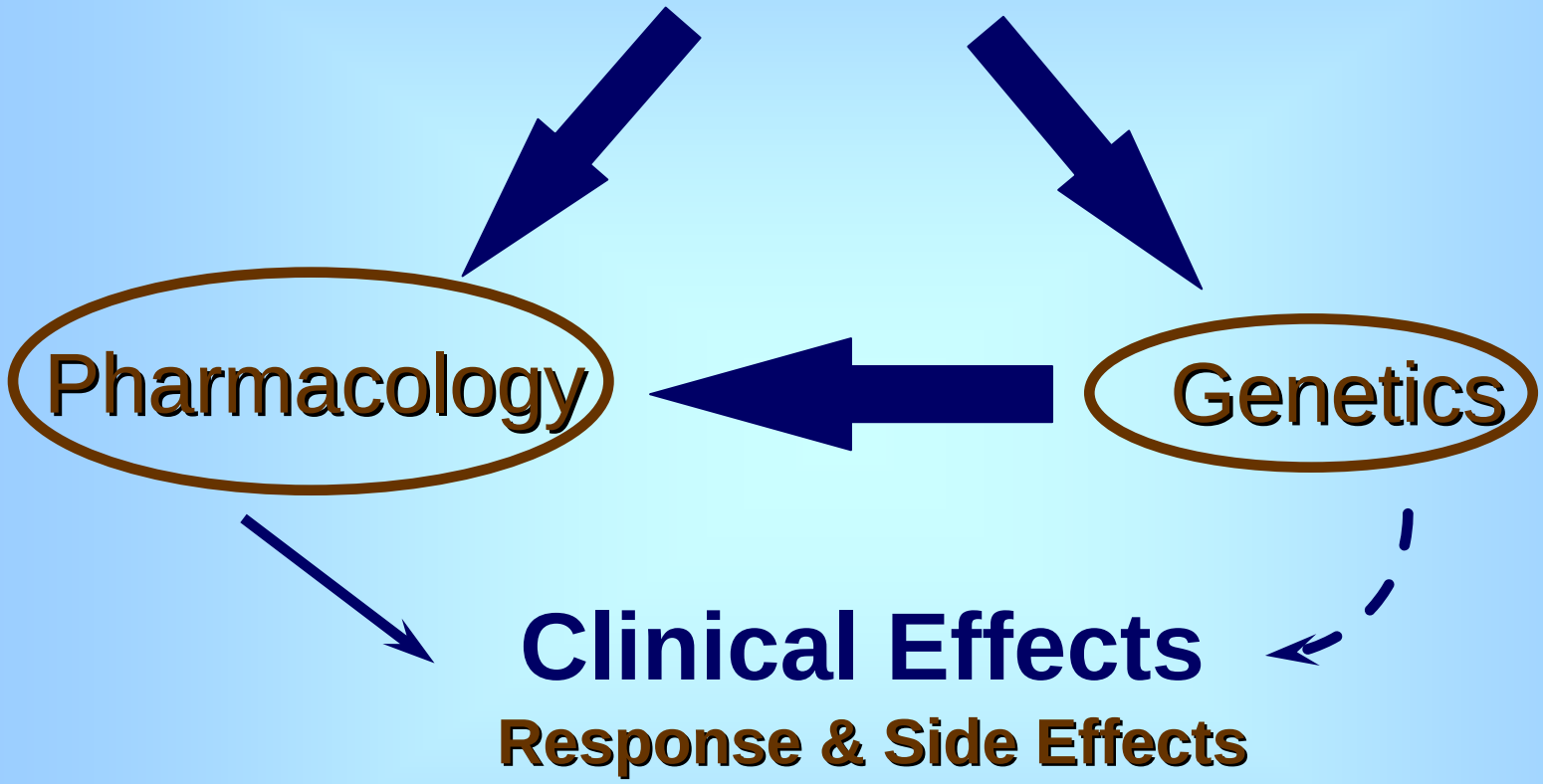
La conoscenza del genoma ci consente di:

- Classificare le neoplasie
- Identificare marker prognostici e predittivi
- Identificare i target molecolari di una terapia
- Condurre una terapia mirata al singolo paziente
- Verificare la singola risposta al farmaco

“The right treatment for the right patient at the right time and the right dose”

(Paul Stoffels)

PHARMACOGENETICS



Genetic make-up may contribute to predisposition to side effects in certain individuals and protection in others.

Pharmacogenomics/genetics **is the science of understanding** the genetic variations influencing the biological effects of drugs

- ⇨ Drug responses
- ⇨ Adverse Drug Reactions

Pharmacogenetics **is the study of the structure of <u>single</u> genes and their effects**

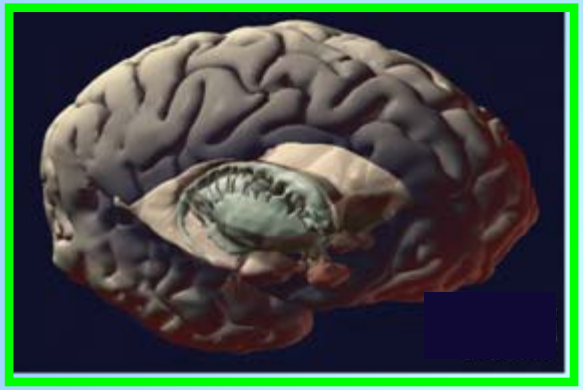
Pharmacogenomics (PGx) **is the study of the functions and interactions of <u>all</u> the genes in the genome**

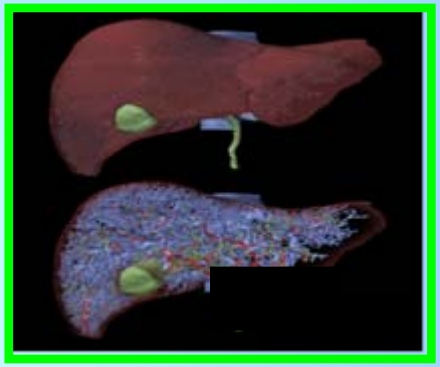
NEJM,2002;347:1512-1520

Pharmacogenetics & Pharmacogenomics: the context

Pharmacodynamics: drug targets

Pharmacokinetics: drug-Metabolizying enzymes And drug transporter





Response & Side Effects

Target molecules

CYP1A2
CYP2D6
etc.

Diet:
-cruciferous veg
-grapefruit

sex

smoking

exercise

ethnicity

age

psychosocial

Environmental Factors

DRUG SAFETY, EFFICACY AND COMPLIANCE PROFILE

Genetic differences impact on medications:

- POSITIVE EFFECT 30%
- NO EFFECT 30%
- SIDE EFFECT 10%
- (MEDICATION NOT TAKEN 30%)

ADVERSE EVENTS		
		US 1994
SERIOUS	6.7%	2.200.000
FATAL	0.3%	106.000

PHARMACOGENOMICS

Definition

A combination of:

FUNCTIONAL GENOMICS

and

MOLECULAR PHARMACOLOGY

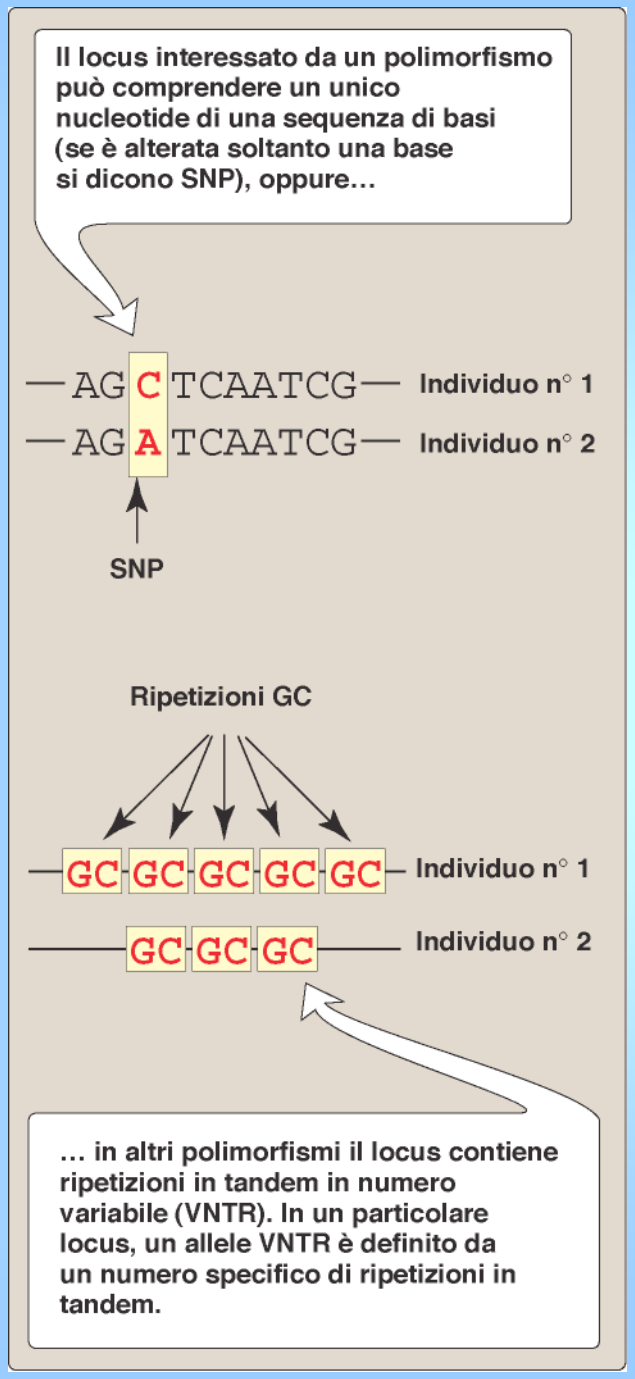
Goal

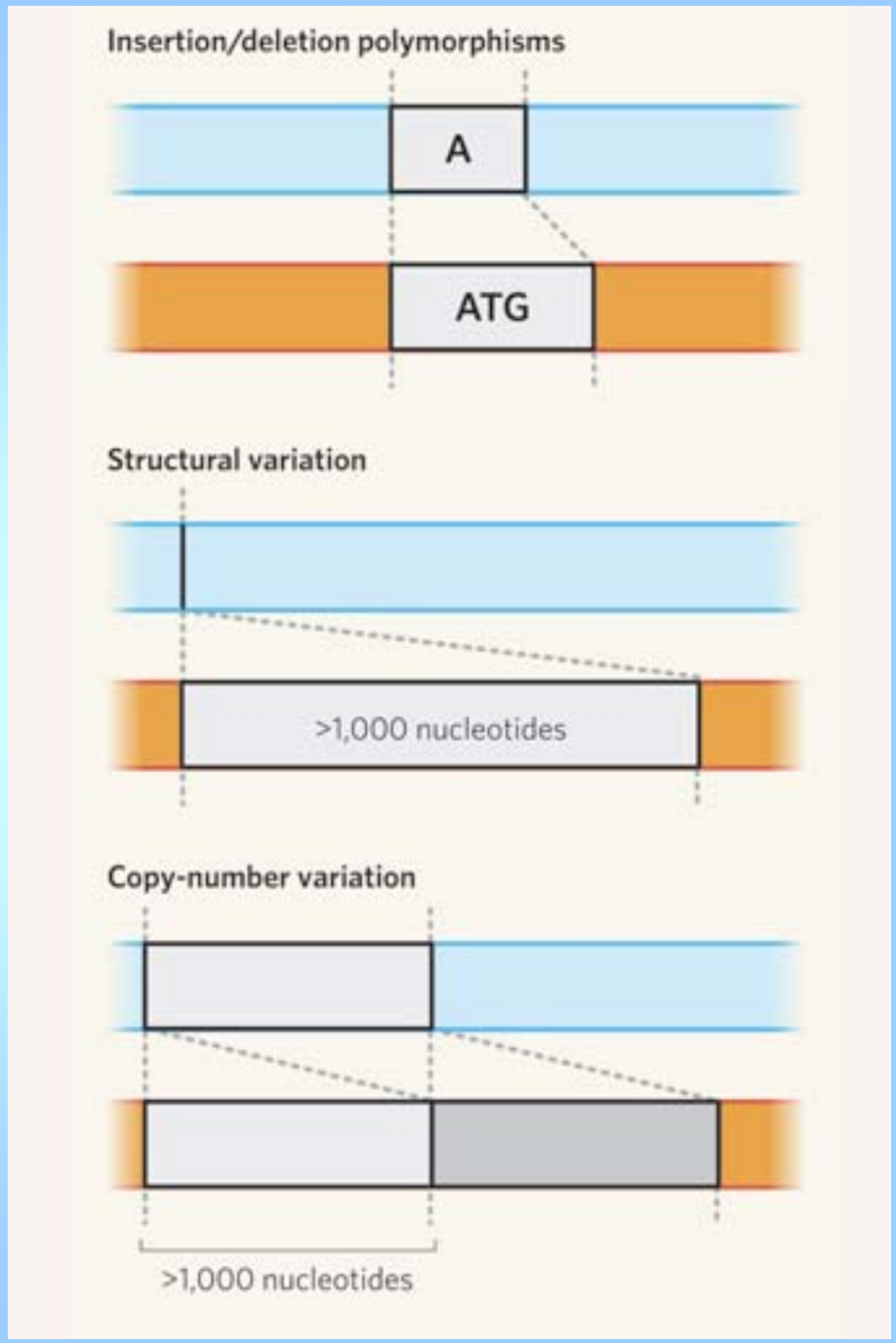
Find correlations between:

THERAPEUTIC *RESPONSES* TO DRUGS

and

GENETIC *PROFILES* OF PATIENTS


Il locus interessato da un polimorfismo può comprendere un unico nucleotide di una sequenza di basi (se è alterata soltanto una base si dicono SNP), oppure…
AG C TCAATCG
Individuo n° 1
AG A TCAATCG
Individuo n° 2
SNP
Ripetizioni GC
GC GC GC GC GC
Individuo n° 1
GC GC GC
Individuo n° 2
… in altri polimorfismi il locus contiene ripetizioni in tandem in numero variabile (VNTR). In un particolare locus, un allele VNTR è definito da un numero specifico di ripetizioni in tandem.


Insertion/deletion polymorphisms
A
ATG
Structural variation
>1,000 nucleotides
Copy-number variation
>1,000 nucleotides

Genetic polymorphisms of drug-metabolising enzymes, transporters, receptors or targets

PHASE I ENZYMES

GENE	REPRESENTATIVE DRUG	CONSEQUENCES FOR DRUG EFFECTS
CYP2C9	WARFARIN	Anticoagulant effect
CYP2C19	OMEPRAZOLE	Peptic ulcer cure rates
CYP2D6	IMIPRAMINE	Dose requirement
CYP2D6	CODEINE	Narcotic side effects
NQO1	MENADIONE	Urolitiasis

Genetic polymorphisms of drug-metabolising enzymes, transporters, receptors or targets

PHASE II ENZYMES

GENE	REPRESENTATIVE DRUG	CONSEQUENCES FOR DRUG EFFECTS
NAT2	ISONIAZID	Neurotoxicity
TPMT	MERCAPTOPURINE, THIOGUANINE	Toxicity, efficacy
UGT	IRINOTECAN	Glucuronidation

Genetic polymorphisms of drug-metabolising enzymes, transporters, receptors or targets

TRANSPORTERS

GENE	REPRESENTATIVE DRUG	CONSEQUENCES FOR DRUG EFFECTS
MDR-1	DIGOXIN	High plasma levels

Genetic polymorphisms of drug-metabolising enzymes, transporters, receptors or targets

RECEPTORS/TARGETS

GENE	REPRESENTATIVE DRUG	CONSEQUENCES FOR DRUG EFFECTS
ß2-ADREN.	ALBUTEROL	Asthma response
CETP	PRAVASTATIN	Atherosclerosis resp.
SEROTONIN	FLUVOXAMINE	Antidepressant resp.
D2 & D3	ANTIPSYCHOTICS	Dyskinesia
APOE4	TACRINE	Alzheimer resp.
RYANODINE	HALOTHANE	Malignant hyperthermia
PROTHROMBIN	CONTRACEPTIVES	Thrombosis

POLYMORPHIC GENES IN POPULATIONS OF DIFFERENT ORIGIN

GENE	GENOTYPE	CAUCASIANS	ASIANS	BLACK AFRICANS	ETHIOPIANS & SAUDI ARABIANS
		POOR METABOLIZERS %			
CYP2C9	Homozygous PM	0.2-1	ND	ND	ND
	Heterozygous	14-37	2-3	0.5	ND
CYP2D6	Homozygous PM	5-13.5	0-1	0-8	2
NAT2	Homozygous (slow)	40-70	9-22	50-60	80
		ULTRARAPID METABOLIZERS %			
CYP2D6	Duplication	1-7	2	2	10-16

RADIOGENOMICS

Table 3 – Large national/international genotyping studies

Study name	Full title	Planned recruitment	Primary	Based	Reference
Gene-PARE	Genetic Predictors of Adverse Radiotherapy Effects	>2000	Breast, prostate, head and neck	USA, Israel, France, Switzerland	[42]
GENEPI	GENEtic pathways for the Prediction of the effects of Irradiation	3000–4000	Breast, prostate, head and neck, rectal	Europe	[37]
RadGenomics	Japanese RadGenomics study	1071	Breast, cervix, prostate, head and neck	Japan	[40]
RAPPER	Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy	2200	Breast, prostate, gynaecological	UK	[38]

Common goal of these studies:
identifying gene expression profiles associated with an increased risk of developing normal tissue radiation toxicity.

NUTRIGENOMICS

Diet (fruits & vegetables, soy, etc.)

and

Lifestyle (daily exercise, etc.)

A 3-month prospective trial

in early prostate cancer:

effects on gene expression profiles

- Several recent studies have examined how ***nutrition*** affects gene expression in the context of obesity and metabolic syndrome (40, 41). These investigations (the FUNGENUT study) profiled gene expression in subcutaneous adipose tissue and found down-regulation of IGF pathway genes and genes related to fat metabolism.

- Results of the GEMINAL study in prostate tissue were very similar: down-regulation of IGF pathway genes [*IGF1 receptor (IGF1R), phosphoinositide-3-kinase, class 2, -polypeptide (PIK3C2A),* and *forkhead box A2 (FOXA2)*] and down-regulation of fat metabolism genes [*acyl-CoA dehydrogenase, long chain (ACADL),* and *phytanoylCoA 2-hydroxylase (PHYH)*].

- In addition, prostate tissue exhibited down-regulation of carbohydrate metabolism genes [*6-phosphofructo-2-kinase (PFKFB1), glycerol-3-phosphate dehydrogenase 1-like (GPD1L),* and *ATP citrate lyase (ACLY)]*.

Will genetics create an information elite ?

- The genetics literature is replete with hints about what genetic differences might mean for health and drug response

- Translating these hints into practical advice requires professional help

- If national healthcare providers are unable to provide this service, only the elite will realize the benefits of genetic research in the near and medium term



"Here's my sequence..."