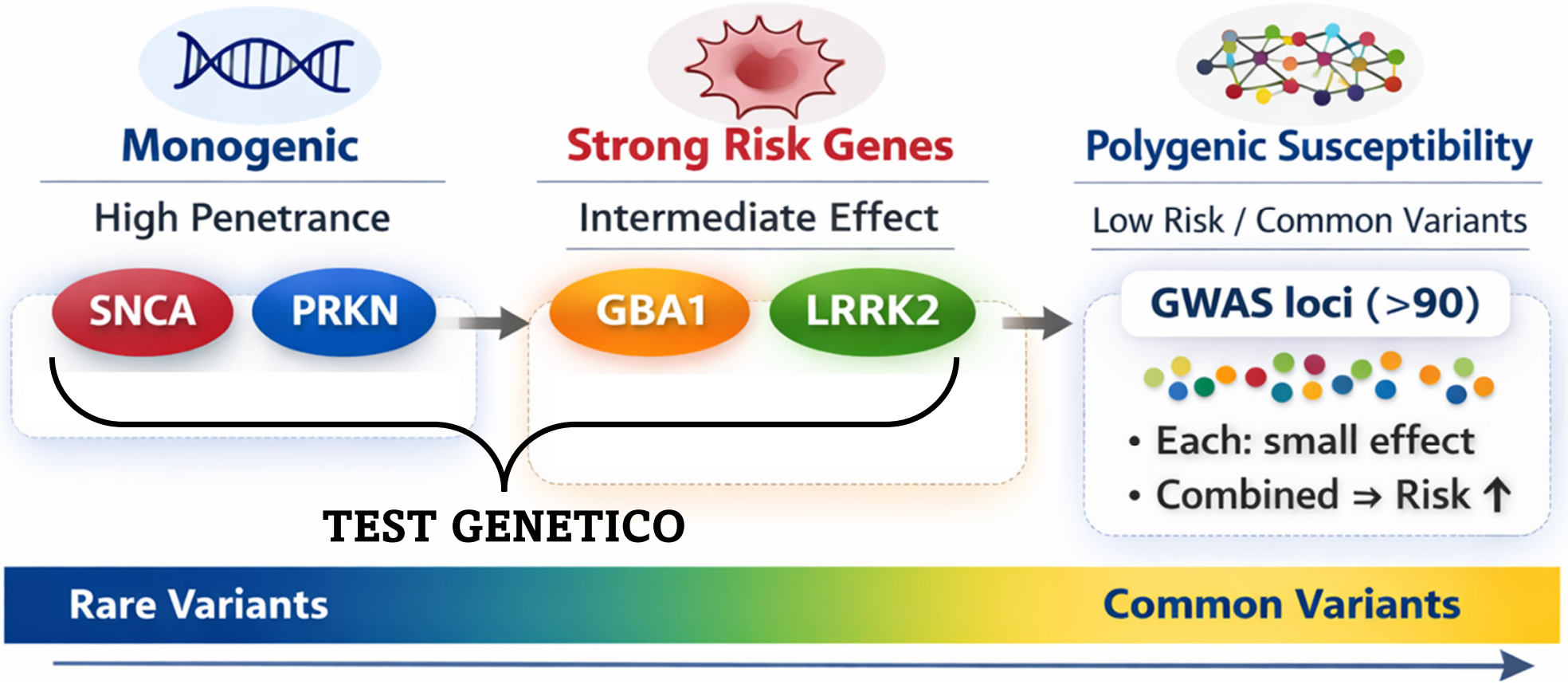
ROMA
17-18 marzo 2026

NEUROYoung
next generation in neurologia
5th edition

Genetica: istruzioni per l'uso

Edoardo Monfrini

Architettura genetica del PD



Forme «genetiche»

Autosomal dominant PD and strong risk factors

Genes	Inheritance	Prevalence	Phenotype	Lewy bodies
GBA1	Risk factor / AD	5-15% of all PD patients (up to 20% in Ashkenazi Jews)	Early and late onset PD	+
LRRK2	Risk factor / AD	1-5% of all PD patients (up to 15% in Ashkenazi Jews and 40% in North African Berbers)	Late onset typical	-/+
RAB32	Risk factor / AD	~0.5% of all PD patients (mediterranean area)	Late onset typical	-
ITSN1	Risk factor	~0.1% of all PD patients	Late onset typical (?)	?
SNCA	AD	Rare	Early and late onset	+
VPS35	AD	Extremely rare	Late onset typical	?

Forme «genetiche»

Autosomal recessive PD

Genes	Inheritance	Prevalence	Phenotype	Lewy bodies
GBA1	Risk factor / AD	5-15% of all PD patients (up to 20% in Ashkenazi Jews)	Early and late onset PD	+
LRRK2	Risk factor / AD	1-5% of all PD patients (up to 15% in Ashkenazi Jews and 40% in North African Berbers)	Late onset typical	-/+
RAB32	Risk factor / AD	~0.5% of all PD patients (mediterranean area)	Late onset typical	-
ITSN1	Risk factor	~0.1% of all PD patients	Late onset typical (?)	?
SNCA	AD	Rare	Early and late onset	+
VPS35	AD	Extremely rare	Late onset typical	?
PRKN	AR	~10% of early-onset PD patients	Early onset typical	-
PINK1	AR	~5% of early-onset PD	Early onset typical	-/+
PARK7 (DJ-1)	AR	Rare	Early onset atypical	+
VPS13C	AR	Extremely rare	Early onset atypical	+
PSMF1	AR	Extremely rare	Early onset atypical	-

Forme «genetiche»

X-linked PD

Genes	Inheritance	Prevalence	Phenotype	Lewy bodies
GBA1	Risk factor / AD	5-15% of all PD patients (up to 20% in Ashkenazi Jews)	Early and late onset PD	+
LRRK2	Risk factor / AD	1-5% of all PD patients (up to 15% in Ashkenazi Jews and 40% in North African Berbers)	Late onset typical	-/+
RAB32	Risk factor / AD	~0.5% of all PD patients (mediterranean area)	Late onset typical	-
ITSN1	Risk factor	~0.1% of all PD patients	Late onset typical (?)	?
SNCA	AD	Rare	Early and late onset	+
VPS35	AD	Extremely rare	Late onset typical	?
PRKN	AR	~10% of early-onset PD patients	Early onset typical	-
PINK1	AR	~5% of early-onset PD	Early onset typical	-/+
PARK7 (DJ-1)	AR	Rare	Early onset atypical	+
VPS13C	AR	Extremely rare	Early onset atypical	+
PSMF1	AR	Extremely rare	Early onset atypical	-
RAB39B	XLR	Extremely rare	Late onset atypical	+

Forme «genetiche»

Genes	Inheritance	Prevalence	Phenotype	Lewy bodies
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VPS13C	AR	Extremely rare	Early onset atypical	+
PSMF1	AR	Extremely rare	Early onset atypical	-
RAB39B	XLR	Extremely rare	Late onset atypical	+

+ PLA2G6, ATP13A2, FBXO7, SYNJ1, DNAJC6, TAF1, PTRHD1, SLC9A6…

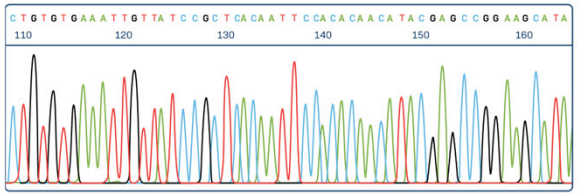
Avanzamento delle tecnologie

Primi anni 2000

Sanger sequencing

Un gene (o un esone)

Selezione clinica del gene più probabile

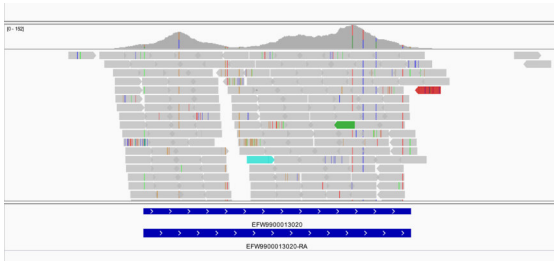


Anni 2010-2020

Next-generation sequencing gene panels

Un pannello di geni

Selezione in base alla classe fenotipica

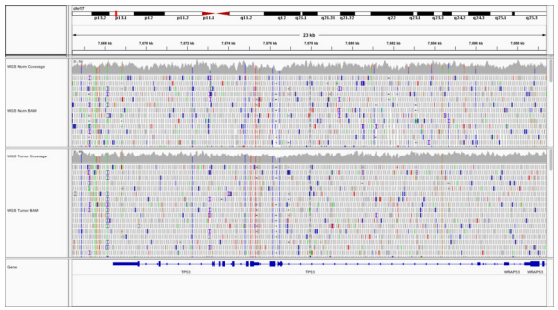


Adesso

Whole-exome o whole-genome sequencing

Tutti i geni

Approcci "*unbiased*"



Utilità diagnosi genetica in PD

DIAGNOSI GENETICA NELLA MALATTIA DI PARKINSON

- **Migliore definizione diagnostica (verso diagnosi biologica – *precision medicine*)**
- **Identificare precocemente manifestazioni cliniche associate**
- **Counseling familiare**
- **Risvolti terapeutici immediati**
- **Reclutamento in sperimentazione cliniche / stratificazione biologica in trials**
- **Avanzamento conoscenze e scoperta nuove terapie**

Migliore definizione diagnosi

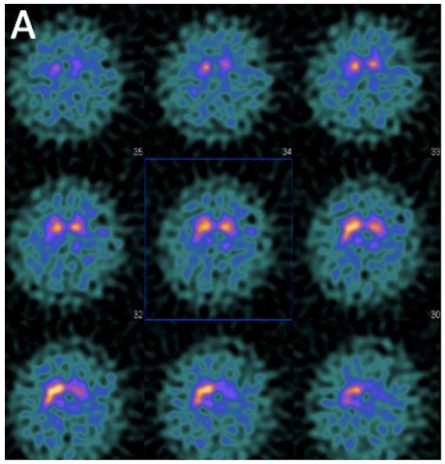
Caso clinico

Esordio 53 aa tremore a dx e bradicinesia

Ottima risposta a levodopa

SPECT DaTscan ++

RM encefalo normale



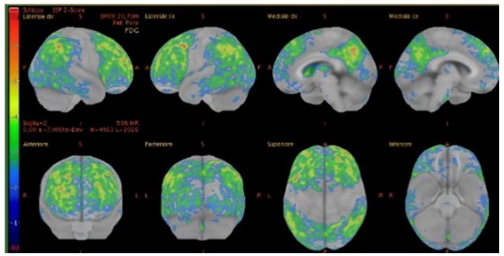
A 5 anni dall'esordio comparsa di gravi fluttuazioni motorie

→ Valutazione per DBS

Analisi genetica mediante whole-exome sequencing:

***GRN* p.Arg110Stop het**

Dopo un anno comparsa di disturbi cognitivi, fino a mutacismo



PET-FDG con ipometabolismo frontoparietale

› J Neurol Sci. 2023 Aug 15:451:120737. doi: 10.1016/j.jns.2023.120737. Epub 2023 Jul 17.

Levodopa responsive asymmetric parkinsonism as clinical presentation of progranulin gene mutation

Niccolò Biagioli [1], Francesco Cavallieri [2], Alessandro Marti [3], Giulia Di Rauso [1], Valentina Fioravanti [3], Edoardo Monfrini [4], Federico Gasparini [3], Daniela Beltrami [3], Sara Grisanti [5], Jessica Rossi [6], Giulia Toschi [3], Alessandro Fraternali [7], Annibale Versari [7], Manuela Napoli [8], Rosario Pascarella [8], Alessio Di Fonzo [4], Franco Valzania [3]

Impatto su decisione follow-up e terapia

Definizione prognosi

	GBA1-PD	LRRK2-PD	PRKN-PD
Clinical features	Dementia, psychosis, non-motor symptoms	Low prevalence of dementia	Absence of hyposmia, absence of dementia, dystonia
Age at onset	Slightly younger	Slightly younger	Early-onset
Clinical course	Fast progression	Intermediate	Slow progression
Neuropathology	Lewy pathology	Lewy pathology, Tau pathology, Pure nigral degeneration	Pure nigral degeneration
CSF αSyn SAA	+	– / +	–
Brain MRI	Cortical atrophy	Intermediate	No cortical atrophy
PET-FDG	Cortical hypometabolism	Intermediate	No cortical hypometabolism

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Counseling familiare

Il Parkinson è una malattia ereditaria?

RISPOSTA SENZA TEST GENETICO:

Rischio doppio nei parenti di primo grado degli affetti.
In una minoranza di casi il PD presenta una forte componente genetica (~10-15%)

RISPOSTA CON TEST GENETICO POSITIVO:

Counseling fatto in modo specifico per la variante genetica identificata

FORME MONOGENICHE	FORME ASSOCIATE A RISK GENES
(ad es. *PRKN* o *SNCA*)	(ad es. *GBA1*)

SE TEST NEGATIVO: In media un rischio lievemente aumentato nei parenti degli affetti (**non si può escludere che ci siano varianti genetiche predisponenti non identificate**)

Risvolti terapeutici immediati

	GBA1-PD	LRRK2-PD	PRKN-PD
Parkinsonism response to therapies	Early drug-related complications	Satisfactory, early diskinesias	Satisfactory (on parkinsonism)
Useful drugs	Rivastigmine (psychosis) Midodrine and Fludrocortisone (orthostatic hypotension)	Amantadine (dyskinesia)	Botulinum toxin (foot dystonia)
Response to DBS	Good on motor features	Generally good (but it depends on the variant)	Optimal (target GPi?)
Response to Duodopa	Good on motor features	Good	Unknown
Additional issues	Early neuropsychological assessments and Tilt test	Increased risk of neoplasia and type 2 diabetes (?)	Work-related issues (early-onset disease) and psychological disturbances

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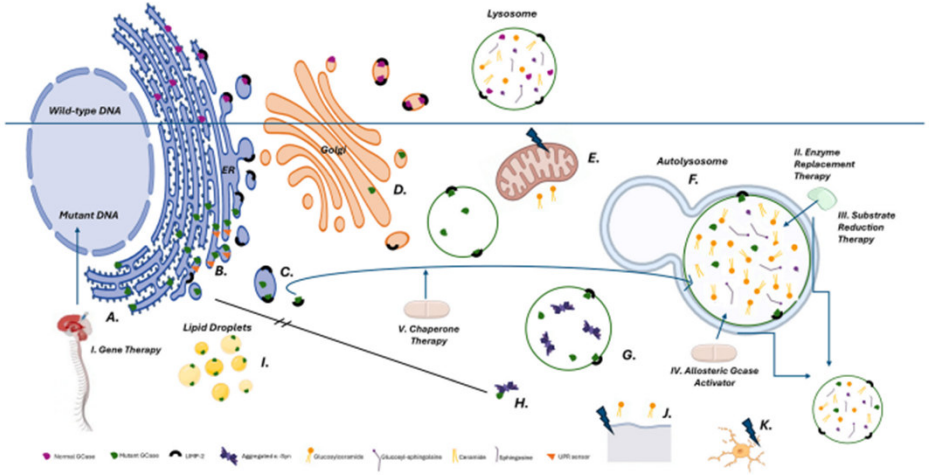
Sperimentazioni cliniche

LRRK2

- Trial Fase 2/3 BIIB122/DNL151 inibitore attività kinasica di LRRK2 N1437H, R1441G, R1441C, R1441H, Y1699C, G2019S I2020T
- Anche in pz senza varianti LRRK2 (LUMA)
- Trial Fase 1: ASO per ridurre espressione LRRK2



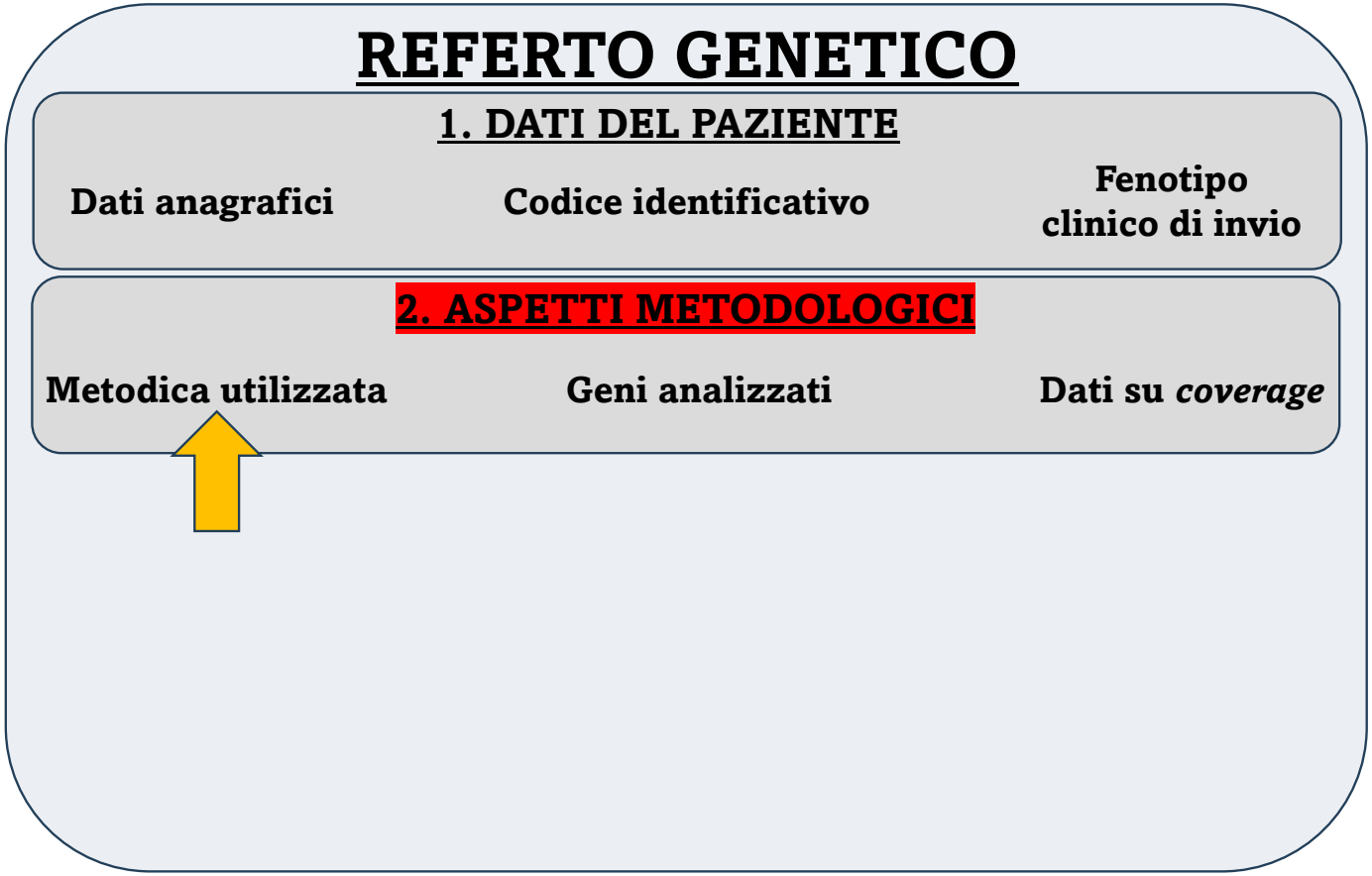
GBA1

- NCT02941822 Ambroxol in disease modification in PD (fase 2) UK
- NCT05778617 Ambroxol in disease modification in PD (fase 3) UK
- NCT05287503 Ambroxol in disease modification in GBA1-PD (fase 2) ITA
- NCT04127578 (gene therapy AAV9-GBA1 intratecale)
- BIA27, Gain Therapeutics: small molecule per stabilizzare o aumentare attività GCase

Cavallieri F, 2023
Colucci F, 2025

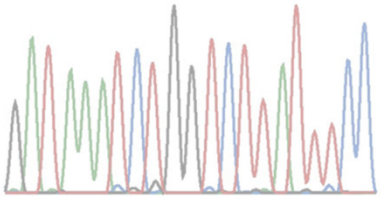
Come interpretare un referto?

Interpretazione referto genetico

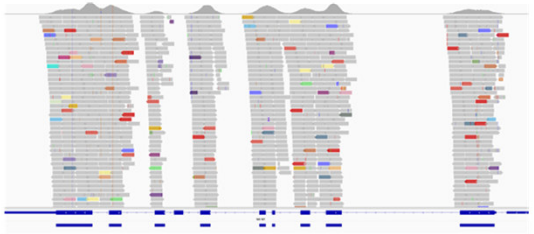


Tecnologia di sequenziamento

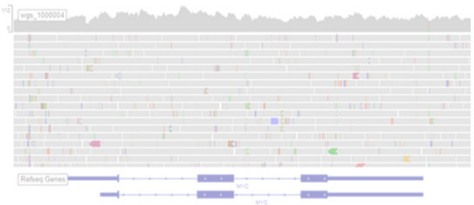
1) Sanger sequencing



2) NGS gene panels



3) Exome sequencing (CES o WES)

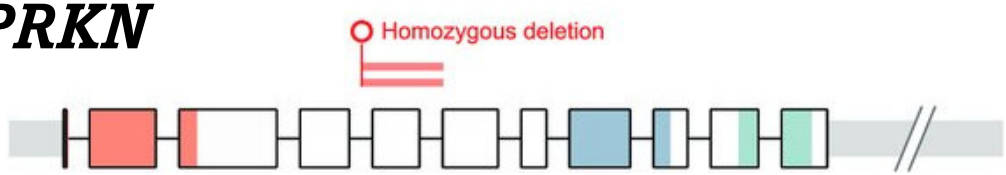


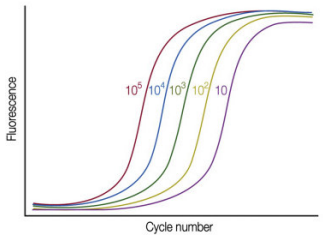
4) Whole genome sequencing

- Short reads
- Long reads

Dosaggio genico?

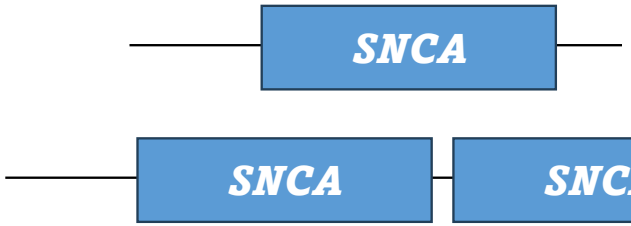
PRKN





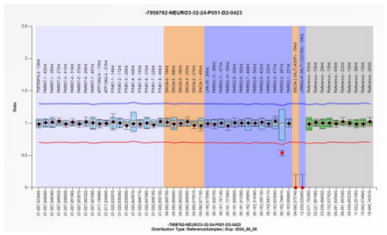
Real Time-PCR

SNCA

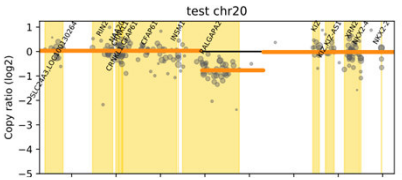


NORMALE

DUPLICATO



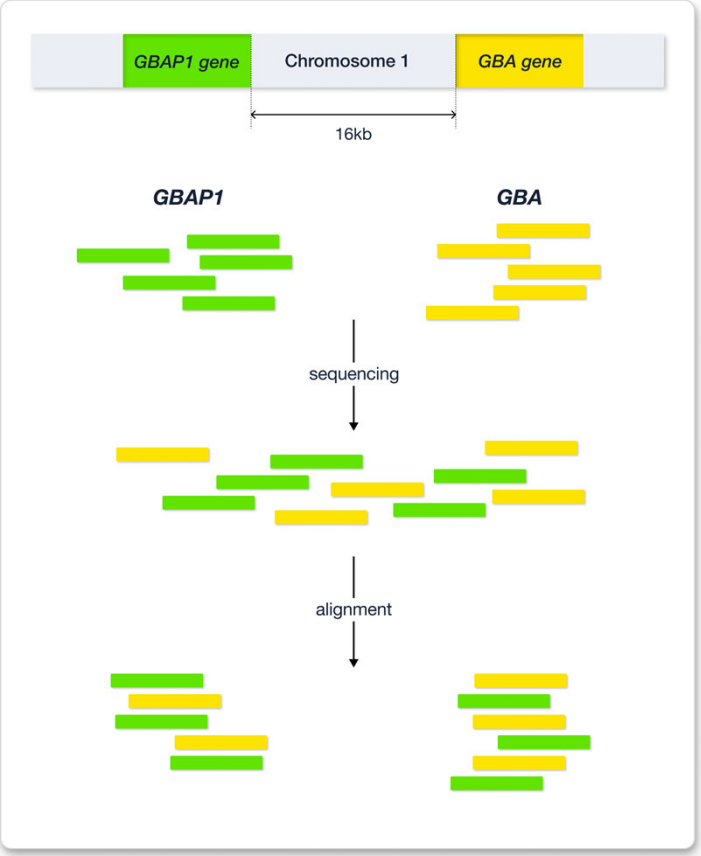
MLPA

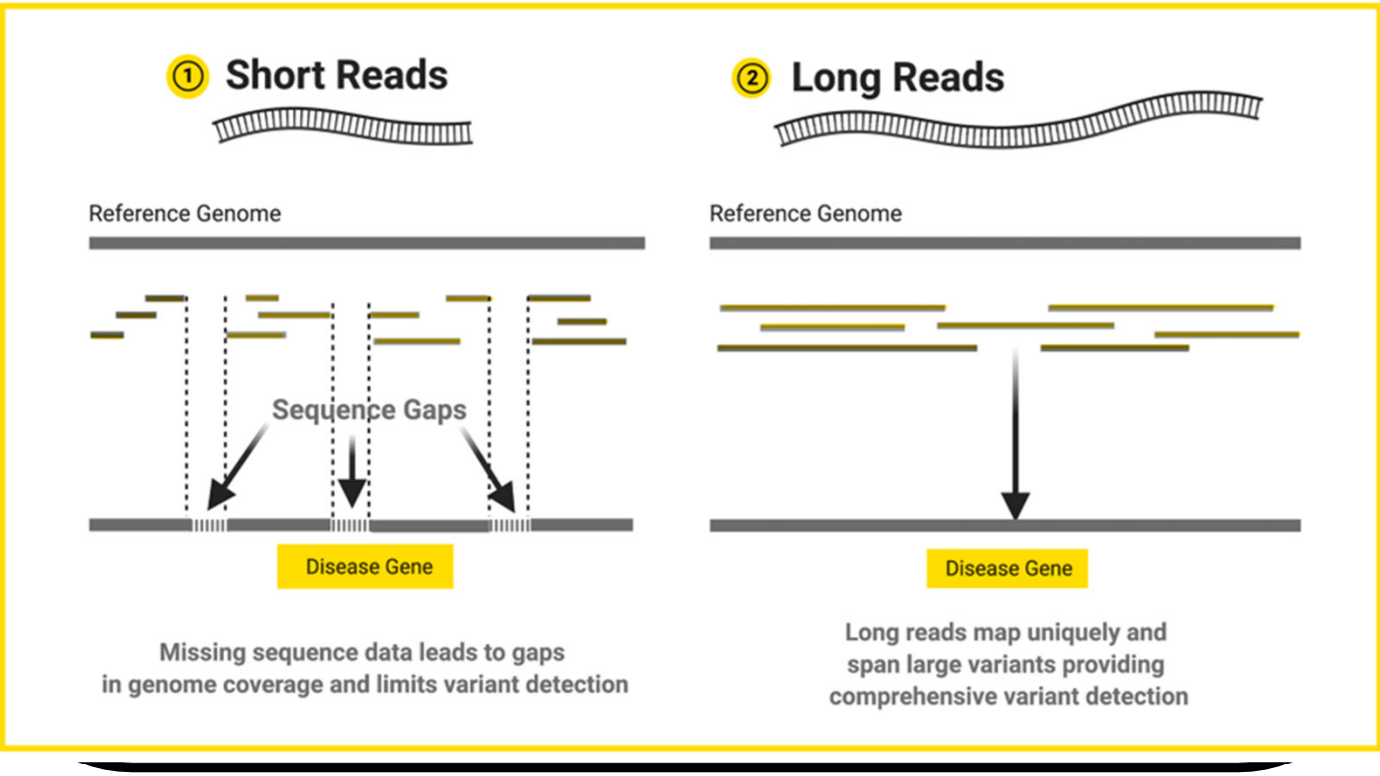


CNVkit

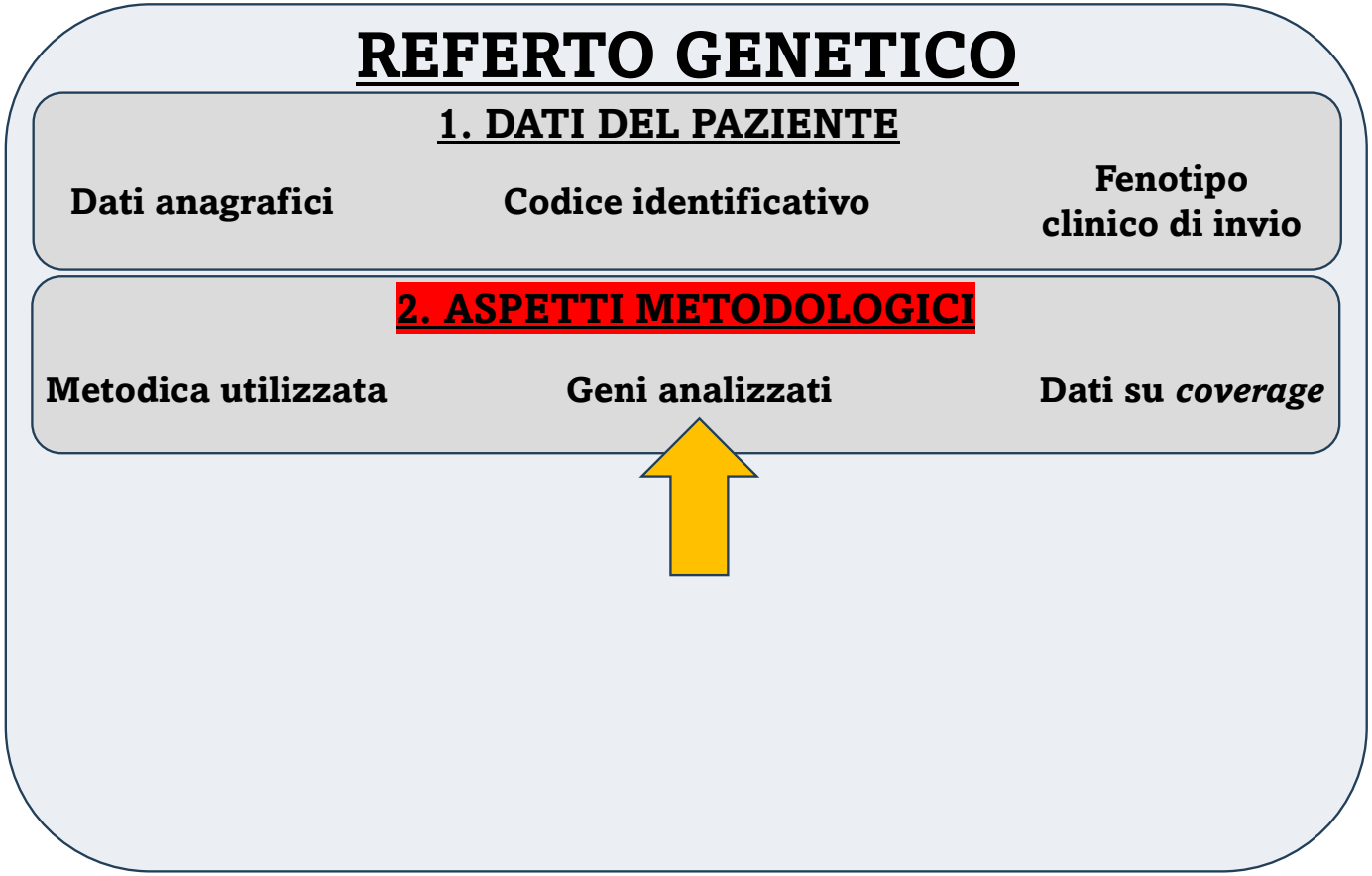
La negatività di un referto va interpretata alla luce dell'esecuzione o meno di tecniche di *dosage assays*

Problema *GBA1*





Interpretazione referto genetico



Laboratori diversi analizzano pannelli di geni diversi per la malattia di Parkinson

MANCA UN CONSENSUS SUI GENI DA INCLUDERE NEI PANNELLI GENETICI PER MALATTIA DI PARKINSON

Questioni irrisolte:

1) L'associazione di alcuni geni al Parkinson è ancora *pending*
(*DNAJC13, LRP10, TWNK, CHCHD2…*)

2) Dovremmo includere i geni associati a fenotipi parkinsoniani atipici?
(*MAPT, C9ORF72, PRNP, GRN, ATP13A2, FBXO7, SYNJ1, DNAJC6…)*

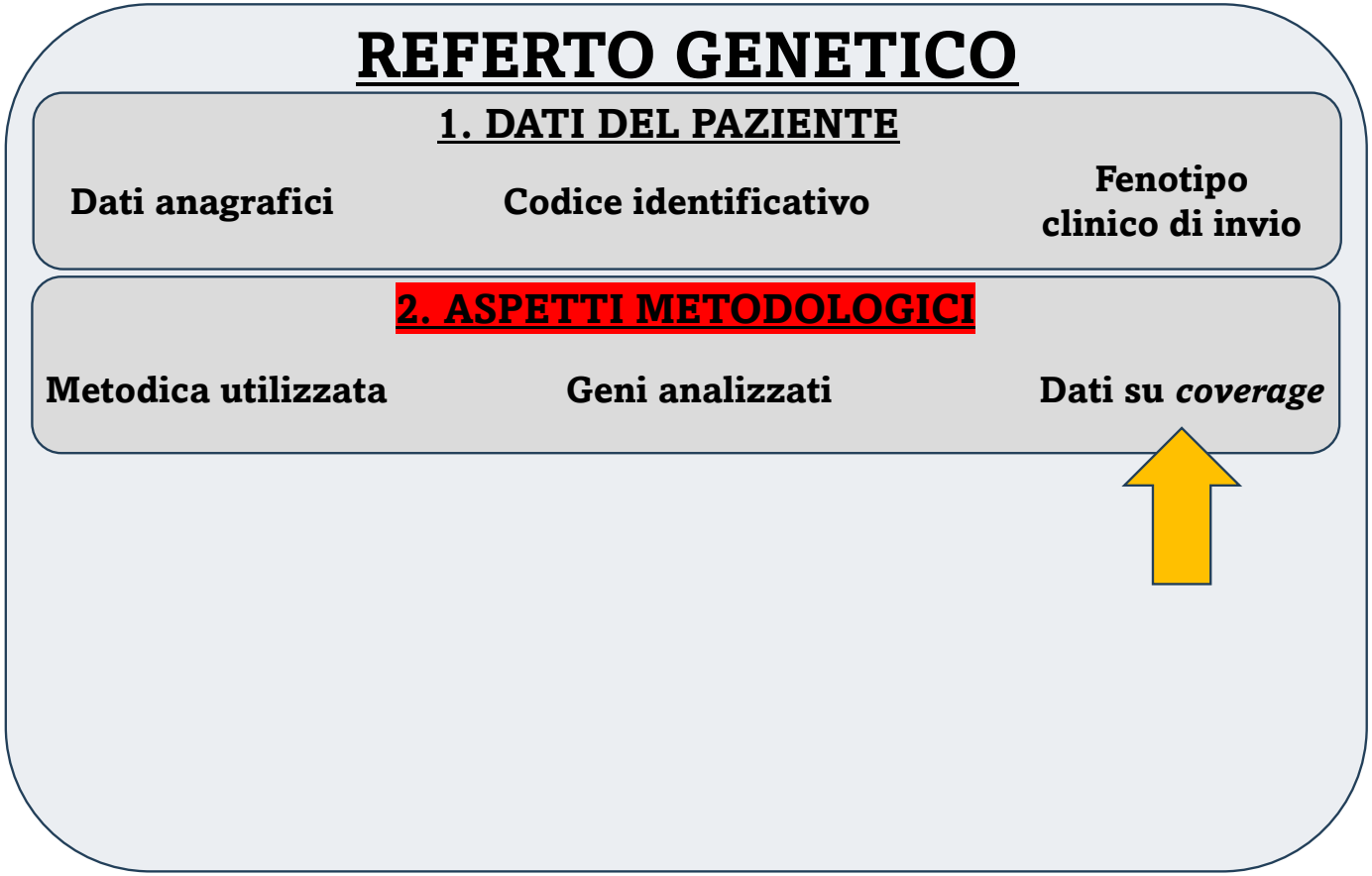
Minimal gene set Parkinson del ParkNet

Gene	Inheritance
GBA1	AD, risk factor
LRRK2	AD, risk factor
SNCA	AD
VPS35	AD
RAB39B	X-linked recessive
PRKN	AR
PINK1	AR
PARK7	AR
ATP13A2	AR
PLA2G6	AR
DNAJC6	AR
SYNJ1	AR
FBXO7	AR
VPS13C	AR
PTRHD1	AR
RAB32	AD, risk factor
PSMF1	AR
ITSN1	risk factor

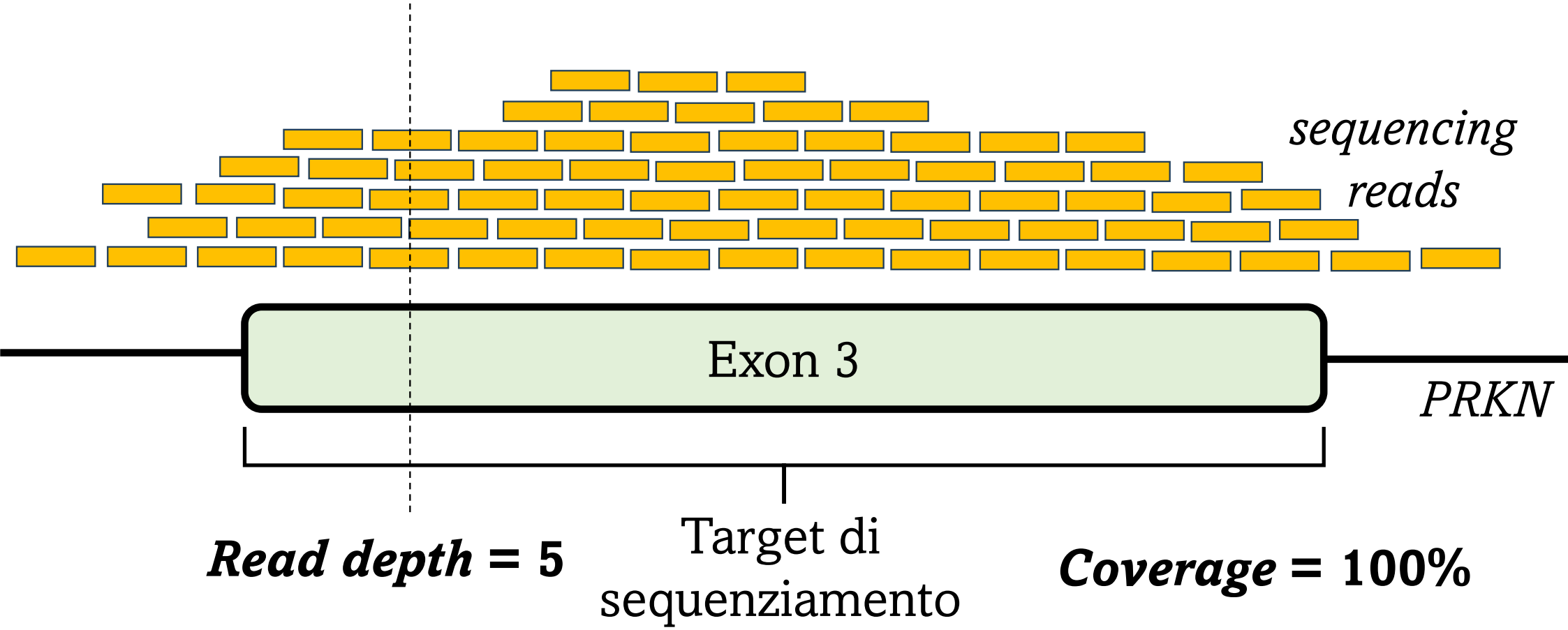
È necessario un consensus internazionale

ClinGen
Clinical Genome Resource

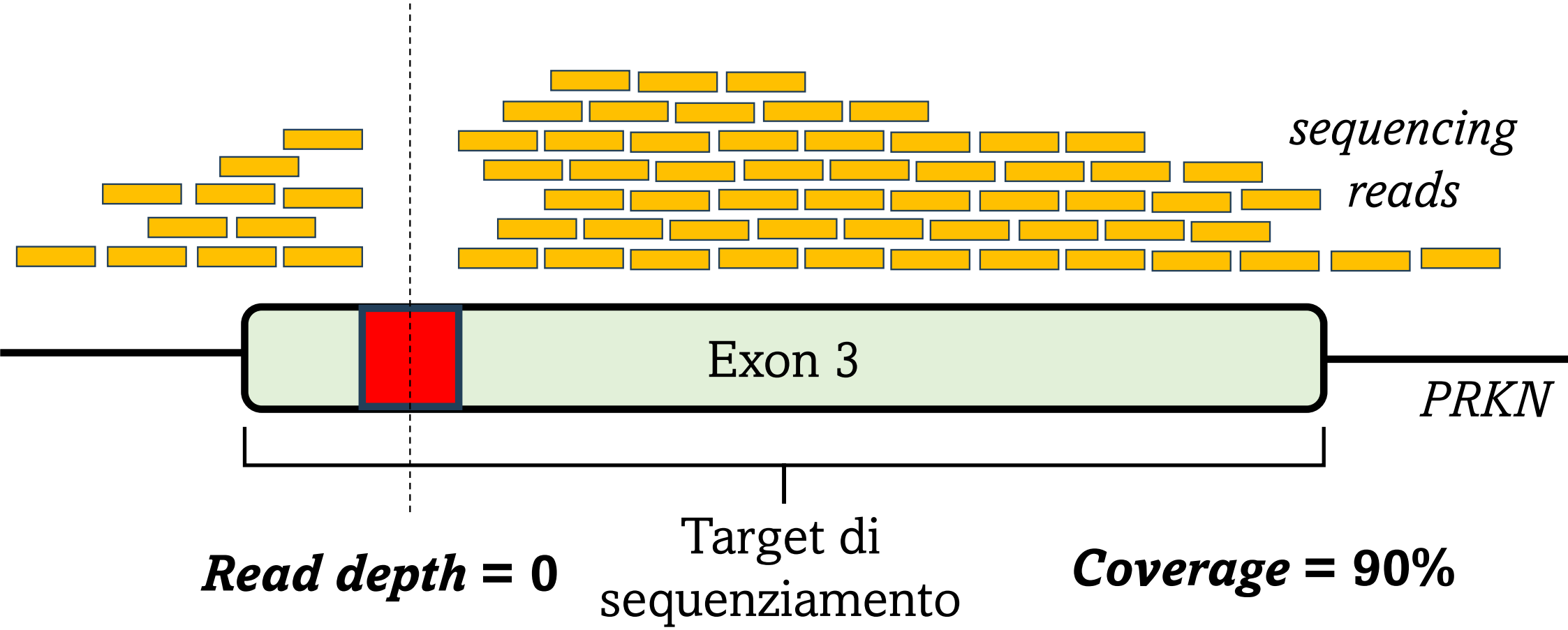
Interpretazione referto genetico



Coverage


sequencing reads
Exon 3
PRKN
Read depth = 5
Target di sequenziamento
Coverage = 100%

Coverage



***Read depth* = 0**

***Coverage* = 90%**

Interpretazione referto genetico

REFERTO GENETICO

1. DATI DEL PAZIENTE

Dati anagrafici | **Codice identificativo** | **Fenotipo clinico di invio**

2. ASPETTI METODOLOGICI

Metodica utilizzata | **Geni analizzati** | **Dati su *coverage***

3. VARIANTI IDENTIFICATE

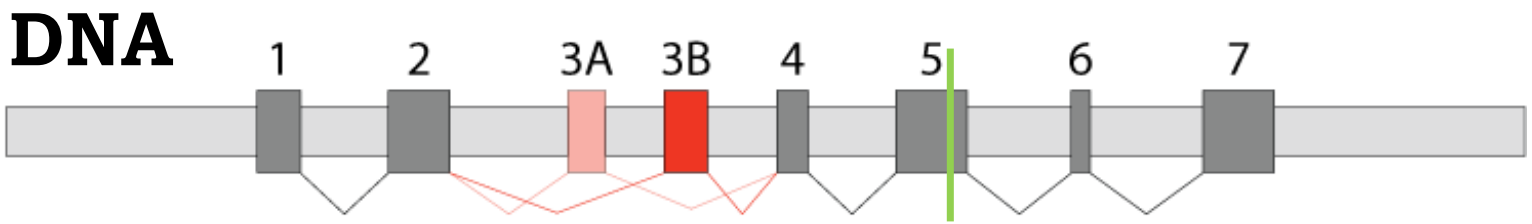
Variante o lista varianti rare clinicamente rilevanti per il paziente

Nomenclatura varianti

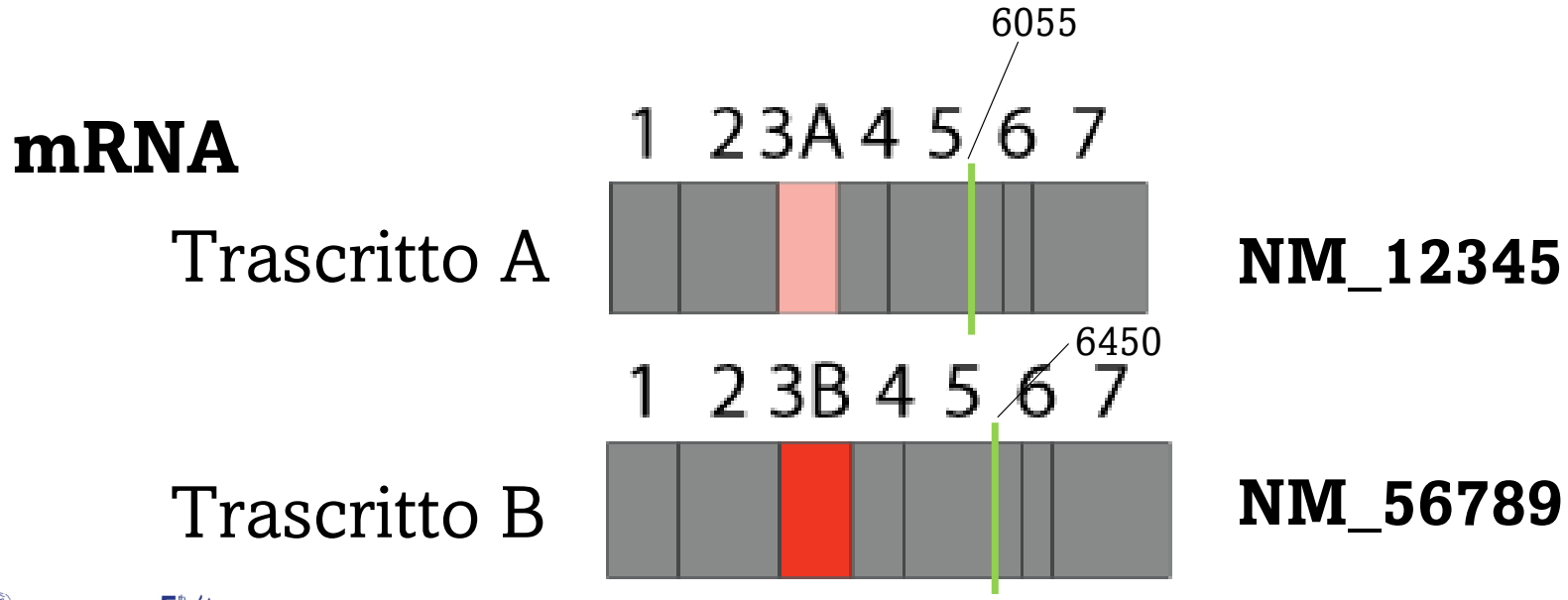
LRRK2 (NM_198578.4) c.6055G>A p.(Gly2019Ser)

Nome del gene	Nome del trascritto	Variante osservata sul DNA	Variante predetta a livello proteico

Un solo gene, diversi trascritti



Splicing alternativo



Interpretazione referto genetico

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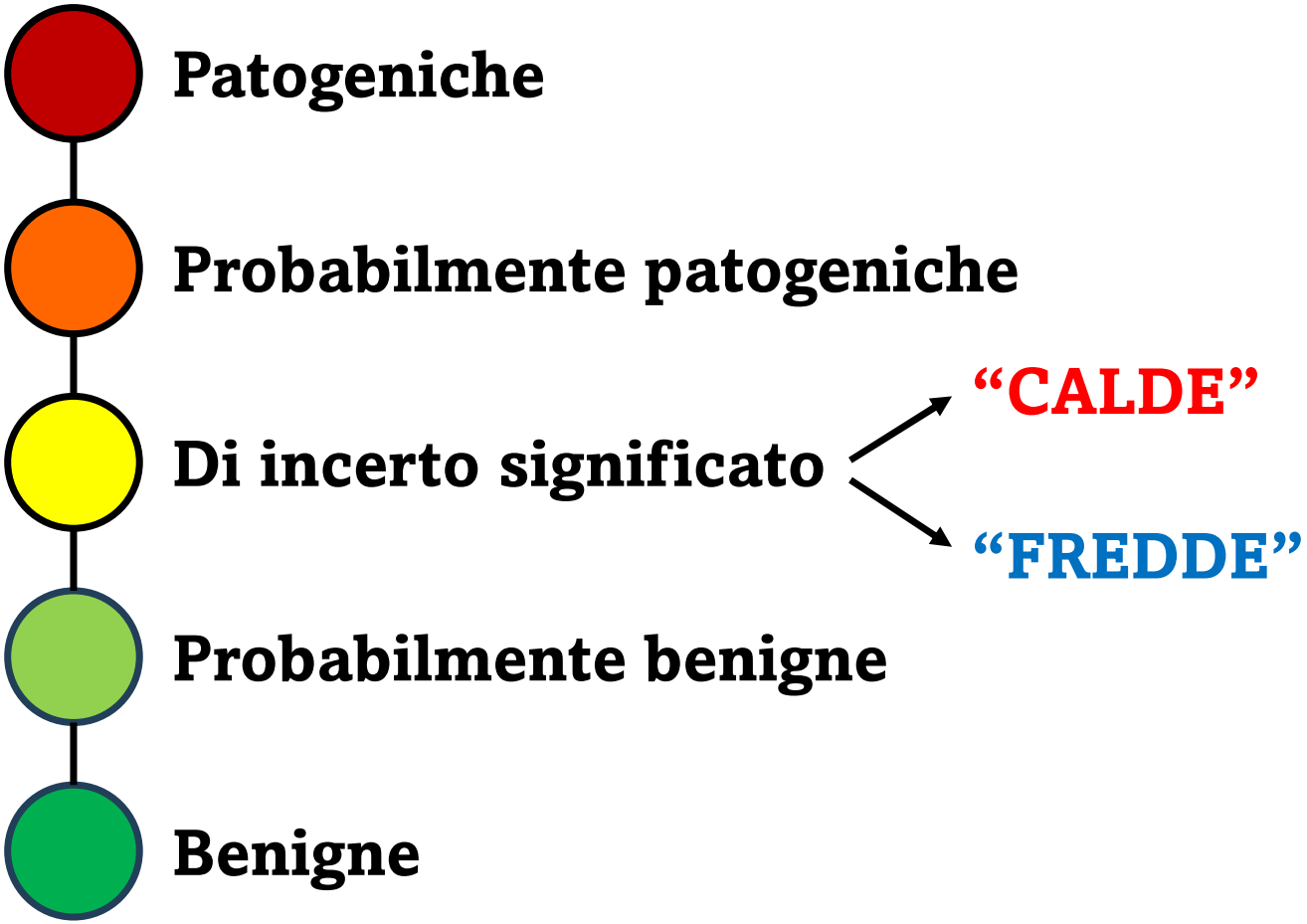
4. INTERPRETAZIONE DEI RISULTATI

Interpretazione delle varianti alla luce dei criteri ACMG, del pattern di ereditarietà e del fenotipo clinico del paziente

Classificazione ACMG varianti



ACMG

Criteri classificazione ACMG

1) Frequenza nella popolazione del paziente	se è rara ↑ patogenicità
2) Predizione dei programmi in silico	se predetta deleteria ↑ patogenicità
3) Dati funzionali a supporto della patogenicità	se effetto deleterio ↑ patogenicità
4) Dati di segregazione familiare	se presente in soli affetti ↑ patogenicità
5) Occorrenza de novo	se presente solo in probando e non in genitori ↑ patogenicità
6) Stato allelico in AR	se associata in trans con variante patogenetica nota ↑ patogenicità
7) Classificazione su database clinici	se Clinvar la classifica come patogenetica ↑ patogenicità
8) Specificità fenotipica	se fenotipo altamente specifico ↑ patogenicità

Classificazione ACMG varianti

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Criteri ACMG

Classificazione automatica

- Pathogenic variant
- Likely pathogenic variant

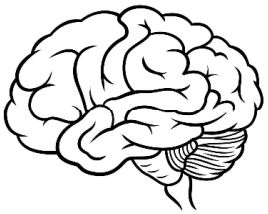
POSITIVO

- Variant of uncertain significance

VUS

- Likely benign variant
- Benign variant

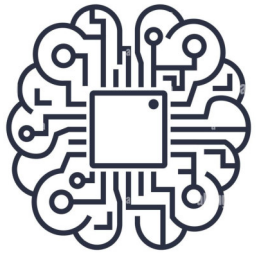
NEGATIVO



Supervisione umana

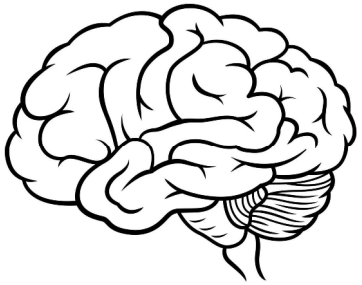
REFERTAZIONE

Classificazione solo automatica? NO

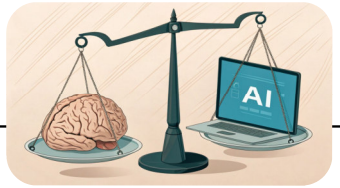


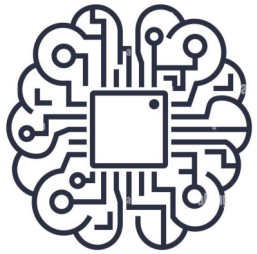
Likely Pathogenic 9 points = 9 P - 0 B

***LRRK2*: c.792_793insTTTAA, p.Arg265Phefs*7**



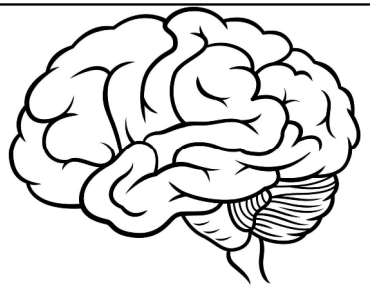
Varianti nonsense di *LRRK2* <u>non</u> sono associate a Parkinson





Benign -8 points = 4 P - 12 B

***GBA1*: c.1093G>A, p.Glu365Lys (E326K)**



GBA1 E326K è un fattore di rischio noto per Parkinson

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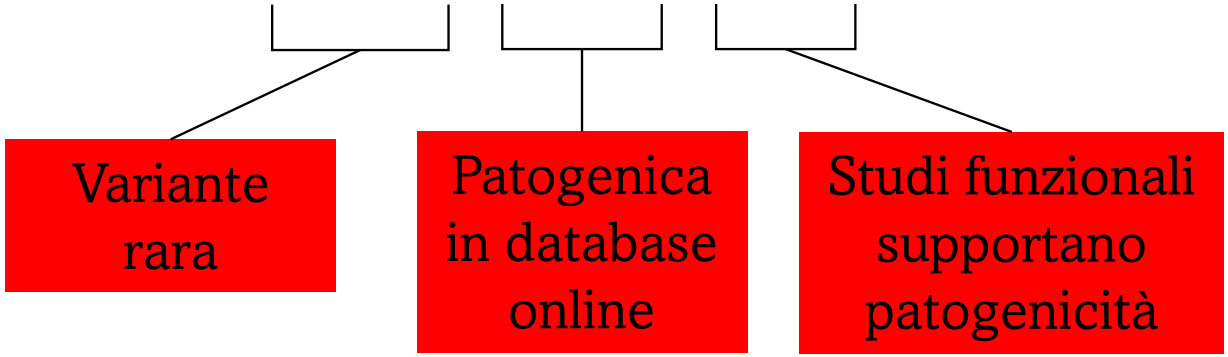
Esempio ACMG / Patogenica

PD familiare (AAO 38y)

SNCA (NM_000345.4): c.157G>A p.(Ala53Thr)

Criteri ACMG: PM2 PP5 PS3



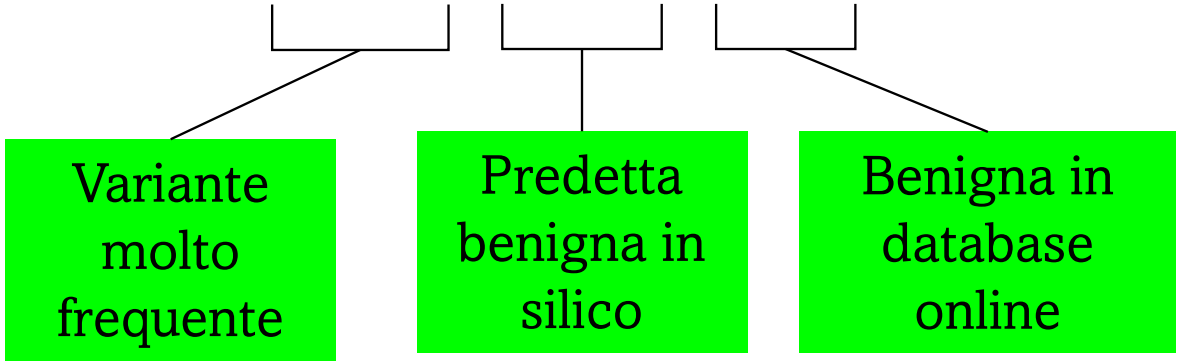
Variante Patogenica

Esempio ACMG / Benigna

PD sporadico (AAO 68y)

LRRK2 (NM_198578.4): c.149G>A p.(Arg50His)

Criteri ACMG: BA1 BP4 BP6



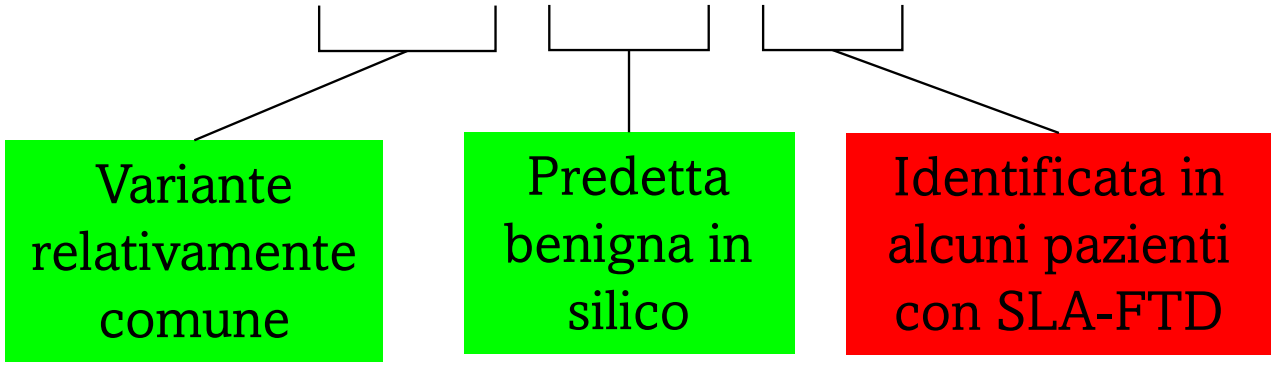
Variante Benigna

Esempio ACMG / VUS

Parkinsonismo-demenza familiare (AAO 63y)

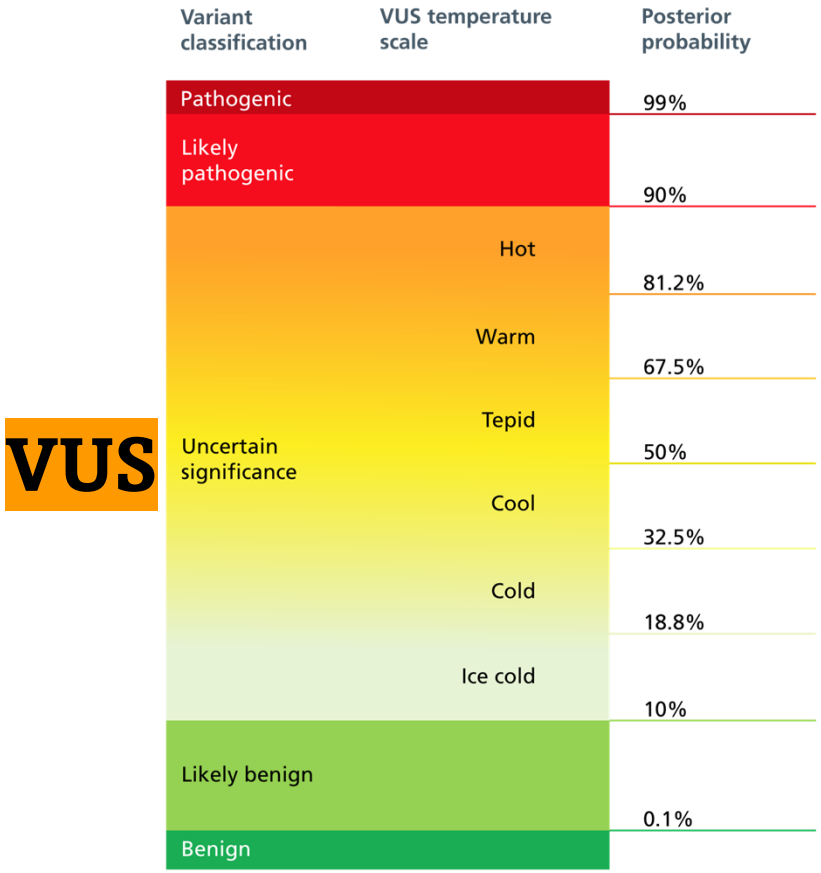
CHMP2B (NM_014043.4): c.85A>G p.(Ile29Val)

Criteri ACMG: BS2 BP4 PP5



Variante di incerto significato clinico

Problema VUS



VUS CALDE

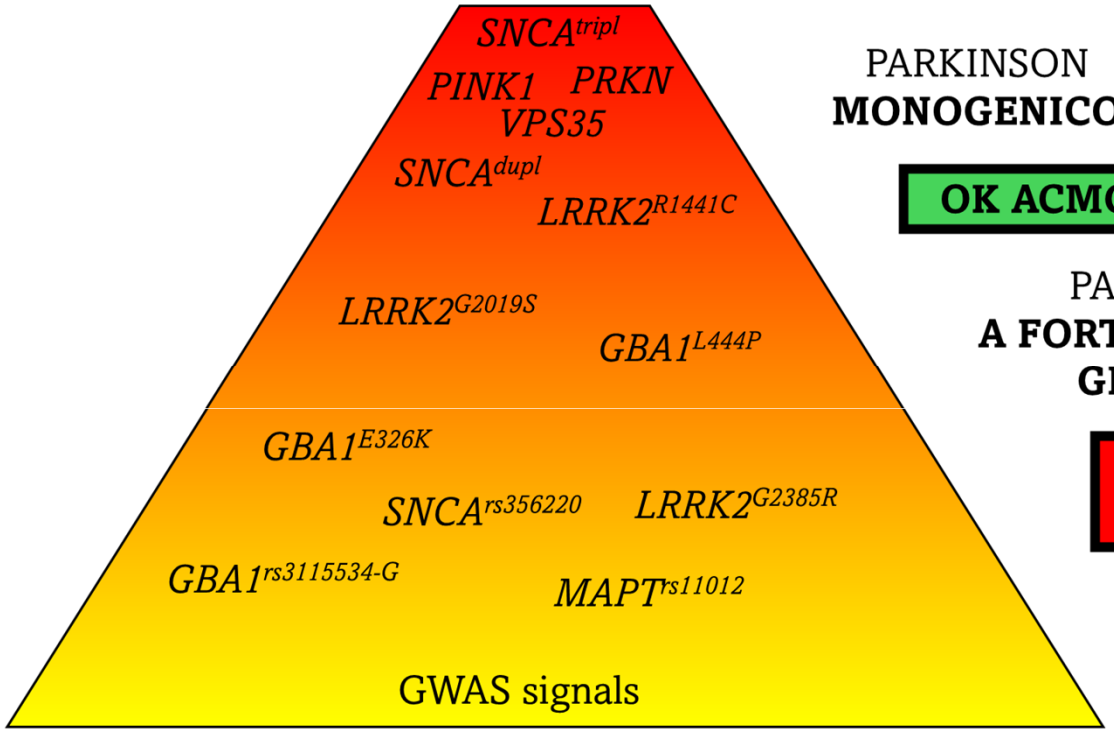
VUS con <u>elevate</u> probabilità di essere patogenetiche

VUS FREDDE

VUS con <u>basse</u> probabilità di essere patogenetiche

Classificazione ACMG e PD

Il sistema di classificazione ACMG è stato creato per forme genetiche monogeniche Mendeliane (AD, AR, XL)



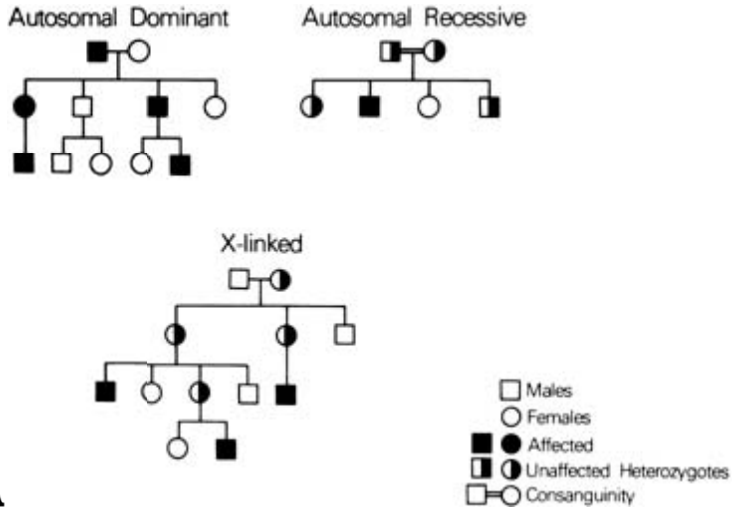
PARKINSON
MONOGENICO

OK ACMG!

PARKINSON
A FORTE IMPRONTA GENETICA

ACMG NON APPROPRIATO

PARKINSON
"IDIOPATICO"



Un possibile futuro…

Whole-genome sequencing

LUISA BIANCHI

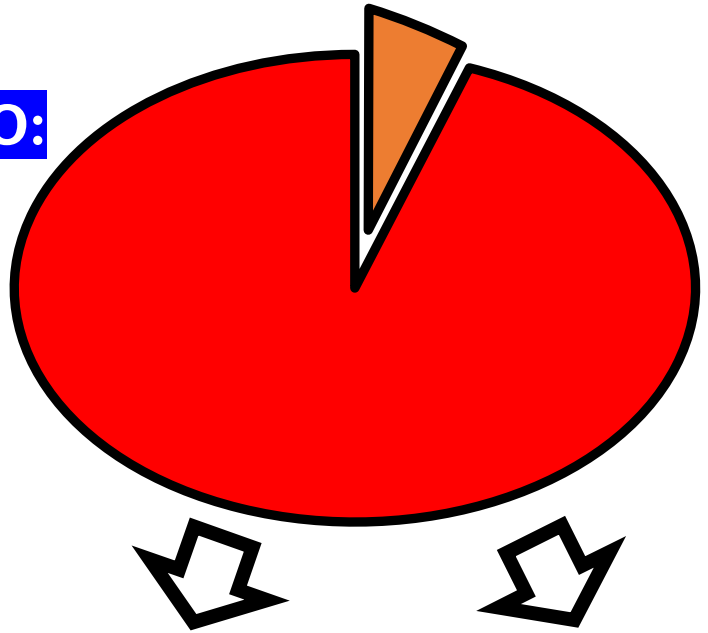
PROFILO DI RISCHIO POLIGENICO:

VARIANTI IN GENI PD LISOSOMIALI:
- *GBA1* E326K eterozigote
- *PSAP* missense eterozigote
- *HGSNAT* missense eterozigote
- *TMEM175* missense eterozigote

VARIANTI IN GENI PD MITOCONDRIALI:
- Nessuna variante

VARIANTI IN GENI PD TRAFFICKING VESCICOLE:
- *LRRK2* M1646T eterozigote

Predisposizione genetica a PD "lisosomiale"



DYSAUTONOMIA
COGNITIVE IMPAIRMENT

TARGETED MOLECULAR THERAPIES

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Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Movement Disorders Clinical and Research Group

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

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Gloria Brescia
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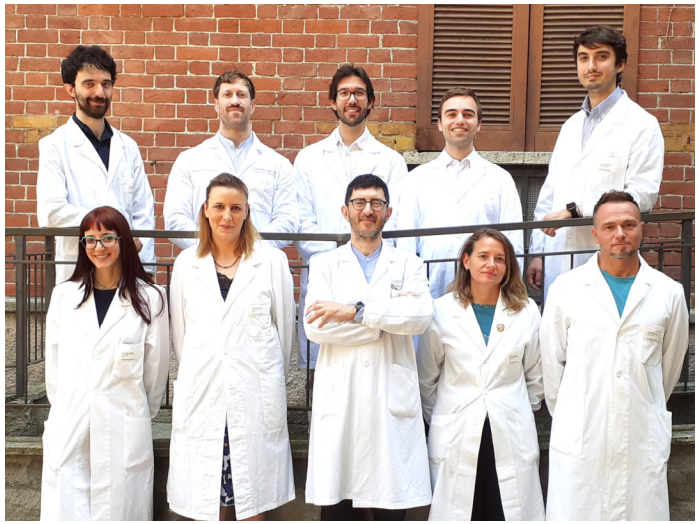

Grazie per l'attenzione!

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Fresco Parkinson Institute

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