

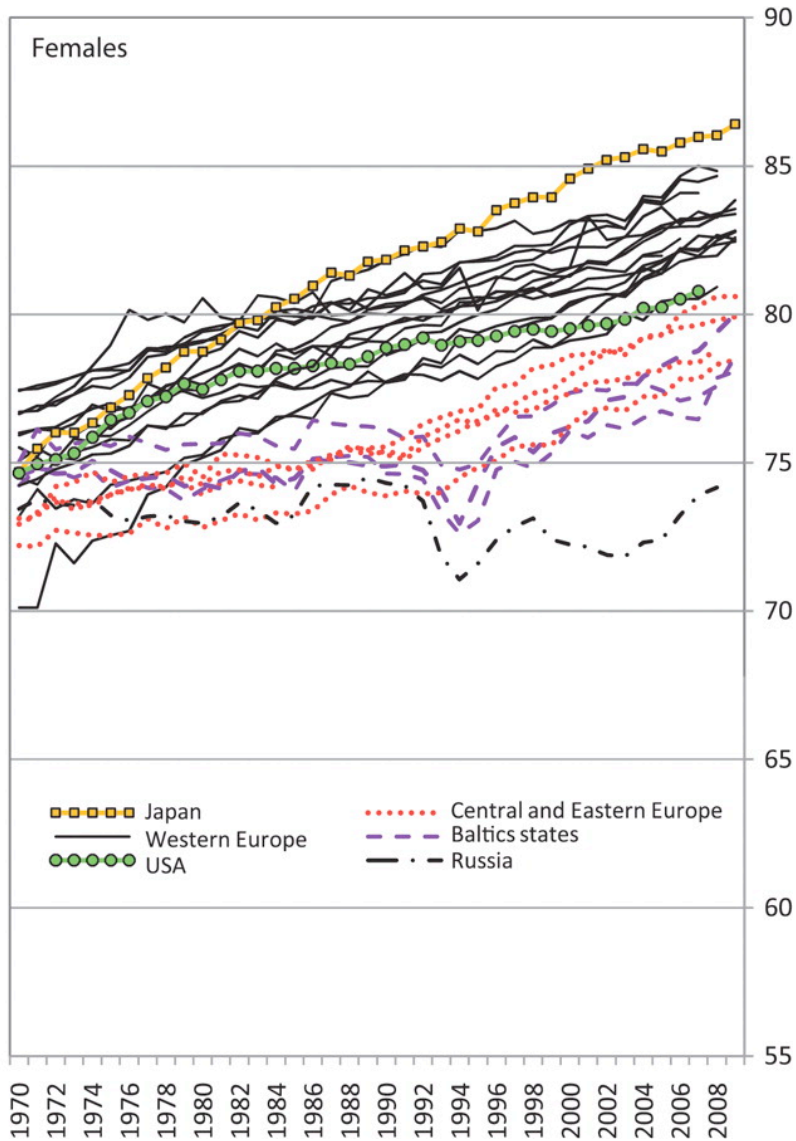
Genetic Parkinson's – studying the few to treat the many



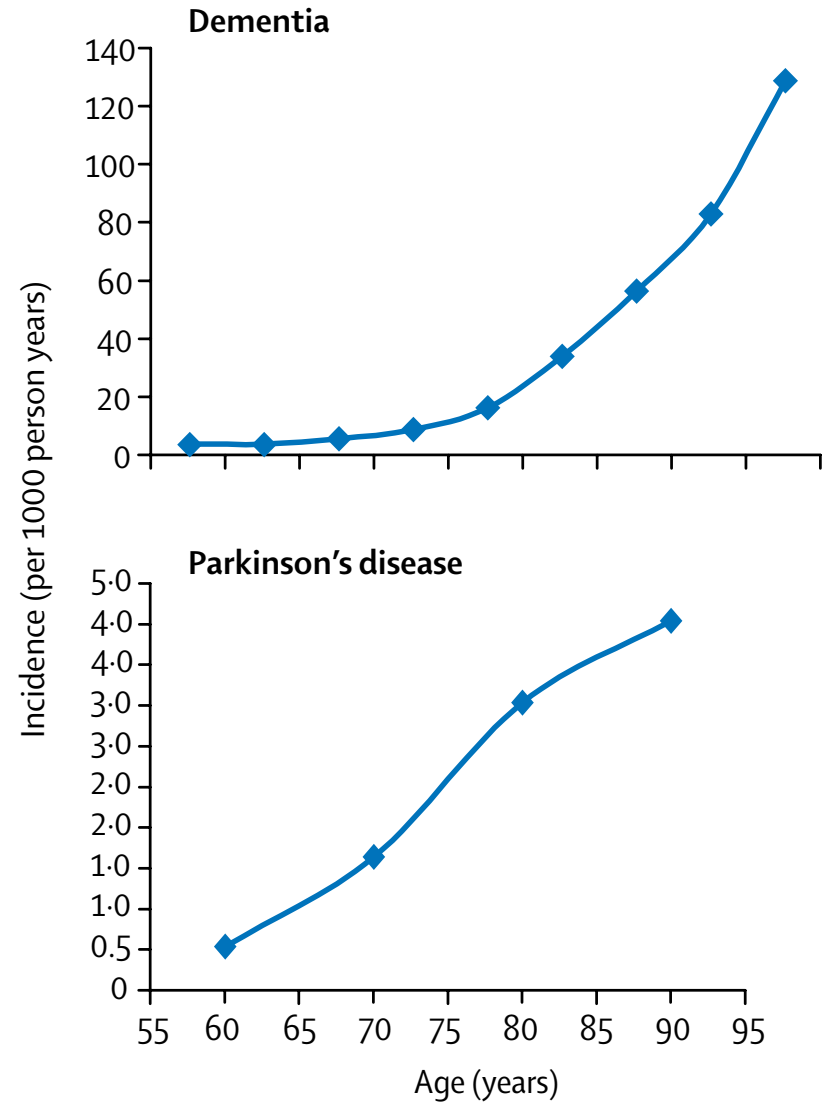
THE MICHAEL J. FOX FOUNDATION FOR
PARKINSON'S
RESEARCH

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MRC Protein Phosphorylation Unit,
University of Dundee

Life Expectancy soaring: the rise and rise of degenerative brain disorders



Leon, I J Epidemiol 2009



Rotterdam study, Lancet Neuro 2006

Neurodegenerative disease: scale of the problem



	Men	Women	Total
Dementia	1 550 000	2 980 000	4 530 000 ←
Stroke	1 620 000	1 690 000	3 310 000
Macular degeneration	720 000	1 210 000	1 930 000
Parkinson's disease	490 000	660 000	1 150 000 ←

Table: Absolute number of neurological diseases in the elderly population of the European Union^{8,9}

Launer & Hofman, Neurology 2000



~127,000 cases in UK



~10,000 cases in Scotland

Parkinson's UK, 2012

Parkinson's disease is a neurodegenerative movement disorder



Frank Netter

Motor

Tremor

Bradykinesia

Rigidity

Non-motor

Depression

Dementia

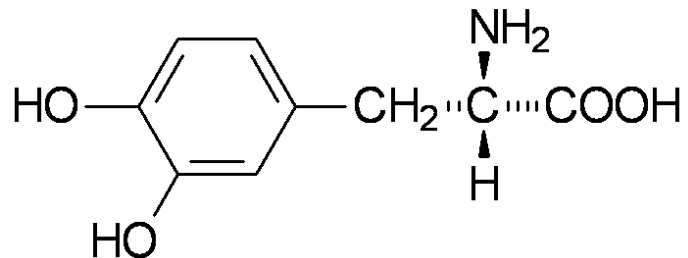
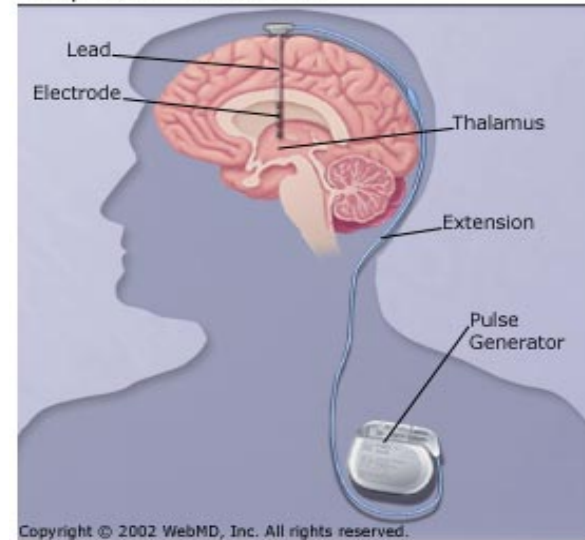
Constipation

Anosmia

Parkinson's remains an incurable disorder

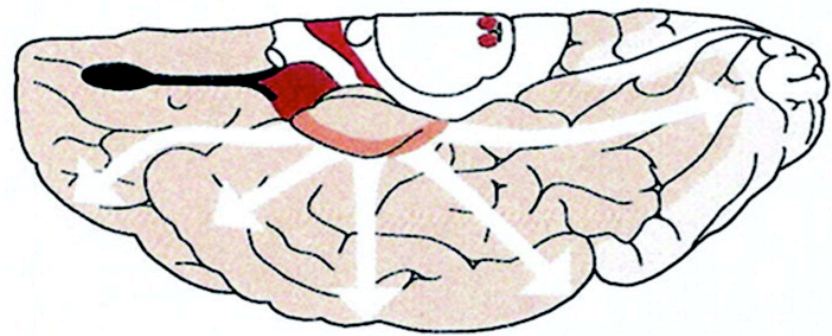
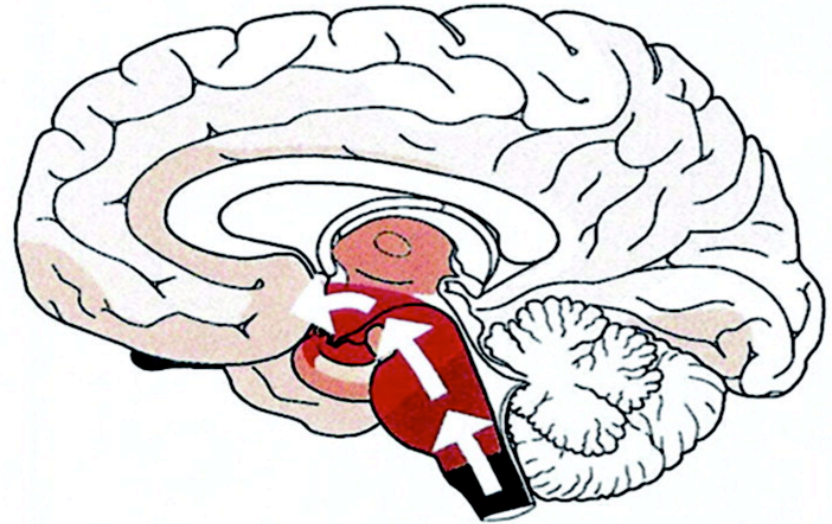
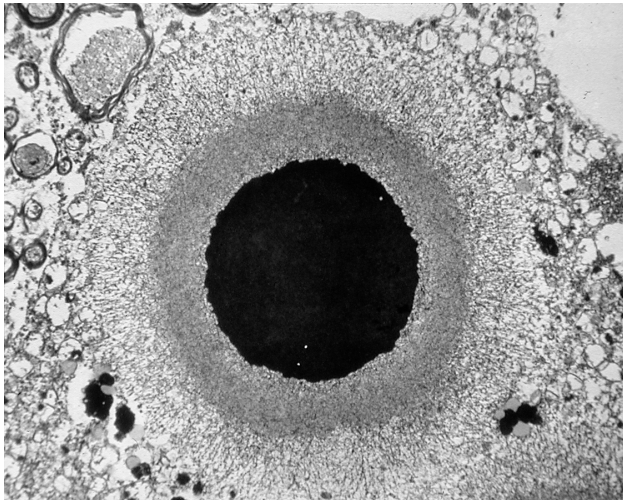
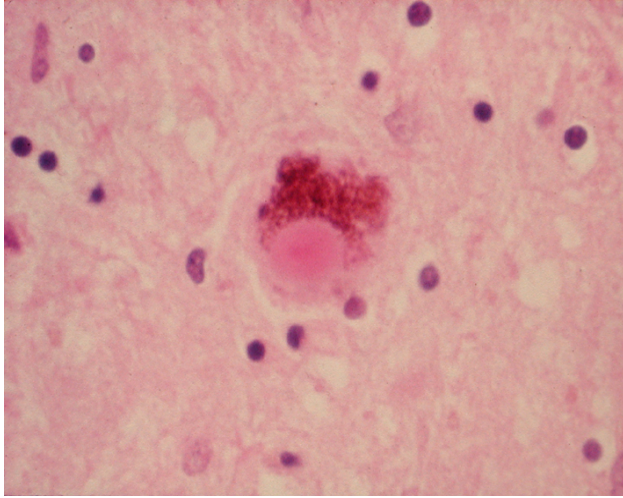


Deep Brain Stimulation



Chemical structure of 3-(3',4'-dihydroxyphenyl)-L-alanine (L-DOPA).

Pathology of Parkinson's



Sir William Gowers FRS

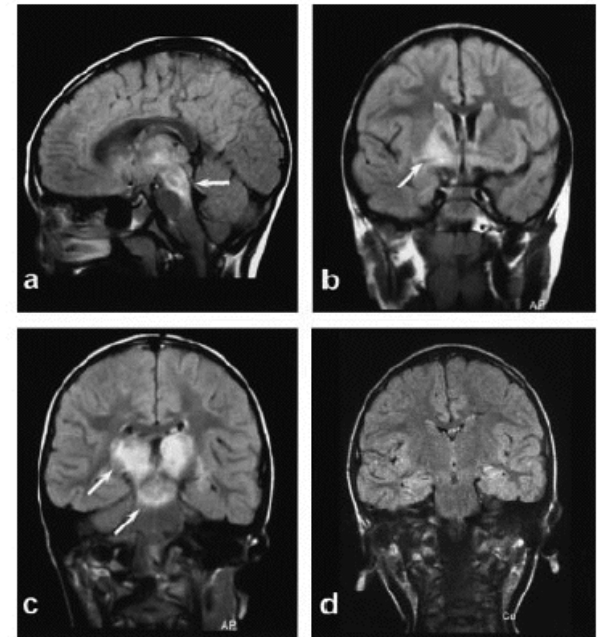
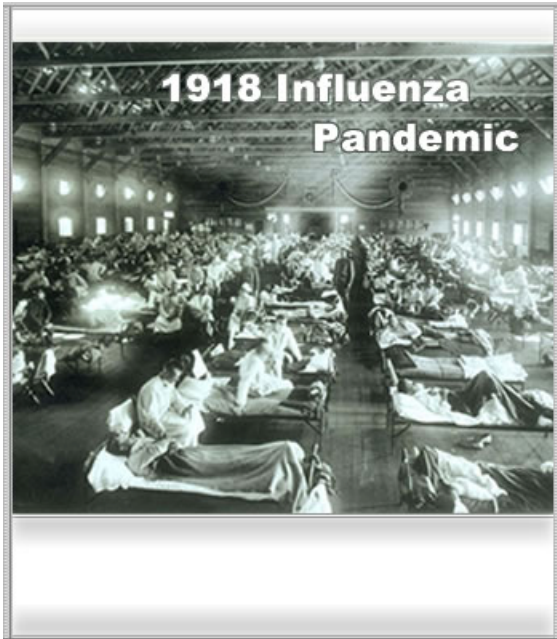
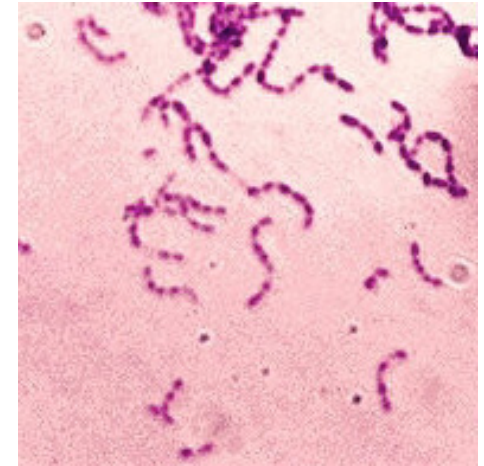
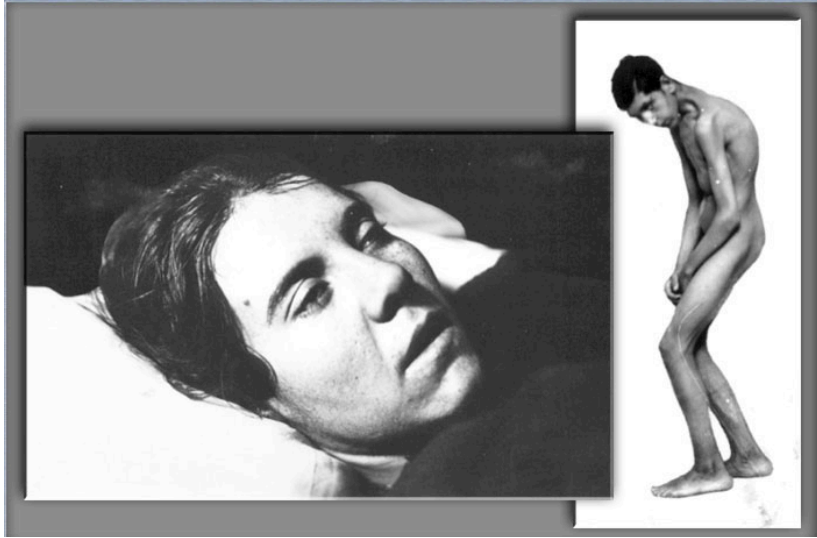


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Staff Group 1886

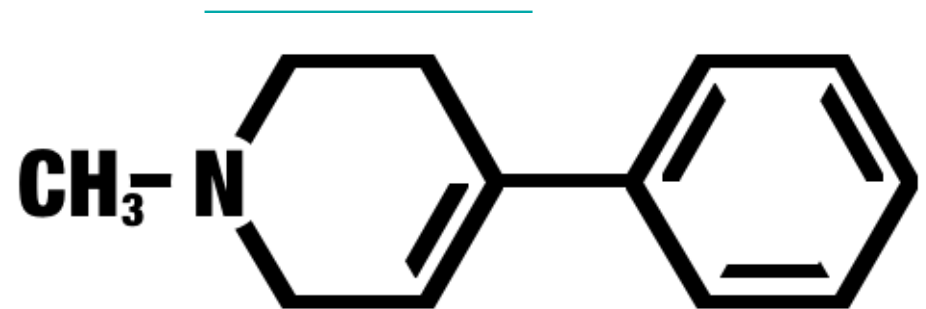
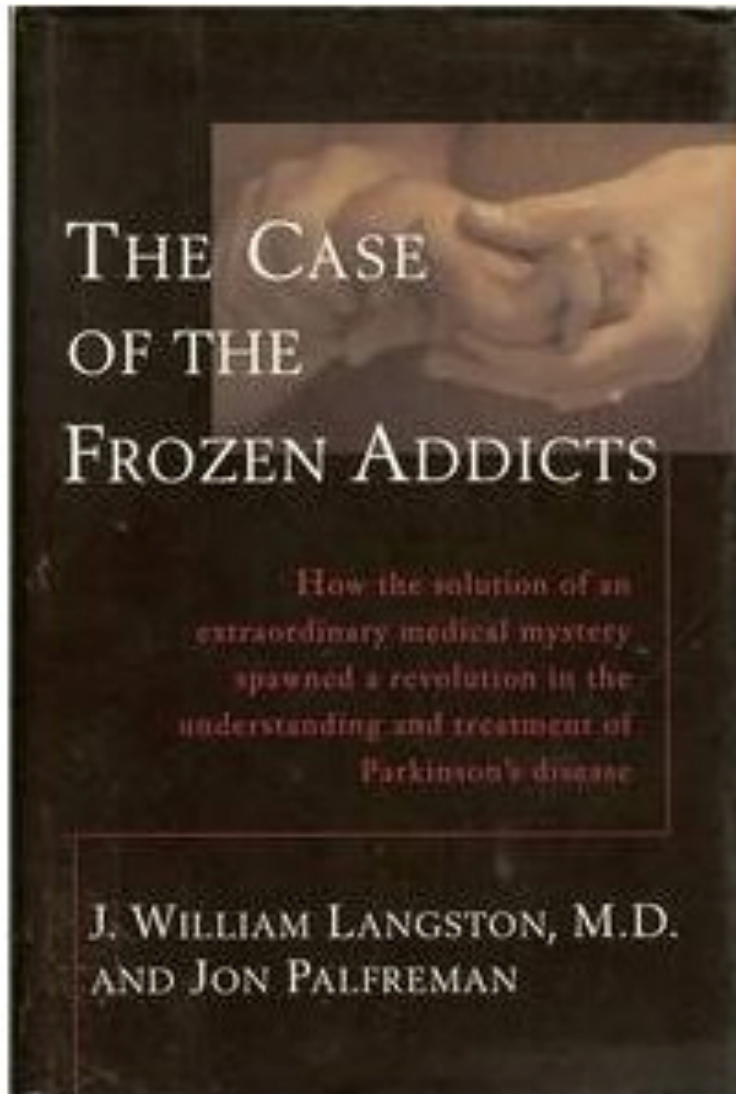
*Back row, left to right: Horsley, Beevor, Cumerbatch, Buzzard, Burdendall Carter, Ormerod, Adams.
Front row: Marcus Gunn, Bastian, Jackson, Ramskill, Radcliffe, Gowers, Semon, Ferrier.*

Encephalitis Lethargica



Twin studies suggest that Parkinson's not very heritable

	Concordant Pairs		Discordant Pairs		Pairwise Concordance		
	MZ	DZ	MZ	DZ	MZ	DZ	Relative Risk (95% CI)
Overall	11 ⁴	10 ¹	60	80	0.155	0.111	1.39 (0.63-3.10)
First twin diagnosed ≤50 y	4 ²	2 ⁰	0	10	1.00	0.167	6.00 (1.69-21.3)
First twin diagnosed >50 y	7 ²	8 ¹	58	68	0.108	0.105	1.02 (0.39-2.67)

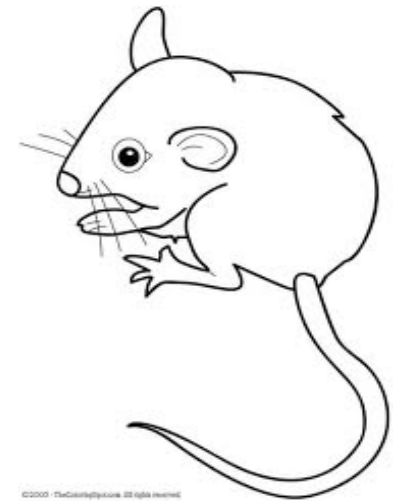
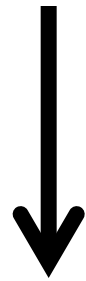


Therapies developed based on toxin models

Environmental trigger(s)

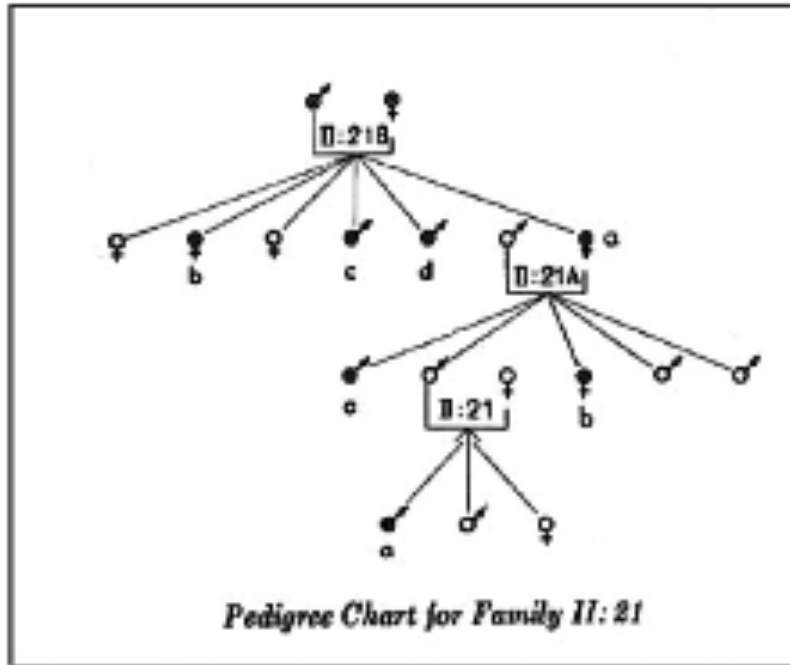


Toxin



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Early genetic studies

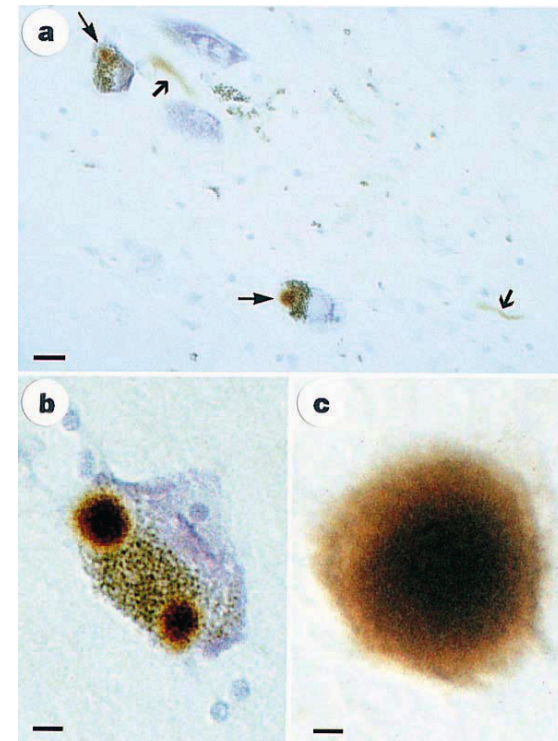
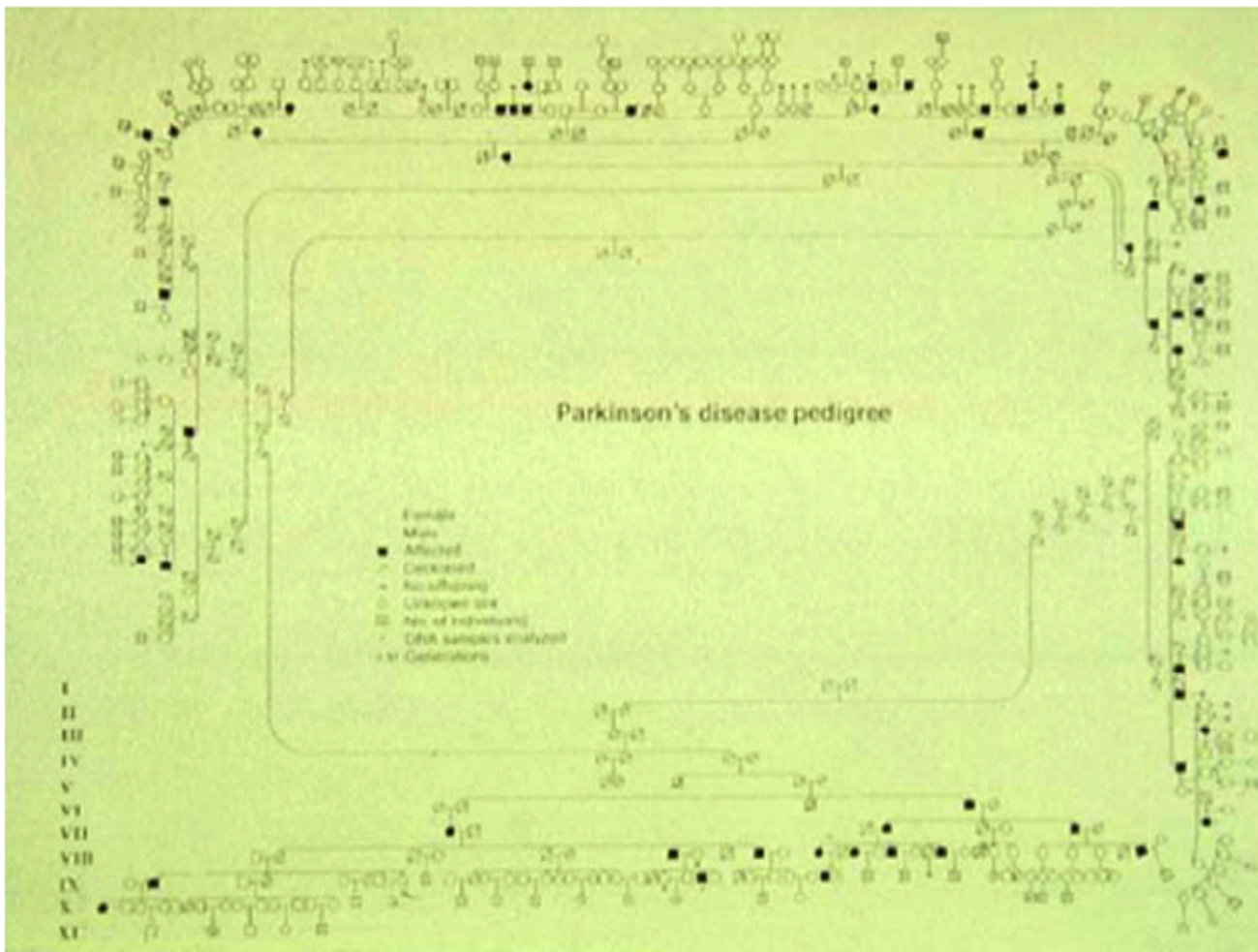


Mjones 1949

**Found 41% of 194 PD patients reported a positive family history,
Concluded that PD could be an autosomal dominant trait with
high penetrance.**

Parkinson's disease genetic loci

LOCUS	MODE	TYPE	GENE	FUNCTION
PARK1/4	AD	LO/EOPD	α -synuclein	Unknown

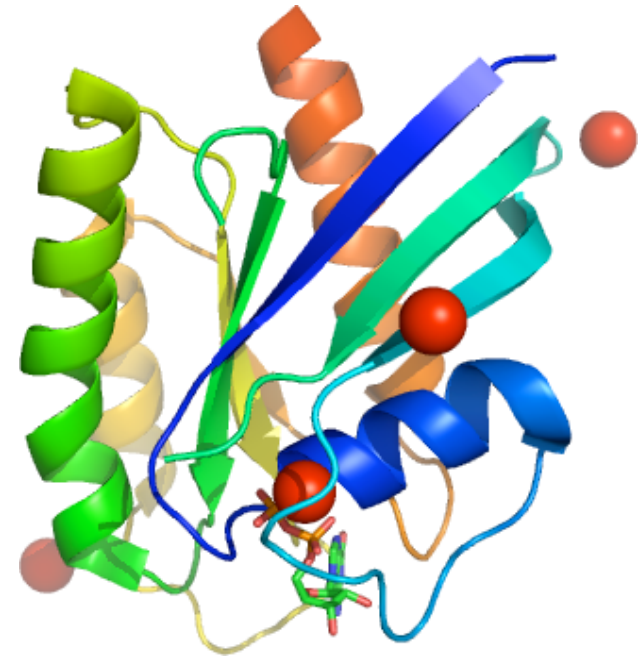
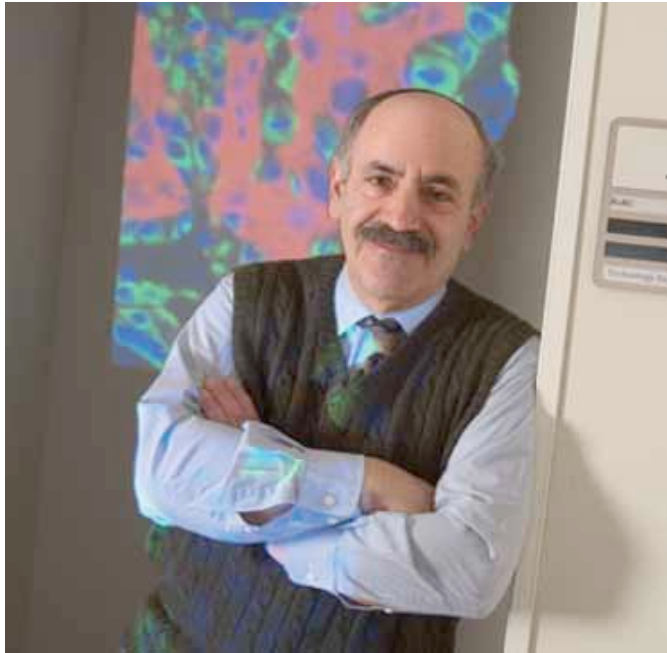


Parkinson's disease genetic loci

LOCUS	MODE	TYPE	GENE	FUNCTION
PARK1/4	AD	LO/EOPD	α -synuclein	Unknown
PARK2	AR	EOPD	Parkin	Ubiquitin ligase
PARK3	AD	LOPD	Unknown	
PARK5	AD	LOPD	UCH-L1	DUB
PARK6	AR	EOPD	PINK1	Kinase
PARK7	AR	EOPD	DJ-1	Oxidative chaperone
PARK8	AD	LOPD	LRRK2	Kinase
PARK9	AR	EOPD*	ATP13A2	ATPase
PARK10	Complex	LOPD	Unknown	
PARK11	Complex	LOPD	<i>G/GYF2</i> (controversial)	
PARK12	X-linked	LOPD	Unknown	
PARK13	AD	LOPD	HtrA2/Omi	Serine protease
PARK14	AR	EOPD*	PLA2G6	Phospholipase A2
PARK15	AR	EOPD*	FBXO7	F Box protein
PARK16	Complex	LOPD	Unknown	
PARK17	Complex	LOPD	GAK	Kinase
PARK18	Complex	LOPD	HLA	immune recognition
PARK19	AD	LOPD	VPS35	endosomal-Golgi trafficking
PARK20	AD	LOPD	EIF4G1	mRNA translation-initiation

* Complex syndrome

Cancer genetics – 30 years ago

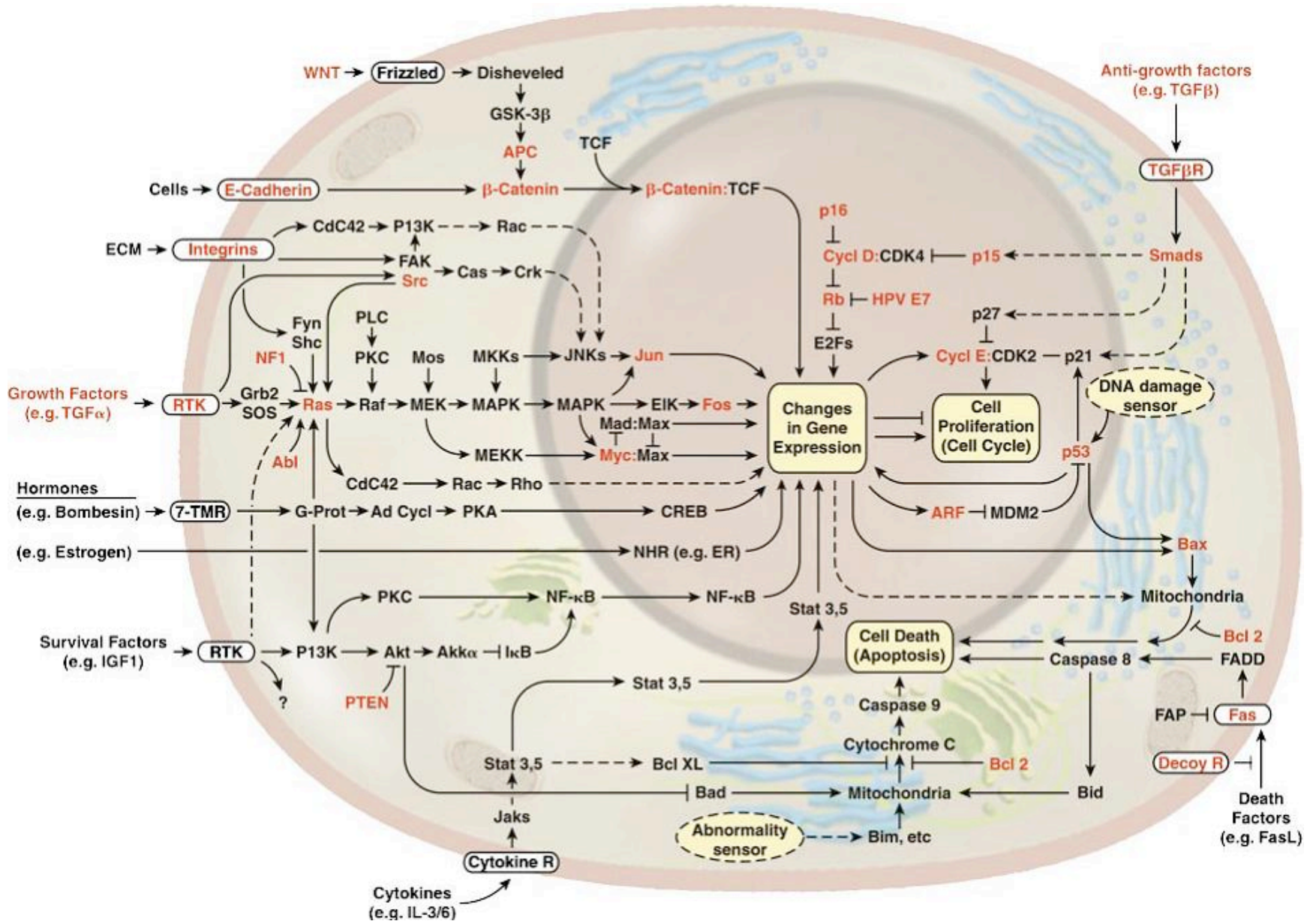


Robert Weinberg discovered first human proto-oncogene, Ras

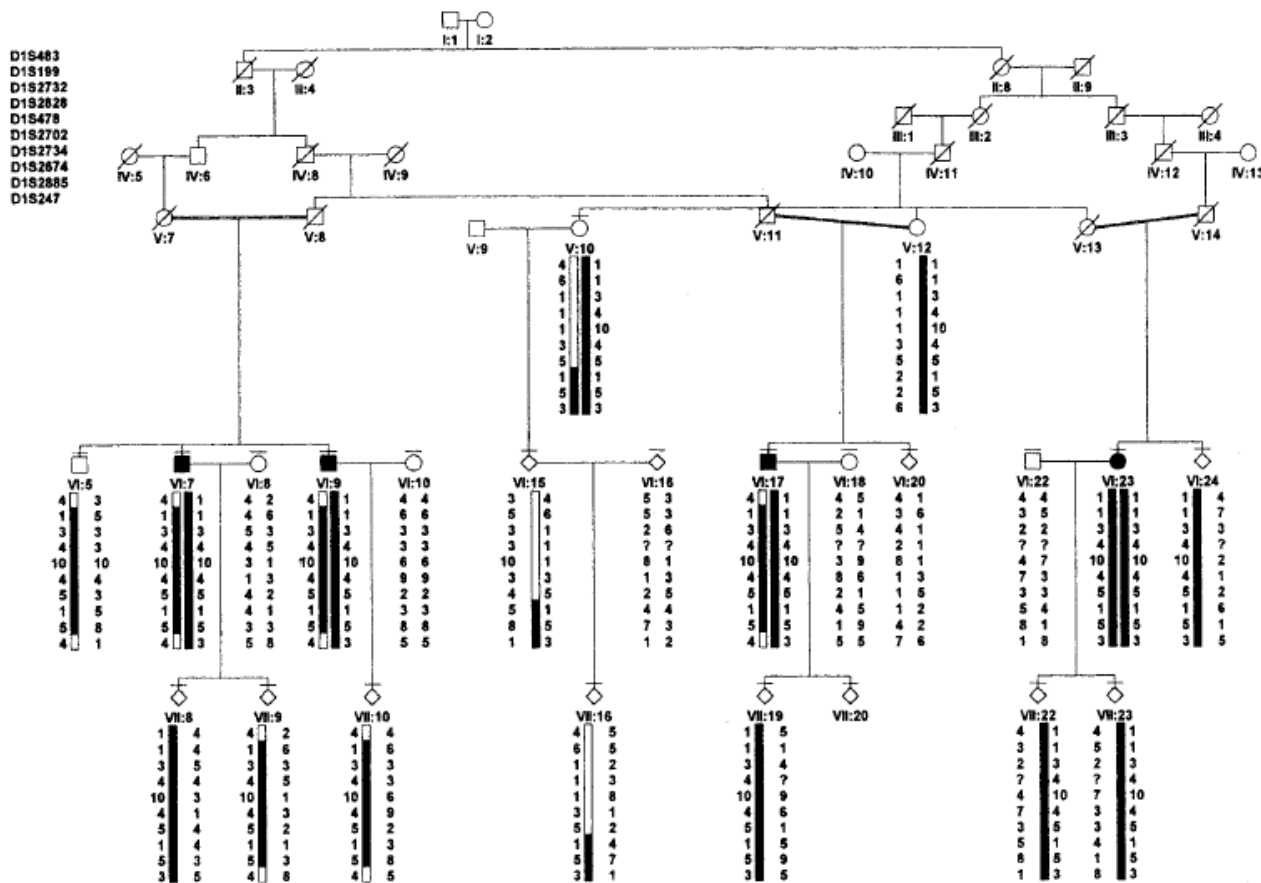
An oncogene is a gene that has the potential to cause cancer – often mutated or expressed at high levels

Ras mutations are found in a large number of human cancers

Ras signaling network in cells



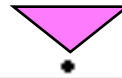
“Marsala Kindred”



Autosomal recessive PD
Early-onset (age at onset 32-47)
Slowly progressive
Sustained response to Levodopa

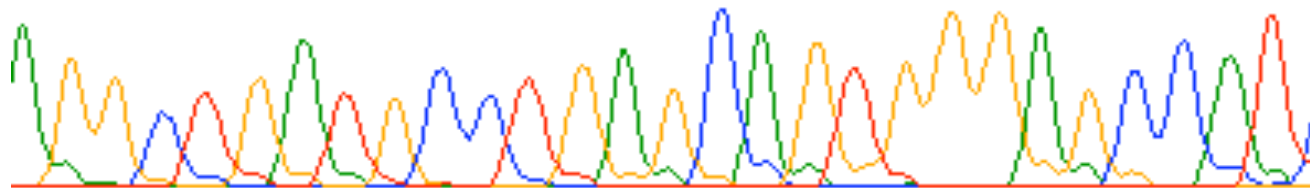
Homozygous Mutations in PTEN-induced kinase 1

Exon 7 W437OPA



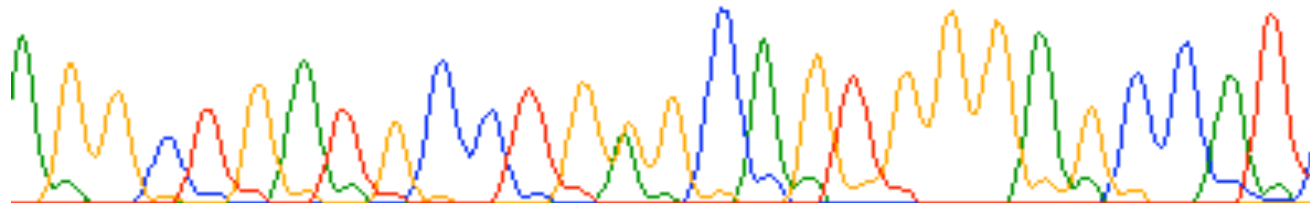
A G G C T G A T G C C T G A G C A G T G G G A G C C A T I

Homo-
zygote



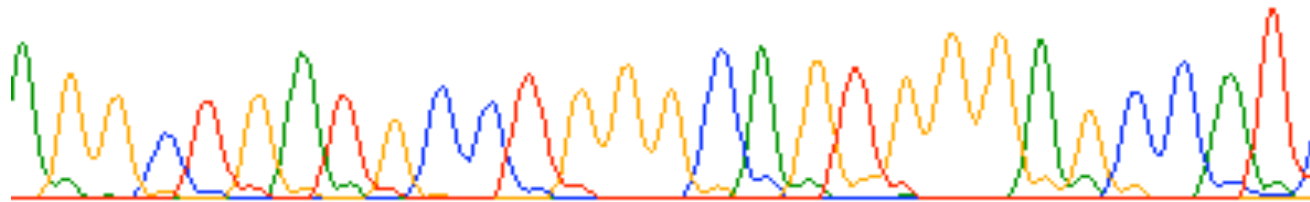
A G G C T G A T G C C T G G G C A G T G G G A G C C A T I

Hetero-
zygote

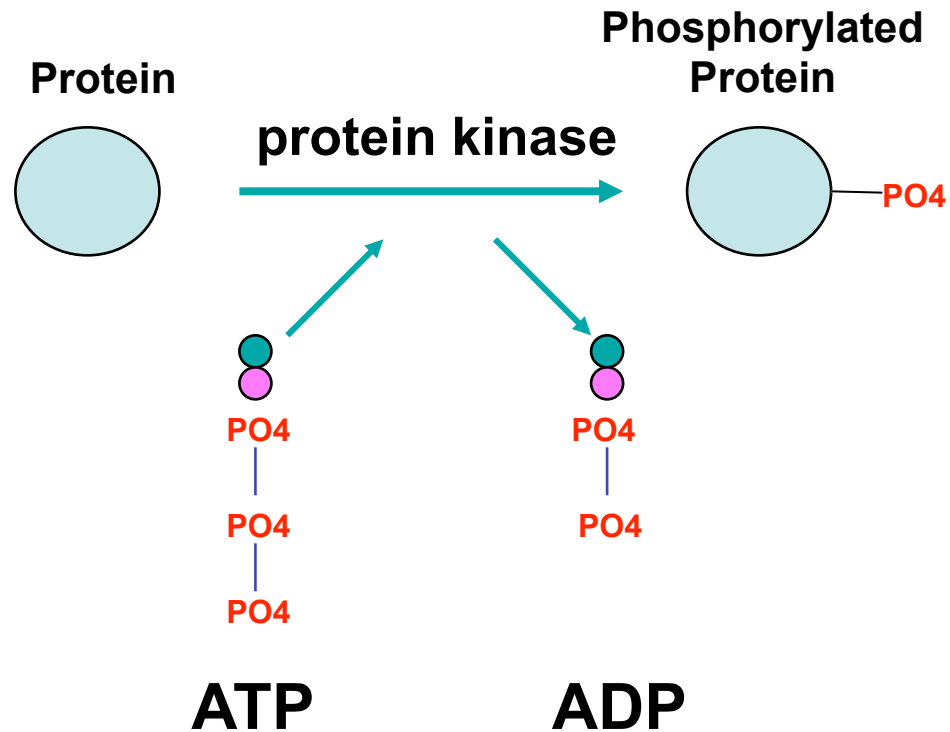


A G G C T G A T G C C T G G G C A G T G G G A G C C A T I

Wild
type



Protein Phosphorylation



Proof of concept in CML

