Genetics of Movement Disorders

- Chorea
-
-
- Dystonia

PD

PD plus

- Myoclonus, Tremor

REVIEW

"Atypical" Atypical Parkinsonism: New Genetic Conditions Presenting With Features of Progressive Supranuclear Palsy, Corticobasal Degeneration, or Multiple System Atrophy—A Diagnostic Guide

Maria Stamelou, MD, PhD,[1,2,3*] Niall P. Quinn, MD,[1] and Kailash P. Bhatia, FRCP[1]

Genetic causes of chorea: HD-like disorders (Aka HD phenocopies)

Characterised by variable presentations of:

- Chorea, dystonia, parkinsonism
- Cognitive impairment (frontal-subcortical)
- Psychiatric disturbance

Genetic HD-like disorders

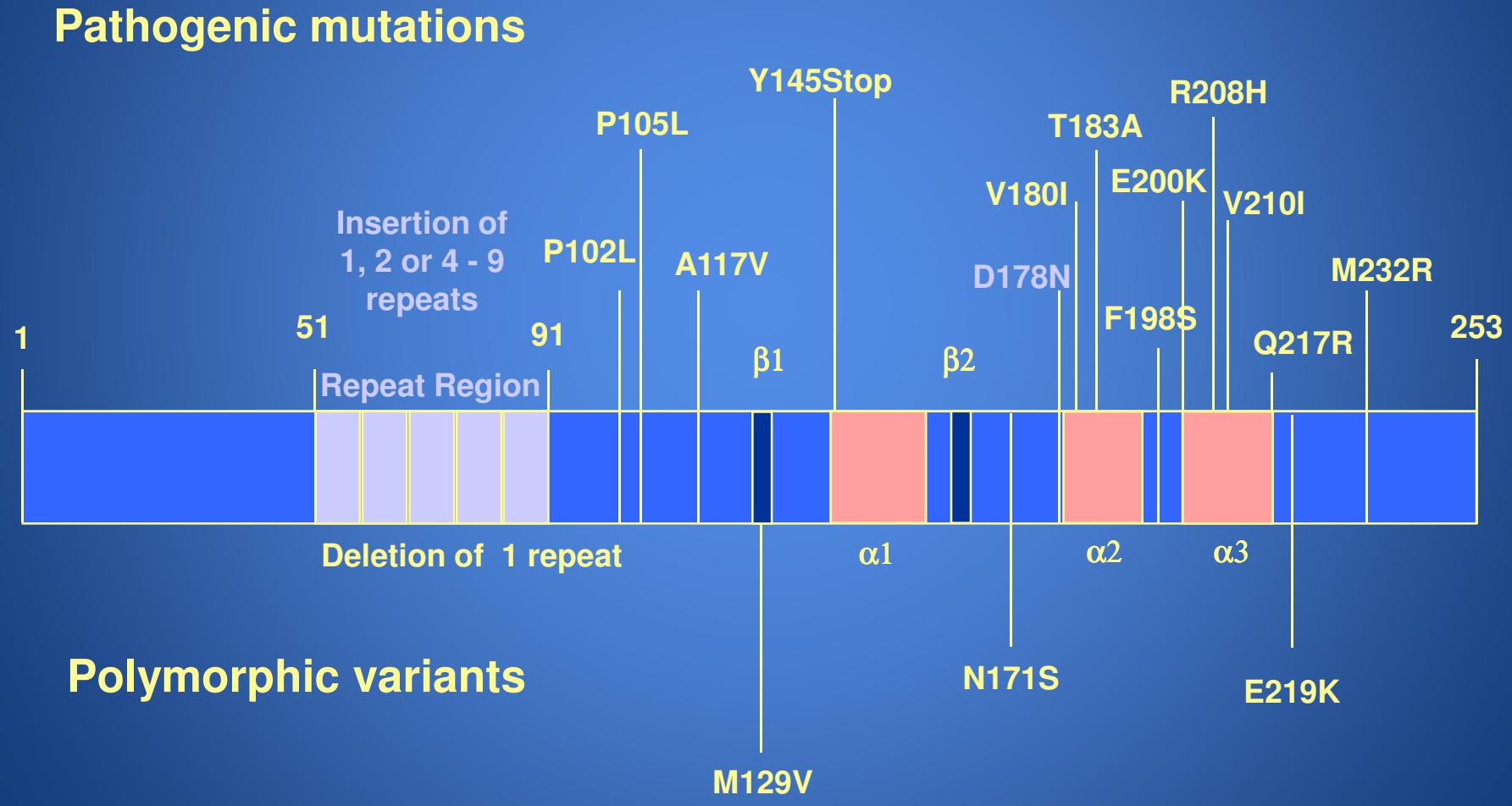
- **HDL1 Inherited prion disease** (includes HDL1)
- **HDL2** (triplet repeat expansion in junctophilin-3 gene)
- ~~**HDL3** (1 family; causative mutation not known)~~
- **SCA17** *aka* HDL4 (triplet repeat expansion in *TBP*)
- **SCA1-3** (triplet repeat expansions)
- **Dentatorubro-pallidoluysian atrophy** (*DRPLA*)
- **Neuroacanthocytosis (choreo-acanthocytosis** (chorein) and **MacLeod's Syndrome** (XK gene – X chromosome)
- **Neuroferritinopathy** (ferritin light chain)
- **NBIA/PKAN** (*PANK2* mutations)

Prion diseases

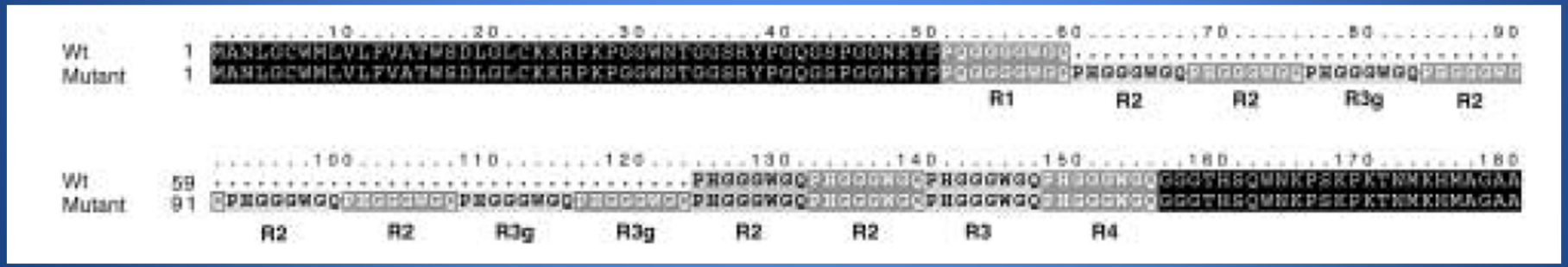
- HDL1
- Inherited prion diseases may present with chorea in addition to ataxia, parkinsonism, myoclonus

- HDL1 is caused by an octapeptide repeat insertion in PRNP (prion protein gene humans)

Polymorphisms and pathogenic mutations in the human prion protein gene



- Sporadic CJD: late-onset
- PrP repeats tend to present younger



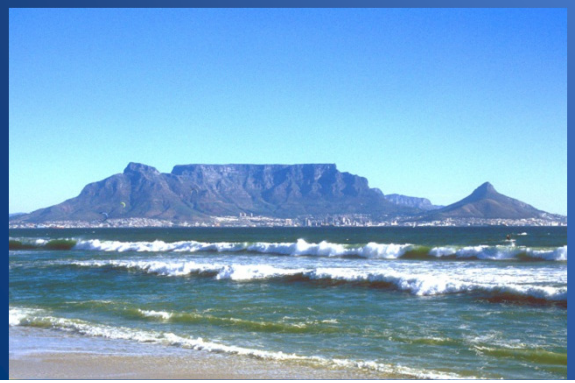
Wild-type human PrP contains one PQGGGGWGQ nonapeptide (encoded by R1) and four PHGGGWGQ octapeptides (encoded by R2-R4), such that the normal sequence is R1-R2-R2-R3-R4. The mutant allele has eight extra PHGGGWGQ repeats: R1-R2-R2-R3g-R2-R2-R2-R3g-R3g-R2-R2-R3-R4.

HUNTINGTON DISEASE GENETICS

- **Huntingtin gene (IT15/HD)**
  - **Chromosome 4p16.3**
  - **>99% of cases worldwide**

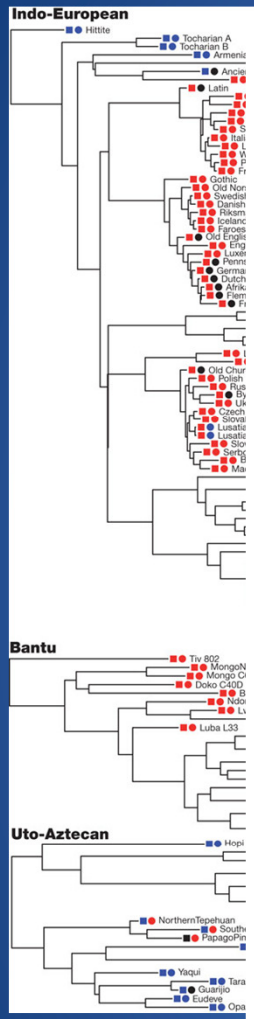
Epidemiology of HDL2

- Most families of definite or probable African ancestry
- HDL2 accounts for ~1% of all HD-negative cases tested in the USA
- “Frequency high in black South Africans and as common as HD”



ORIGIN OF HDL2 PREDISPOSING HAPLOTYPE

- HDL2 patients share extended haplotype
  - Strong evidence for founder effect
    - Single origin of mutation
    - Present in Africans & African-Americans
      - Old sub-Saharan African mutation
        - African slave trade to USA = 300 years


Indo-European
Hittite
Tocharian A
Tocharian B
Armeni
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Gothic
Old Nor
Swedish
Danish
Riksm
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Faroes
Old Engli
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Germa
Afrik
Flem
Old Chur
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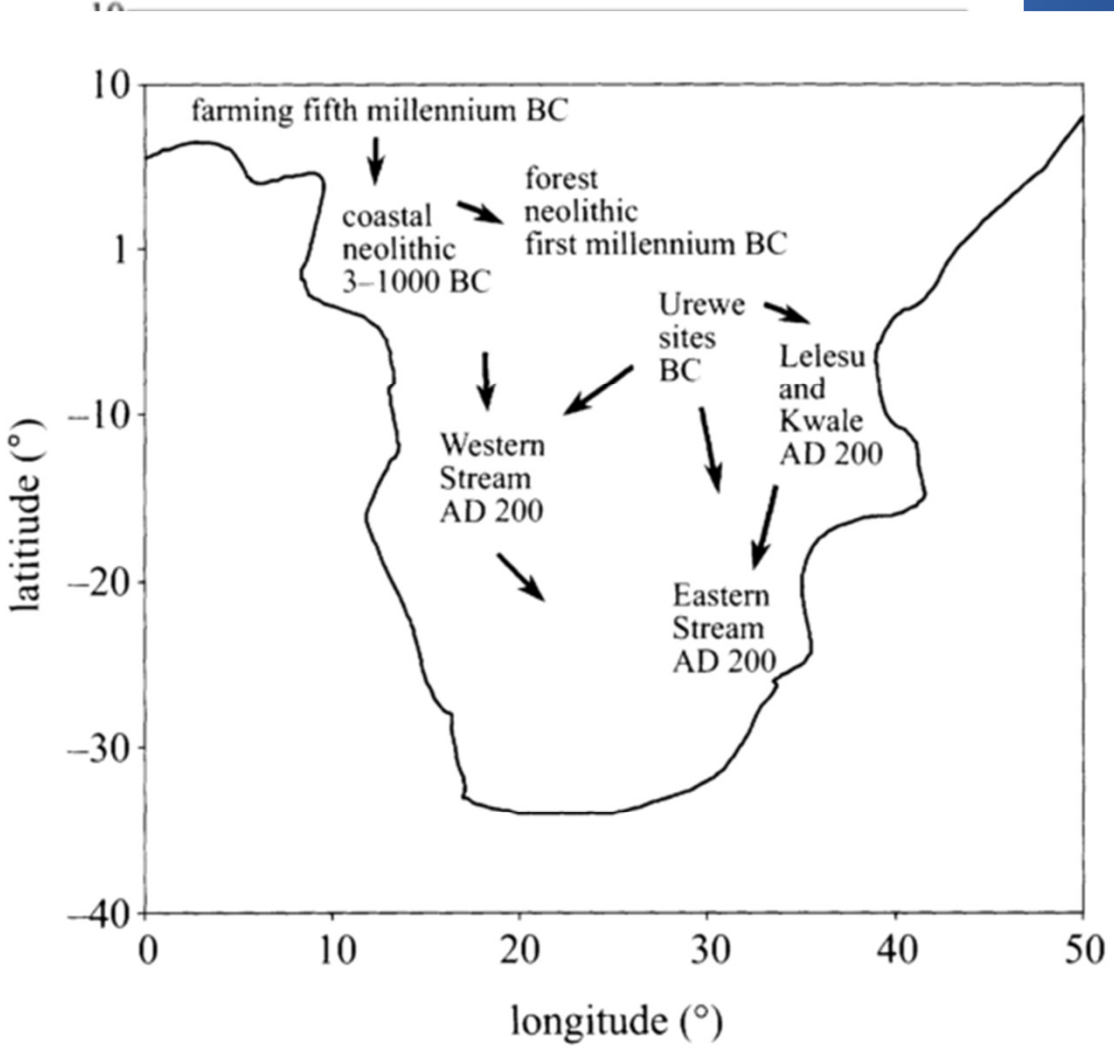
NorthernTepehuan
South
PapagoPim
Yaqui
Tara
Guarijio
Eudeve
Opa


farming fifth millennium BC
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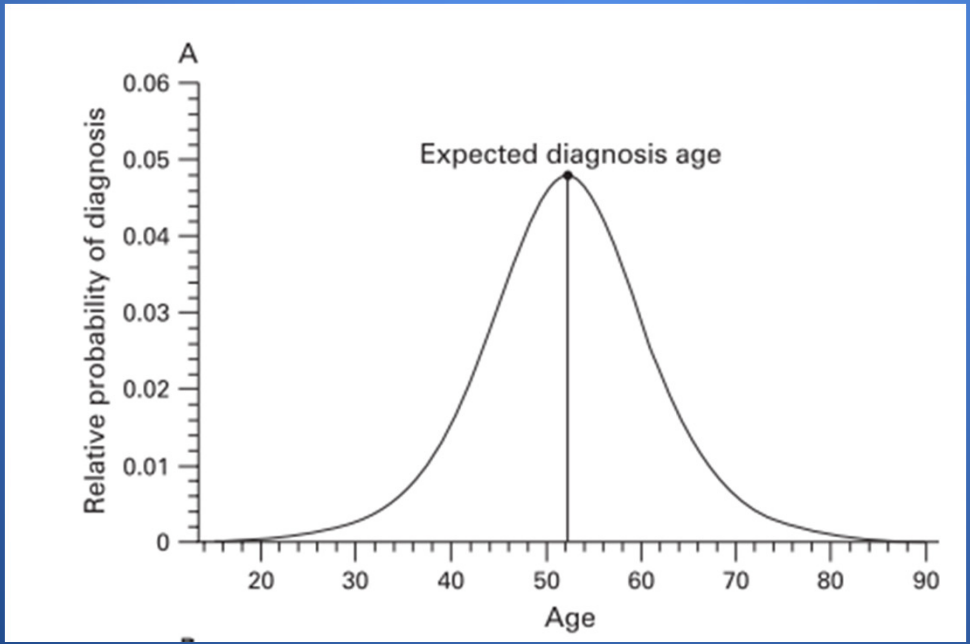
+ West Bantu, equatorial
▲ West Savannah
△ East Bantu, East Africa
× East Bantu, southeast

Detection of Huntington's disease decades before diagnosis: the Predict-HD study

J S Paulsen,[1] D R Langbehn,[1] J C Stout,[2] E Aylward,[3] C A Ross,[4] M Nance,[5] M Guttman,[6] S Johnson,[2] M MacDonald,[7] L J Beglinger,[1] K Duff,[1] E Kayson,[8] K Biglan,[8] I Shoulson,[8] D Oakes,[9] M Hayden,[10] The Predict-HD Investigators and Coordinators of the Huntington Study Group[11]

- Predict time of diagnosis by age and CAG repeat length: 440 patients



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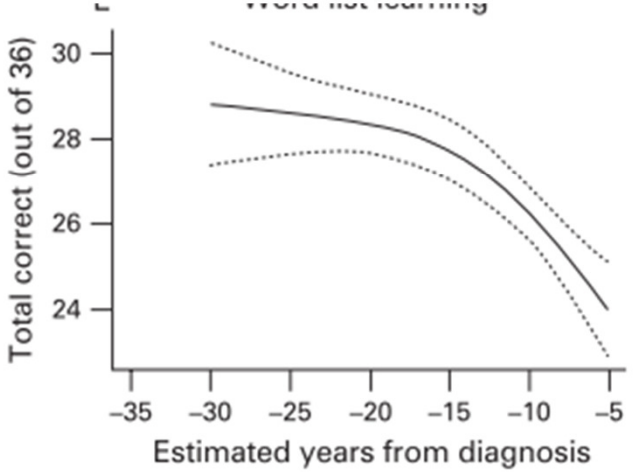
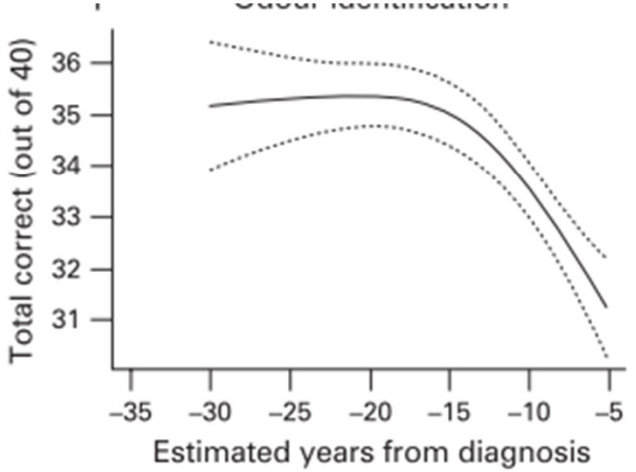
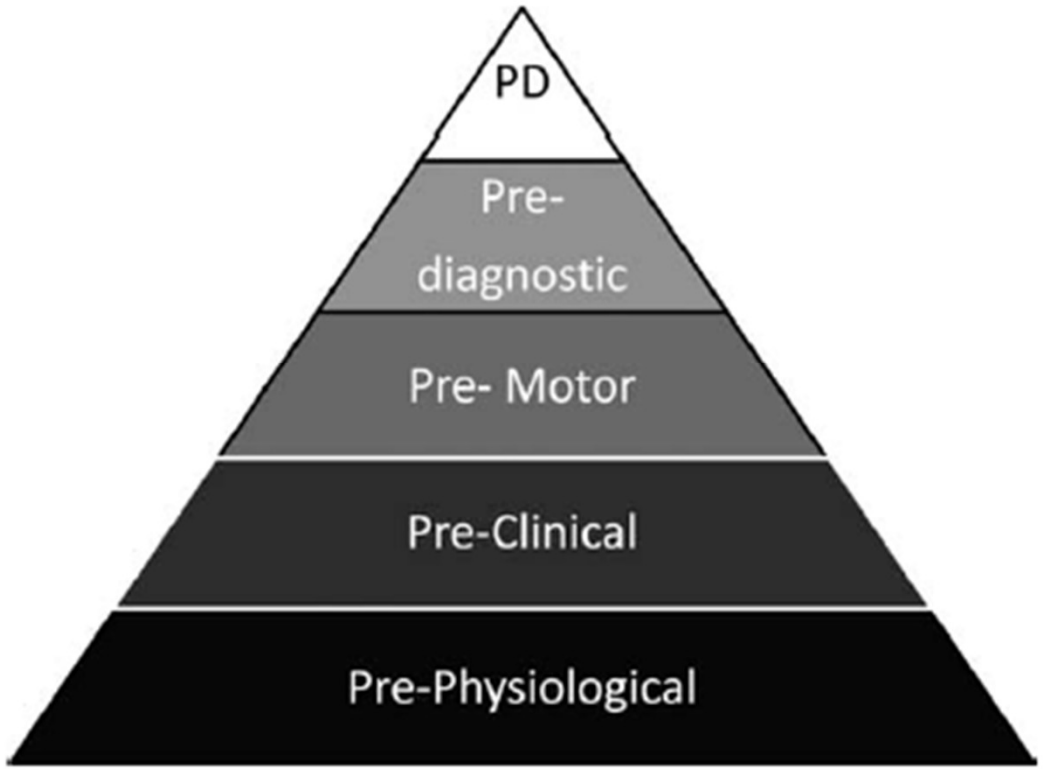





PD
Pre-
diagnostic
Pre- Motor
Pre-Clinical
Pre-Physiological

- CAG repeats translate into a polyglutamine (polyQ) stretch in the amino terminus of the huntingtin (htt) protein.
- Unusually long CAG stretches (>50)
  - juvenile HD (JHD)
  - more widespread pathology.

a | Diagram representing huntingtin protein. Amino-acid numbering is for the human sequence (accession number NP 002102). A stretch of glutamine (Q) residues near the N terminus (23Q) is expanded (polyQ) in individuals affected with Huntington's disease. Unaffected individuals typically have 6–35 CAG repeats that encode the polyQ stretch, whereas individuals with the disease have >40 repeats. Cys214 is the site of palmitoylation in huntingtin. The N-terminal 548 amino acids of huntingtin are sufficient for binding huntingtin-interacting protein-14 (HIP14)[88]. **b** | Predicted membrane topology and domain structure of the huntingtin protein acyltransferase (PAT), HIP14 (also known as DHHC17)[21, 88]. HIP14 is a polytopic integral membrane protein with N-terminal ankyrin repeats and a DHHC–Cys-rich domain, which confers PAT activity[20, 21].

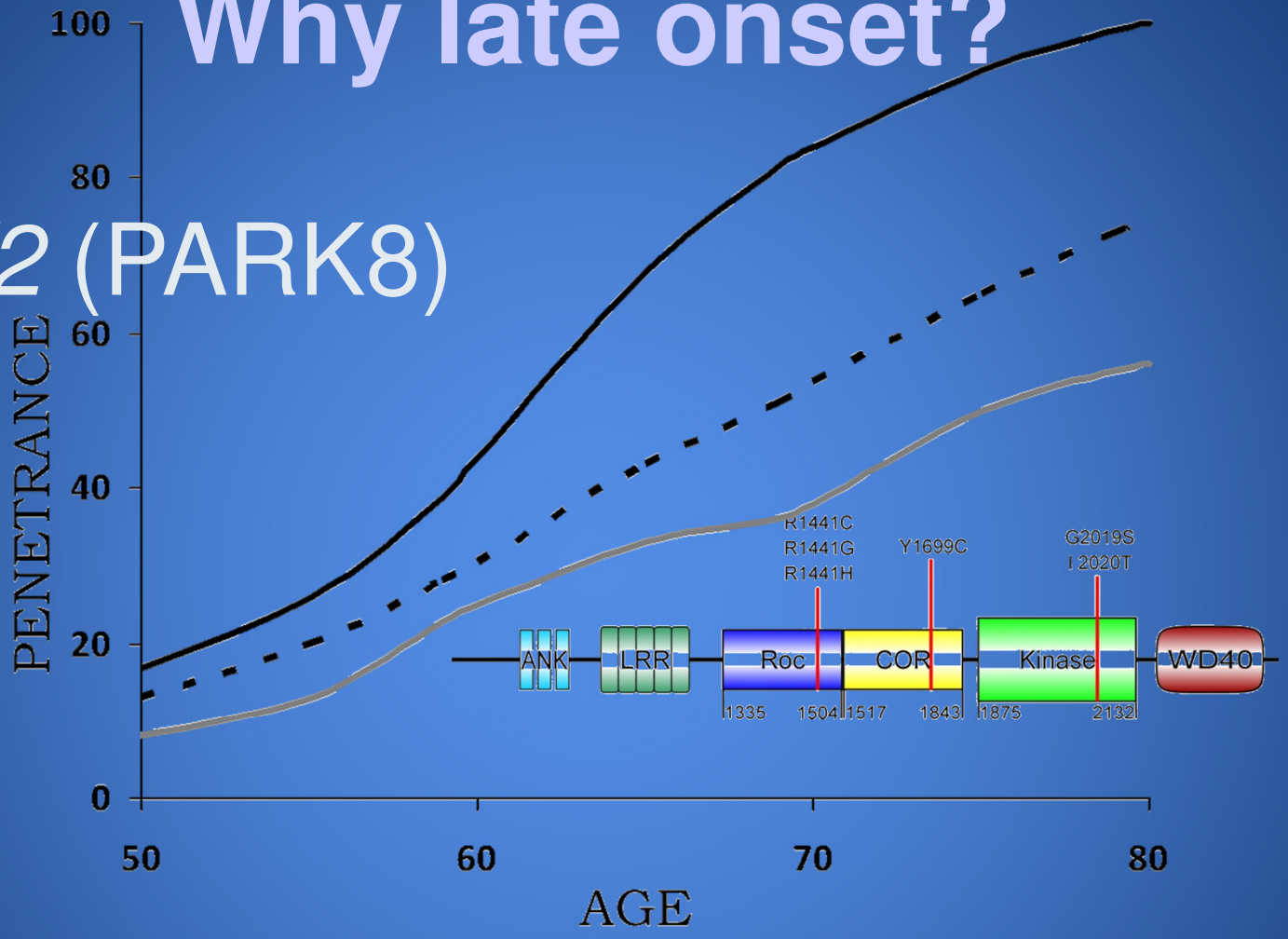
HD Genetics

- Spontaneous mutation rate?

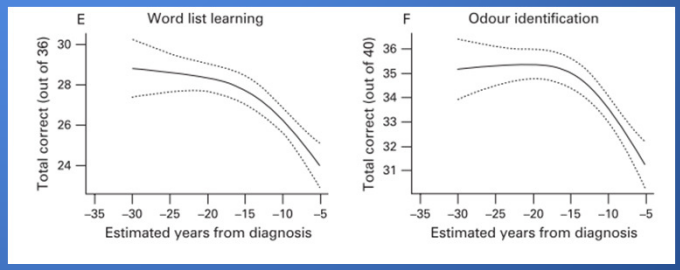
- 10%
- HD range: > 36 repeats
- Parents and/or siblings of all confirmed new mutations had an allele size between 27 and 35 CAG repeats.
- : “intermediate alleles”

Why late onset?

LRRK2 (PARK8)



- CNS has extra capacity before symptoms manifest
- Compensation: upregulation (certainly in PD)
- Use of symptoms to detect AAO is arbitrary



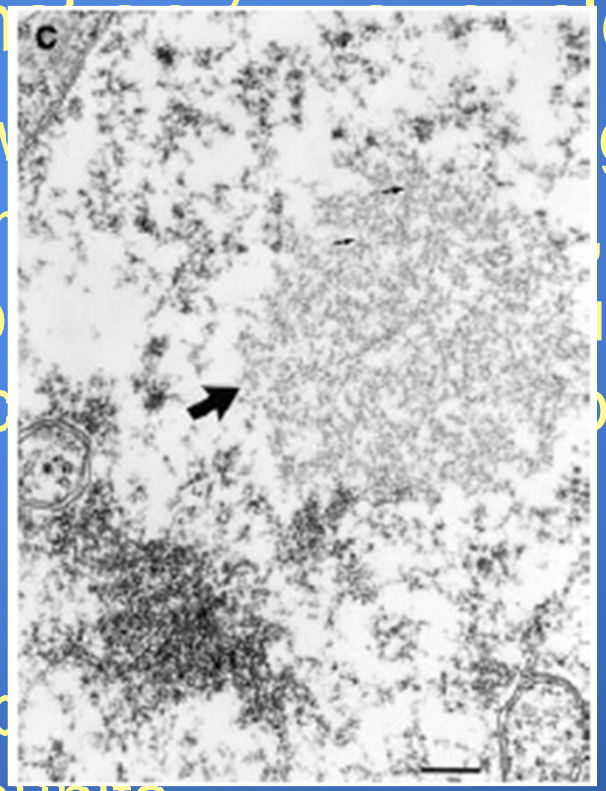
'one-hit' biochemical model

- Mutation imposes a mutant steady state on the neuron
- A single event randomly initiates cell death.

- HD mutation reduces the overall viability of cells, ↑ susceptible to apparently random stresses.
- Cumulative cell loss over time eventually uses up the nervous system's excess capacity/exceeds its mechanisms to cope with cell loss.
- Aging may further reduce the overall ability of cells to withstand random stresses

HD: proteopathy

- Accumulation of mutant protein, HTT
- Toxic gain of fun ein)
  - polyglutamines v gate, initially by formin , and oligomers, depo sion bodies in the nucleus, c cesses of neurons.
  - IBs contain chap proteasome subunits.



Pathogenesis:

- Functions of HTT not fully understood
- Cytoplasmic protein
- HTT important in regulation of vesicle transport and recycling via interactions with HAP's (Huntington-associated protein) and dynein.

HDL2

CLINICAL COMPARISON OF HD AND HDL2

- HDL2 two clinical presentations:
  - Probably reflect opposite ends of a spectrum

    - Weight loss and poor coordination, with fairly rapid development of rigidity, bradykinesia and dystonia
      - Similar to juvenile-onset Huntington
      - Chorea may be mild

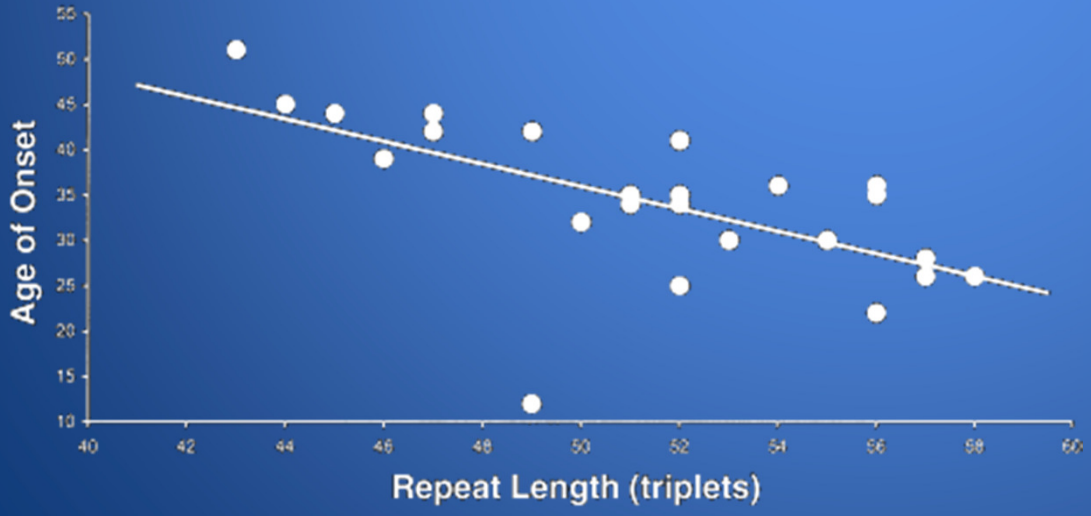
    - Chorea with a somewhat less rapidly progressive course.
      - Corresponds to typical HD
      - Onset is generally in the fifth decade and beyond

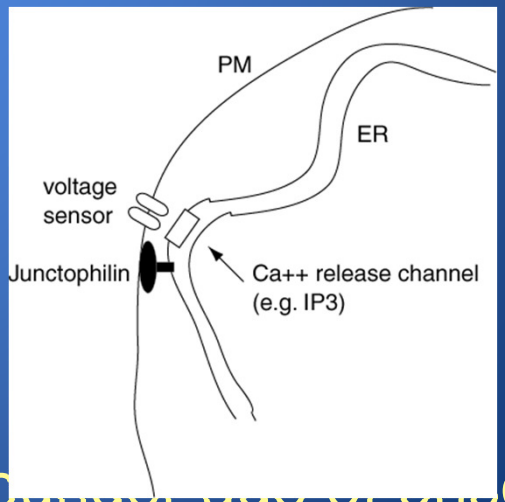
http://www.ncbi.nlm.nih.gov/books/NBK1529/


Segment 1
Patient 3
Movement Disorders
(c)2008 The Movement Disorder Society

Genetics of HDL2

- CAG/CTG repeat expansion in JPH3 (junctophilin 3) (Holmes *et al.* 2001)
- Normal 8-28 repeats, disease 40-59 repeats
  - Junctional complexes between the plasma membrane and endoplasmic/sarcoplasmic reticulum-mediate cross talk between cell surface and intracellular ion channels.





younger age of onset

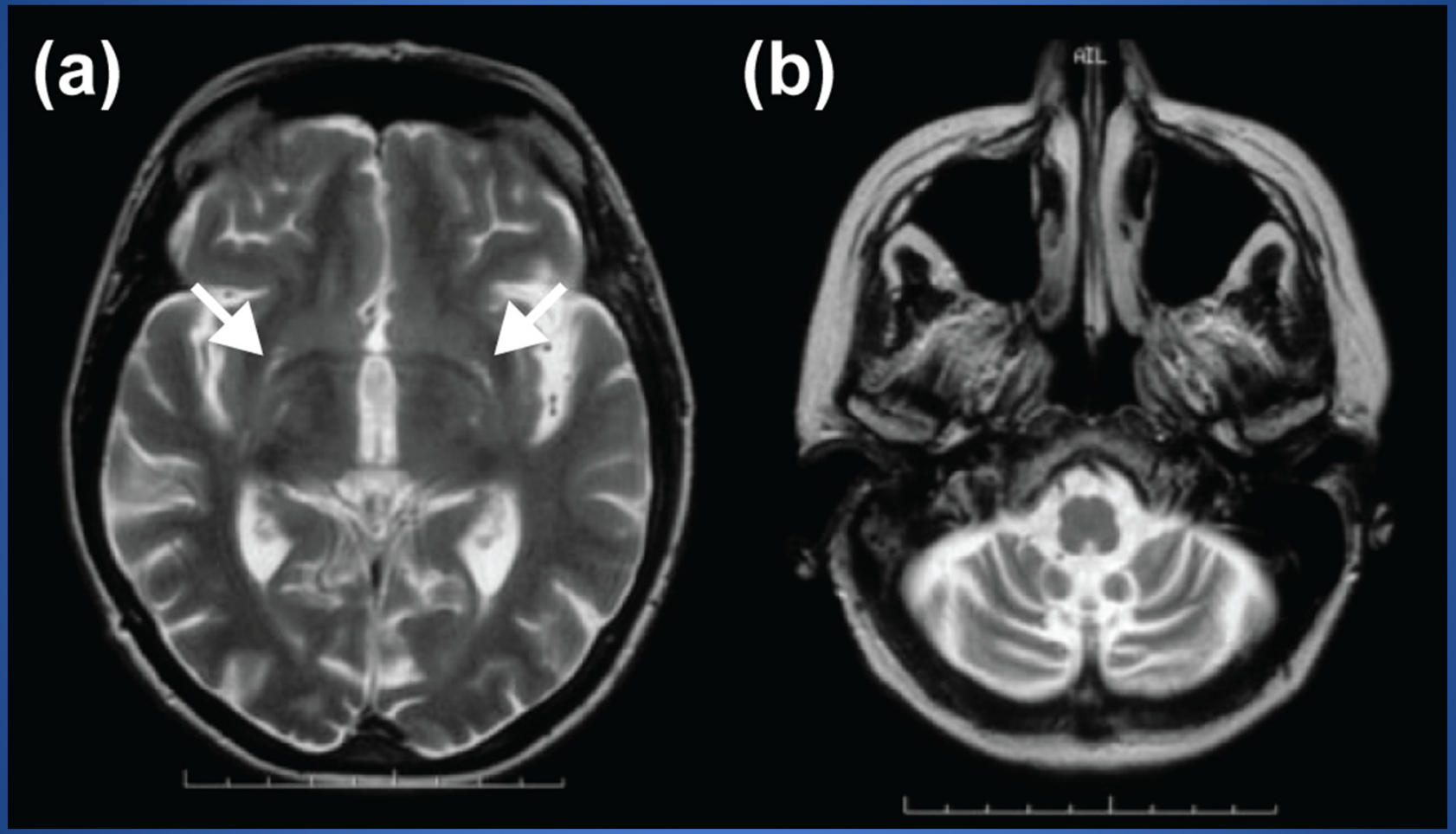
SCA 17

Spinocerebellar ataxia 17(HDL4)

- SCA17 presents with a variable combination of:
  - Ataxia (commonest typical presentation)
  - Dementia,psychiatric features, chorea
  - Dystonia
  - Oculomotor abnormalities common (like HD)
  - Epilepsy

Video 1 – HD-like SCA17 family (Schneider et al 2006)

T2-weighted axial brain MRI in SCA17

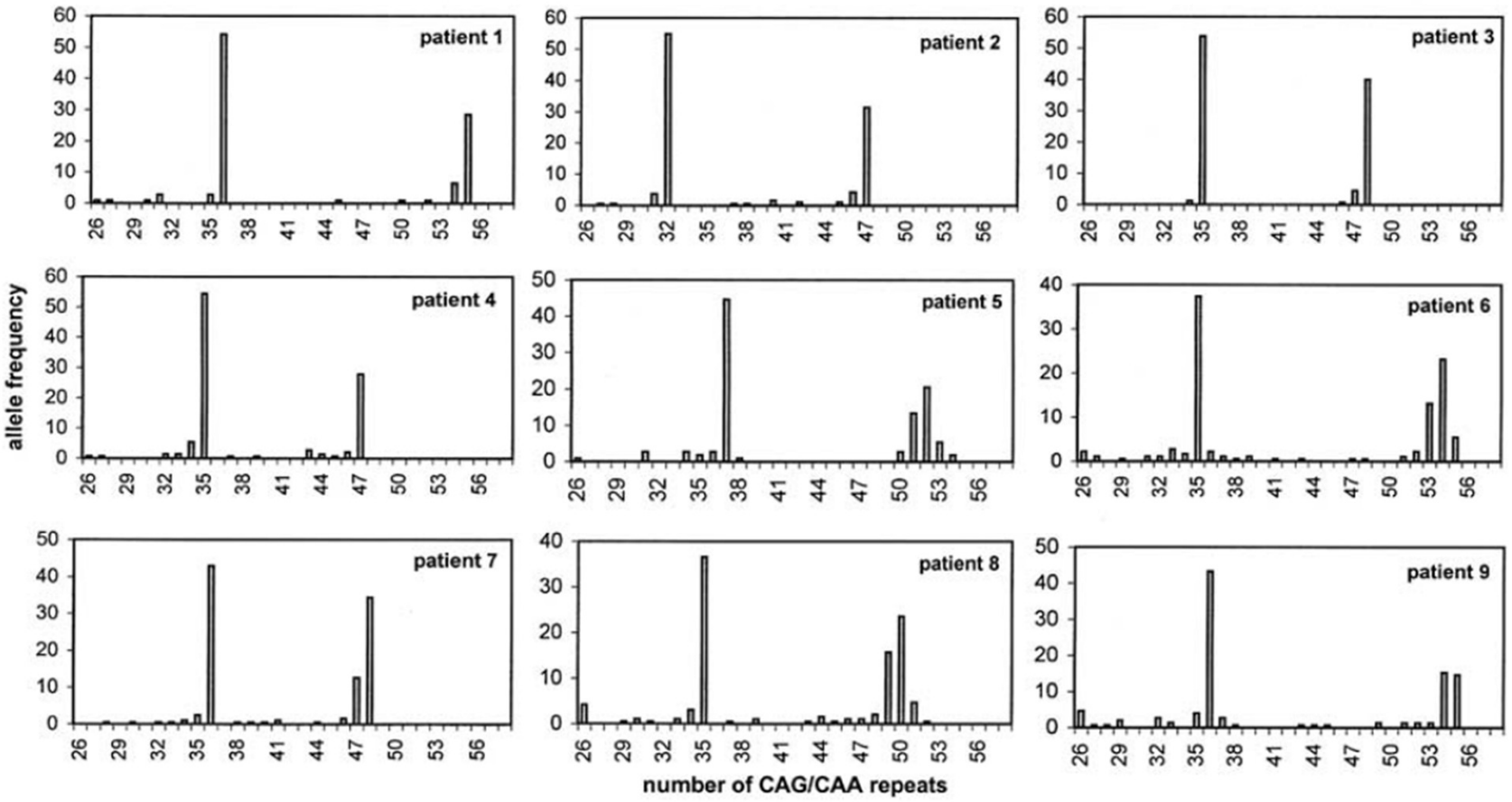


- Imaging useful as commonly shows cerebellar atrophy
- Putaminal signal change reported (Loy *et al.* 2005)

Genetics of SCA17

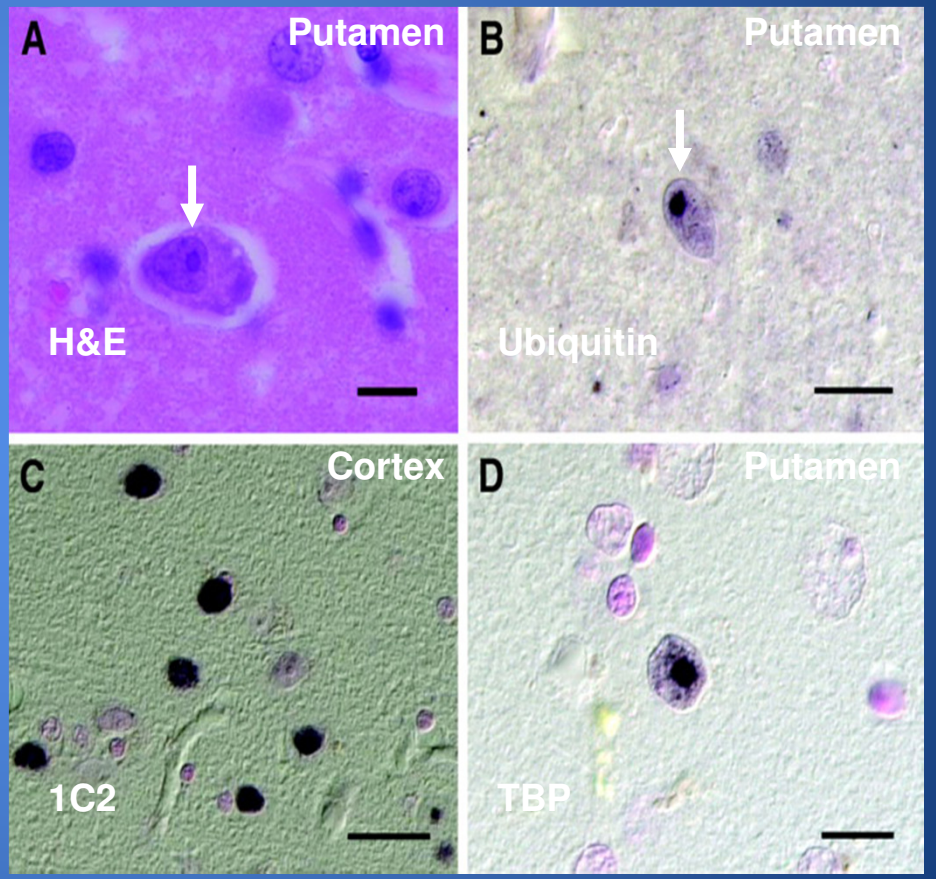
- Autosomal dominant
- CAA/CAG repeat expansion in the TBP (TATA binding protein) (Koide *et al.* 1999)
- Disease range is >43 CAG repeats
- Similar intergenerational instability to HD: anticipation, especially with paternal transmission (Rasmussen *et al.* 2007, Gao *et al.* 2008)
- Reduced penetrance range reported: 44-48 repeats in asymptomatic mutation-transmitting parents (Zulkhe *et al.* 2003, Oda *et al.* 2004)

Pure CAG // *or* CAA interruptions



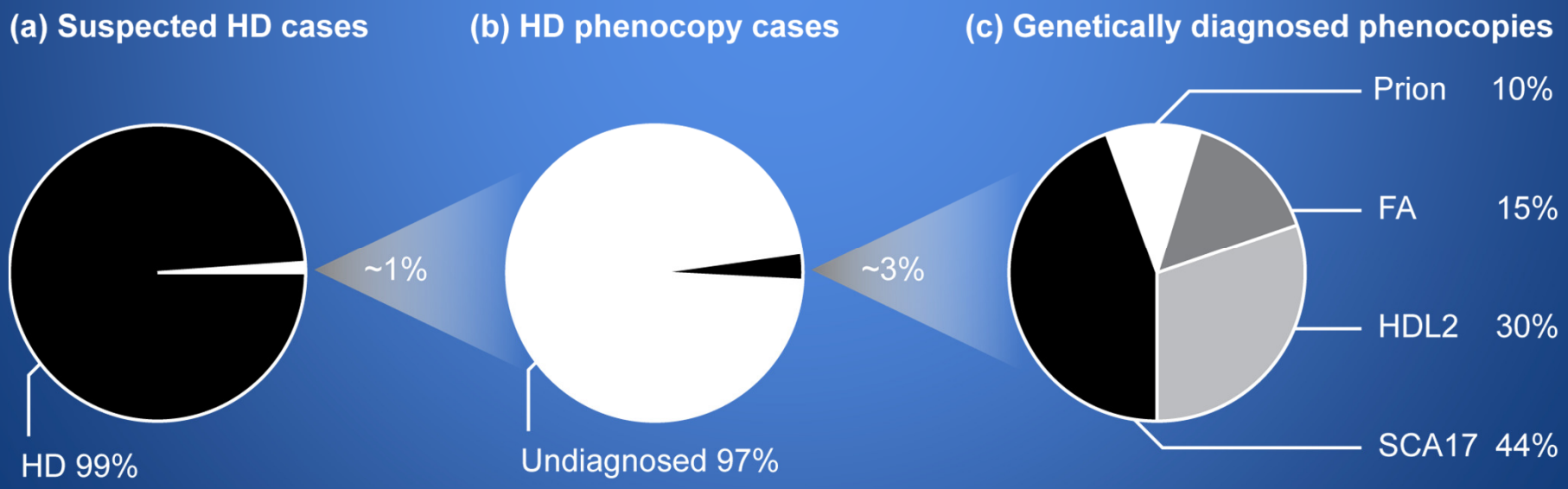
Pathology and pathogenesis of SCA17

- TBP positive intranuclear inclusions



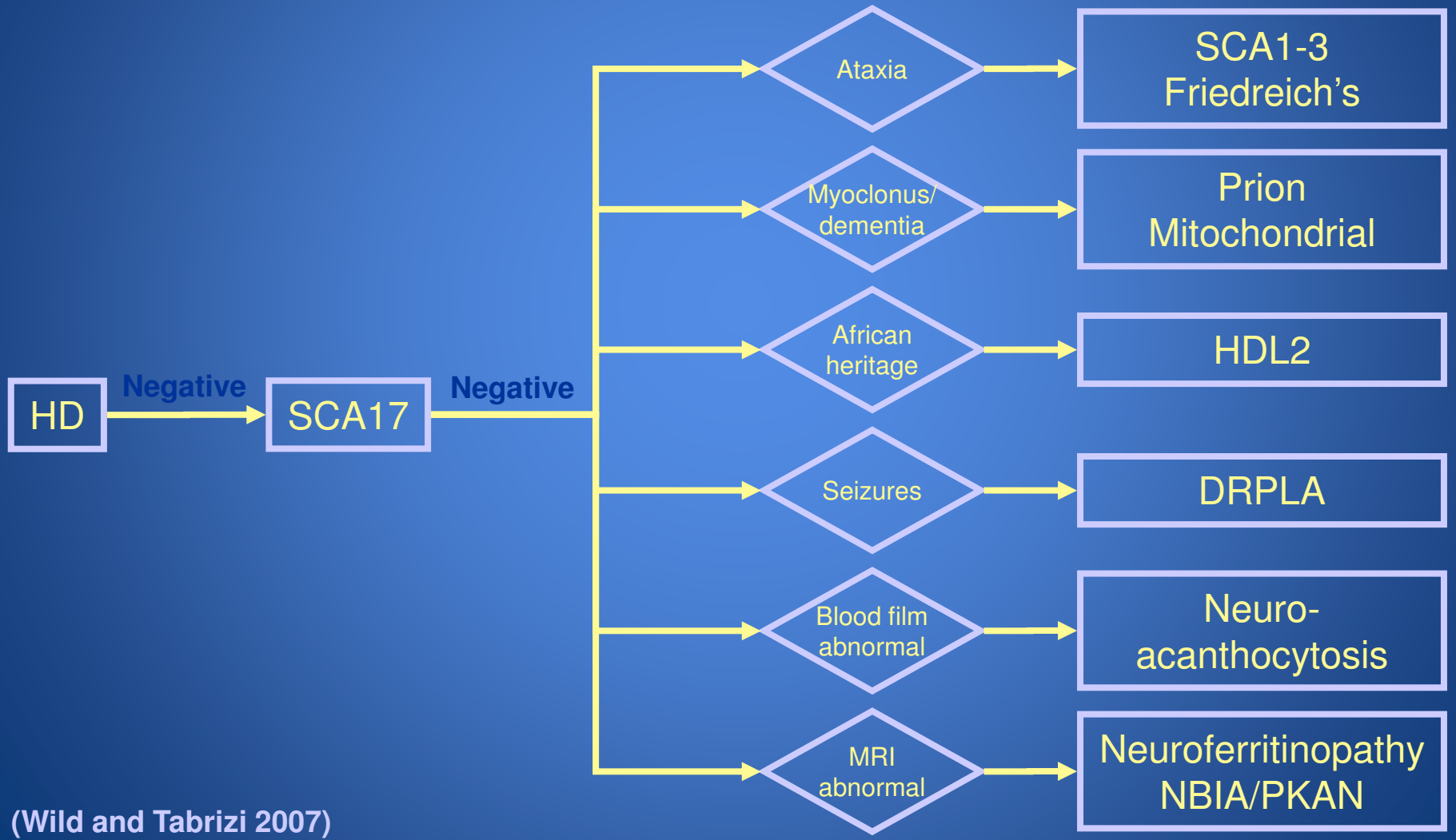
Heterogeneity of HD phenocopies

- 285 subjects who tested negative for HD
- Screened for 9 HD-like genetic disorders
- 5 cases of SCA17, 1 prion disease,1 HDL2 and 1 Friedreich's ataxia
- Reviewed all published HD phenocopy series, and pooled the data which are schematically illustrated below:



(Wild *et al.* 2008)

Approach to genetic testing of the choreic patient



(Wild and Tabrizi 2007)

DYSTONIA

REVIEW

Genetics of Dystonia: What's Known? What's New? What's Next?

Katja Lohmann, PhD, and Christine Klein, MD*

Institute of Neurogenetics, University of Luebeck, Luebeck, Germany

Designation	Clinical category	Clinical characteristics	Mode of inheritance	Gene locus	Gene	OMIM number
DYT1	Isolated dystonia	Early-onset generalized	Autosomal dominant	9q	*TOR1A*	128100
DYT2	Isolated dystonia	Early-onset generalized	Autosomal recessive	Unknown	Unknown	224500
DYT3	Combined, persistent dystonia	X-linked dystonia parkinsonism; "lubag"	X-chromosomal recessive	Xq	*TAF1*	314250
DYT4	Isolated dystonia	Whispering dysphonia	Autosomal dominant	19p	*TUBB4*	128101; 602662
DYT5	Combined, persistent dystonia	Dopa-responsive dystonia; Segawa syndrome	Autosomal dominant	14q	*GCH1*	128230
DYT6	Isolated dystonia	Adolescent-onset mixed phenotype	Autosomal dominant	8p	*THAP1*	602629
DYT7	Isolated dystonia	Adult-onset focal	Autosomal dominant	18p	Unknown	602124
DYT8	Combined, paroxysmal dystonia	Paroxysmal nonkinesigenic dyskinesia 1	Autosomal dominant	2q	*MR-1*	118800
DYT10	Combined, paroxysmal dystonia	Paroxysmal kinesigenic dyskinesia 1	Autosomal dominant	16p-q	*PRRT2*	128200
DYT11	Combined, persistent dystonia	Myoclonus-dystonia	Autosomal dominant	7q	*SGCE*	159900
DYT12	Combined, persistent dystonia	Rapid-onset dystonia-parkinsonism	Autosomal dominant	19q	*ATP1A3*	128235
DYT13	Isolated dystonia	Adolescent-onset multifocal/segmental	Autosomal dominant	1p	Unknown	607671
DYT15	Combined, persistent dystonia	Myoclonus-dystonia	Autosomal dominant	18p	Unknown	607488
DYT16	Combined, persistent dystonia	Early-onset generalized with parkinsonism	Autosomal recessive	2p	*PRKRA*	603424
DYT17	Isolated dystonia	Adolescent-onset	Autosomal recessive	20pq	Unknown	612406
DYT18	Combined, paroxysmal dystonia	Paroxysmal exertion-induced dyskinesia	Autosomal dominant	1p	*SLC2A1 (GLUT1)*	612126
DYT19	Combined, paroxysmal dystonia	Paroxysmal kinesigenic dyskinesia 2	Autosomal dominant	16q	Unknown	611031
DYT20	Combined, paroxysmal dystonia	Paroxysmal nonkinesigenic dyskinesia 2	Autosomal dominant	2q	Unknown	607488
DYT21	Isolated dystonia	Adult-onset generalized/multifocal	Autosomal dominant	2q	Unknown	614588
DYT23	Isolated dystonia	Adult-onset cervical dystonia	Autosomal dominant	9q	*CIZ1*	614860
DYT24	Isolated dystonia	Adult-onset craniocervical dystonia	Autosomal dominant	11p	*ANO3*	615034
DYT25	Isolated dystonia	Adult-onset cervical dystonia	Autosomal dominant	18p	*GNAL*	615073

Dominantly inherited, early-onset dystonia

- Mutations in the
  - TOR1A11 (DYT1) or
  - THAP112 (DYT6) gene.

  - Penetrance of mutations in both these genes is markedly reduced, as low as 30%.

DYT11

- Myoclonus-Dystonia
- “Essential myoclonus & alcohol-sensitive myoclonic dystonia”
- Mutations in the epsilon- sarcoglycan (SGCE) gene
- Childhood onset
- Responsive to alcohol
- Upper body: dystonia largely neck and writer’s cramp

- Neuropsychiatric disease
- Depression, anxiety, compulsive obsessive disorders, addictive behavior or, more rarely, psychosis


Segment 1
Pre-operative
(c)2009 The Movement Disorder Society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Pre-OP
state
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- Important because of DBS

Figure 1. The Patient Lying in a Dystonic Posture at 32 Years of Age.

with little improvement. As a result of the failure of medication trials she underwent a left and subsequently a right ventrolateral thalamotomy at the Montreal Neurological Institute. Movement of her right arm improved after the left-sided surgery, but there was little additional improvement after the right-sided surgery. Two months after the left-sided procedure she became dysarthric and then aphonic. She did not speak for 18 months.

There were also episodes of periodic breathing and acute opisthotonic posturing lasting up to six hours, associated with tonic–clonic movements and a decreased level of consciousness. However, electroencephalograms taken during these episodes showed no seizure discharges. During a particularly severe "seizure," treated with intravenous diazepam, the patient had a respiratory arrest, which led to placement of a tracheostomy tube. She reported constant pain from the dystonic spasms, leading to the use of narcotic analgesics

The rapid progression led to consideration of a nursing home placement. Just before this decision was to be implemented, the patient awoke one morning and started to speak with normal volume and articulation. She appeared to be delusional and hallucinating, although her psychotic symptomatology was perceived as histrionic and manipulative. She was transferred to the psychiatric unit of Johns Hopkins Hospital, where behavior modification techniques were used. One day later she sat up, and within a week she began using both her arms. She also walked for the first time in two years, although maintaining an equinus gait. Her psychotic symptoms disappeared. Medications were stopped without worsening of her

- Family history (only in 50% in one series)
- Reduced penetrance on maternal transmission of the disease allele: maternal genomic imprinting of the SGCE gene.
- Majority of affected individuals inherit their disease gene from their fathers, whereas those inheriting the mutated allele from their mothers will likely remain unaffected throughout their lives

Table 3. Published Mutations in the *SGCE* Gene in Individuals with Myoclonus-Dystonia

Exon	Mutation	Family History	Reference
2	164delG	Yes	Hedrich et al [2004]
2	H60P	No	Hedrich et al [2004]
3	276delG	No	Asmus et al [2002]
3	R97X	Yes	Zimprich et al 2001
3	R102X [1]	Yes [2]	Zimprich et al [2001], Asmus et al [2002], Han et al [2003], Hedrich et al [2004]
3	233-1G>A	Yes	Asmus et al [2002]
4	484delAATT	Yes	Marechal et al [2003]
4	463+6T>C	No	Asmus et al [2002]
4	488-97del	Yes	Zimprich et al [2001]
5	565delA	Yes	Zimprich et al [2001]
5	625insG	Yes [2]	Muller et al [2002], Kock et al [2004]
5	L196R	Yes	Klein et al [2002]
6	R237X	Yes	Doheny et al [2002]
6	733delAATT	Yes	Asmus et al [2002]
6	907+1G>A	Yes	Zimprich et al [2001]
7	832delAAAAC	Yes	Han et al [2003]
7	835delACAAA	Yes	Klein et al [2002]
7	855insT	Yes	Foncke et al [2003]
7	966delT	Yes	Muller et al [2002]
7	974delC	Yes	Hjermind et al [2003]
7	Q286X	Yes	Asmus et al [2002]
7	1037+5G>A	Yes	Asmus et al [2002]
All	Interstitial del 7q21	No	DeBerardinis et al [2003]

1. This mutation has been reported in nine unrelated families.
2. The proband appeared to be a simplex case, but the mutation was found in their unaffected father due to reduced penetrance (only one of the R102X cases appeared simplex [Hedrich et al 2004]).

Testing

- Young age at onset of motor symptoms, especially in association with psychiatric disturbance, are strongly predictive for SGCE positivity

Defining the Epsilon-Sarcoglycan (SGCE) Gene Phenotypic Signature in Myoclonus-Dystonia: A Reappraisal of Genetic Testing Criteria

Miryam Carecchio, MD,[1,2] Monia Magliozzi, BSc,[3] Massimiliano Copetti, PhD,[4] Alessandro Ferraris, MD, PhD,[3] Laura Bernardini, PhD,[3] Monica Bonetti, BSc,[3‡] Giovanni Defazio, MD,[5] Mark J. Edwards, PhD,[1] Isabella Torrente, BSc,[3] Fabio Pellegrini, MSc,[4,6] Cristoforo Comi, MD, PhD,[2] Kailash P. Bhatia, MD, FRCP,[1] Enza Maria Valente, MD, PhD[3,7*]

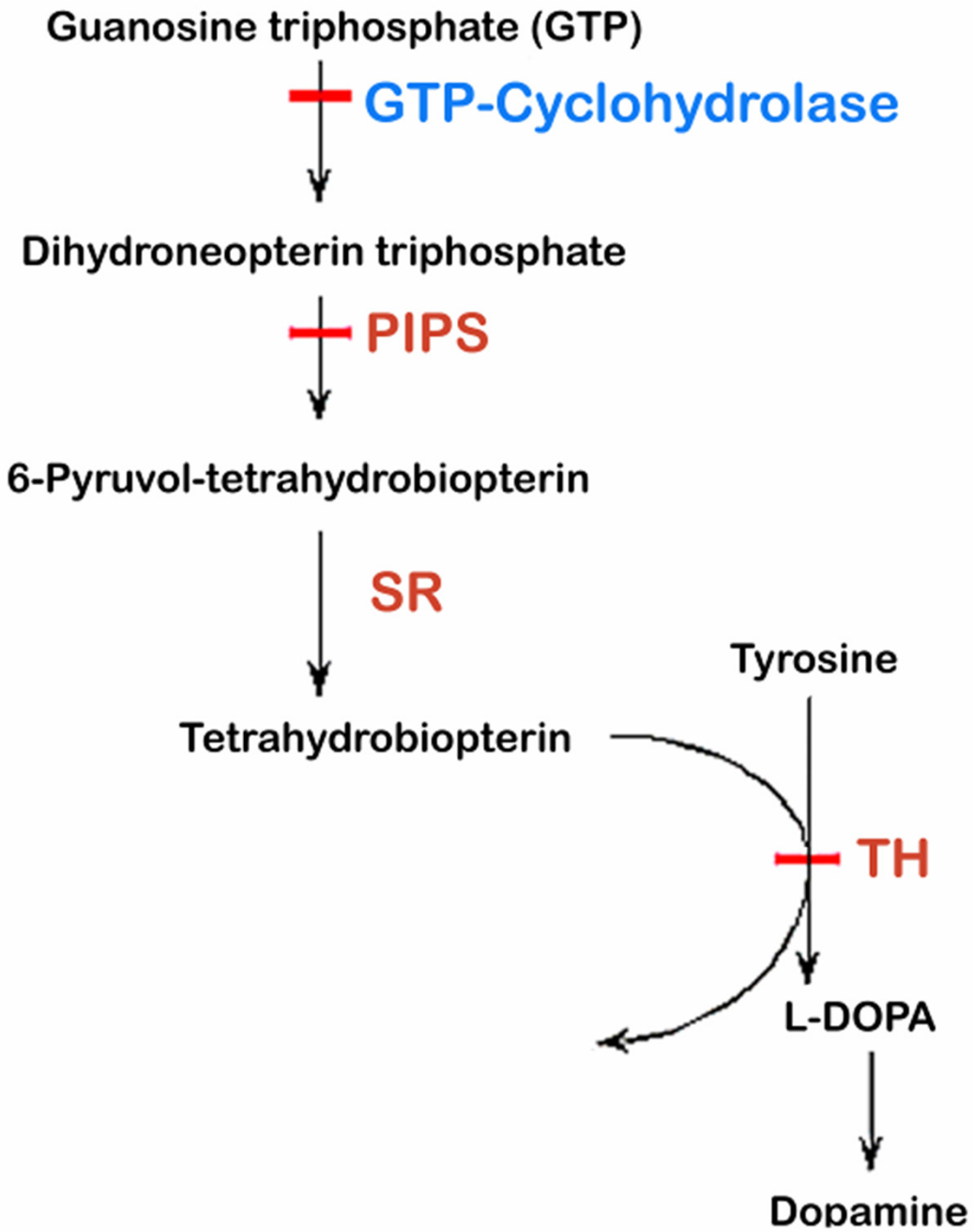
DYT5: Dopa-Responsive Dystonia

Dopa-responsive dystonia (DRD)

- Usually presents in early childhood as dystonia of the lower limbs
- Dramatic and sustained response to low doses of levodopa therapy.
- AD inheritance with reduced penetrance.

DRD

- C14q
- Mutations in GTP cyclohydrolase gene:
  - GCH1 is the rate limiting enzyme in the conversion of GTP to tetrahydrobiopterin (BH4), a cofactor for tyrosine hydroxylase.
- TOHase: the rate-limiting step for dopamine synthesis


Guanosine triphosphate (GTP)
GTP-Cyclohydrolase
Dihydroneopterin triphosphate
PIPS
6-Pyruvol-tetrahydrobiopterin
SR
Tetrahydrobiopterin
Tyrosine
TH
L-DOPA
Dopamine

GCH1

M1X
E2fs
A8X
P23L
Q48X
A50fs
E56X
E61X
E65X
L71fs
L71Q
A74V
Y75X

S77-L82del
L79P
G83A
Q87P
R88W
R88G
R88P
R88-Q89del
Q89X
L91R
T94K
W96X
M102K
M102R
Q103fs
G103P
T106I
T106ins
G108D
G108V
Q110fs
Q110X
S114X
D115N

L117fs
D134V
I135K
C141R
C141W
H144P

H153P
N159fs
L163R

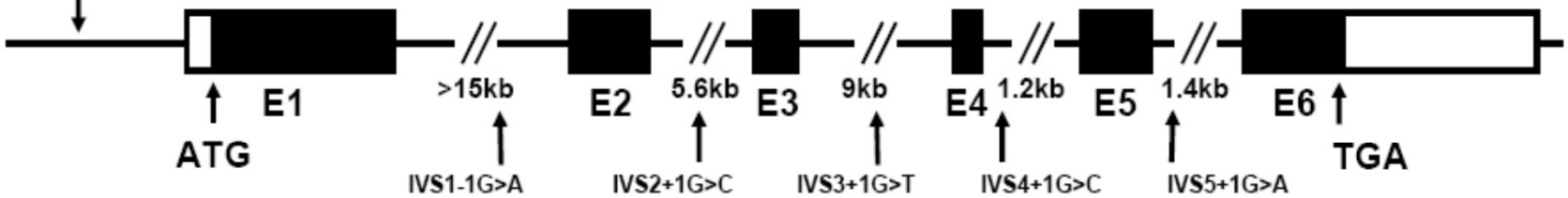
I171fs
S176T
R178G
R178S
Q180X
Q180R

Q182X
R184C
R184H
L185R
T186fs
A190fs
V191I
S196A
P199A
P199S
P199L
G201R
G201E
V202I
G203R
V205G
V206fs

M211fs
M211I
M211V
M213T
R216X
V218fs
M221T
S223R
K224R
K224X
V226A
L231fs
F234S
R241W
E243fs
R249S
X251R

Black = missense, non-coding
Red = HPA
Blue = nonsense
Green = frameshifts
Deletions = orange
Insertions = pink

-22C>T
-39C>T/-132C>T



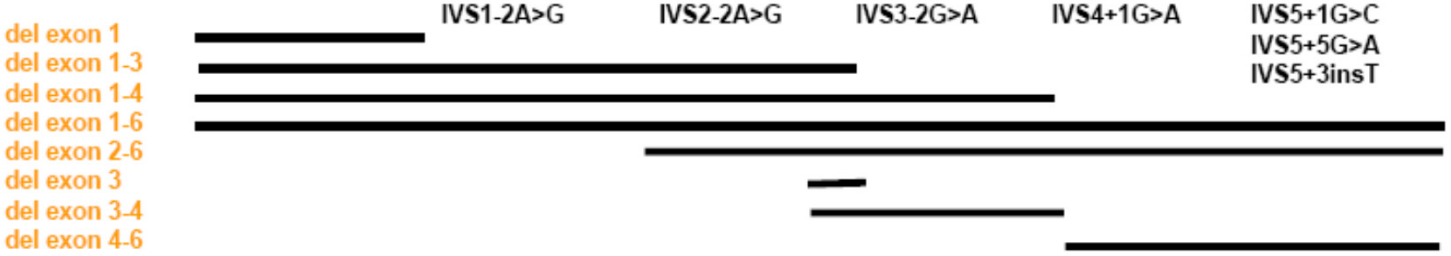
IVS1-1G>A
IVS1-2A>G

IVS2+1G>C
IVS2-2A>G

IVS3+1G>T
IVS3-2G>A

IVS4+1G>C
IVS4+1G>A

IVS5+1G>A
IVS5+1G>C
IVS5+5G>A
IVS5+3insT



DRD: what is the spectrum?

Table 4 *Atypical presentations in patients with mutations in the GTPCH I gene*

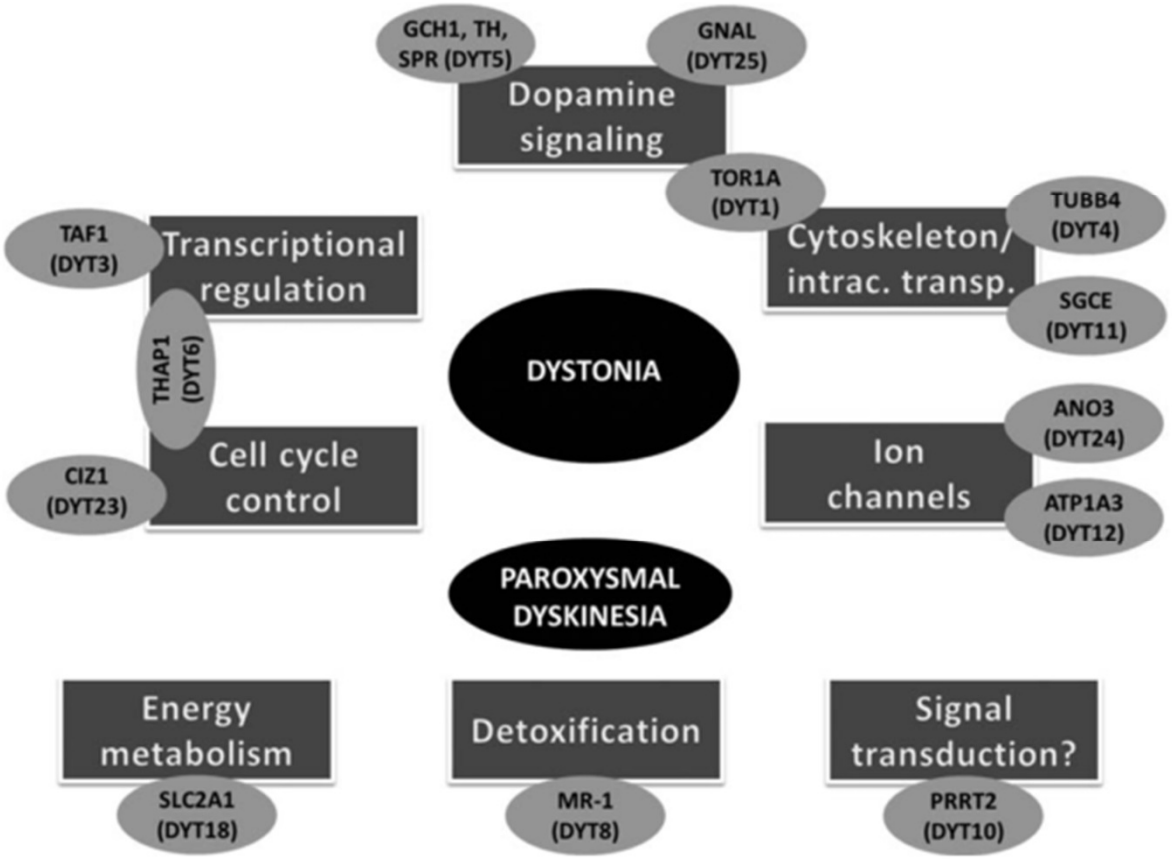
Atypical presentation	Amino acid change	Reference
Very early onset (feeding problems in the 1st week of life)	Gly83Ala	Bandmann *et al.*, 1998
Relapsing–remitting course of dystonic features	Lys224Stop	Bandmann *et al.*, 1996
Inversed diurnal fluctuations (improvement during the day)	Leu71Glu	Bandmann *et al.*, 1998
Guitarist's cramp	Arg216Stop	Bandmann *et al.*, 1998
Oromandibular dystonia	Ala196Ser	Steinberger *et al.*, 1999
Severe motor delay, lack of speech development	351delA/Met221Thr	Furukawa *et al.*, 1998
Paroxymal dystonia, oculogyric crises	Cys108Asp/Lys224Arg	Furukawa *et al.*, 1998
Levodopa-induced dyskinesias	Gln180Stop Met211Val (Stop249)	Present study

Table 2 *Clinical features of 27 patients from 12 families with DRD according to the mutation in the GTPCH I gene on chromosome 14*

Patient	Sex	Age (years)	Age at onset (years)	Location of dystonia	Additional features	LL reflexes	Plantar reflex	Response to low dose of levodopa (%)
Truncating mutation								
SAL-37-1	F	46	7	LL	Painful dystonia	N	F	100
SAL-37-3	F	14	7	LL	Painful dystonia	N	F	100
SAL-426-15	M	25	9	LL	Some UL dystonia	N	F	90
SAL-426-17	F	24	7	Generalized	LL spasticity	N	ND	100
SAL-444-17	F	57	10	Generalized	Writer's cramp	N	F	50
SAL-444-37	F	45	42	LL	None	ND	ND	NT
SAL-444-130	F	21	18	UL	None	ND	ND	NT
SAL-444-132	M	15	11	Generalized	Scoliosis, mental retardation	N	F	90
SAL-444-194	F	20	10	Generalized	None	Increased	E	90
SAL-444-209	M	68	52	None	Tremor, axial rigidity, amimia	N	F	NT
SAL-445-4	F	10	5	Torticollis, writer's cramp	None	Increased	F	80
SAL-609-7	F	47	12	None	LL spasticity, postural and rest tremor	Brisk	F	90*
SAL-609-14	F	12	8	Writer's cramp	LL spasticity, scoliosis	Brisk	E	90*
SAL-704-1	F	76	57	None	Parkinsonian syndrome, major instability, dementia	Brisk	EF	100*
SAL-704-4	M	39	10	LL	Facial grimacing, writer's cramp	N	F	90
SAL-704-7	M	37	13	LL, writer's cramp	None	N	F	90
SAL-704-42	M	66	55	None	Parkinsonian syndrome	N	F	ND
SAL-704-62	M	15	10	LL	Intermittent	N	F	NT
n = 18	11F/7M	35 ± 21	19 ± 18			5I/11N	13F/3E	
Missense mutation								
SAL-424-3	M	21	9	LL	None	ND	ND	100
SAL-438-1	M	57		LL	LL spasticity	Increased	E	NT
SAL-438-5	F	27	10	Generalized	None	Increased	F	100
SAL-438-6	M	25		None	Exercise-induced LL stiffness	Increased	F	0
SAL-452-11	F	10	5	Generalized	LL spasticity	Brisk	E	90
SAL-452-12	M	8		LL	None	N	F	>30
MON-132-3	F	14	8	LL	None	ND	ND	100
CLE-150-5	F	54	7	Generalized	Bradykinesia and tremor	N	F	80
n = 8	4F/4M	27 ± 19	8 ± 2			4I/2N	4F/2E	
Mutation in 5′-untranslated region								

- DYT1: Mutations in TorsinA have been shown to disturb the endoplasmic reticulum, the nuclear envelope, and/or cytoskeletal dynamics
- Link between dystonia and the cytoskeleton: mutations in the tubulin TUBB4 (DYT4)
- SGCE (DYT11): considered part of the dystrophin-glycoprotein complex that links the cytoskeleton to the extracellular matrix

GENETICS OF DYSTONIA



Young Onset PD: 21-40

- Tends to be genetic
- Commonest: Parkin mutations
  - nearly 80% of patients with onset < 30 years.

alpha-Synuclein (PARK1, PARK4)

Parkin (PARK2)

PINK1 (PARK6)

DJ-1 (PARK7)

LRRK2 (PARK8)

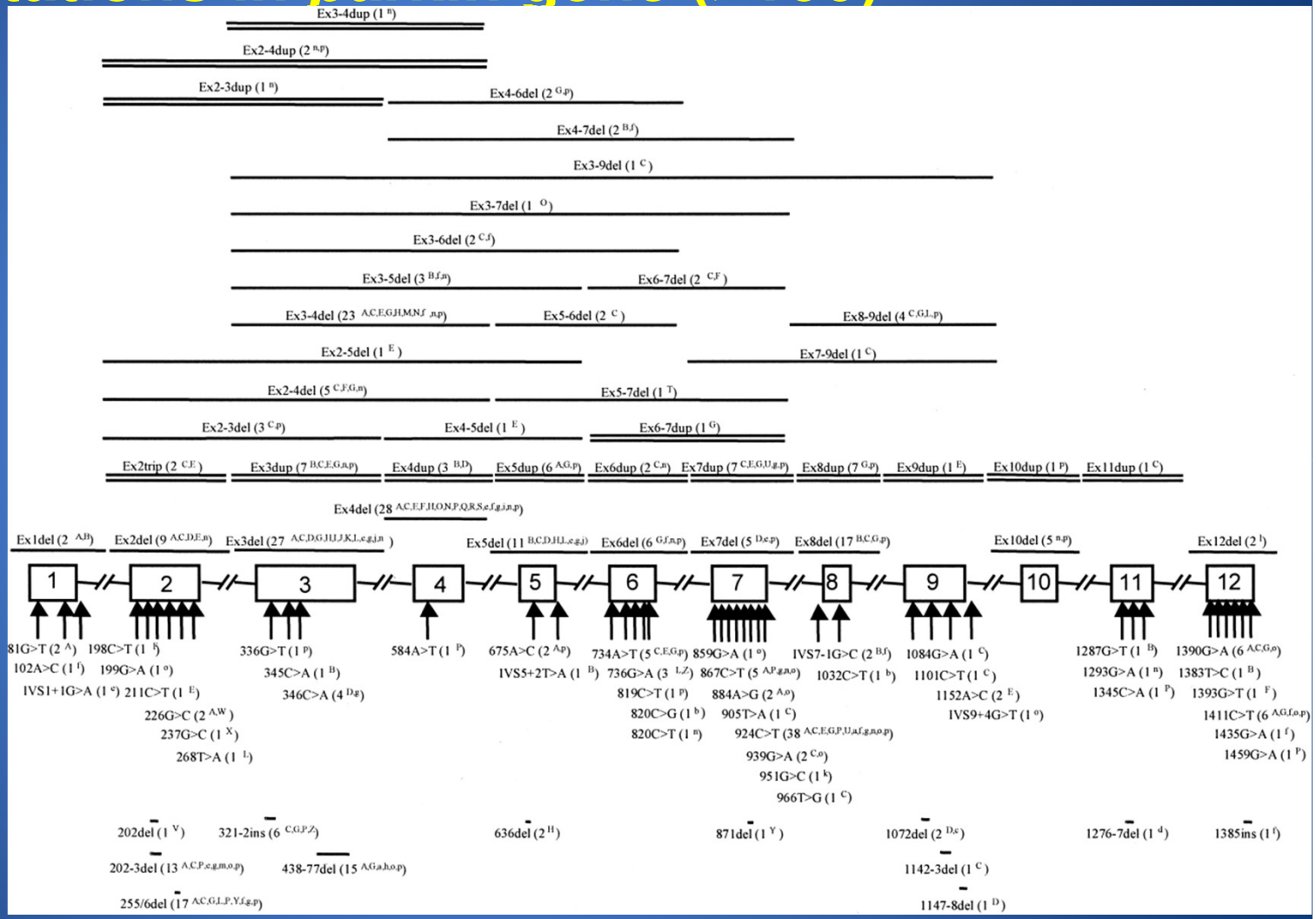
Parkin (PARK2)

Mutations in *parkin* gene (>100)

Whole exon deletions & insertions

12 EXONS

Point mutations



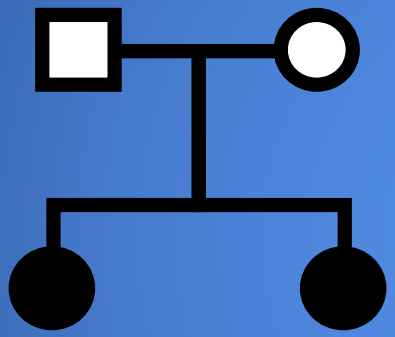
- Involved in protein degradation pathway

Hedrich et al. Mov Disord 2004

Parkin (PARK2)

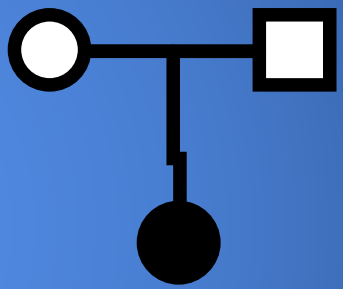
Results

Homozygous whole exon deletions



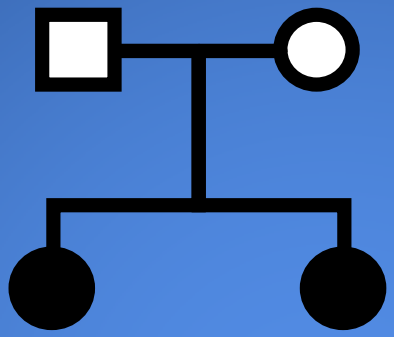
Exon 4 deleted

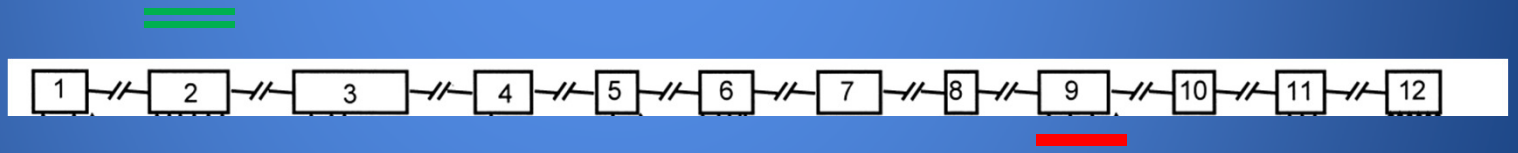
- AAO both 27 years
- Prominent dystonia



Exons 3 & 4 deleted

- Mixed ancestry
- AAO 27 years
- Foot dystonia/ mild symptoms




1
2
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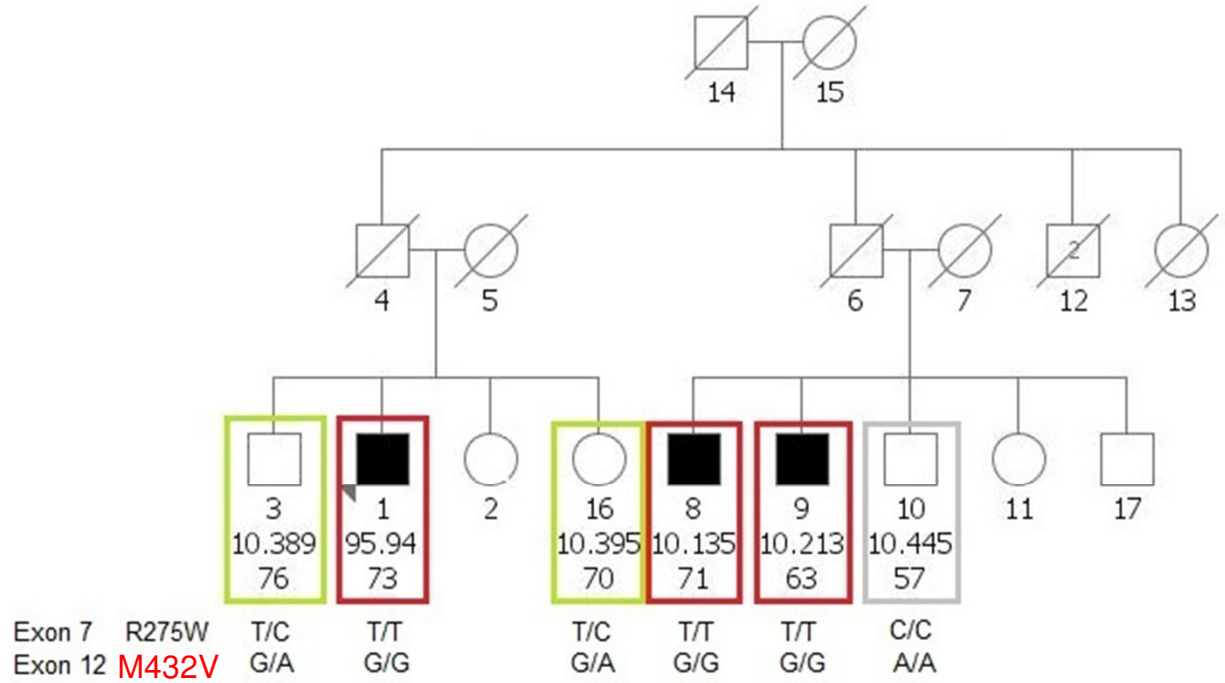
Oct 24 2013

Family 340 South Africa

Exon 7 R275W**pathogenic Chr6:162206852

Exon 12 M432V Chr6:161771235



SCA

- Extrapyramidal features may occur as a prominent sign in SCA2, SCA3, SCA8,and SCA17 or as a mild, additional feature in SCA6.
- SCA2 mutations, a CAG/CAA repeat, may cause classical, L-dopa-responsive PD
- Asian origin: 10% of familial parkinsonism
- SCA3: typically have peripheral neuropathy & spasticity

SCA6

alpha-Synuclein (PARK1, PARK4)

Parkin (PARK2)

PINK1 (PARK6)

DJ-1 (PARK7)

LRRK2 (PARK8)

- Synuclein:
  - gene dosage
  - A53T mutation is associated with an approximately 10-year earlier age at onset than the other 3 known missense mutations
  - No gene dosage: carriers of heterozygous vs homozygous leucine-rich repeat kinase 2 (LRRK2) mutations 6.
  - No genotype-phenotype correlation emerged in a recent meta-analysis of>1000 Parkin mutation carriers.

Major risk factor= age

LRRK2 (PARK8)

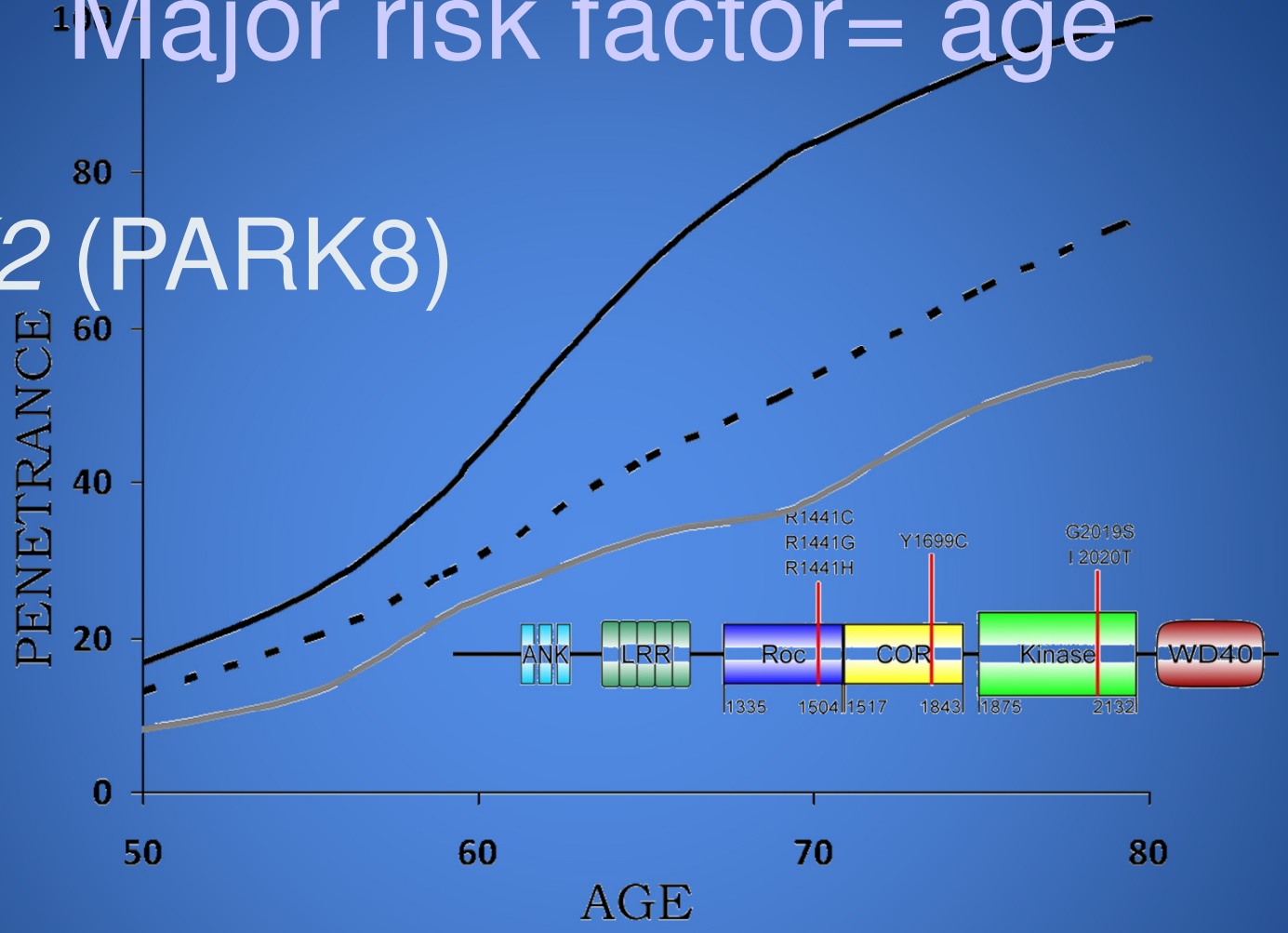


Figure 1. Penetrance of the G2019S mutation from three separate studies.
Kachergus ; Healey --- ; Latourelle

Rare and recessive

- ATP13A2 (PARK9)
- PLA2G6 (PARK14)
- FBXO7 (PARK15)
- Very early onset (<30 years)
- Atypical clinical features (e.g., pyramidal, dystonic, ocular movement, and cognitive disturbances).

GBA mutations

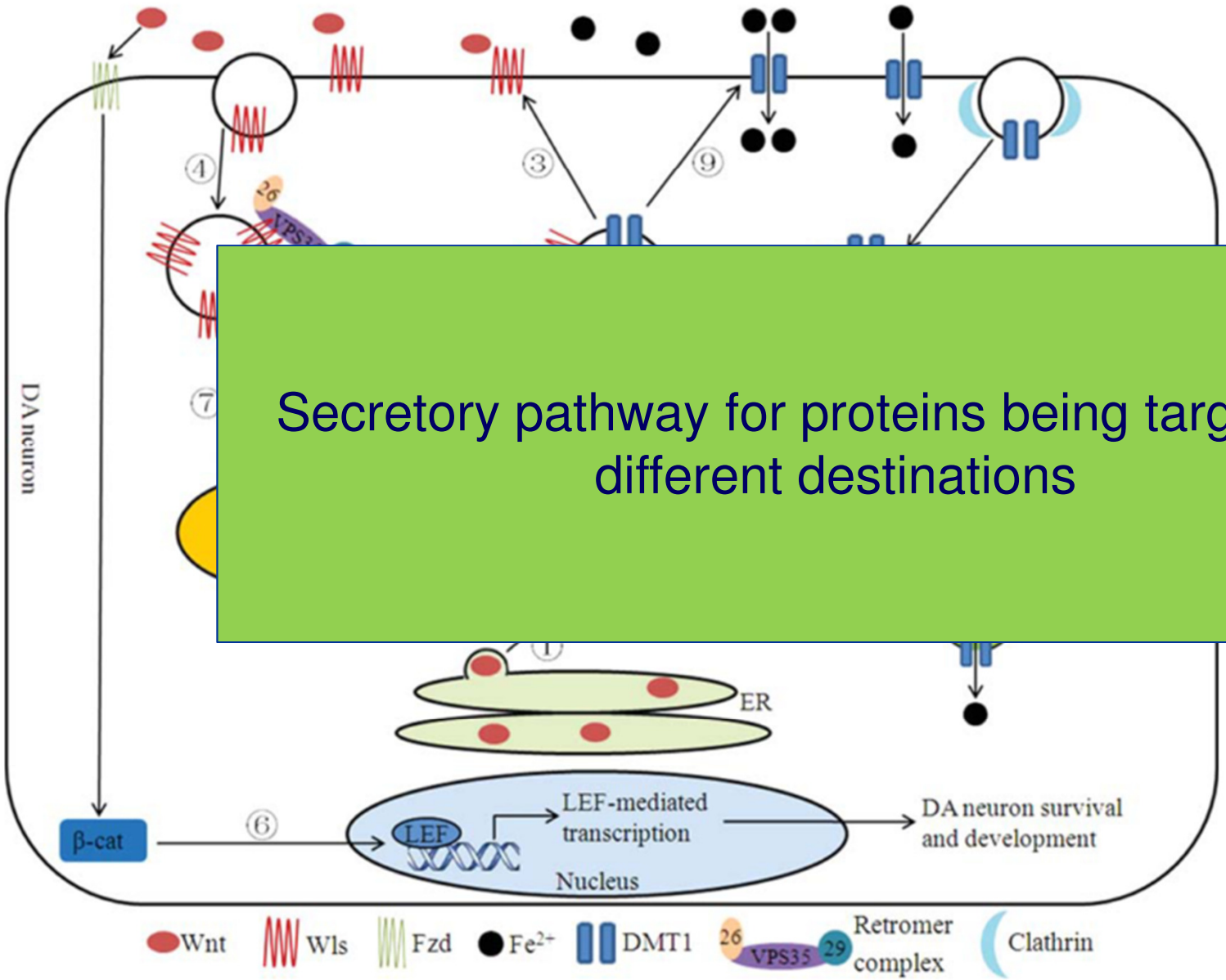
- AR disorder, Gaucher disease (GD), is a lysosomal storage disorder caused by mutation of the gene encoding glucocerebrosidase (GBA).
- Report indicated that GD patients may also infrequently display signs and symptoms of parkinsonism.
- Carriers of a single GBA mutation appeared to be at a much higher risk for PD.

GD

- Large meta-analysis of sequencing studies clearly showed that a single GBA mutation increases risk for PD by approximately 5-fold.

Exome Sequencing

- Swiss kindred: AD late-onset PD
- Mutations in the gene for vacuolar protein sorting 35 (VPS35 c.1858G>A; Asp620Asn).
- VPS35 is a central component of the tripartite retromer cargo-recognition complex, involved in recycling membrane proteins.



Secretory pathway for proteins being targeted to different destinations

GWAS

- SNCA: risk variants
- Nominal association between alleles of the REP1 polymorphism in the promoter region of SNCA, & risk for disease.
- (1.4 x risk)

GWAS

- LRRK2: risk variants
- ? mutation (p.G2385R) in Taiwanese family.
- Relatively common in the general Asian population
- 2-fold increase in risk for PD.

GWAS

- Most recent analysis includes data on more than 12,000 cases// 20,000 controls
- Evidence for 16 independent risk loci
- Alleles at each of the loci represent small risk or protective factors, conferring 1.1- to 1.4-fold increases in risk.
- (equally, protective alleles)

July, 2013

- Even the sum of all genetic variability detected so far probably accounts for not more than 10% to 20% of attributable risk in most populations.

EDITORIAL

Parkinson's Disease: Is It All in the Genes?

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