Genetic Studies of Neurological Disorders & Biomarkers for Neurodegenerative Diseases: an experience in Thailand

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รพ.รามาธิบดี มหาวิทยาลัยมหิดล

Neurological diseases

- Genetic risk factors
- Access susceptible individuals
- Biomarkers
- Prevention
- Treatment

Neurogenetic diseases

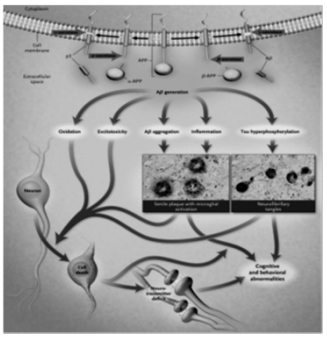
- Identify primary cause
- Genetic diagnosis
- Genetic counselling
- Molecular pathogenesis
- Treatment

GWAS in Neurology

- Alzheimer's disease
- Parkinson's disease
- Neuromyelitis optica
- Lone AF
- Intracranial aneurysm
- Susceptible to infections
- Respond to medications

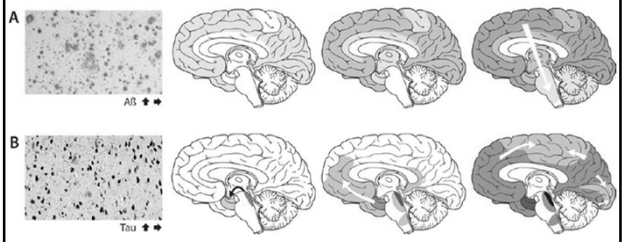
Neurodegenerative diseases

Amyloid cascade hypothesis



Cummings JL. N Engl J Med 2004

Alzheimer's disease

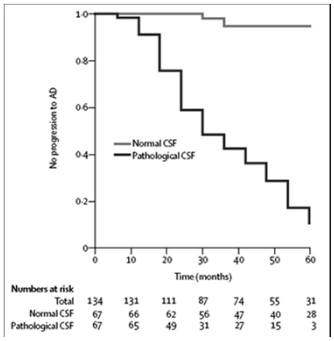


Jucker M & Walker LC. Ann Neurol 2011

CSF biomarkers

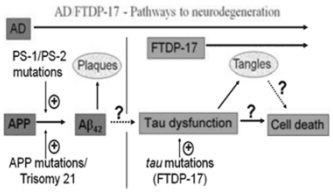
- β-Amyloid 1-42 ($A\beta_{42}$)
- Tau
- Phosphorylated tau (p-tau)

MCI progression to AD



Hansson O, et al. Lancet Neurol 2006

APP, PS1, PS2

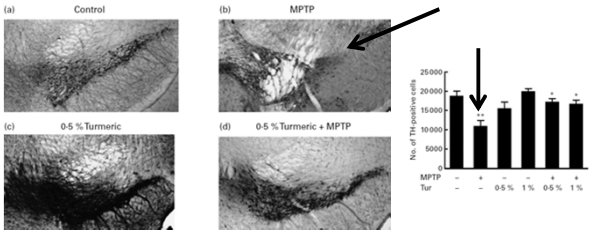


Hardy J. J Neruochemistry 2009

Parkinson's disease

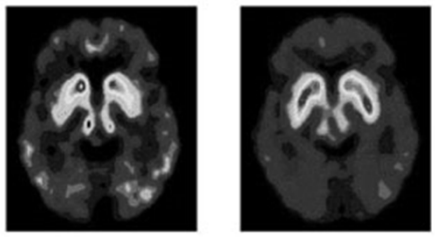
PD control

Early treatment



Mythri R.B., et al. Br J Neutri 2011

Biomarkers



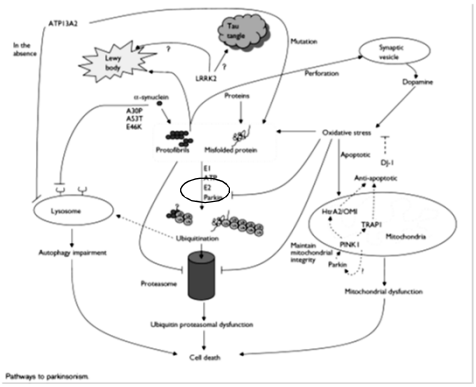
PD control

Parkinson's disease

- 2nd commonest neurodegenerative dz in human
- Prevalence 80-130/100,000 in Asians
  - (160-200/100,000 in Caucasians)
- Prevalence 1-2% over 65 y.o.
- Thai ~ 80,000-100,000 cases

Familial PD

Locus	Inheritance	Chromosomal locus	Gene
PARK1/ PARK4	AD	4q21-q23	*α-Synuclein*[41,43]
PARK2	AR	6q25.2-q27	*Parkin*[72]
PARK3	AD	2p13	ยังไม่ทราบ[122]
PARK5	AD	4p14	*UCHL1*[67]
PARK6	AR	1p35-p36	*PINK1*[93]
PARK7	AR	1p36.23	*DJ1*[89,90]
PARK8	AD	12p11.2-q13.1	*LRRK2/Dradarin*[80]
PARK9	AR	1p36	*ATP13A2*[100]
PARK10	Disease susceptibility	1p32	ยังไม่ทราบ[123,124]
PARK11	AD, familial PD	2q36-q37	*GIGYF2*[69,70]
PARK12	Disease susceptibility	Xq21-q25	ยังไม่ทราบ[125]
PARK13	AD	2p12	*HTRA2*[71]
PARK14	Disease susceptibility	18q11	ยังไม่ทราบ[120]
PARK15	AR	22q12-13	*FBXO7*[101]
PARK16	Disease susceptibility	1q32	ยังไม่ทราบ[121]



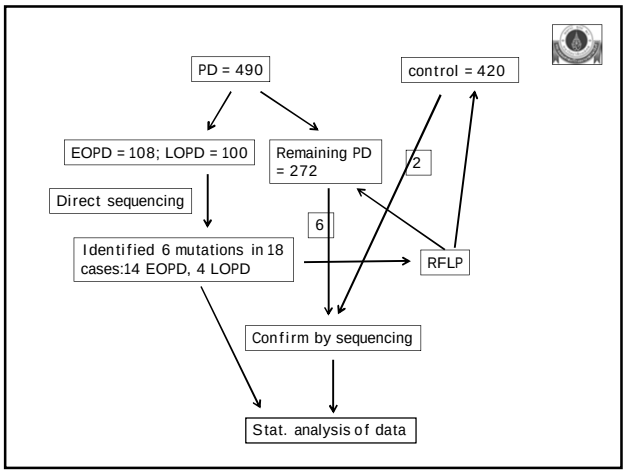
Yang, Wood & Latchman. Neuroreport 2006

Sporadic PD

- *LRRK2* – mutations & polymorphisms
- *GBA*1 - mutations
- SCA2 & SCA3 – triplet repeat expansions
- Alfa-synuclein – Rep1, duplication & triplication
- Familial – *Parkin, PINK1, DJ1, GIGYF2, HTRA2*

Glucocerebrosidase (*GBA*)

- Lysosomal enzyme
  - glycolipid glucosylceramide -> glucose + ceramide
- Homozygous/ compound heterozygous mutations:
  - Autosomal recessive paediatric neurological & multi-system disorder with parkinsonism is the main feature
- Common mutations: L444P, N370S, R120W, D409H, R463C
- Carriers: develop PD in adult-life
- PD cohorts: hetero. mutations associated with ↑ risk of PD
  - L444P – 30% of carriers develop PD ≤ 70 yo (30 times > normal)

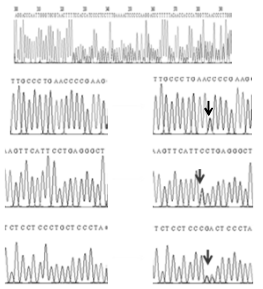


GBA mutations

- Known mutations: L444P (13/1), IVS2+1G>A (1/0)
- Novel mutations:
  - c.1309delG (1/0) -> V437fsX443
  - c.1275C>A (1/0) -> N386K
  - c.1399C>T (2/1) -> P428S
  - IVS10-9_10GT>AG (3/0)

Acceptor site predict score: 0.98 -> 0.54

  - IVS3+1G>C



GBA

Logistic regression analysis of factors associated with EOPD and PD with age at onset after 50 years.

Disease groups	Factors	Univariate analysis			Multivariate analysis		
		OR	*P*	95%CI	OR	*P*	95%CI
Sequencing data	GBA mutation	4.82	0.016[a]	1.34–17.30	4.64	0.022[a]	1.25–17.16
EOPD (108) vs. AAO > 50y–PD (100)	Male vs. Female	0.66	0.141	0.38–1.15	0.67	0.200	0.37–1.23
	Thai vs. Thai-Chinese	1.45	0.230	0.79–2.68	2.35	0.034[a]	1.06–5.18
	Chinese vs. Thai-Chinese	1.20	0.671	0.52–2.73	1.88	0.246	0.65–5.48
	Family History vs. none	2.72	0.045[a]	1.02–7.27	2.58	0.071	0.92–7.21
	Smoking vs. non-smoking	0.60	0.173	0.28–1.26	0.65	0.303	0.29–1.47
RFLPs data	*GBA mutation*	5.19	0.041[a]	1.07–25.17	2.88	0.240	0.49–16.89
AAO > 50y–PD (272) vs. control (395)	Male vs. Female	1.67	0.001[a]	1.22–2.28	2.38	<0.001[a]	1.66–3.43
	Thai vs. Thai-Chinese	1.81	0.003[a]	1.22–2.68	1.74	0.009[a]	1.15–2.62
	Chinese vs. Thai-Chinese	1.45	0.176	0.85–2.48	1.20	0.522	0.68–2.13
	Family History vs. none	15.63	<0.001[a]	4.72–51.87	16.30	<0.001[a]	4.79–55.37
	Smoking vs. non-smoking	0.70	0.104	0.46–1.07	0.46	0.002[a]	0.28–0.75

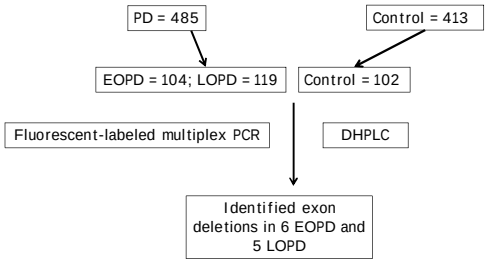
Comparison PD with GBA mut & without

Association between *GBA* mutations and clinical characteristics of PD.

Clinical characteristics	GBA mutation		*P*	OR	95%CI
	Yes	No			
	n = 17 (%)	n = 191 (%)			
Age at onset (mean ± SD)	43.1 ± 10.2	54.4 ± 13.9	0.002[a]	0.94	0.90–0.98
Disease duration (mean ± SD)	7.4 ± 4.9	8.7 ± 4.7	0.283	1.05	0.96–1.15
Family history	4 (24)	18 (9)	0.088	2.96	0.87–10.02
Bradykinesia	17 (100)	189 (99)	1.000	--	--
Rigidity	16 (94)	187 (98)	0.350	0.34	0.04–3.25
Rest tremor	15 (88)	172 (90)	0.684	0.83	0.16–3.90
Postural instability	6 (35)	46 (24)	0.379	1.71	0.60–4.90
Unilateral onset	16 (94)	178 (93)	1.000	1.17	0.14–9.51
Persistent asymmetry	13 (76)	123 (64)	0.428	1.80	0.56–5.74
Progressive disorder	16 (94)	169 (88)	0.700	2.08	0.26–16.48
≥10-year duration	4 (24)	27 (14)	0.291	1.87	0.57–6.15
Excellence response to L-dopa	13 (76)	137 (72)	0.785	1.28	0.40–4.10
Dopa-responsive ≥ 5 years	11 (65)	73 (38)	0.040[a]	2.96	1.05–8.36
Hoehn and Yahr staging ≥ 3	11 (64)	58 (30)	0.006[a]	4.20	1.48–11.91
Schwab-England ADL score (mean ± SD)	74.4 ± 17.1	81.0 ± 18.08	0.162	0.98	0.96–1.01
Duration of L-dopa treatment (months; median (range))	60 (0–204)	48 (0–240)	0.133	1.00	0.99–1.02
Wearing-off/on-off	8 (47)	82 (43)	0.801	1.18	0.44–3.19
Freezing	2 (12)	21 (11)	1.000	1.08	0.23–5.05
Dopa-induced Dyskinesia	7 (41)	24 (13)	0.006[a]	4.87	1.69–14.00

Parkin (PARK2)

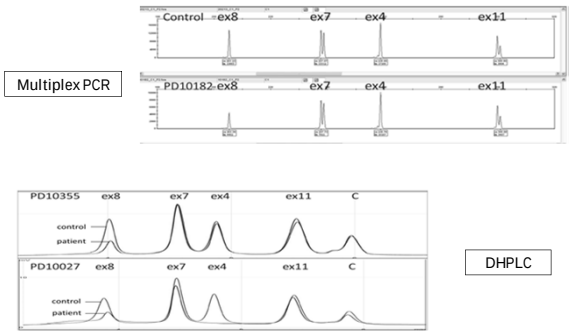
- E3 ubiquitin ligase
  - ubiquitin-mediated proteolytic pathway
  - Intracellular protein aggregation -> cell death
- Associate with mitochondria:
  - ↓mt complex I activity and ATP production
  - altered morphology & ↑susceptibility to mt toxins
- Homozygous/ compound heterozygous mutations:
  - Autosomal recessive early-onset Parkinson disease
- Common mutations: exon deletions/duplications, point mutations
- Heterozygous mutations: contribute to idiopathic PD



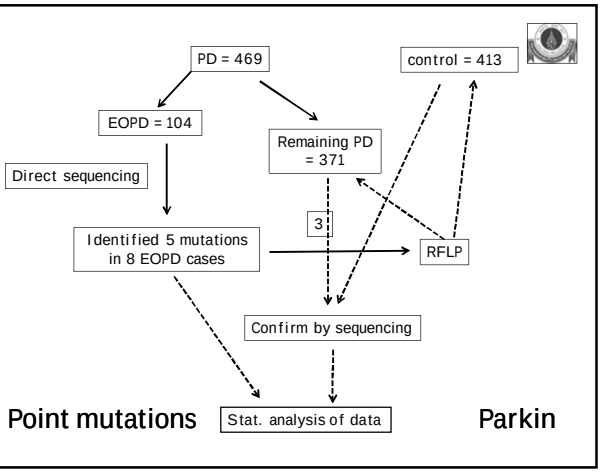
Exon deletions

Parkin

Parkin exon deletions

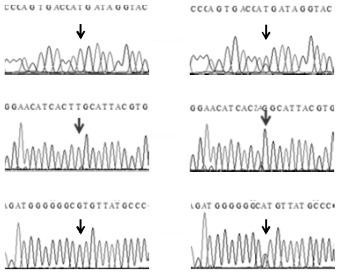


	EOPD				LOPD			
	10027	10110	10317	10355	10081	10166	10182	10309
Mutations								
Ex3 del	Homo	Hetero	-	-	-	-	-	-
Ex4 del	Homo	-	-	-	-	-	-	-
Ex5 del	-	-	Hetero	-	Hetero	-	-	-
Ex8 del	Hetero	-	-	Hetero	-	Hetero	Hetero	Hetero
Sex	M	F	M	F	M	F	M	F
Ethnic	Thai	Thai	Thai	Thai	Thai	Thai	Thai	T-C
*Thai-Chinese (T-C)								
Age at onset	26	46	41	43	60	60	68	79
Duration	3	5	7	4	4	9	2	6
Family history	-	-	-	-	+	-	-	-
Clinical features								
Bradykinesia	+	+	+	+	+	+	+	+
Rigidity	+	+	+	+	+	+	+	+
Rest tremor	-	+	+	+	+	+	+	+
Postural instability	-	-	-	-	-	+	-	-
Unilateral onset	+	+	+	+	+	+	+	+
Persistent asymmetry	-	-	-	-	-	+	+	-
Excellent resp to L-dopa	+	Not use	+	+	+	+	+	+
Hoehn-Yahr staging	2	1	3 (off)	3 (off)	1	4 (off)	2	2
Scwab & England ADL	90	90	70 (off)	50 (off)	100	30 (off)	90	70
Motor complications								
Wearing-off	-	-	+	+	-	+	-	-
On-off	-	-	+	-	-	-	-	-
Freezing	-	-	-	+	-	+	-	-
Dyskinesia	-	-	-	-	-	+	-	-



Parkin point mutations

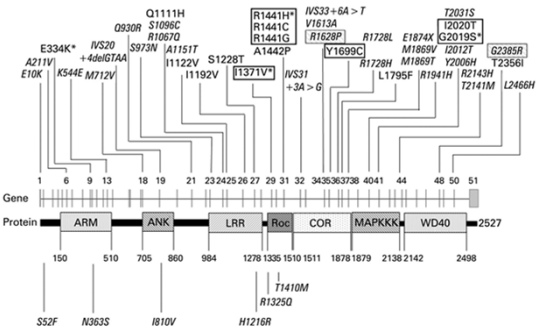
- Known mutations: Q34R (4), M458L (1)
- Novel mutations:
  - M1T (4)
  - C238G (1 homozygous)
  - V330M (1)



Leucine-rich repeat kinase 2 (*LRRK2*)

- 5 functional domains:
  - e.g. signaling pathways for axon guidance, synapse formation, and neuronal maintenance
  - Interact with several proteins inc. parkin
- Autophagic activity -> ↑LRRK2 siRNA knockdown:
  - Inhibition of autophagy -> prevented cell death
- 2° mitochondrial (mt) dysfunction - ↑mt fragmentation
- Mutations: most common causes of inherited PD (AD)
- Sporadic PD in East Asia: R1628P, G2385R

LRRK2 variants and Parkinson's disease



Lesage S, et al. J Med Genet 2009

LRRK2 R1628P (4883G>C)

Group	N	Genotype frequency (%)			Allele frequency (%)	
		G/G	G/C	C/C	G	C
PD	154	139 (90.26)	14 (9.09)[a]	1 (0.65)	292 (94.81)	16 (5.19)[b]
Control	156	151 (96.79)	5 (3.21)	0 (0.00)	307 (98.40)	5 (1.60)

P-value[a] = 0.02, P[b] = 0.01. (Fisher's exact test)

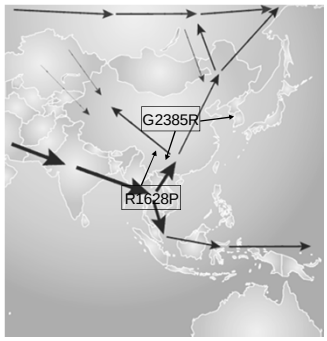
Odds ratio[a] = 3.24; 95%CI = 1.09-11.72; p = 0.02

Estimated PAR of 9.43%.

Pulkes, et al. JNNP 2011

DNA No.	group	Ethnic	R1628P	L153L 457T>C	G1624G 4872C>A	K1637K 4911A>G	S1647T 4939T>A	M2397T 7190T>C
5	PD	T	CG	CT	AC	GA	AT	CT
27	PD	T	CG	CT	AA	GG	AT	CT
28	PD	C	CG	CT	AA	GG	AT	CT
47	PD	TC	CG	CC	AA	GG	AA	CC
94	PD	T	CC	CC	AA	GG	AA	CC
96	PD	T	CG	CT	AC	GA	AT	CT
100	PD	T	CG	CC	AC	GG	AT	CC
110	PD	T	CG	CT	AC	GA	AT	CT
116	PD	C	CG	CT	AC	GA	AT	CT
132	PD	T	CG	CT	AC	GA	AT	CT
137	PD	T	CG	CT	AC	GA	AT	CT
144	PD	T	CG	CC	AA	GG	AA	CC
145	PD	C	CG	CC	AC	GG	AA	CC
159	PD	T	CG	CT	AC	GA	AT	CT
161	PD	T	CG	CC	AC	GG	AA	CC
178	CS	T	CG	CT	AC	GA	AT	CT
192	CS	T	CG	CT	AC	GG	AT	CC
209	CS	T	CG	CT	AC	GA	AT	CT
305	CS	T	CG	CT	AC	GA	AT	CT
315	CS	T	CG	CT	AC	GA	AT	CT
		Shared Alleles		C	A	G	A	C

R1628P and G2385R in East Asians



Association of *LRRK2* exonic variants with susceptibility to Parkinson's disease: a case–control study

Japan (173 vs 95)
Korea (844 vs 587)
Taiwan (369 vs 300)
Overall Asian series (1386 vs 982)

Age at onset (years) 54 (14; 20-85) NA

rs33949390	R1628P	C	+	+	+	C	1·2%	0·62 (0·36-1·07)	0·087	–	–	–

Ross, et al. Lancet Neurol 2011

LRRK2 R1628P

- Estimated sample size = 958 alleles or 479 samples/group

Logistic regression analysis of *LRRK2* genotypes and other factors associated with PD.

Factors	Univariate analysis		Multivariate analysis	
	OR	95%CI	OR	95%CI
LRRK2 genotypes				
CC/GC	1.95	1.22–2.12	1.81	1.10–2.97
GG	1			
Male vs Female	1.81	1.40–2.34	1.84	1.41–2.41
Ethnicity				
Thai	1.71	1.25–2.35	1.61	1.16–2.24
Chinese	1.56	1.00–2.43	1.47	0.92–2.34
Thai-Chinese	1			
Family History vs none	19.09	9.52–61.58	20.42	6.29–66.25
Smoking vs non-smoking	0.76	0.53–1.08	–	–

Comparison R1628P group & without

Association between *LRRK2* p.R1628P and clinical characteristics of PD.

Clinical characteristics	*LRRK2* R1628P genotype		*P*	OR	95%CI
	Yes *n* = 54 (%)	No *n* = 431 (%)			
Age at onset (mean ± SD)	56.0 ± 13.0	60.1 ± 12.2	0.021*	–	–
Disease duration (mean ± SD)	6.0 ± 4.5	5.6 ± 4.6	0.568	–	–
Family history	7 (13)	45 (10.4)	0.639	1.27	0.55–2.99
Bradykinesia	54 (100)	429 (99.5)	1.000	–	–
Rigidity	52 (96.3)	416 (96.5)	1.000	0.94	0.21–4.22
Rest tremor	47 (87)	388 (90)	0.478	0.74	0.32–1.75
Postural instability	12 (22.2)	105 (24.4)	0.866	0.89	0.45–1.75
Unilateral onset	49 (90.7)	496 (91.9)	0.792	0.87	0.32–2.32
Persistent asymmetry	30 (55.6)	259 (60.1)	0.558	0.83	0.47–1.46
Progressive disorder	48 (88.9)	343 (79.6)	0.142	2.05	0.85–4.95
≥10-year duration	9 (16.7)	53 (12.3)	0.386	1.43	0.66–3.10
Excellence response to L-dopa	37 (68.5)	311 (72.2)	0.631	0.84	0.45–1.55
Dopa-responsive ≥5 years	22 (40.7)	122 (29.5)	0.117	1.65	0.92–2.94
Hoehn and Yahr staging (mean ± SD)	3.0 ± 0.5	2.5 ± 0.8	<0.001*	–	–
Schwab-England ADL score (mean ± SD)	72.9 ± 18.0	81.9 ± 15.4	<0.001*	–	–
Duration of L-dopa treatment (months; mean ± SD)	53.4 ± 49.4	46.4 ± 45.1	0.287	–	–
Wearing-off/on-off	12 (22.2)	92 (21.3)	0.861	0.99	0.49–2.01
Freezing	8 (14.8)	34 (7.9)	0.118	2.03	0.89–4.66
Dopa-induced Dyskinesia	6 (11.1)	46 (10.1)	0.819	1.05	0.42–2.58

Summary

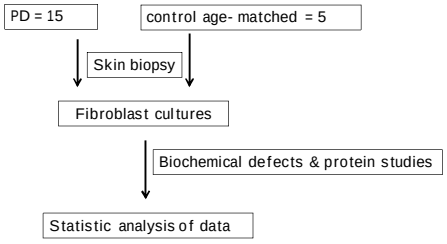
- GBA + parkin mutations + LRRK2 R1628P variant:
  - Association OR ~ 1.8 -25
  - 97 patients (20%)
  - 3 patients with GBA mut. + 1 with parkin mut. also had R1628P
  - Most of the mutations are unique.
- Patients with GBA mutations:
  - Earlier onset + more frequent positive family history + dyskinesia
- Parkin mutations may not be as common as in Europeans, Japanese
- LRRK2 R1628P: Confirmation of the association
  - Earlier onset + more rapid progression

Discussion

- Genetics factors as important risk of PD
- Specific genotypes –vary widely among diff. ethnics
- Key factor of successful treatment: Rx at the early stage
- Genetic tools + other biomarkers + neuroimaging

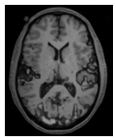
  → identify people at risk in the asymptomatic stage

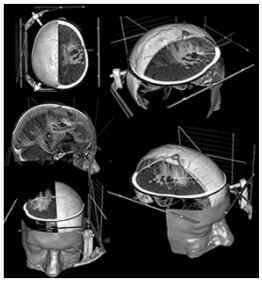
Fibroblast cultures



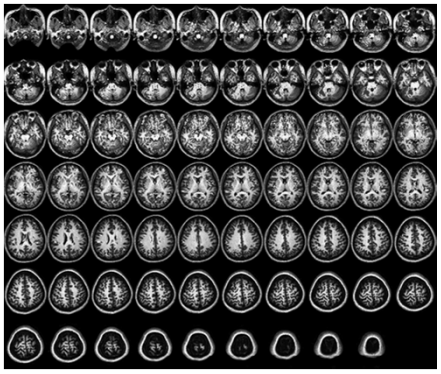
Neuroimaging

- Diffusion tensor imaging, Functional MRI





Neuroimaging: DTI_LOPD



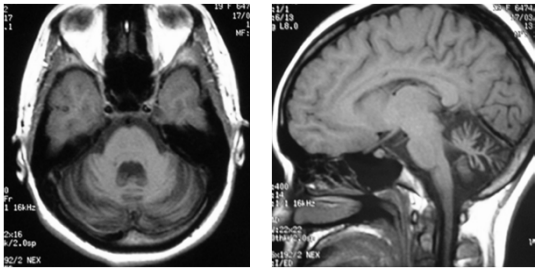
Neurogenetic diseases

Epidemiological data

- Identify common diseases/ risk alleles
- Education/ training
- Healthcare system
  - Specialists
  - Referral system
  - Lab
- Registration/ systematic database

Spinocerebellar Ataxias

Genotype-phenotype



Frequencies (%) of familial ataxias

(No. of Families)	SCA1	SCA2	MJD	SCA6	SCA7	DRPLA
China (84, 120)	5, 6	6, 7	48, 49	0, 3	0, 1	0, 0
India (42, 77)	8, 16	26, 25	5, 3	0, 0	0, 3	0, 0
Japan (202, 330)	3, 6	5, 2	43, 28	11, 26	NT, 1	20, 7
Korea (87)	0	13	5	7	0	3
Singapore (58)	11	33	42	6	0	6
Thailand (86)	21	12	47	7	0	0
Taiwan (74)	5	11	47	11	2.7	1
Australia (88)	16	6	12	17	2	0
France (146)	15	10	**32**	1	NT	NT
Germany (77)	9	10	42	22	NT	NT
Italy (116, 183)	24, 21	47, 24	0, 1	2, 1	2, 1	<1, 1
Portugal (269)	<1	2	52	<1	1	5
UK (19)	37	47	5	NT	NT	NT
USA (178)	6	15	21	15	4	NT
South Africa (54)	41	13	4	2	22	NT

*NT = not test

Adult-onset SCAs

Table 1 Frequencies of the common spinocerebellar ataxias in Thai patients

	Familial group (%) N = 86	Sporadic group (%) N = 179	Total (%) n = 265
SCA1	19 (22.10)	19 (10.61)	38 (14.34)
SCA2	10 (11.63)	12 (6.70)	22 (8.30)
MJD	40 (46.51)	21 (11.73)	61 (23.02)
SCA6	6 (6.98)	4 (2.23)	10 (3.77)
Total	75 (87.21)	56 (31.28)	131 (49.43)
Patients without mutation	11 (12.79)	123 (68.72)	134 (50.57)

SCA in Thailand

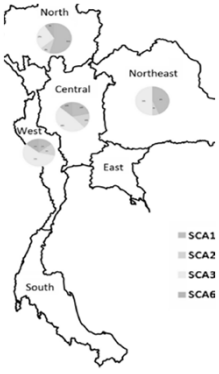


Table 2 Comparison of clinical profile and features of unrelated Thai patients with SCA1, SCA2, MJD and SCA6

	SCA1	SCA2	MJD	SCA6	*p*-value*
Total numbers	21	15	39	8	
Sex (M/F)	11/10	8/7	14/25	4/4	0.500
Age at onset (years)					
Mean age at onset	38.43	41.47	39.97	43.5	0.715
SD	10.14	13.01	12.17	6.76	
Range	15 – 55	19 - 60	16 - 64	34 - 58	
Duration (years)					
Mean duration	5.43	3.93	6.62	6	0.328
SD	5.13	2.99	5.01	5.90	
Range	1 - 20	1 - 10	0.25 - 22	1 - 18	
Positive family history (%)	16 (76.2)	13 (86.7)	32 (82.1)	7 (87.5)	0.900
CAG repeat size (repeats)					
Mean	50.14	37.40	69.97	21.88	
SD	6.27	4.47	4.04	0.83	
Range	41 – 65	32 - 52	62 - 78	21 - 23	
Clinical features (%)					
Slow saccade	12 (57.1)	7 (46.7)	21 (53.8)	2 (25)	0.454
Horizontal nystagmus	5 (23.8)	4 (26.7)	34 (87.2)	6 (75)	**0.0000002****
Vertical nystagmus	0 (0)	1 (6.7)	6 (15.4)	3 (37.5)	**0.026****
Opthalmoparesis	6 (28.6)	3 (20.0)	26 (66.7)	2 (25)	**0.002****
Pale optic disc	1 (4.8)	0 (0)	2 (5.1)	1 (12.5)	0.610
Hyperreflexia	19 (90.5)	5 (33.3)	26 (66.7)	7 (87.5)	**0.002****
Babinski's sign	11 (52.4)	5 (33.3)	17 (43.6)	5 (62.5)	0.310
Areflexia	0 (0)	5 (35.7)	9 (23.1)	0 (0)	**0.011****
Sensory impairment	4 (19.0)	3 (20.0)	9 (23.1)	0 (0)	0.630
Parkinsonism	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Dystonia	1 (4.8)	0 (0)	1 (2.6)	0 (0)	0.475
Chorea	0 (0)	0 (0)	1 (2.6)	0 (0)	1.000
Dementia	0 (0)	1 (6.7)	0 (0)	1 (12.5)	0.074
Facial fasciculation	2 (9.5)	0 (0)	5 (12.8)	0 (0)	0.579
SARA					
Mean scale	16.97	13.18	16.76	15.71	0.767
SD	7.45	3.66	7.27	7.24	
Range	4 - 30	9 - 20	8 - 35	3.5 - 27	

Huntington's disease

- CAG repeats
  - < 27 asymptomatic
  - 27-35 Intermediate
  - 36-39 HD incomplete penetrance
  - >39 HD complete penetrance

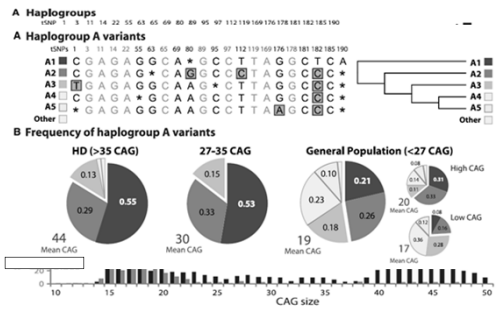
Huntington's disease

Comparison of the distributions of triplet repeats in the control and HD chromosomes in the Chinese and white populations

	Boston (Duyao et al[6])	Cardiff (Snell et al[5])	Vancouver (Kremer et al[4])	Taipei (This study)
Normal controls	545	1160	600	159
Range of repeat numbers	11–34	9–34	10–39	9–29
Mean	19·71	18·29	18·4	17·36*
Median	19		18	17
SD	3·21	3·13		1·97
HD mutant genes	425	440	995	35
Range of repeat numbers	37–86	16–70	36–121	40–58
Mean	46·42	41·88	45·3	44·94†
Median	45		44	44
SD	6·68	6·67		4·15

Soong BW, Wang JT. J Med Genet 1995

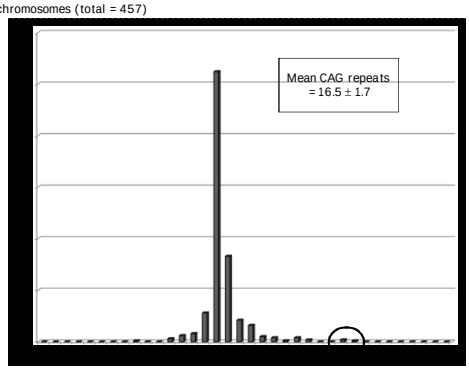
Huntington's disease



Warby SC, et al. Am J Hum Genet 2009

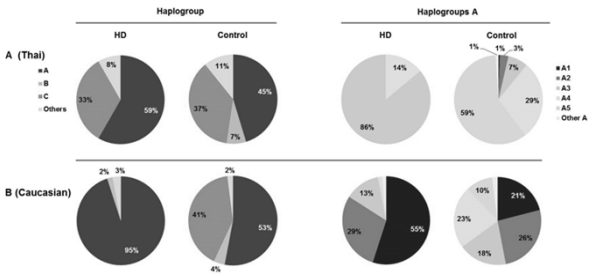
Huntington's disease

N of chromosomes (total = 457)

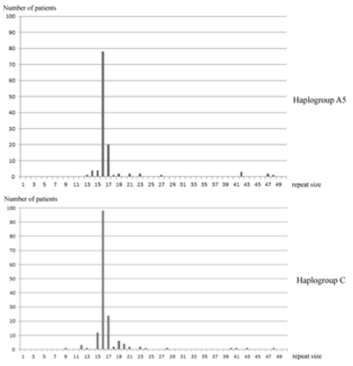


CAG repeat numbers

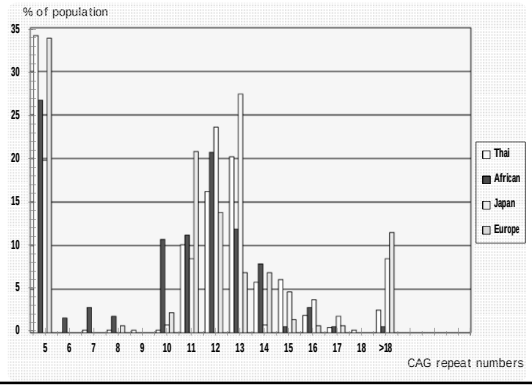
Huntington's disease



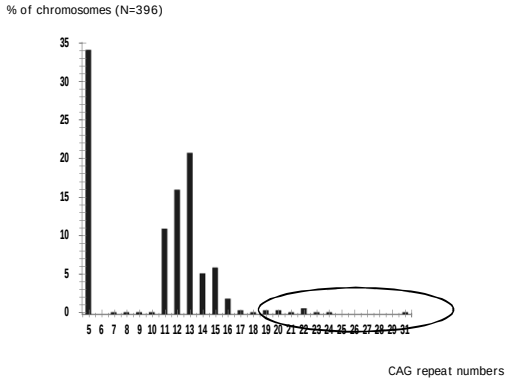
Huntington's disease



Myotonic dystrophy type 1



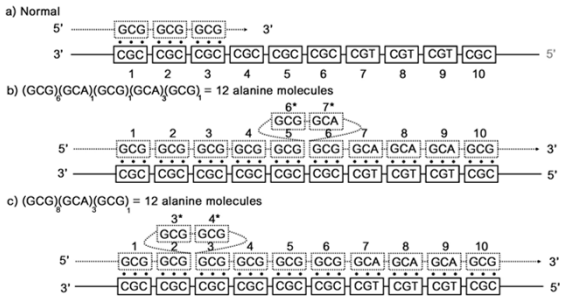
Myotonic dystrophy type 1



Myotonic dystrophy type 1

No. of CTG repeats	Thai	Africa	Taiwan	Japan	Europe	χ^2 Yates Thai-Africa (P-value)	χ^2 Yates Thai-Taiwan (P-value)	χ^2 Yates Thai-Japan (P-value)	χ^2 Yates Thai – Europe (P-value)
5-18	389	417	489	97	115	3.919	1.393	5.84	14.415
> 18	11	3	7	9	15	(0.0477)*	(0.2379)	(0.0157)*	(0.0001)*
Prevalence of DM	?	Almost 0	1/200000	1/20,000	1/8,000				

Oculopharyngeal muscular dystrophy



Oculopharyngeal muscular dystrophy

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Clinical Study

Mutation and haplotype analysis of oculopharyngeal muscular dystrophy in Thai patients

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ABSTRACT

Oculopharyngeal muscular dystrophy (OPMD) is an inherited neuromuscular disease associated with a short trinucleotide repeat expansion in Exon 1 of the *PABPN1* gene. OPMD is uncommon in East Asian populations, and there have been no previous reports of Thai patients. We studied clinical and molecular genetic features of six unrelated Thai patients with autosomal dominant OPMD. All patients had expansions of the guanine-cytosine-guanine (GCG) repeat ranging from three to seven additional repeats in the *PABPN1* gene. Haplotype analysis showed that these mutations might have originated independently. Analysis of the size of the GCG repeat in the *PABPN1* gene in 200 Thai control patients showed that 0.5% of the control subjects possessed $(GCG)_7$, thereby suggesting that the prevalence of autosomal recessive OPMD in the Thai population was approximately 1 in 160,000. In conclusion, our data suggest that OPMD in Thailand may be more common than previously thought.

To fight against genetic diseases

- Epidemiological data
- Risk alleles of complex genetic diseases
  - Specialist team
  - Standard lab
  - Funding

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