ジストニアいろいろ

東京都立神経病院神経小児科
熊田聡子

本日の内容

- 瀬川病
- チロシン水酸化酵素欠損症
- ドパミンの受け手側(線条体投射神経細胞)の機能異常による運動異常症

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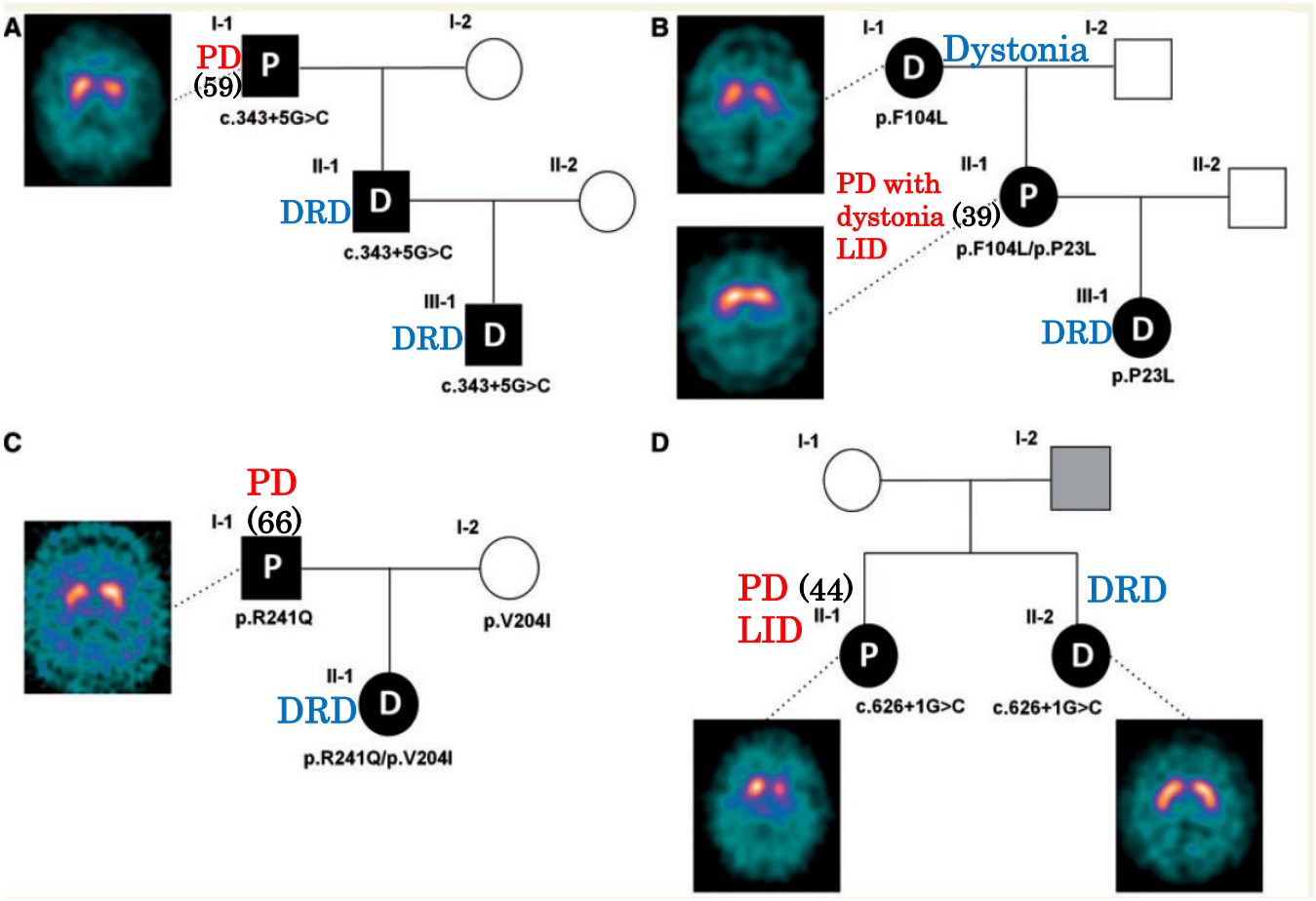
瀬川病（著明な日内変動を伴う遺伝性進行性ジストニア）

- GTPシクロヒドロラーゼⅠ（*GCH-1*）遺伝子異常に伴う常染色体優性遺伝性ジストニア.
- 通常小児期に発症（平均6歳）.
- 症状は女性に優位.
- ジストニアは四肢から発症，一側下肢の内反足による歩行障害を初発症状とすることが多い.
- 症状は進行性で10代半ばにはジストニアは全肢に及びその後も程度が増悪.
- 30代以降は症状の進行はほとんど認めなくなるが，振戦を主とするパーキンソン症状が出現.
- 約80%の患者で症状に著明な日内変動がある(年齢とともにめだたなくなる).
- 正常の知能をもち，小脳や感覚や自律神経系の障害は認めない.
- L-dopa少量で劇的にそして持続的に効果があり，長期投与に伴う運動障害を認めない.
- 病理学的には中脳黒質のメラニン含有細胞の減少のみを認める.

Parkinson's disease in GTP cyclohydrolase 1 mutation carriers.

(Mencacci NE, et al., Brain 2014)



DRD; dopa-responsive dystonia
PD; Parkinson's disease
LID; levodopa-induced dyskinesias
( ); age at onset

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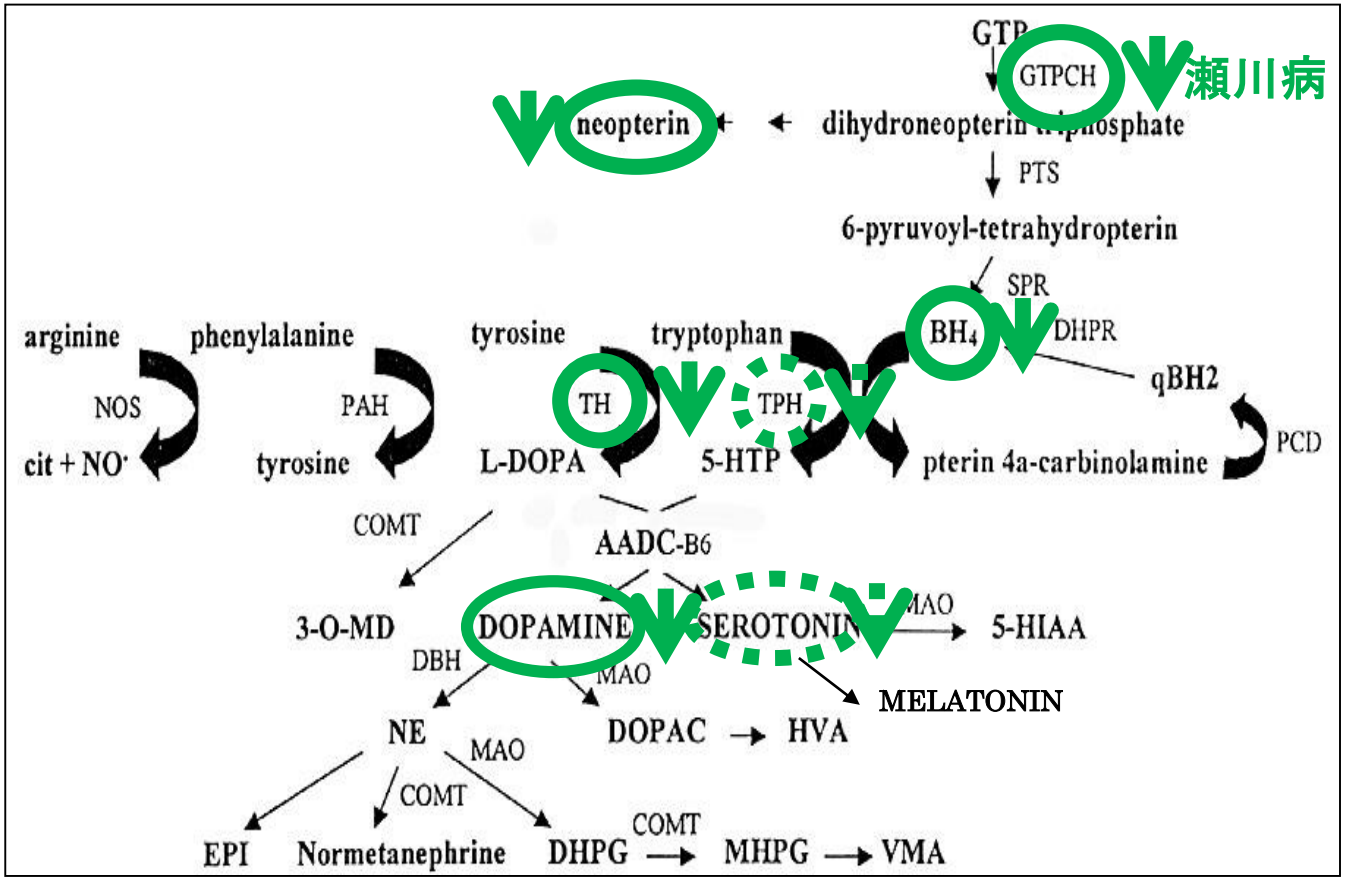
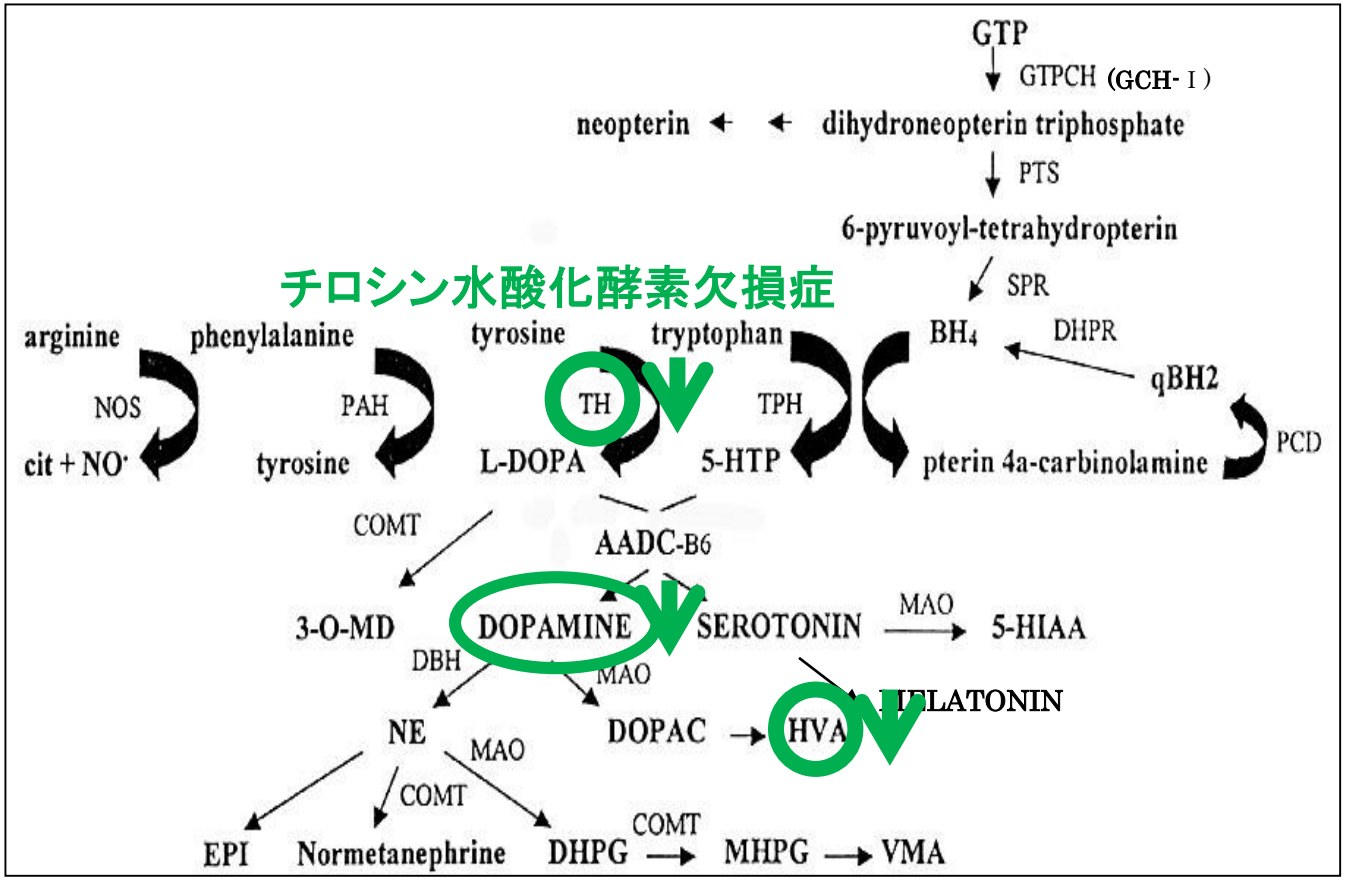
モノアミン代謝異常症


GTP
GTPCH
瀬川病
neopterin
dihydroneopterin triphosphate
PTS
6-pyruvoyl-tetrahydropterin
SPR
arginine
phenylalanine
tyrosine
tryptophan
BH4
DHPR
qBH2
NOS
PAH
TH
TPH
cit + NO·
tyrosine
L-DOPA
5-HTP
pterin 4a-carbinolamine
PCD
COMT
AADC-B6
3-O-MD
DOPAMINE
SEROTONIN
MAO
5-HIAA
DBH
MAO
MELATONIN
NE
DOPAC
HVA
MAO
COMT
COMT
EPI
Normetanephrine
DHPG
MHPG
VMA

モノアミン代謝異常症


GTP
GTPCH (GCH-Ⅰ)
neopterin
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PTS
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SPR
チロシン水酸化酵素欠損症
arginine
phenylalanine
tyrosine
tryptophan
BH4
DHPR
qBH2
NOS
PAH
TH
TPH
PCD
cit + NO·
tyrosine
L-DOPA
5-HTP
pterin 4a-carbinolamine
COMT
AADC-B6
3-O-MD
DOPAMINE
SEROTONIN
MAO
5-HIAA
DBH
MAO
MELATONIN
NE
DOPAC
HVA
MAO
COMT
COMT
EPI
Normetanephrine
DHPG
MHPG
VMA

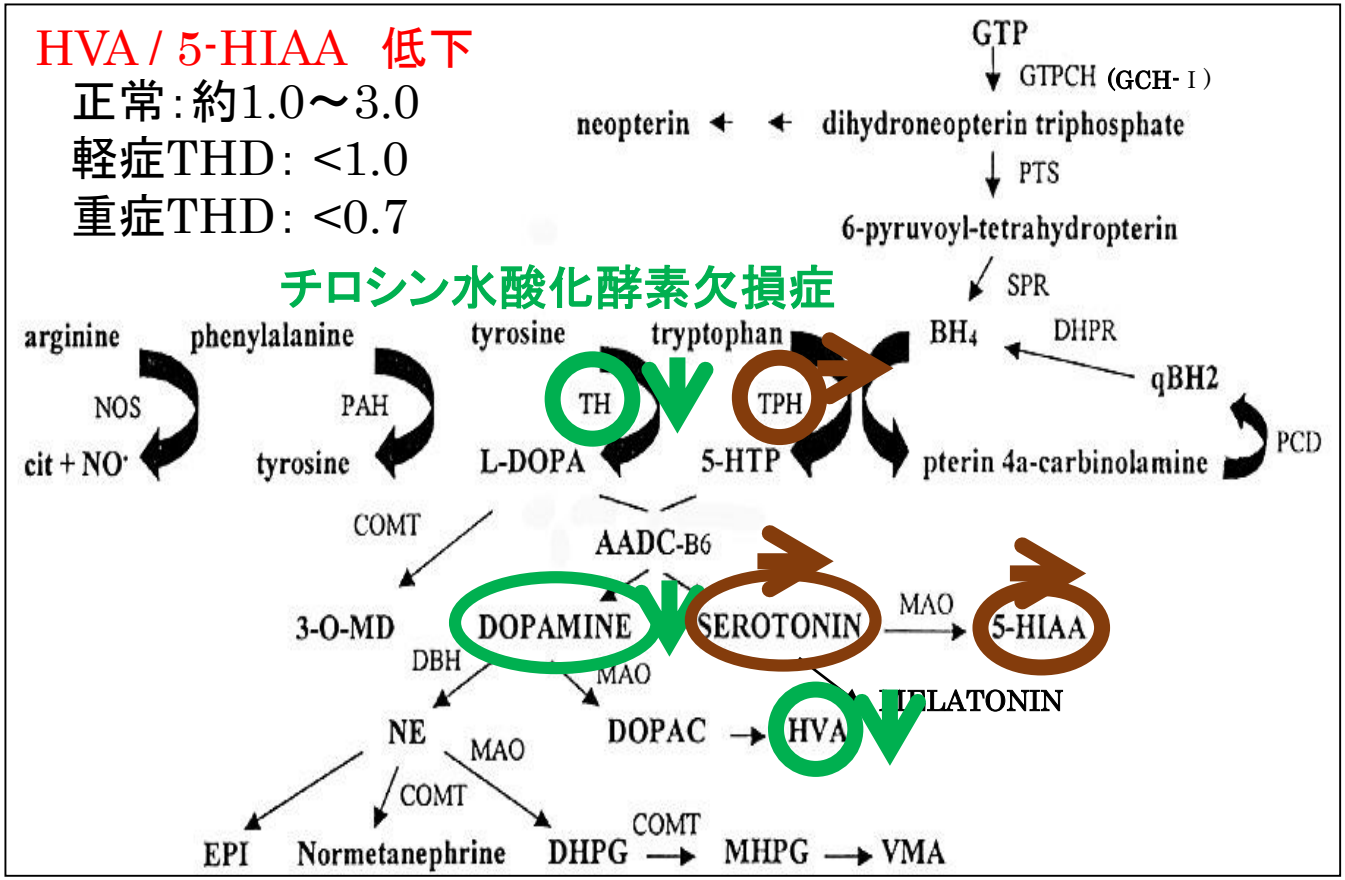
モノアミン代謝異常症

HVA / 5-HIAA　低下

正常：約1.0～3.0

軽症THD：<1.0

重症THD：<0.7



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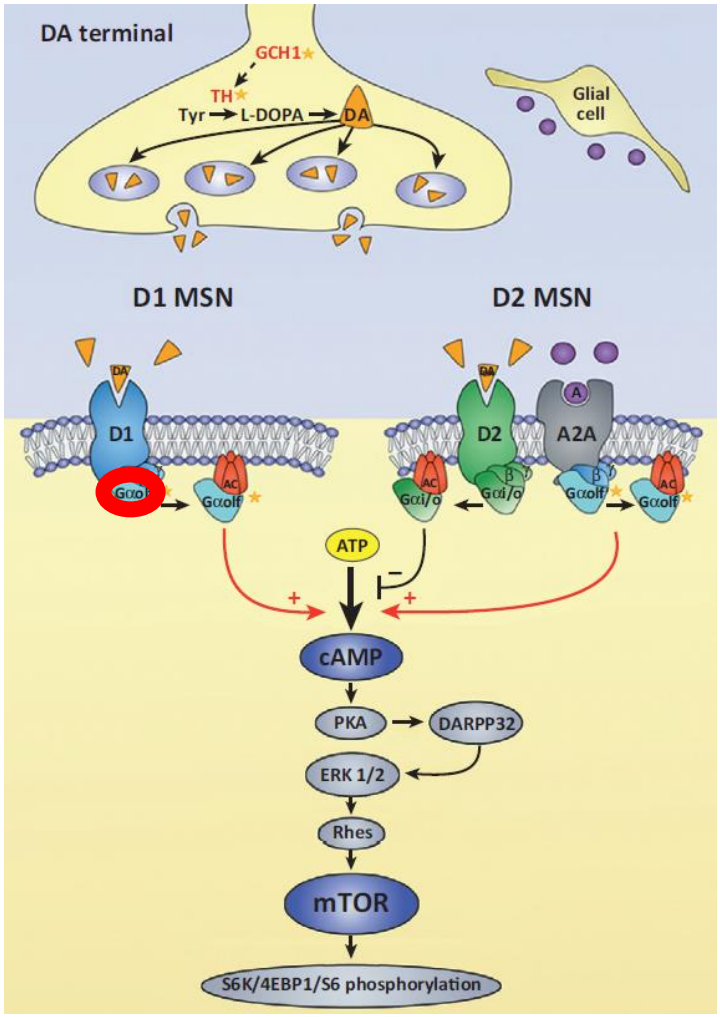
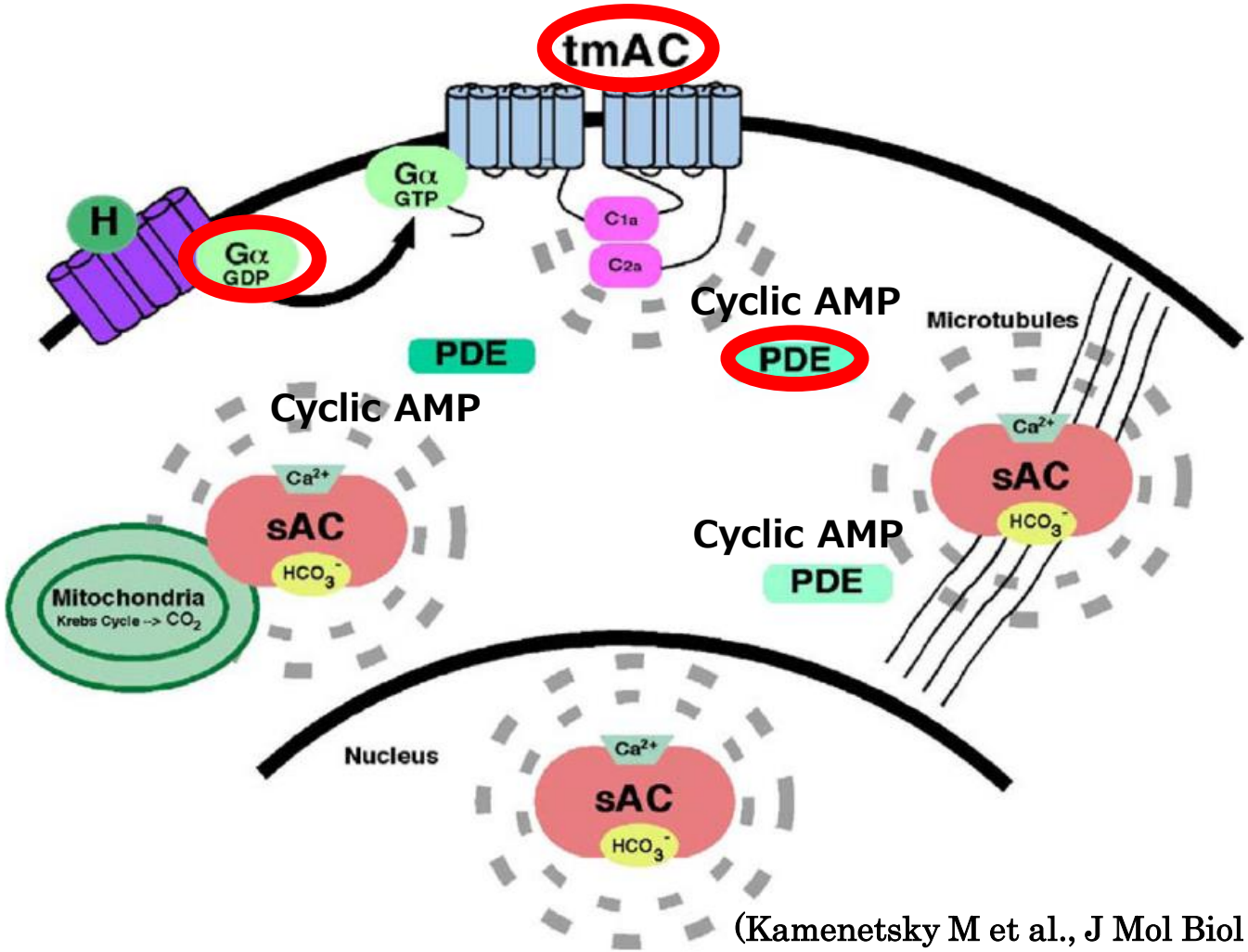
GNAL:

- Encodes a stimulatory α subunit for heterotrimeric G-protein complexes,
  - ✓ Selectively expressed in the striatal neurons.
  - ✓ Activates adenylyl cyclase to produce cAMP, following stimulation of the D1 receptor.
- Loss of function mutations cause
  - ✓ autosomal dominant,
  - ✓ focal~generalized dystonia,
  - ✓ characterized by cranio-cervical involvement.



(Goodchild RE, et al., Trends Neurosci 2013)



(Kamenetsky M et al., J Mol Biol 2006 より改変.)

ADCY5:

- Encodes transmembrane adenylyl cyclase highly expressed in striatum and myocardium.
- Mutations cause autosomal dominant, paroxysmal or non-paroxysmal, chorea-myoclonus-dystonia, with or without facial twitches.
- Normal brain MRI.

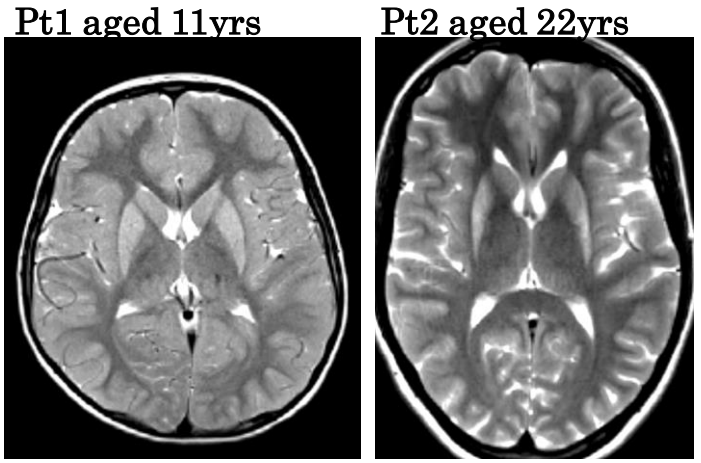
(Mencacci NE et al., Neurology 2015)

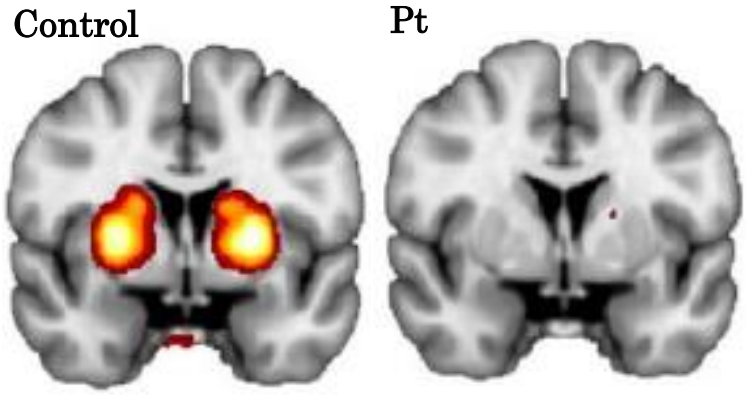
PDE10A

- Encodes a phosphodiesterase highly and selectively present in medium spiny neurons in striatum.

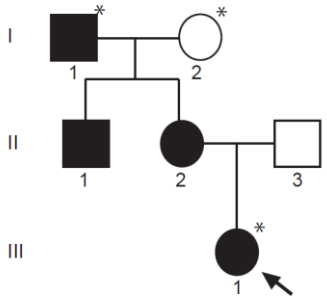
- Heterozygous mutations cause child-onset chorea with bilateral striatal lesions.
  No other neurological abnormalities including intellectual disability.
  Normal basal PDE10A activity, but disrupted activation by cAMP.
  (Mencacci NE, et al. Am J Hum Genet 2016)

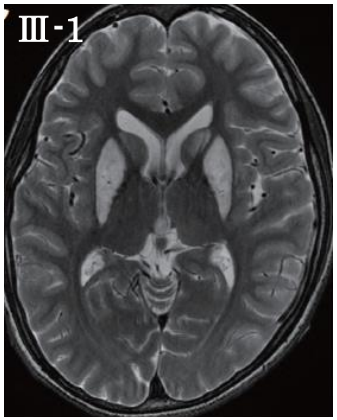
- Homozygous mutations cause early infantile-onset generalized dyskinesia, axial hypotonia, dysarthria, dysphagia with normal brain MRI findings.
  Mentality: normal ~ mildly affected. Epilepsy in one patient.
  Reduction in PDE10A level.
  (Diggle CP, et al., Am J Hum Genet 2016)

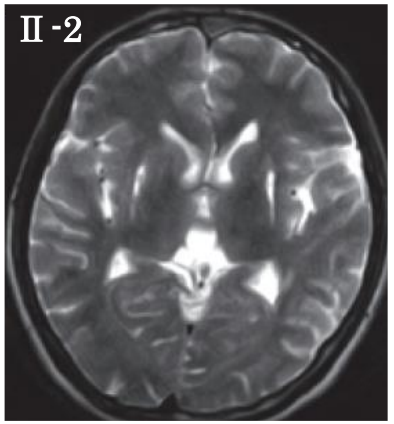




Autosomal dominant *PDE10A*-associated chorea with bilateral striatal lesions

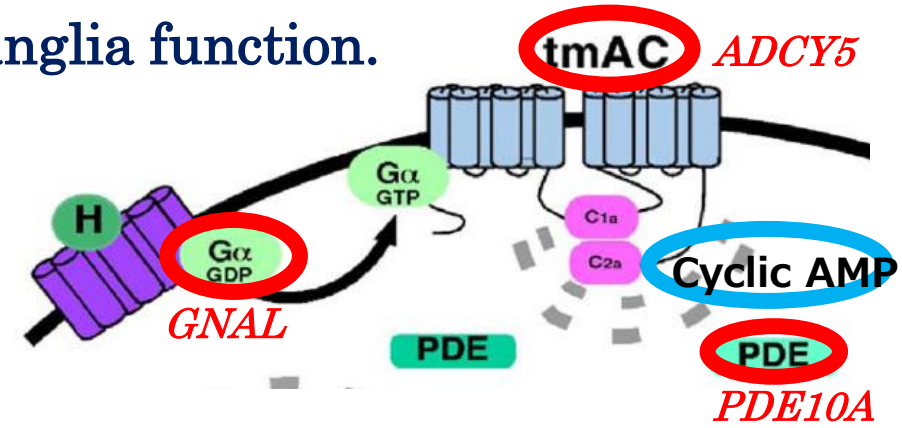






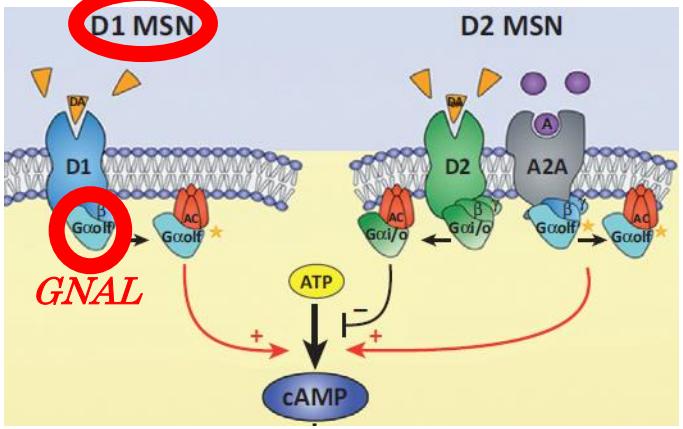
cAMP may play a key role in basal ganglia function. But how?

- Deficiency vs. Excess?
  - ✓ *GNAL* mutations → Deficiency
  - ✓ *ADCY5* mutations (gain of function?) → Excess?
  - ✓ *PDE10A* mutations → Excess

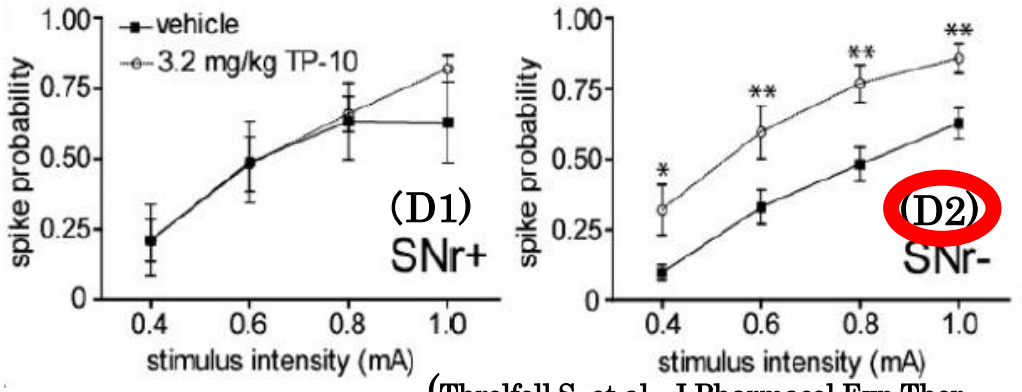


- ✓ PDE10A inhibitors improve cortico-basal ganglia function in Huntington disease mouse models.
- ✓ Decreased PDE10A in Huntington disease.

- D1 pathway vs. D2 pathway?



Effect of PDE10A inhibitor in Huntington mouse model



(Threlfell S, et al., J Pharmacol Exp Ther 2009)