Movement Disorder

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== Contents ==

1. Diagnostic criteria of PD
2. Genotype vs Phenotype
3. Targeting α-synuclein: novel treatment for Parkinson disease

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Diagnostic criteria for PD

Movement Disorders, Vol. 30, No. 12, 2015

REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[11] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

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Diagnostic criteria for PD

UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
- And at least one of the following:
  - muscular rigidity
  - 4–6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

(Hughes et al. 1992)

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Diagnostic criteria for PD

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

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Diagnostic criteria for PD

- Prerequisite: Presence of **Parkinsonism**

Bradykinesia — Bradykinesia is defined as slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts) as movements are continued.

AND

Rest tremor

and/or

Rigidity — 'lead-pipe' resistance. Cogwheeling without 'lead-pipe' rigidity (X)

Postural instability... → Not included in new criteria. Its presence early in disease suggest and alternative diagnosis

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Diagnostic criteria for PD

Diagnosis of **Clinically Established PD** requires:
1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of **Clinically Probable PD** requires:
1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion
   If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Although MDS-UPDRS rates PD, it does not define PD…

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Diagnostic criteria for PD

- Supportive Criteria
  1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
     a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
     b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
  2. Presence of levodopa-induced dyskinesia
  3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)
  4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

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Diagnostic criteria for PD

Absolute exclusion criteria: The presence of any of these features rules out PD:
- ☐ 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystagmus, macro square wave jerks, hypermetric saccades)
- ☐ 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
- ☐ 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
- ☐ 4. Parkinsonian features restricted to the lower limbs for more than 3 y
- ☐ 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
- ☐ 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
- ☐ 7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
- ☐ 8. Normal functional neuroimaging of the presynaptic dopaminergic system
- ☐ 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

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Diagnostic criteria for PD

Red flags
- ☐ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
- ☐ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
- ☐ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
- ☐ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
- ☐ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
  b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
- ☐ 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
- ☐ 7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
- ☐ 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep maintenance insomnia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, symptomatic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
- ☐ 9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
- ☐ 10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

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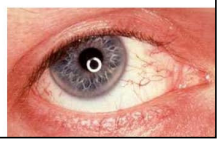
Genotype vs Phenotype

- Ataxia telangiectasia (AT)
  - Onset age 2-3 years and progressive
  - Oculomotor apraxia, dysarthria, truncal ataxia
  - Oculocutaneous telengiectasia (do not develop in the first years of life)
    : Conjunctiva, face, ears, and flexor crease
  - Immunodeficiency: decreased IgA and IgG
  - Increased risk for malignancy: leukemia, lymphoma
  - Elevated α-fetoprotein, decreased IgA and IgG
  - Cerebellar atrophy is typical
  - ***ATM*** gene: a protein kinase involved in DNA repair pathway
    → mutation cause null allele

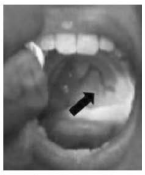


Genotype vs Phenotype

- Ataxia telangiectasia (AT)

Prominent Oromandibular Dystonia and Pharyngeal Telangiectasia in Atypical Ataxia Telangiectasia

Fatima Carrillo · Susanne A. Schneider · A. Malcolm R. Taylor · Venkataramanan Srinivasan · Raj Kapoor · Kailash P. Bhatia



Pat/ref no	Onset age (years)	Clinical features	Telangiectasia	AFP
Our patient	15	Predominantly craniocervical dystonia with oromandibular involvement; no ataxia	Pharyngeal wall only	↑
Bodensteiner [11]	9	Cervical (later generalized) dystonia, facial dyskinesias, myoclonus, "ataxia masked by dystonia"	Face, neck, trunk	↑
Koepp [13]	2	"Ataxic cerebral palsy", segmental dystonia (age 4), facial grimacing, ataxic gait	Conjunctival	↑
Goyal [12]	12	Cervical (then generalized) dystonia, myoclonus, chorea	Conjunctival	↑
Stell [14]	7	Arm and leg dystonia, myoclonus (age 9), ataxia (age 20), facial choreiform movements	Conjunctival	↑
Aguilar [10]	1.5	Recurrent pneumonia, truncal dystonia, oculomotor apraxia, cerebellar speech	Conjunctival, ears	n.d.

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Genotype vs Phenotype

- Ataxia telangiectasia (AT)

Ataxia telangiectasia presenting as dopa-responsive cervical dystonia

Gavin Charlesworth, MRCP
Mahavir D. Mohire, DM
Susanne A. Schneider,

ABSTRACT

Objective: To identify the cause of cervical dopa-responsive dystonia (DRD) in a Muslim Indian family inherited in an apparently autosomal recessive fashion, as previously described in this journal.

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Genotype vs Phenotype

- *ADCY5*
  - 1 of 9 membrane-bound adenylyl cyclases that convert ATP to cAMP
  - First described in 2001, "Familial dyskinesia and facial myokymia"
  - Familial choreoathetosis with exacerbations during drowsiness
  - Paroxysmal dyskinesia
  - Myoclonus dystonia
  - Benign hereditary chorea

Chorea, facial dyskinesia, dystonia, axial hypotonia, myoclonus, spasticity, upward gaze palsy, motor regression, intellectual disability…..

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Genotype vs Phenotype

- *ANO3* (encoding a Ca^{++}-gated chloride channel)

Mutations in *ANO3* Cause Dominant Craniocervical Dystonia: Ion Channel Implicated in Pathogenesis

Gavin Charlesworth,[1] Vincent Plagnol,[2] Kira M. Holmström,[1] Jose Bras,[1] Una-Marie Sheerin,[1] Elisavet Preza,[1] Ignacio Rubio-Agusti,[3,4] Mina Ryten,[1,8] Susanne A. Schneider,[5] Maria Stamelou,[3] Daniah Trabzuni,[1,6,8] Andrey Y. Abramov,[1] Kailash P. Bhatia,[3,7,*] and Nicholas W. Wood[1,2,7,*]

The American Journal of Human Genetics 91, 1041–1050, December 7, 2012

- Cervical dystonia followed by laryngeal dystonia
  : usually remain focal/segmental, but evolution to generalized dystonia has been reported
- Tremor (leading to misdiagnosis as essential tremor)
- Subcortical myoclonus (leading to myoclonus dystonia)
- Dysarthria + blepharospasm + motor tics

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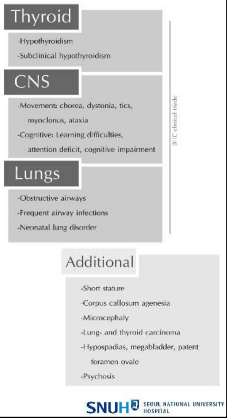
Genotype vs Phenotype

- Benign hereditary chorea
  - *NKX2-1* (TITF-1) mutation
  - Autosomal dominant
  - Early onset chorea and often hypotonia and delayed motor developement
  - Minimal or no disease progression
  - No MRI abnormality



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Genotype vs Phenotype

- Benign hereditary chorea

Diagnose[a]	Gene	Genetic clues[a]	Main clinical features
Benign hereditary chorea (BHC)	*NKX2-1*	AD, early onset	Hypotonia, chorea, lung and thyroid symptoms
Myoclonus dystonia (DYT11)	*SGCE*	AD, maternal imprinting	Myoclonus of short duration (<150 ms), dystonia
BHC like disorder	*ADCY5*	AD	Paroxysmal choreic/dystonic movements, facial myokymia
Huntington's disease[b]	*HTT*	AD, anticipation	Chorea, athetosis, worsen over time, psychiatric symptoms and dementia
Huntington's disease - like disorder 1–4[c]	*PRNP, JPH3, TBP*	AD/AR	Chorea, athetosis, worsen over time, psychiatric symptoms and dementia
Other Huntington's - like disorders	*RNF216*	AR	Cerebellar ataxia, behavioral problems, dementia, white matter lesions, hypogonadotropic hypogonadism, in some families chorea and athetosis
Ataxia telangiectasia	*ATM*	AR	Oculomotor apraxia, telangiectasia, dystonia
AOA1 (Ataxia with oculomotor apraxia 1)	*APTX*	AR	Early-onset cerebellar signs, sensory neuropathy, cognitive decline, and oculomotor deficits
Friedreich ataxia	*FXN*	AR	Sensory disturbances, spaticity, hyporeflexia, rare presentations with chorea and myoclonus
Hereditary ataxias (SCA1,2,3,6,7,17, DRPLA)	*ATXN1–3, CACNA1A, ATXN17, TBN, ATN1*	AD	Progressive ataxia, cerebellar (and brainstem) atrophy
Glucose transporter type 1 deficiency	*SLC2A1*	AD	Chorea and often mental retardation associated with a combination of paroxysmal ataxia, dystonia and/or epilepsy
Neurodegeneration with brain iron accumulation (NBIA)[d]	*PANK2*	AR/X-linked/AD	Typical MRI findings, dystonia, progression, cognitive decline

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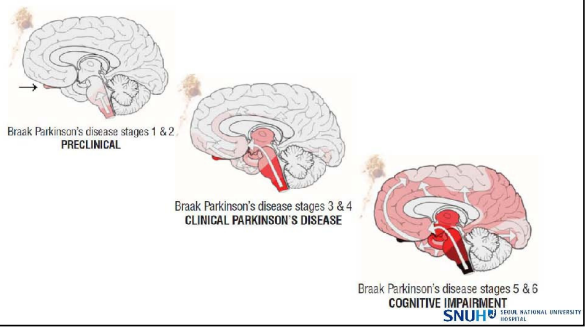
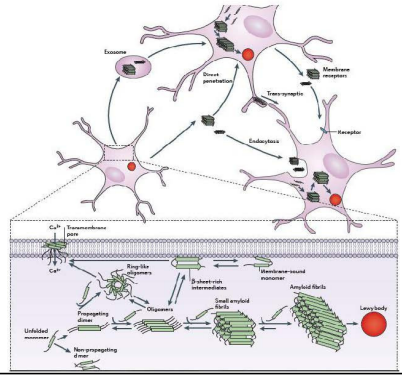
Targeting α-synuclein

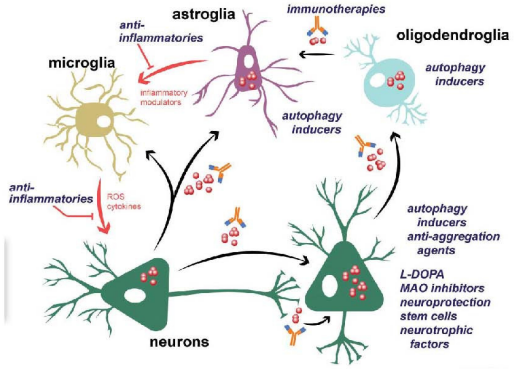
- Progression of PD pathology



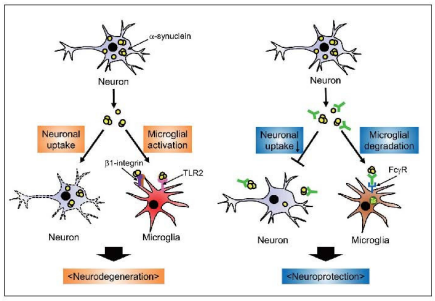
Targeting α-synuclein



Targeting α-synuclein



Anti-α-synuclein immunotherapy for Parkinson disease



"Clearance and Blocking"

⇩

Reduce aggregation
Reduce cellular toxicity
Reduce spreading of pathology