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## Movement Disorders

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**W**e provide an update on the state of translational research in movement disorders, using examples of Huntington disease, Parkinson disease, and dystonia. While substantial progress in our understanding of these disorders has been achieved, development of neuroprotective treatments remains an unrealized goal. Here we highlight some of the emerging research areas that show the most promise for translational research in Huntington disease, Parkinson disease, and dystonia. Aetiology and pathogenesis, biomarker directions, and causal treatment opportunities are discussed for each disease, followed by a brief discussion drawing attention to important translational initiatives.

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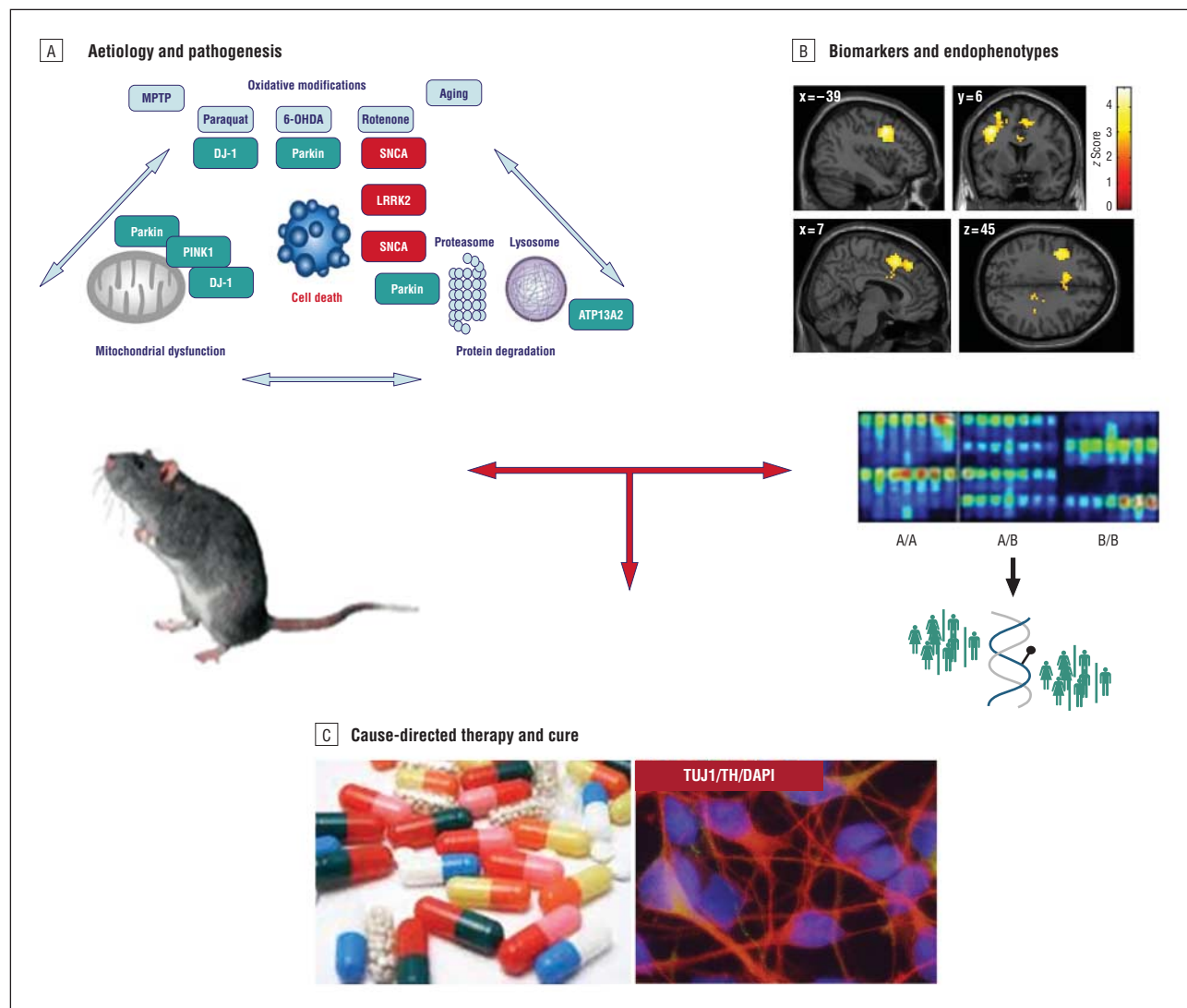
While Huntington disease (HD) is a monogenic disorder that is pathologically relatively defined, neurogenetic and clinico-pathological studies have shown that there is considerable heterogeneity in Parkinson disease (PD) and dystonia. Most cases of PD and dystonia represent complex diseases presumed to be caused by the interaction of genetic susceptibilities and environmental triggers. Despite these differences, there are important commonalities in disease pathogenesis and research goals. It is imperative to identify critical disease mechanisms within each disorder to develop neuroprotective therapies. Moreover, biomarkers are urgently needed to aid diagnosis, monitor disease progression, and, as new medicines are introduced, detect the patient's response to treatment. These biomarkers could be divided into trait markers that evaluate risk of disease in presymptomatic individu-

als, state markers assessing the presence of established (often covert or premanifest) disease, and rate markers capable of evaluating the progression of the disease. Herein, we provide the reader with an "ABC"-type progress report on HD, PD, and dystonia. We categorized recent developments according to aetiology and pathogenesis, biomarkers, and cause-directed therapy (**Figure 1**). Each disease section is concluded by a brief discussion that highlights specific research initiatives and translational mandates. Owing to the uniform aetiology of HD and the relatively advanced level of basic research for this disorder, we focused on clearance of mutant huntingtin (Htt) as the most logical therapeutic target, whereas both the PD and dystonia sections provide a more general overview on translational efforts and future perspectives.

### HUNTINGTON DISEASE

Huntington disease is a monogenic disorder. It is caused by an expansion of the CAG trinucleotide repeat coding for a polyglutamine tract in the Htt protein<sup>1</sup> with a well-described inverse correlation between repeat numbers, age at onset, and

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**Figure 1.** An “ABC”-type scheme to categorize recent developments of translational research in movement disorders. Translational developments were grouped according to aetiology and pathogenesis, biomarkers and endophenotypes, and cause-directed therapy and cure. A, The identification of the Huntington disease gene and of monogenic forms of Parkinson disease and dystonia has greatly advanced our understanding of underlying disease mechanisms, as illustrated here for the “Bermuda Triangle” of Parkinson disease, consisting of oxidative modification, mitochondrial dysfunction, and impaired protein degradation. B, Biomarker development efforts range from the identification of cerebrospinal fluid markers and gene expression profiles to electrophysiological imaging and neuroimaging (endophenotypes). The latter approach is exemplified by a functional magnetic resonance imaging experiment resulting in z score maps that delineate voxels with relative overactivity during internally selected movements in asymptomatic carriers of a single mutant *Parkin* allele relative to healthy noncarriers. C, Using animal models on the one hand and genetically well-characterized individuals on the other has resulted in the development of some still-experimental cause-directed therapies. Some of the limitations imposed by the incomplete success in reproducing human disease(s) in animal models and the paucity of brain tissue from living patients may be overcome by the engineering of human fibroblasts into neurons via induced pluripotent stem cells.

the presence of polyglutamine protein-containing inclusions.

### Aetiology and Pathogenesis

**Mutant Htt Disrupts Multiple Cellular Pathways.** Following the discovery of the *Htt* gene in 1993, various cell culture and animal models of HD have been developed to study pathological functions of the mutant protein. These studies revealed that expression levels of mutant Htt strongly correlate with phenotype severity, as best demonstrated through a conditional mouse model where elimination of mutant Htt expression resulted in reversal of the pathological phenotype.<sup>2</sup> The accumulation of mutant Htt presumably leads to alterations in multiple

cellular pathways including gene transcription, energy metabolism, axonal transport, synaptic transmission, and vesicle release.<sup>1</sup>

**Accumulation and Clearance of Mutant Htt.** The presence of intracellular aggregates in the HD brain suggests a key role for aggregate formation in HD pathogenesis, but a direct causal link has not been established. Recent studies indicate that soluble forms of mutant Htt may be more toxic than insoluble aggregated forms.<sup>3</sup> Similarly, sequestration of toxic forms of mutant Htt into insoluble aggregates can be protective because it prevents monomeric or oligomeric mutant Htt from exerting its toxic effects and provides the cell with an opportunity of delayed protein degradation.<sup>1,3</sup>

It remains controversial whether the ubiquitin proteasome system, which is responsible for selectively degrading damaged or misfolded proteins, can also degrade mutant Htt. While proteasomal inhibitors lead to the formation of Htt aggregates<sup>4</sup> and ubiquitin has been found in Htt-containing inclusion bodies, other studies have suggested that polyglutamine tracts cannot be degraded by the proteasome.<sup>5</sup> An alternative method of degradation that removes damaged or aggregated long-lived proteins or organelles is the autophagy-lysosome pathway. Here, cytoplasmic content is sequestered in double-membrane autophagosomes that fuse to lysosomes for degradation.<sup>6</sup> The importance of basal autophagic activity in neurons has been demonstrated by the presence of ubiquitinated protein inclusions and neurodegeneration in mice with deficient neuronal autophagy.<sup>6</sup> While autophagy appears to play an important protective role in HD,<sup>6</sup> current approaches to modulate autophagy result in its global and nonspecific activation that could have deleterious consequences in neurons in the context of long-term treatment.

### Biomarkers

While the diagnosis of HD (state) currently involves a genetic test, which has 100% sensitivity, standard clinical tools for assessing progression (rate) are not useful for distinguishing between symptomatic benefit and disease modification. Numerous disease-modifying treatments that have been shown to have efficacy in animal models of HD await clinical trials in humans.<sup>1</sup> Several candidate HD biomarkers have emerged in recent years.<sup>1</sup> For example, structural magnetic resonance imaging studies demonstrate widespread cerebral changes and white matter abnormalities in the HD brain. These studies also suggest that striatal volume loss may be a useful surrogate marker of disease progression.<sup>1</sup> Functional magnetic resonance imaging is sensitive to very early striatal dysfunction, suggesting that it could be used to identify neural degeneration even before the onset of clinical symptoms.<sup>1</sup> In addition to neuroimaging studies, other strategies are used to identify biomarkers in bodily fluids. Unbiased proteomic, genomic, and metabolomic approaches have revealed significant alterations in peripheral blood that in some cases appear to correlate with disease progression.<sup>1</sup> Most biomarker studies are still in the early stages of development, and their universal approval will depend on validation of putative markers in larger longitudinal clinical studies.

### Cause-Directed Therapy

**Stimulation of Autophagy to Degrade Mutant Htt.** Recent data suggest that selective targeting of the mutant protein for degradation can be achieved through specific posttranslational modifications.<sup>7,8</sup> For example, acetylation and phosphorylation of mutant Htt promote formation of more degradable or less toxic species of mutant Htt.<sup>7</sup> Of the various posttranslational modifications studied in HD, acetylation of mutant Htt appears particularly amenable to therapeutic interventions. Protein acetylation is very dynamic and maintained by 2 classes of functionally antagonistic enzymes: the protein acetyl-

lases (histone acetyltransferases) and the deacetylases (histone deacetylases).<sup>9</sup> Interestingly, histone deacetylase inhibitors that promote acetylation have been previously shown to be neuroprotective in various HD models,<sup>9</sup> but their precise mechanism of protection has not been elucidated. For therapeutic purposes in HD, it would be advantageous to identify histone deacetylase inhibitors that primarily promote clearance of mutant Htt. Although it is presently unclear whether class-specific or isoform-specific inhibitors will be more effective, it is anticipated that they would have fewer adverse effects and thus be better tolerated during long-term administration.<sup>9</sup>

**Elimination of Mutant Htt by Interfering With RNA Translation.** Synthetic small interfering RNAs leverage the naturally occurring process of RNA interference by directing sequence-specific degradation of messenger RNA (mRNA) after entry into cells.<sup>10</sup> Antisense oligonucleotides are single-stranded short nucleotides that suppress synthesis of the targeted protein.<sup>10</sup> Although delivery remains a key challenge for translational success with long-term therapy, these approaches provide promising new therapeutic strategies through reduced production of mutant Htt. Allele-specific silencing of mutant Htt by targeting associated single-nucleotide polymorphisms represents an attractive strategy because it spares the wild-type protein.<sup>10</sup> On the other hand, partial suppression of both wild-type and mutant Htt was found to be both effective and well tolerated. While these studies support the therapeutic potential of simultaneous partial suppression of wild-type and mutant Htt, the ultimate validation of these approaches for HD will only be revealed as they progress into clinical trials.

### Discussion

Intracellular protein aggregation is a hallmark of a wide array of neurological disorders, including tauopathies, synucleinopathies, TDP-43 proteinopathies, and polyglutamine disorders. Although the precise relationship between protein aggregation and disease pathogenesis is unclear, several studies using mouse genetics, lentiviral technologies, and RNA interference have shown that elimination of the accumulation-prone proteins permits symptomatic reversal in different neurodegenerative models. While these studies do not establish a causative link between protein aggregation and neurodegeneration, they clearly suggest that elimination of accumulated (or to-be-misfolded) proteins may alleviate underlying cellular dysfunction and potentiate recovery across different disorders. Preclinical studies in animal models of HD have confirmed that small interfering RNAs delivered by direct central nervous system administration silence mutant Htt and ameliorate neuropathology and abnormal behaviors. Practical considerations for allele-specific approaches that target the mutant allele include degree of discrimination between mutant and wild-type Htt in the HD population, selectivity for Htt mRNA over other transcripts, and doses required for silencing mutant Htt in vivo. Similarly, in the case of autophagy-based therapeutics, selectivity must be achieved to degrade only accumulations of mutant Htt and not functional cellular structures. Posttranslational modifications

of the mutant protein offer a promising opportunity for such selective clearance. Translational success for all approaches will depend on selective delivery of the therapeutic agent to the target region of interest and safety with long-term exposure in patients with HD.

## PARKINSON DISEASE

It is now recognized that PD is not a single nosological entity but that instead there are several forms of typical PD. Most feature formation of Lewy inclusion bodies containing insoluble  $\alpha$ -synuclein (SNCA) aggregates in cell bodies, dystrophic neurites, and presynaptic terminals.

### Aetiology and Pathogenesis

**Several Variants of Typical PD.** Parkinsonism encompasses conditions of either genetic or environmental aetiology, or a combination of both.<sup>11</sup> Under the former category, it is believed that rare SNCA gene mutations together with aging (but without an environmental trigger) promote widespread neurodegeneration and inclusion formation, where SNCA production inversely correlates with age at onset. At the other extreme, a singular environmental hit (eg, a neurotoxin with basal ganglia tropism) may precipitate parkinsonism irrespective of genetic susceptibility.<sup>11</sup>

In contrast, late-onset idiopathic PD, its most common variant, represents a complex disease that results from an interaction between susceptibility loci and environmental modifiers.<sup>11</sup> Braak et al<sup>12</sup> hypothesized a neurotoxin or infectious pathogen as the environmental trigger, proposed a unique staging model for PD evolution, and placed evidence of early SNCA misprocessing at the interface of host and environment, ie, the digestive and olfactory systems. The transsynaptic progression of PD from gut to brainstem is thought to take decades.

Various events can alter the processing of wild-type SNCA as facilitated by its abundance, long half-life, and propensity to misfold. Many conditions have been associated with Lewy body formation, thereby highlighting their lack of specificity. Therefore, Lewy inclusion bodies share important elements with tau-containing neurofibrillary tangles; both can be caused by mutations in the respective genes of their major constituents (SNCA; MAPT) but are also associated with other diseases. Intriguingly, recent genome-wide association studies link SNCA and MAPT sequence variations to altered PD risk. Inspired by protein-induced neurotoxicity studies in HD and Alzheimer disease, numerous posttranslational modifications have been explored in synucleinopathy models. To date, 3 pathogenic events have emerged, ie, elevated SNCA steady state, soluble oligomer formation, and C-terminal truncation.

**LRRK2 and GBA Function Upstream of SNCA—Focus on Autophagy.** Mutations in the dominantly inherited leucine-rich repeat kinase 2 (LRRK2)—encoding LRRK2 gene underlie more than 2% of all late-onset, typical PD cases; there, they typically promote synucleinopathy, but LRRK2-linked PD also can occur without inclusion formation.<sup>13</sup> Most investigators have postulated a gain-in-

kinase-function effect for LRRK2 mutants. However, its physiological function remains elusive. Recently, autophagy changes with subsequent SNCA misprocessing were demonstrated in kidneys (but not the brain) of LRRK2-deficient mice,<sup>14</sup> thereby raising an alternative scenario in which LRRK2 mutants promote loss of autophagy function.

Heterozygous mutations in the GBA gene, which encodes the enzyme acid  $\beta$ -glucocerebrosidase (GBA), currently represent the most frequent genetic risk factor for typical PD and dementia with Lewy bodies.<sup>15</sup> Loss of GBA activity underlies Gaucher disease, a relatively common lysosomal storage disorder. Only a few such patients ever develop parkinsonism, and subjects with PD who have GBA mutations rarely have Gaucher disease.<sup>15</sup> The mechanisms underlying this paradoxical association of a single lysosomal enzyme with 3 human diseases remain unknown. Autopsy evidence demonstrated that all mutant GBA allele-carrying patients with PD (and dementia with Lewy bodies) show classic synucleinopathy, which strongly suggests that mutant GBA expression facilitates SNCA misprocessing. Of note, the recent identification of homozygous mutations in the P-type lysosomal adenosine triphosphatase—encoding ATP13A2 gene as the cause of early-onset parkinsonism with dementia further points to lysosomal dysfunction as a pathogenic event in some variants of parkinsonism.

**Recessive Forms of Typical PD—Focus on Mitophagy.** Mutations in both alleles of the *Parkin*, *PINK1*, or *DJ-1* genes underlie most cases of known recessive parkinsonism and frequently mimic typical PD. Most (but not all) *Parkin*-linked cases studied revealed dopamine cell loss without inclusion formation. No cases of *DJ-1*-related PD have come to autopsy to our knowledge, while a single case with *PINK1* mutations featured Lewy body formation. Disappointingly, the first animal model deficient in the 3 recessive PD genes (*parkin*  $-/-$ , *pink1*  $-/-$ , *dj-1*  $-/-$ ) failed to induce any detectable cell loss in the midbrain. However, aged triple knockout mice showed evidence of dysregulated dopamine turnover, possibly reflecting a presymptomatic stage of PD.<sup>16</sup>

Recent cell biological evidence placed PINK1 function upstream of Parkin in a linear pathway that regulates the degradation of impaired human mitochondria through mitophagy.<sup>17</sup> It remains to be seen whether the multifunctional DJ-1 protein acts in concert with PINK1 and/or Parkin and whether mitophagy represents the essential function by which neuroprotection is conferred in humans. Of note, 2-year-old *parkin*  $-/-$ , *pink1*  $-/-$ , *dj-1*  $-/-$  mice did not reveal any structural evidence for altered brain mitochondria.<sup>16</sup> Nevertheless, an important direction for future translational studies in PD is to determine whether lysosomal impairment in postmitotic neurons promotes mitochondrial dysfunction and, vice versa, whether mitochondrial impairment reduces efficiency of autophagic and lysosomal degradation.

### Biomarkers

Research in PD biomarkers has seen a surge in activity fueled by 4 insights: (1) its misdiagnosis in early inter-



vention trials; (2) its molecular heterogeneity (even when correctly diagnosed as typical PD); (3) the lack of inexpensive laboratory tools for disease monitoring; and (4) the absence of objective, validated surrogates to reflect target engagement (eg, brain SNCA levels).<sup>18</sup> Select examples of recently explored biomarker candidates are neurophysiology based (eg, heart rate variability loss, rapid eye movement sleep behavior disorder, hyposmia), brain structure based (eg, hyperechogenicity on midbrain sonography, distinct magnetic resonance imaging changes), biological fluid based (eg, abnormal cerebrospinal fluid SNCA levels, dysregulated plasma metabolome), or molecular in nature (eg, genetic susceptibility, altered transcriptome).<sup>19</sup> Most of these PD biomarker candidates require careful and independent validation such as in recently announced multicentered, longitudinal cohorts.<sup>18</sup>

### Cause-Directed Therapy

Currently available treatment options for PD provide only symptomatic therapy. Deep brain stimulation (DBS) of the subthalamic nucleus represents a significant translational achievement based on primate studies that showed a preeminent role of this nucleus in regulating basal ganglia outflow. As expected from neuropathological evidence, DBS probably does not confer disease modification. Viral vector deliveries under experimental protocols that increase striatal dopamine concentrations also fall under symptomatic or augmentative therapy. Currently ongoing multicenter trials are aimed at neuroprotection and include, for example, the administration of the following: (1) coenzyme Q10 to aid mitochondrial function; (2) inosine to increase the antioxidant uric acid level; and (3) isradipine, an L-type calcium ion channel blocker that confers protection of midbrain neurons. Trophic therapies (direct application or via viral vectors) could be classified both as protective and as regenerative or restorative. Neurorestorative efforts using fetal cell transplants have improved motor deficits in select cases but have also caused substantial adverse effects in others.<sup>20</sup> Strikingly, the transmission of synucleinopathy disease from host to grafted cells was recently documented in transplant recipients living for more than 11 years after surgery. This discovery has suggested mechanisms of disease pathogenesis and spread (eg, prionlike) and has provided an independent measure for the rate of disease propagation as previously postulated by neuropathologists and epidemiologists.

One could argue that as long as the elusive environmental triggers are not delineated, real breakthrough cannot occur in cause-directed therapy. Translational success may arrive earlier in rare, monogenic variants of PD such as in carriers of 4 SNCA copies. Several laboratories are aiming to reduce brain SNCA concentrations as their target in preclinical validation, for example, through autophagy induction and mRNA interference; others are pursuing specific SNCA modifications such as oligomer and protofibril formation. The emerging interface between GBA mutations and synucleinopathy risk has led to repositioning efforts of Gaucher-specific drugs for future PD trials. Although the exploration of therapeutic

targets in PINK1- and/or Parkin-related pathways is in its infancy, the recent finding of a systemic reduction in peroxisome proliferator-activated receptor  $\gamma$  coactivator 1- $\alpha$ -dependent mRNA species in subjects with PD<sup>19</sup> highlighted the importance of mitochondrial biogenesis and energy production across PD variants.

### Discussion

Cause-directed PD therapy will likely arrive when 3 prerequisites have been met: (1) successful delineation of the pathogenic events in 1 or more forms of typical PD; (2) validation of specific targets in preclinical models, thereby facilitating drug development; and (3) differentiation of typical PD variants based on objective biological tools. The process of stratification using biological markers is essential to ultimately match a drug with its proper target in the correct patient cohort. This should have a profound effect on the success rate for putative disease-modifying therapies<sup>18</sup> (**Figure 2**).

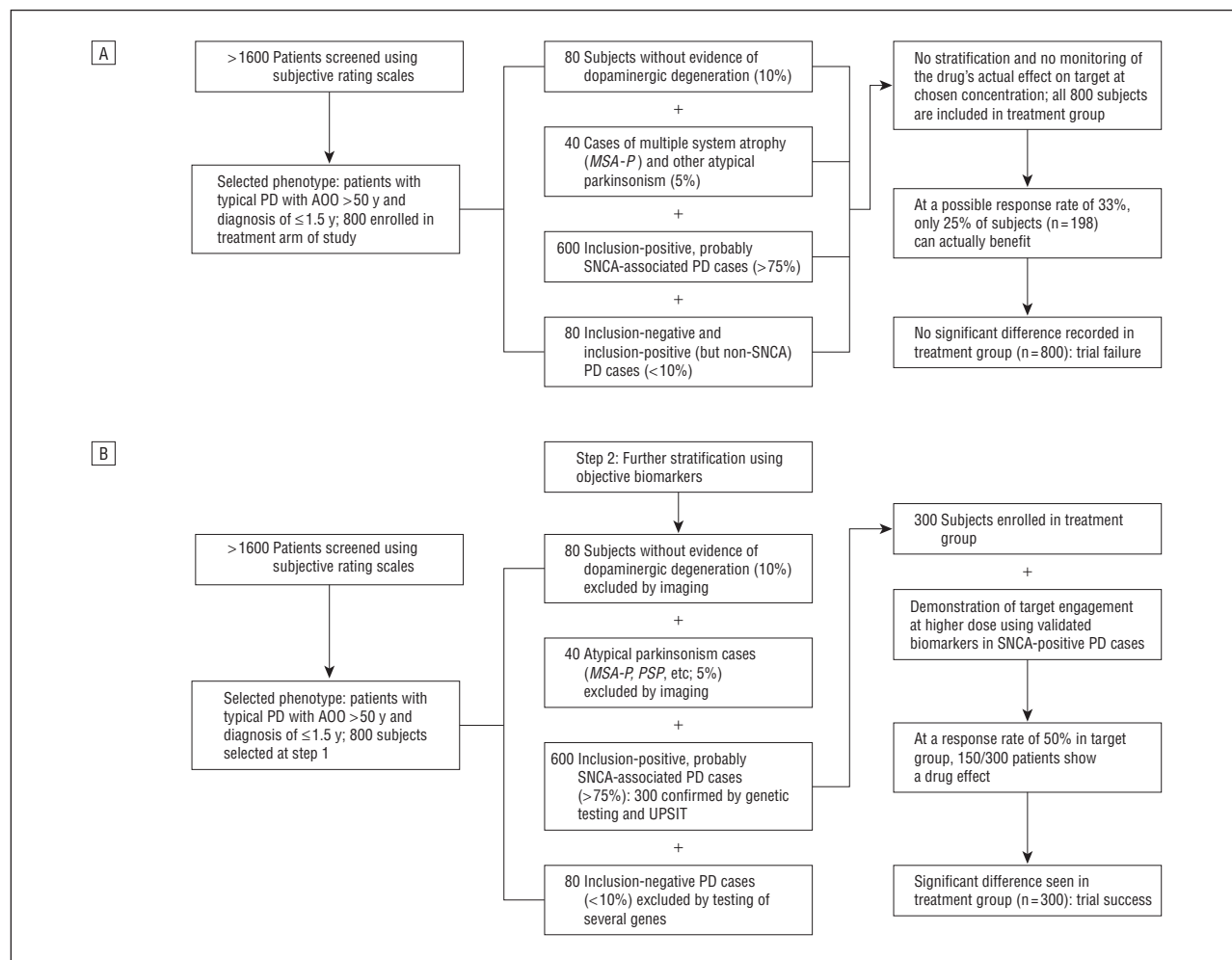
### DYSTONIA

Even more than PD, dystonia is a clinically and etiologically heterogeneous condition. This section will mainly focus on the following 2 forms of dystonia: (1) monogenic primary torsion dystonia caused by mutations in the *DYT1* and *THAP1* genes, also frequently referred to as DYT1 and DYT6 dystonia, respectively; and (2) adult-onset primary torsion dystonia without a known genetic cause, ie, the most common form of dystonia.

### Aetiology and Pathogenesis

**Monogenic Causes of Dystonia.** While a monogenic cause has been identified for a number of different dystonias designated as DYT, including the primary dystonia genes *DYT1* (DYT1) and *THAP1* (DYT6), the understanding of their pathophysiology is incomplete. These forms of dystonia are largely nondegenerative and appear to be the result of neuronal functional defects. The *DYT1* gene product, TorsinA, belongs to the superfamily of adenosine triphosphatases associated with a variety of cellular activities. It has chaperonelike functions, participates in the processing of proteins through the secretory pathway (which includes synaptic vesicle recycling), and is involved in the regulation of the organization of the nuclear envelope and the endoplasmic reticulum.<sup>21</sup> Recently, proteasome-mediated endoplasmic reticulum-associated degradation has been implicated in the clearance of monomeric, mutant TorsinA. The THAP1 protein is thought to act as a transcription factor involved in endothelial cell proliferation and proapoptotic processes.

**Linking DYT1 and DYT6 Functions.** Intriguingly, it has recently been demonstrated that wild-type but not mutant THAP1 binds to the core promoter of *DYT1* where it represses its expression.<sup>22,23</sup> These data suggested 2 novel concepts: (1) transcriptional dysregulation may be the primary cause of a dystonia; and (2) DYT6 and DYT1 proteins define a heretofore unknown pathway.



**Figure 2.** Importance of patient stratification in Parkinson disease (PD) trials, showing scenarios for current (A) and future (B) enrollment strategies in a hypothetical, placebo-controlled, randomized trial for typical PD. A single concentration of the experimental drug is tested, where the target is a toxic species in the metabolism of  $\alpha$ -synuclein (SNCA). Patients with an age at onset (AAO) older than 50 years and with their diagnosis established within the last 18 months are enrolled with either no stratification (A) or following a series of stratification steps (B).<sup>18</sup> The latter encompasses already available biological and surrogate markers, including results from structural and functional neuroimaging tests, testing for the presence of commonly encountered mutations in the *GBA* gene, and a smell test (eg, University of Pennsylvania Smell Identification Test [UPSIT]). Note that in the first scenario (A), 800 patients with various forms of typical PD were included in the treatment group; in the second scenario (B), only 300 patients were selected following stratification. The latter have a high likelihood of inclusion-positive, SNCA-associated PD. Only patients in 1 arm of the trial (ie, the treatment group) are shown. An equal number of participants are enrolled in the placebo arm. A, The lack of enrichment of the most suitable patient population for the drug under investigation leads to 198 responders in 800 subjects treated (25%). B, The corresponding rate after stratification is 150 responders in 300 subjects treated (50%). These 150 responders could be identified by a biological fluid-based marker that signals the successful engagement of the target by the experimental drug at the chosen concentration.

**Is Primary Dystonia a Complex Disease?** Most of our current knowledge on motor circuit abnormalities resulting in dystonia is derived from secondary dystonia, where focal lesions have been found in a variety of structures including the putamen, globus pallidus, caudate, thalamus, brainstem, and possibly even the cerebellum. Importantly, in primary dystonia, abnormal functions have been documented in nearly every region of the central nervous system relevant for motor control and sensorimotor integration.

A sizable number of patients with sporadic primary dystonia of segmental or focal type have affected relatives, suggesting dominant transmission with very low penetrance. This assumption has been strengthened by cases of familial musician's dystonia, previously considered to be a purely occupational dystonia. However, with the rare exception of *DYT1* and *THAP1* mutations causing seemingly sporadic focal or segmental dystonia, the

origin of most adult-onset primary dystonias remains elusive. In contrast to PD, no genome-wide association study has yet been published for dystonia, and candidate association studies have yielded inconsistent results.

**Animal Models of Dystonia.** Transgenic and heterozygous knock-in mouse models of *DYT1* dystonia do not display any readily identifiable changes in posture or tone. Caytaxin, the defective protein underlying the dystonic rat model, is highly expressed in the cerebellum; cerebellectomy reverses the motor syndrome. This strongly supports the hypothesis of cerebellar involvement in dystonia.<sup>21</sup>

## Biomarkers

**Biomarker Studies in *DYT1* and *DYT6* Dystonia.** Structural and functional neuroimaging studies strengthen the

concept that DYT1 and DYT6 dystonia are neurodevelopmental circuit disorders involving cortico-striatal-pallido-thalamo-cortical and related cerebellar-thalamo-cortical pathways. Abnormalities in the latter circuit have been found in both manifesting and nonmanifesting mutation carriers. Additional changes in the thalamocortical tract were present only in nonmanifesting mutation carriers, although it is not clear whether these changes represent a compensatory effect (providing an explanation for reduced penetrance) or signal a preclinical stage.<sup>24</sup> Intriguingly, mRNA expression profiling in peripheral blood was able to distinguish between manifesting and nonmanifesting mutation carriers with 87% sensitivity and 100% specificity.<sup>25</sup> Furthermore, from a mechanistic and biological marker perspective, it will be important to discern how a single coding polymorphism in the *DYT1* gene can protect against disease manifestation.<sup>26</sup>

**Endophenotypes in Primary Dystonia.** Based on the hypothesis that adult-onset focal dystonia is dominantly inherited with very low penetrance, various potential endophenotypes such as abnormalities in central sensory processing have been explored as possible preclinical markers of genetic susceptibility. Indeed, temporal discrimination threshold testing appears to reliably identify such endophenotypes.<sup>27</sup> In primary dystonia without known genetic cause, no predictor of disease course and/or of severity is currently available to our knowledge. However, careful clinical studies have revealed a tight correlation between age at onset, the spread of dystonia, affected body part(s), and disease severity.

### Cause-Directed Therapy

**Symptomatic Treatment.** The vast majority of dystonias are treated symptomatically and rather nonspecifically with drugs or brain surgery. Consistent with alterations in dopaminergic and muscarinic cholinergic neurotransmission and reduced  $\gamma$ -aminobutyric acid-mediated inhibition in dystonic brains, dystonias can respond to high doses of anticholinergic compounds,  $\gamma$ -aminobutyric acid agonists, and dopaminergic agents. Providing evidence for a possible link to dopaminergic neurotransmission, the dopamine D<sub>2</sub> receptor dysfunction of a DYT1 dystonia mouse model was rescued by adenosine A2A receptor antagonism.<sup>28</sup> Deep brain stimulation of the globus pallidus internus, the principal basal ganglia output structure, improves many forms of dystonia. This effect, however, does not elucidate the origin of dystonias as it likely offsets disturbances in several regulatory elements of motor circuitry. In contrast to the immediate effect of DBS in PD, patients with dystonia tend to show more gradual improvement over weeks and months, in keeping with secondary plasticity changes in the brain. DYT6 dystonia may respond less favorably to globus pallidus internus DBS than other forms of dystonia, suggesting pathophysiological differences between them.

**Experimental Therapies.** DYT1 dystonia is caused by a distinct 3-base pair GAG deletion in almost all affected carriers. Successful allele-specific knock-down of mu-

tant TorsinA using lentivirus-mediated RNA interference in a neural cell model of DYT1 dystonia has defined a promising potential therapeutic strategy.<sup>29</sup> A first screen for small-molecule therapeutics, which used multiple activity-based readouts for TorsinA in *Caenorhabditis elegans*, identified 2 classes of antibiotics, quinolones and aminopenicillins. TorsinA-dependent secretory function was improved significantly by ampicillin in the fibroblasts of patients with DYT1 dystonia (or with a *DYT1* mutation), suggesting that small-molecule-induced changes could potentially augment TorsinA activity in vivo.<sup>30</sup>

### Discussion

Recent data on THAP1 regulating transcriptional control of the *DYT1* gene suggest that the role of *DYT1* may extend well beyond its direct involvement in DYT1 dystonia, where it is both disease causing and disease modifying through its effect on penetrance. It will therefore be crucial to aim future research efforts at further exploring the function of the *DYT1* gene and its product, TorsinA. Indeed, we have learned from several other DYT<sub>s</sub> that a better understanding of the pathophysiology may be key to effective treatment and/or improved genetic counseling. Examples include levodopa treatment in dopa-responsive dystonia (DYT5); the use of a ketogenic diet in DYT18 dystonia; and the imprinting mechanism of specific *SGCE* gene (DYT11) alleles, allowing for more than 90% certainty in the prediction of mutation penetrance. In fact, variable expressivity and reduced penetrance may be among the most important issues to explore in dystonia research to unmask potential compensatory mechanisms at play in individuals not developing dystonia signs despite the presence of a mutation. Various ex vivo (eg, gene expression) and in vivo (eg, neuroimaging) studies have proven to be effective tools to address this important question. Despite the clear epidemiological evidence of a familial contribution even in late-onset primary dystonia, which appears to be even stronger than in PD, no gene or genetic risk factor has yet been identified for this most common form of dystonia. Genome-wide association studies in unrelated individuals and next-generation sequencing of affected members from multiplex families affected by dystonia are urgently needed.

### COMMENT

The 3 main themes in today's translational research arena, ie, delineation of aetiology and pathogenesis, identification of validated biomarkers, and development of cause-directed therapy, have become inseparable. Each of these is at a different stage in the 3 disorders we have highlighted. To date, the more uniform aetiology of HD has not translated into effective treatments. However, there are some extremely promising prospects that are being actively pursued. In HD, it is likely that it will be possible to combine all mutation carriers (ie, at-risk individuals and early-symptomatic individuals) in pursuit of disease-modifying therapies. The more heterogeneous disorders of PD and dystonia will probably require a greater degree of splitting and recognition of different disease mechanisms that underlie

distinct phenotypes. Here, pursuing individualized interventions based on objective stratification may finally pave the way to translational success in our search for effective disease-modifying treatments.

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