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Locus Pocus

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The International Parkinson Disease and Movement Disorders Task Force for Nomenclature of Genetic Movement Disorders recently proposed a new approach for nomenclature.¹ The traditional approach has numerous problems, and the task force should be congratulated for trying to fix them. The new approach is markedly different from the existing one. Like a good magician, the task force has put a bunch of ugly rats into a hat, and pulled out a beautiful bird. The task force pointed out some of the weaknesses of the new plan, but its logic reveals some further problems.

In the proposed plan, assigning a prefix (DYT, PARK, SCA, etc...) requires that the phenotype be a *prominent* feature in the *majority* of cases. What is *prominent* or a *majority* is subject to debate. For example, Lesch-Nyhan disease was conferred DYT/CHOR-*HPRT1*, to emphasize the prominence of dystonia and chorea. However, chorea is not usually prominent, and does not occur in the majority.^{2, 3} Spasticity is nearly as prominent as chorea, so why not add HSP to make DYT/CHOR/HSP-*HPRT1*? Another example is myoclonus-dystonia, designated DYT-*SCGE* to emphasize the dystonia. Dystonia is often minor or absent, yet myoclonus is universal.^{4, 5} So why not MYOC-*SCGE*, or MYOC/DYT-*SCGE*? Also, there currently is no prefix for tremor. Once tremor genes are delineated and a TREM prefix is created, will we need to add TREM to many existing disorders including PARK, DYT, and SCA?

The proposed plan also permits a prefix only after confirmation by *two independent groups*. For rare disorders, most reports are initially based on very small cohorts. The discovery of a genetic defect almost invariably leads to appreciation of a broader phenotype, or alternative phenotypes that are quite distinct. What if two groups do not agree? This means the prefix will be subject to frequent change, and frequent dispute.

The proposed plan also assigns a prefix based exclusively on the movement disorder, overlooking other phenotypic features, which are sometimes more important. For example, all patients with Lesch-Nyhan disease have severe self-injurious behavior, cognitive disability and overproduction of uric acid. For myoclonus-dystonia, psychiatric features are

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prominent and frequent. So why not add prefixes for these problems? Will others outside of movement disorders use a system that focuses only on movement?

Historically, the traditional *locus* nomenclature aimed at designating a gene's approximate *location* in the genome. It was not designed for classification of phenotypes. The new plan attempts to link phenotypes and genotypes. However, there are already better tools for linking phenotypes and genotypes. The new plan will create confusion because nomenclature will be unstable due to subjective and arbitrary phenotype assignments, constant evolution with expanding knowledge, and almost certain disagreement among experts. Also unclear is who will have authority to adjudicate disagreements and render decisions. Before adopting the new plan, we must ask whether it is merely replacing old problems with new ones (Table 1). Instead of fixing the broken locus nomenclature system, perhaps we should put it into our magician's hat, and make it disappear.

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Table 1

Limitations of old and new genetic locus nomenclature

Traditional system	Proposed system
Fails to discriminate risk genes from disease genes	Fails to discriminate risk genes from disease genes
Failure of some disorders to be assigned a locus prefix	Failure of some disorders to be assigned a locus prefix
Unconfirmed link between some locus prefixes and some disorders	Unconfirmed link between some genes and some disorders
Greatly oversimplifies relationship between phenotype and gene	Moderately oversimplifies relationship between phenotype and gene
Inconsistent relationship between locus prefix and implied phenotype	Complex and evolving relationship between locus prefix and phenotype
Erroneous prefix due to improper phenotypic ascertainment	Arbitrary and incomplete prefixes based only on movement disorder
More than one prefix assigned for the same disorder	Multiple prefixes conferred simultaneously to the same disorder
Prefix assigned without identification of locus or gene	Prefix assigned based on incomplete knowledge of phenotype that frequently evolves
Some phenotypes missing (e.g. tremor)	Addition of phenotypes will require revision of substantial numbers of existing assignments
No clear authority for curating errors	No clear authority for curating errors
No clear authority for adjudicating differences of opinion	No clear authority for adjudicating differences of opinion
Clinical value limited because of poor correspondence between prefix and phenotype	Clinical value limited because of confusion created by arbitrary and changing prefixes