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Attenuated variants of Lesch–Nyhan disease

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Lesch–Nyhan disease is a neurogenetic disorder caused by deficiency of the enzyme hypoxanthine–guanine phosphoribosyltransferase. The classic form of the disease is described by a characteristic syndrome that includes overproduction of uric acid, severe generalized dystonia, cognitive disability and self-injurious behaviour. In addition to the classic disease, variant forms of the disease occur wherein some clinical features are absent or unusually mild. The current studies provide the results of a prospective and multi-centre international study focusing on neurological manifestations of the largest cohort of Lesch–Nyhan disease variants evaluated to date, with 46 patients from 3 to 65 years of age coming from 34 families. All had evidence for overproduction of uric acid. Motor abnormalities were evident in 42 (91%), ranging from subtle clumsiness to severely disabling generalized dystonia. Cognitive function was affected in 31 (67%) but it was never severe. Though none exhibited self-injurious behaviours, many exhibited behaviours that were maladaptive. Only three patients had no evidence of neurological dysfunction. Our results were compared with a comprehensive review of 78 prior reports describing a total of 127 Lesch–Nyhan disease variants. Together these results define the spectrum of clinical features associated with hypoxanthine–guanine phosphoribosyltransferase deficiency. At one end of the spectrum are patients with classic Lesch–Nyhan disease and the full clinical phenotype. At the other end of the spectrum are patients with overproduction of uric acid but no apparent neurological or behavioural deficits. Inbetween are patients with varying degrees of motor, cognitive, or behavioural abnormalities. Recognition of this

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spectrum is valuable for understanding the pathogenesis and diagnosis of all forms of hypoxanthine–guanine phosphoribosyltransferase deficiency.

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Abbreviations: ADHD = attention-deficit hyperactivity disorder; BFM = Burke–Fahn–Marsden scale; HPRT = hypoxanthine–guanine phosphoribosyltransferase; LND = Lesch–Nyhan disease

Introduction

Complete deficiency of the purine recycling enzyme, hypoxanthine–guanine phosphoribosyltransferase (HPRT), causes Lesch-Nyhan disease (LND). Affected individuals typically suffer from overproduction of uric acid that may lead to hyperuricaemia, nephrolithiasis, gout or subcutaneous deposits of tophi (Lesch and Nyhan, 1964; Jinnah and Friedmann, 2001). Neurologically, all patients have severe motor disability that is dominated by dystonia, with occasional choreoathetosis or spasticity (Jinnah *et al.,* 2006). Most also exhibit recurrent self-injurious behaviour, often with other difficult behaviours such as impulsivity, striking or spitting at others, or use of socially unacceptable language (Nyhan, 1976; Anderson and Ernst, 1994; Schretlen *et al.,* 2005). Finally, most have intellectual disability (Anderson *et al.,* 1992; Matthews *et al.,* 1995; Schretlen *et al.,* 2001).

Although complete HPRT deficiency typically results in the stereotypical LND syndrome, partial deficiency more often causes a phenotype in which some features are attenuated or absent (Kelley *et al.,* 1969; Emmerson and Thompson, 1973; Jinnah and Friedmann, 2001; Puig *et al.,* 2001). Collectively, these patients are labelled LND variants. All of these patients produce excess uric acid, but broad variations in the neurological and behavioural features have been described. Because all patients overproduce uric acid, efforts to classify the spectrum of disease have focussed on differences in neurological and behavioural manifestations. Initial attempts classified patients in two groups, including those with the complete phenotype, and those with only minor neurobehavioural manifestations (Kelley *et al.,* 1969). However, increasing recognition of cases with intermediate severity led to later classification systems that involved three or four groups, based on specific neurobehavioural features. The earliest of these focussed on differences in intellectual function (Page *et al.,* 1981; Hersh *et al.,* 1986; Page and Nyhan, 1989). This focus proved difficult because of challenges inherent in comprehensive cognitive assessments, together with wide variations in normal individuals. More recent proposals have focussed on variations in the motor disorder (Sege-Peterson *et al.,* 1992; Jinnah *et al.,* 2000; Puig *et al.,* 2001).

Most proposed nosological classification systems were derived from relatively small numbers of patients evaluated at individual centres, each with different assessment protocols and varying expertise with the many manifestations. These studies have led to different opinions on the relative importance of individual clinical features for classification. The goal of the current studies was to delineate more comprehensively the spectrum of neurological abnormalities in an international multi-centre study of a large group of LND variants.

Materials and methods

Patients

All 46 LND variants were recruited after referral to centres with expertise in the evaluation and management of LND and related conditions. The diagnosis of a variant form of LND required evidence for an *HPRT* gene mutation or reduced HPRT enzyme activity in a male patient without the self-injurious behaviour typical of classic cases. Self-injurious behaviour was defined as any self-directed behaviour leading to tissue injury. Neurological and/or behavioural difficulties were not required in the LND variants.

Since the main focus was the LND variants, classic cases of LND were excluded. The diagnosis of classic LND was made in accordance with prior studies (Jinnah *et al.,* 2006) and included expression of the full phenotype with evidence for overproduction of uric acid, severe motor disability, cognitive dysfunction and self-injurious behaviour. The diagnosis of classic LND was supported by documentation of an *HPRT* gene mutation predicting null activity or reduced HPRT enzyme activity in fibroblasts or blood cells. Although classic LND cases were not evaluated for this study, data from our previously published cases are presented for comparisons (Jinnah *et al.,* 2006).

Evaluation

The first author directly evaluated 37 patients. Nine others were evaluated by clinicians who worked with the first author on other cases, and videotapes were prepared for review. The evaluation included a detailed history with attention to early development and behaviour. It also included a complete neurological examination with specific attention to the motor features as previously described (Jinnah *et al.,* 2006). Because dystonia was the most common and severe problem, the Burke–Fahn–Marsden (BFM) rating scale was used to estimate overall severity of motor dysfunction (Burke *et al.,* 1985). Results from neuropsychological or diagnostic testing were summarized when available from the clinical records or prior studies (Schretlen *et al.,* 2001).

Literature review

The Medline database through July 2009 was searched for reports with the keywords 'Lesch–Nyhan', 'hypoxanthine–guanine phosphoribosyltransferase', or 'Kelley–Seegmiller'. Other reports were found through the bibliographies of these articles.

Among 78 articles describing 127 LND variants retrieved, four were from the French literature, two were from the German literature, one was from the Spanish literature and the rest were in English. To avoid

redundancy, multiple reports for the same case were combined, and any cases that were re-evaluated and presented as part of the prospective evaluation were excluded from the summary of prior reports, leaving 109 unique cases in 60 reports.

Prospective evaluation

Demographics

All 46 LND variants were male, ranging from 3 to 65 years of age (Table 1). Most were taking allopurinol to reduce uric acid, and three were taking antihypertensives. Other medications occasionally used to reduce excess muscle tone included baclofen, benzodiazepines and trihexyphenidyl.

Presentation

Information concerning presenting signs was available for 44 cases (96%). The most frequent presenting problems were neurological, in 26 cases (Table 1). Delayed acquisition of motor or speech skills in early childhood was common. Another 18 patients came to medical attention as a result of overproduction of uric acid. Among these were eight with gout, six with problems involving the kidneys or urogenital tract, four with asymptomatic hyperuricaemia and one with a tophus.

Motor function

Motor abnormalities occurred in 42 patients (91%). Functional severity varied from incapacitating to barely detectable with specific tasks. The most seriously affected cases exhibited a motor syndrome indistinguishable from classic LND, with profoundly disabling and generalized dystonia. Among the LND variants with prominent dystonia, two had chorea and ballism and two had dystonic myoclonus. Moderately affected patients were less disabled but exhibited dystonia with repetitive abnormal posturing of the limbs and overflow posturing. Mildly affected cases had dystonic overflow only when performing specific tasks, or exercise-induced dystonia. The least severely affected cases had subtle motor signs that were clearly abnormal but not readily classified as dystonic. Examples included slight slowing or clumsiness of fine dexterous movements of the fingers and hands, or an awkward or stiff-appearing gait. Overall, obvious dystonic movements were evident in 27 (58.7%), probable dystonia limited to overflow posturing was seen in five (10.9%), and possible dystonia defined only by slow or awkward movements without overt twisting or posturing occurred in seven (15.2%).

Although slight slowing of movements was common, significant bradykinesia was evident only for four. Other parkinsonian features included resting tremor in two, rigidity without cogwheeling in two, rigidity with cogwheeling in one, hypomimia in two, and hypophonia in one. Mild postural or kinetic tremors occurred in two. Three had tic-like movements.

Pyramidal signs also were common. Hyperreflexia occurred in 23 (50%), being limited to the legs in 12 and the arms in one. Clonus occurred in 14, limited to the ankles. Only three had a rate-dependent increase in limb tone with a catch indicative of spasticity. The frequency of the extensor plantar reflex was not summarized because it could not be discriminated reliably from the dystonic toe response (Nausieda *et al.,* 1980; Ashour *et al.,* 2005).

Some patients also exhibited irregular timing and coordination of movements suggestive of cerebellar ataxia, for example overshooting a target on finger-to-nose pointing or irregular hand tapping. However, all of these patients also had severe generalized dystonia, and their irregular movements seemed more related to dystonic dysfunction than true cerebellar ataxia. More definitive features indicative of cerebellar involvement were absent, including isolated ataxia, ocular hypermetria or nystagmus, or scanning speech.

Speech

Dysarthria occurred in 35 cases (76%), developing in all during early childhood. The most severely affected had obvious dystonic dysarthria with slow and laboured articulation accompanied by overactivity of orolingual and jaw muscles, with overflow to other craniofacial muscles. In these patients, speech often was limited to single words or short phrases, and was difficult to follow. Moderately affected patients exhibited speech that was slow and laboured, often with overflow muscle activation typical of dystonia. A task-specific jaw dystonia occurred with speaking in three, and six had stuttering or hesitant speech. Less severely affected patients had speech that was difficult to characterize, being only slightly indistinct or slow. The least severely affected patients had histories of transient speech impediment during childhood or transient decompensation as adults during periods of stress or fatigue.

One patient had a high-pitched nasal voice suggestive of spastic dysarthria. Eleven had normal speech. Vocal cord involvement suggestive of spasmodic dysphonia was absent.

Gait

A gait disorder occurred in 33 cases (72%), emerging typically during childhood. Those most severely affected could not stand or walk, with the dominating problem being hypotonia with superimposed dystonic posturing of the legs and trunk with attempts to stand or walk. In these cases, muscle bulk was significantly reduced distally in the legs due to disuse. Moderately affected patients could stand with support, but independent ambulation was difficult due to leg or trunk posturing. Less severely affected cases exhibited a very laboured and stiff-appearing gait, with overflow activation of truncal or limb muscles. In the least severely affected cases, the gait had a stiff or heavy appearance without other obvious signs of dystonia. Thirteen had normal gaits.

Cognition

Cognitive skills varied from moderately impaired to above normal. Some type of learning impediment was evident in 31 cases (67%). This impediment was expressed as a need for special education, or being recognized as a slow learner in school. Attention-deficit hyperactivity disorder (ADHD) was diagnosed in seven. Several others were described by parents as having problems with attention but were not formally diagnosed.

Formal neuropsychological testing was available for 21 patients (Table 2). Most fell in the mildly impaired to low-average range. Only seven had IQ scores of 90 or above, and two of these were diagnosed with ADHD. No case had severe cognitive disability. The most seriously affected case was also unusual with dysmorphic features suggestive of a superimposed congenital defect (Table 1).

Behaviour

Overt self-injurious behaviour was absent because it was an exclusion criterion. However, some LND variants exhibited potentially related behaviours. For example, severe onychophagia was evident in six cases. Obsessive-compulsive disorder and an anxiety disorder were diagnosed in one patient each. Other psychosocial problems included five with impulsivity (including two severe enough to quality for impulse control disorder), four with clinically apparent problems with

Table 1 Case demographics

Case-family	Other identifiers	*HPRT* mutation	Consequence	Residual function[a]	Presenting problem	Presenting age (years)	Age last seen (years)	Non-neurologic problems	Medications	Prior reports
1–1	None	239-240delGA insTT	D80F	ND (EL)	Motor delay and posturing	0.5	3.4	Multiple scars on hands	Allopurinol, diazepam	None
2–2	PB	IVS4-1G>A	Splice error	ND (EL)	Nephrolithiasis	0.25	7		Allopurinol	None
3–3	JLY	IVS1+1G>A	Splice error	0.1% (EL)	Hypotonia	0.5	7	Nephrolithiasis, hydronephrosis	Allopurinol, baclofen	(Marcus *et al.*, 1993)
4–4	Zarazoga I	G397A	V133M	9.4% (EL), 54% (LE)	Renal failure	Infancy	8	Renal insufficiency	Allopurinol	(Jinnah *et al.*, 2000 Torres *et al.*, 2000; Puig *et al.*, 2001)
5–5	NF	T203C	L68P	ND (EL)	Motor delay	0.5	9	Nephrocalcinosis	Allopurinol	None
6–6	DoA	G143A	R48H	ND (EL)	Motor delay	2	9	Nephrolithiasis	Allopurinol	None
7–7	JW	C193T	L65P	10% (EL)	Motor delay	6	10	Hypertension	Allopurinol, cetirizine	(Srivastava *et al.*, 2002)
8–8	P4	None	mRNA decrease	6% (EL), 98% (LE)	Hyperuricaemia	10	10	NA		(Garcia *et al.*, 2008)
9–5	DiA	T203C presumed	L68P	7% (EL)	Motor delay	2	11	NA	Allopurinol	None
10–8	P3	None	mRNA decrease	6% (EL), 98% (LE)	Hyperuricaemia	12	12	NA		(Garcia *et al.*, 2008)
11–9	JF	T548C	I183T	<1% (EL) 8% (LF)	Motor delay	Infancy	14	NA	Allopurinol	(Hersh *et al.*, 1986; Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000;)
12–8	P2	None	mRNA decrease	6% (EL), 98% (LE)	Hyperuricaemia	15	16	NA	NA	(Garcia *et al.*, 2008)
13–10	IRdL	IVS4-2A>G	Splice error	ND (EL), 0.1% (LE)	Motor delay	16	16	NA	Allopurinol	(Torres *et al.*, 2010)
14–11	RB	G601A	D201N	60% (LF)	Crystalluria	0.5	17	Nephrolithiasis	Allopurinol, metoprolol, amlodipine	(Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000;)
15–9	BF	T548C	I183T	<1% (EL) 8% (LF)	Crystalluria	1	17	NA	Allopurinol	(Hersh *et al.*, 1986; Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000)
16–12	Madrid I	G212T	G71V	ND (EL), 0.2% (LE)	Motor delay	1	17	Nephrolithiasis, hypertension, macrocytic anaemia	Allopurinol, baclofen, nifedipine	(Bouwens-Rombouts *et al.*, 1993; Torres *et al.*, 2000)
17–13	BT	G599C	R200T	0-26% (EL)[b]	Hypotonia	2	17	Nephrolithiasis, macrocytic anaemia	Allopurinol	(Hidalgo-Laos *et al.*, 1997; Jinnah *et al.*, 2000)
18–14	TH	G143A	R48H	ND (EL), 39% (LF)	ADHD	6	17	Macrocytosis	Allopurinol	None
19–15	None	G500C	R167T	8.7% (LL)	Nephrolithiasis, gout	10	17	Nephrolithiasis, cystitis, gout	Allopurinol	None
20–16	VC	G143A	R48H	ND (EL)	Motor delay	<1	18	NA	Allopurinol	(Larovere *et al.*, 2007)
21–17	None	A584C	Y195S	ND (EL)	Uric acid crystal in finger	14	18	NA	NA	(Larovere *et al.*, 2004, 2007)
22–18	MM	IVS1+1 G>T	Splice error	5% (EL), 1% (LF)	Motor delay	1	20	Multiple scars on chin	Allopurinol, trihexyphenidyl, balcofen, diazepam	(Jinnah *et al.*, 2000)
23–14	GH	G143A	R48H	15% (LF)	Clumsiness	2.5	20	Macrocytosis	Allopurinol	None
24–19	P1	None	Decreased mRNA	5% (EL), 64% (LE)	Hyperuricaemia	14	20	Hypothyroidism	Allopurinol	(Garcia *et al.*, 2008)
25–20	Santona (family S2)	T125C	I42T	ND (EL), 0.6% (LE)	Motor delay, dystonic postures	14	21	NA	Allopurinol	(Puig *et al.*, 2001)
26–21	None	A602G	Splice error[c]	NA	Gout	2	23	Gout, migraines, macrocytic anaemia	Allopurinol, baclofen	None
27–22	None	A584C	Y195S	ND (EL)	Motor delay	2	24	Tophi, renal insufficiency, nephrolithiasis, dysphornism[d]	Allopurinol, enalapril	(Larovere *et al.*, 2004, 2007)

(continued)

Table 1 Continued

Case-family	Other identifiers	*HPRT* mutation	Consequence	Residual function[a]	Presenting problem	Presenting age (years)	Age last seen (years)	Non-neurologic problems	Medications	Prior reports
28–23	Madrid II (family G)	G143A	R48H	0.3% (EL), 9.2% (LE)	Dystonic gait	13	24		Allopurinol	(Andres *et al.*, 1987; Puig *et al.*, 2001)
29–5	HA	T203C	L68P	AFM	Motor delay	2.3	27	Nephrolithiasis	Allopurinol	None
30–24	DD	G143A	R48H	20% (LF)	NA	29	29	NA	Allopurinol	(Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000)
31–25	Tsou	G152A	R51Q	NA	Gout	13	30	Tophi	Allopurinol	(Chang *et al.*, 1999)
32–26	DM; GM 1622	E2-3 duplication	Partial reversion	ND (EL), 1.6% (LF)	Motor delay	0.5	31	Multiple scars on all limbs	Allopurinol	(Gottlieb *et al.*, 1982; Yang *et al.*, 1984,1988; Sege-Peterson *et al.*, 1992; Adler and Wrabetz, 1996; Jinnah *et al.*, 2000)
33–27	Sardinia	C463T	P155S	ND (EL or LE), 2-4% (LF)	Motor delay	1–2	32	Gout, nephrolithiasis, G6PD deficiency	Allopurinol	(Cossu *et al.*, 2002, 2006)
34–28	LW	G148C	A50P	2.5 (LF)	Motor delay	0.6	34	Nephrolithiasis	Allopurinol, diazepam	(Sege-Peterson *et al.*, 1992)
35–22	None	A584C	Y195S	ND (EL)	Gout	19	35	NA		(Larovere *et al.*, 2004, 2007)
36–16	None	G143A presumed	R48H	AFM	Motor delay	1.5	37	Gout, recurrent tophi, nephrolithiasis	Allopurinol	(Larovere *et al.*, 2007)
37–29	Salamanca	T128G, G130A	M34R, D44N	7.8% (LF)	Motor delay	1.5	42	NA	Allopurinol	(Page *et al.*, 1987; Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000; Torres *et al.*, 2000; Puig *et al.*, 2001)
38–30	LP	T596G	F199C	8% (EL)	Motor delay	2.3	43	Nephrolithiasis, gout	Allopurinol	(Ea *et al.*, 2009)
39–29	Salamanca	T128G, G130A	M34R, D44N	7.8% (LF)	Motor delay	6	45	NA	Allopurinol	(Page *et al.*, 1987; Sege-Peterson *et al.*, 1992; Jinnah *et al.*, 2000 Torres *et al.*, 2000; Puig *et al.*, 2001, 2008)
40–25	Tsou	G152A	R51Q	NA	Gout	30	45	Tophi	Allopurinol	(Chang *et al.*, 1999)
41–31	Arlington	A239T	D80V	ND (EL)	Motor delay	5	46	Hypertension, migraines	Allopurinol	(Davidson *et al.*, 1989)
42–32	Chia-yi	T93G	D31E	5% (EL)	Gout	27	53	Nephrocalcinosis	Allopurinol	(Wu *et al.*, 2007)
43–16		G143A	R48H	AFM	Tophus on knee	28	56	Tophi, nephrolithiasis, renal insufficiency, diabetes mellitus	Allopurinol, glibencamide	(Larovere *et al.*, 2007)
44–33	Moosejaw	C582G	D194E	10.8% (EL)	NA		58	NA	Allopurinol	(Jinnah *et al.*, 2000; Lightfoot *et al.*, 1994; Snyder *et al.*, 1984)
45–34	Marseille	T407C	I136T	1.4% (EL), 5.4% (L)	Gout	40	60	Severe gouty arthritis, urate nephropathy, scoliosis	Allopurinol	(Dussol *et al.*, 2004)
46–33	Moosejaw	C582G	D194E	8.4% (EL)	Haematuria	22	65	Gout, tophi, macrocytic anaemia, renal insufficiency	Allopurinol	(Snyder *et al.*, 1984; Lightfoot *et al.*, 1994; Jinnah *et al.*, 2000)

Some information was not available (NA) because knowledgeable informants or records could not be located. For nosological classification, a BFM score of 6 or more was used to define patients as having HPRT-related neurological dysfunction (HND), while those with scores of 5 or below were considered to have HPRT-related hyperuricaemia (HRH).

[a]Results are shown as percent of normal control from different assays used in different clinical laboratories as noted: AFM = testing conducted in affected family member only; EL = erythrocyte lysates, FL = fibroblast lysates, LE = live erythrocytes, LF = live fibroblasts, LL = lymphocyte lysates. If normal controls were presented as a range, the percent of control was based on the lower limit of normal.

[b]The test result varied according to phosphoribosyl pyrophosphate substrate applied.

[c]Genomic DNA revealed the base substitution A602G predicting D201G, but mRNA showed exclusion of exon 8, suggesting a coding region error leading to a splicing defect.

[d]Dysmorphic features included coarse facial features and hair, very short thumbs and great toes, and clubbed first and second fingers.

Table 2 Neurological features

Case-family	Speech	Gait	Extrapyramidal features	BFM	Other motor features	Cognition	Behaviour	Evolution
1–1	Moderate dystonic dysarthria	Limited by dystonic posturing but stands with support	Moderate generalized dystonia affecting face, trunk, limbs	48	Brisk leg reflexes, ankle clonus	NA	Aggressive	Hypotonia and posturing at 6 months; stable by 2 years
2–2	Severe dystonic dysarthria	Severe posturing prevents standing or walking	Severe generalized dystonia affecting face, neck, trunk, limbs	66	Brisk leg reflexes, ankle clonus	NA	Aggressive, coprolalia, 'likes to flirt with danger'	Motor and speech delay noted by 1 year; involuntary movements by 2 years; stable thereafter
3–3	Severe dystonic dysarthria	Severe posturing prevents standing or walking	Severe generalized dystonia affecting face, neck, trunk, limbs	82.5	Mild leg spasticity	Poor attention	Oppositional behaviour	NA
4–4	Normal	Normal	Mild overflow posturing of hands	2		Poor attention, IQ = 89	Normal	Floppy head noted at 6 months; normal thereafter
5–5	Severe dystonic dysarthria	Severe posturing prevents standing or walking	Severe generalized dystonia affecting face, neck, trunk, limbs; rare myoclonic jerks	47	Brisk arm and leg reflexes	Special education	Inappropriate affection, even with strangers	Motor and speech delay noted by 1 year; stable thereafter
6–6	Moderate dystonic dysarthria, hesitant, telegraphic	Normal but awkward running and hopping	Mild generalized dystonia	19	Brisk leg reflexes	Special education, IQ = 79	Impulsive, oppositional	Motor and speech delay noted by 2 years; stable thereafter
7–7	Transient childhood speech disorder	Normal	Mild hand clumsiness with overflow posturing	8		ADHD, IQ = 108	Onychophagia, impulsive, Asperger syndrome	Persistent stable clumsiness noted by 1 year; transient speech disorder
8–8	Normal	Normal	Chronic tic disorder	0		Normal, IQ = 146	Normal	None
9–5	Moderate dystonic dysarthria	Independent but very slow and laboured with very stiff appearance	Moderate generalized dystonia with mild rigidity and myoclonic jerks	34	Brisk leg reflexes, ankle clonus	Special education	Normal	Motor and speech delay noted by 2–4 years; stable thereafter
10–8	Normal	Normal	Slightly slow/clumsy hand movements with exercise-induced dystonia	7[a]		ADHD, IQ = 117	Normal	None
11–9	Normal	Independent but heavy appearance, awkward	Slow hand movements, overflow hand posturing	2	Brisk leg reflexes, ankle clonus,	IQ = 82	Normal	Transient hypotonia in infancy
12–8	Slight dystonic dysarthria	Slightly slowed, reduced arm swing	Slow hand movements	1	None	Normal, IQ = 134	obsessive-compulsive disorder	None

(continued)

Table 2 Continued

Case-family	Speech	Gait	Extrapyramidal features	BFM	Other motor features	Cognition	Behaviour	Evolution
13–10	Moderate dystonic dysarthria	Leg spasms prevent standing or walking	Severe generalized dystonia	NA	Brisk leg reflexes, ankle clonus	Special education	Normal	Drinks 3l/day of water
14–11	Slightly indistinct	Independent but heavy appearance, cannot edge walk	Slow/clumsy limb movements, rare facial twitches	3	Ankle clonus	IQ = 56	Normal	None
15–9	Tongue–jaw synkinesis and transient childhood speech disorder	Normal	Slow hand movements, tic-like shoulder shrug and head roll	0.5	Brisk leg reflexes, ankle clonus	IQ = 66	Normal	Transient childhood speech impediment
16–12	Moderate dystonic dysarthria	Truncal hypotonia with dystonic leg posturing prevents standing or walking	Moderate generalized dystonia affecting face, neck, trunk, limbs; bradykinesia and rigidity without cogwheeling	22.5	Two seizures during childhood	IQ = 86	Normal	Motor and speech delay noted by 1 year; involuntary movements 2–4 years; progressive gait disability from 8 years
17–13	History of stress-induced dysarthria	Normal	None	0	Brisk arm and leg reflexes, ankle clonus	Poor school performance, IQ = 86	Severe onychophagia sometimes to bleeding	Motor delay and sialorrhea noted by 2 years; resolved thereafter
18–14	Normal	Normal	None	0	None	ADHD, IQ = 89	Onychophagia, impulsive, bad behaviors (lying, stealing, etc.)	None
19–15	Mild dystonic dysarthria	Normal but cannot edge walk	Slightly slowed/clumsy hand movements	7.5	Brisk leg reflexes, ankle clonus	Normal	NA	NA
20–16	Slightly slow and indistinct	Slightly slowed	Hypomimia, slow hand movements with overflow posturing	6	Brisk leg reflexes, ankle clonus	Significantly impaired	Normal	Motor and speech delay noted by 2 years; stable thereafter
21–17	Hypophonic	Normal	Slightly slowed hand movements	2	None	Repeated 1st grade	Aggressive, labile mood, 'rebellious'	NA
22–18	Severe dystonic dysarthria	Severe posturing prevents standing or walking	Severe generalized dystonia affecting face, neck, trunk, limbs	60	Brisk arm and leg reflexes, reduced distal muscle bulk	IQ = 67	None	Motor and speech delay noted by 1 year; progressive gait disability with falls from 6 to 12 years

(continued)

Table 2 Continued

Case-family	Speech	Gait	Extrapyramidal features	BFM	Other motor features	Cognition	Behaviour	Evolution
23–14	Sightly slowed and indistinct, intermittent jaw dystonia, childhood stuttering	Normal except overflow hand posturing	Slow/clumsy hand movements	7	None	IQ = 83	None	Clumsiness progressively apparent from 3 to 8 years; stable thereafter
24–19	Normal	Reduced arm swing	Slow arm and hand movements	NA	None	IQ = 97	Normal	None
25–20	Severe dystonic dysarthria	Extreme leg spasms prevent standing or walking	Severe generalized dystonia	12.5	Brisk arm and leg reflexes, ankle clonus	ADHD, IQ = 86	Anxiety disorder	None
26–21	Moderate dystonic dysarthria, childhood stuttering	Independent but very slow and laboured with very stiff appearance	Moderate generalized dystonia affecting face, neck, trunk, limbs; bradykinesia	39	None	ADHD, special education, IQ = 78	Incarcerated for inappropriate behaviour	Motor and speech delay noted by 2 years; stable clumsiness until 9 years when stuttering speech began; progressive gait disability with falls at 18 years
27–22	Slightly indistinct	Normal but can't edge-walking	Slow/clumsy hand movements	6	Brisk arm and leg reflexes, ankle clonus	Marked cognitive impairment	Aggressive	Motor and speech delay noted by 2 years; stable thereafter
28–23	Slight dystonic dysarthria	Mildly dystonic	Hypomimia, mild generalized dystonia, affecting face, trunk, limbs	NA	Brisk leg reflexes	Special education	Normal	None
29–5	Moderate dystonic dysarthria with jaw dystonia	Independent but hyperlordotic with very slow and laboured stiff appearance	Moderate generalized dystonia affecting face, trunk, limbs with bradykinesia, rigidity	37	Brisk leg reflexes, ankle clonus	Special education	Normal	Motor and speech delay noted at 2–4 years; stable thereafter
30–24	High-pitched nasal voice	Moderately slow with stiff appearance	Mild generalized dystonia affecting face and limbs	16	Brisk arm and leg reflexes, ankle clonus	IQ = 96	Onychophagia when stressed	NA
31–25	Normal	Normal	Postural and kinetic tremor	NF	None	NA	Normal	None
32–26	Severe dystonic dysarthria	Severe posturing prevents standing or walking	Severe generalized dystonia affecting face, neck, trunk, limbs; occasional chorea and ballismic limb flailing	61	Reduced distal muscle bulk	IQ = 87, 77	None	Motor and speech delay noted at 1 year; involuntary movements progressively apparent from 2 to 4 years; stable thereafter
33–27	Moderate dystonic dysarthria	Independent but very slow and stiff appearance with rare skip-like postural adjustments	Moderate generalized dystonia affecting face, trunk, limbs; bradykinesia	16	None	ADHD, IQ = 74	Normal	Motor delay by 1 year, progressive clumsiness from 2–4 years, progressive gait disability beyond 20 years

(continued)

Table 2 Continued

Case-family	Speech	Gait	Extrapyramidal features	BFM	Other motor features	Cognition	Behaviour	Evolution
34–28	Severe dystonic dysarthria	Truncal hypotonia with dystonic leg posturing prevents standing or walking	Resting hypotonia, severe generalized dystonia affecting face, neck, trunk, limbs; occasional choreiform and ballismic limb flailing	68	Brisk arm reflexes	IQ = 49	Sits on arms to avoid hitting bystanders, story fabrication	Motor and speech delay with involuntary movements noted by 1 year; involuntary movements increasingly apparent through 30 years
35–22	Normal	Normal	Minor overflow posturing of one hand	1	None	Mild executive syndrome	Normal	None
36–16	Moderate dystonic dysarthria	Slightly slowed and heavy appearance	Slow/clumsy limb movements, stereotypical action-induced elevation of one shoulder	11	Brisk arm and leg reflexes, neuropathy	Poor school performance	Onychophagia	Motor and speech delay noted at 2–4 years; stable until >20 years when additional disability due to joint deformity began
37–29	Mild dystonic dysarthria with slight stuttering	Independent but hyperlordotic and stiff appearance	Slow/clumsy hand movements with overflow posturing	14.5	None	ADHD, could not finish public school, IQ = 68	Onychophagia	Motor and speech delay noted at 2–4 years; stable clumsiness thereafter
38–30	Slightly slowed and indistinct	Slowed and stiff appearance; desires support at all times	Mild generalized dystonia with slow/clumsy hand movements	22.5	Brisk arm and leg reflexes	Frontal syndrome	Normal	Motor and speech delay by 2 years, sudden gait decline at 30 years after dropping daughter[b]
39–29	Mild dystonic dysarthria with severe jaw dystonia and stuttering	Independent but hyperlordotic and stiff appearance	Blepharospasm	5	None	IQ = 68	Normal	Motor and speech delay noted at 2–4 years; stable clumsiness thereafter
40–25	Normal	Impaired by joint deformities from tophaceous gout	None	0	None		Normal	Progressive disability due to joint deformity
41–31	Slightly slowed and indistinct	Extreme leg spasms prevent standing or walking[b]	Painful transient leg spasms, postural and kinetic tremor	6	None	Slow learner	Impulsive	Leg braces from 5 to 6 years, mild dystonic posturing until sudden decline at 40 years due to painful leg spasms
42–32	Normal	Normal	None	0	None	NA	Normal	None
43–16	Moderate dystonic dysarthria	Slightly slowed, cannot toe or heel walk due to joint deformity from tophaceous gout		NF	Brisk leg reflexes, peripheral neuropathy	NA	Emotional lability	Progressive hand disability due to joint deformity

(continued)

Table 2 Continued

Case-family	Speech	Gait	Extrapyramidal features	BFM	Other motor features	Cognition	Behaviour	Evolution
44–33	Slightly indistinct	Normal	Slight cogwheeling and slowing of hand movements	5	Brisk arm and leg reflexes, mild spasticity	Slow learner, IQ = 78	Normal	None
45–34	Normal	Impaired by joint deformity from tophaceous gout	None	4		Normal, no testing	Normal	Progressive disability due to joint deformity beyond age 40 years
46–33	Slightly indistinct with intermittent stuttering	Normal	Slight slowing of hand movements	5	Brisk arm and leg reflexes, mild spasticity	Slow learner, IQ = 93	Normal	Stable stuttering since early childhood

Some information was not available (NA). BFM = Burke–Fahn–Marsden dystonia rating scale; NF = not feasible because of severe tophaceous gout with joint deformity precluding meaningful motor exam or other confounding problems. The extensor plantar reflex was not included among the pyramidal signs because it could not be unequivocally distinguished from the dystonic toe response.

[a]BFM score taken at baseline, not after exercise.

[b]Functional decline suspected to be psychogenic. One patient developed sudden deterioration of gait with examination features suggestive of fear of falling after he dropped his infant daughter. The other suddenly developed incapacitating painful leg spasms that were inducible following a minor knee injury. In both, there was no evidence for parallel deterioration of speech or hand skills.

aggression, three others considered oppositional by parents, one who was incarcerated for inappropriate social behaviour, and one with Asperger syndrome.

Multiple scars under the chin from 'repeated falls' were seen in one case, and two others had multiple scars on their limbs from 'accidents' due to 'bad wheelchair driving'. These patients and their caregivers did not view the scars as evidence of unwanted self-injurious behaviour. However, the stereotypical location in the case with chin scars and the unusually large numbers of limb scars in the other two are not typical of patients with other similar motor handicaps, leading the examiners to question whether they qualified as self-injurious behaviour.

Development and progression

Among the cases where sufficient information regarding early development could be obtained, the most common pattern involved a delay in motor or speech development in early childhood. The most severely affected cases were identified during their first year of life with hypotonia or delayed acquisition of motor milestones. Involuntary movements evolved between 6 months and 4 years. Less severely affected cases were not identified until 2–6 years of age when persistent clumsiness or overflow posturing became increasingly apparent with the increasingly complex motor skills expected during development. The least severely affected cases had transient motor or speech impediments during early childhood.

In most cases, motor disability worsened only during early childhood and remained static thereafter. Adult-onset disability did not occur, and there was no evidence of dementia with ageing. The lack of progression was supported by the lack of any significant correlation of either BFM dystonia score or IQ with age. However, worsening motor function with advancing age was evident for 10 cases. In three of these, progressive gait or hand disability was attributable to obvious joint destruction from tophaceous gout. In two others a psychogenic process was suspected due to sudden onset after a traumatic event (Table 2). The remaining five had worsening motor disability suggestive of evolution of their neurological disorder. For example, four with signs of mild motor delay during the first year of life eventually became ambulatory, albeit with slightly clumsy gaits. Walking became progressively awkward later in childhood or adolescence, with development of falls severe enough to require wheelchairs by early adulthood.

Previously reported cases

Presentation

Among 109 LND variants published, the age at presentation was noted for 78. The average age was 12.4 years, with a range of <1 month to 55 years. Initial presenting problems were reported for 97 patients (Table 3). Among these, 67 (69%) presented with issues related to the overproduction of uric acid. There were 38 cases with urological presentations including renal colic, renal failure, nephrolithiasis, haematuria, or crystalluria. Gout was the presenting problem for 26, and asymptomatic hyperuricaemia was the initial clue for three. Only 19 (20%) presented with neurological abnormalities. Most common were signs of delayed motor development during early childhood.

Motor abnormalities

At any time during the illness, the most commonly reported motor problem was dysarthria, in 19 cases (Table 4). Extrapyramidal signs included dystonia or choreoathetosis in nine each, and athetosis in

Table 3 Presenting features in previously reported cases

Presenting feature	Number ($n = 97$)	Percent of total
Neurological	19	19.6
Motor delay	12	12.4
Seizures	3	3.1
Speech impediment	2	2.1
Encephalopathy	1	1.0
Toe walking	1	1.0
Urological	38	39.2
Colic	17	17.5
Renal failure	13	13.4
Crystalluria	9	9.3
Haematuria	8	8.2
Nephrolithiasis	7	7.2
Dysuria	2	2.1
Other urate-related	29	29.9
Gout	26	26.8
Hyperuricemia	3	3.1
Miscellaneous	11	11.3
Affected relative	7	7.2
Failure to thrive	2	2.1
Screening program	1	1.0
Fevers	1	1.0

Presenting features in 97 of the 109 unique cases where information concerning presentation was available. The subgroups may sum to more than the total since some cases presented with more than one problem.

Table 4 Neurological features in previously reported cases

Feature	Number ($n = 47$)	Percent of total
Extrapyramidal	18	38.3
Choreoathetosis	9	19.1
Dystonia	9	19.1
Athetosis	4	8.5
Pyramidal	19	40.4
Hyperreflexia	14	29.8
Spasticity	11	23.4
Clonus	2	4.3
Other	28	59.6
Dysarthria	19	40.4
Seizures	7	14.9
Ataxia	2	4.3
Tremor	2	4.3

Neurological features in 47 of the 109 unique cases were information was presented. The subgroups may sum to more than the total since some cases presented with more than one problem. The table is based on originally reported terminology with no effort to re-interpret accuracy when the term conflicted with actual clinical descriptions.

four. Pyramidal signs included hyperreflexia in 14, spasticity in 11 and clonus in two.

Less frequent problems included seizures in seven, and postural or kinetic tremors in two. One case was reported as having ataxia, and two others were reported as suffering from a spinocerebellar syndrome. Another 11 were described as being clumsy or poorly coordinated, or as having 'minor' neurological problems. Notably absent were bradykinesia, resting tremor or cogwheel rigidity, tics or myoclonus.

Cognitive abnormalities

Among 44 cases where cognition was addressed, formal neuropsychological testing yielded IQ scores below 90 for eight. In 16 others, cognitive impairments were suspected on the basis of poor school performance or other clinical benchmarks. IQ scores of 90 or greater were documented for only four cases. Another 15 cases were considered to be cognitively normal on the basis of clinical impressions.

Behavioural abnormalities

Overt self-injurious behaviour was absent among the cases reviewed because it was an exclusion criterion for defining a variant form of LND. However, several potentially related problems were reported. Habitual fingernail biting was noted for five cases. Impulsivity was a problem for five cases, including one in whom the impulses were destructive. One patient was diagnosed with hyperactivity, one with obsessive-compulsive disorder, and another was institutionalized in a psychiatric ward for unspecified reasons.

Discussion

The LND variants are defined by HPRT deficiency without self-injurious behaviour, a hallmark feature of classic LND. The current study provides the largest and most comprehensive summary of the neurological features of these variants to date. The relatively large number of patients permits the delineation of a characteristic phenotype with a graded spectrum of severity, rather than a variable assortment of unrelated abnormalities (Fig. 1). The spectrum of variation is evident for each of the major clinical features. Below we summarize this phenotypic spectrum, its relevance for nosological classification of HPRT deficiency, and its biological basis. Finally, we review the implications of phenotypic variation for diagnostic assessment and treatment.

The spectrum of motor abnormalities

The results of our evaluations are compatible with the literature, with small differences attributable to methodology. A shared conclusion is that motor abnormalities are common in the LND variants, with a spectrum that ranges from subtle clumsiness to severe disability. While prior reports suggest the majority of LND variants present with problems related to uric acid, our results suggest the majority present with neurological problems. Our studies also suggest a higher frequency of motor abnormalities in comparison to prior reports, with a high proportion of patients having some form of dystonia. The most likely explanation for these differences is that the current study involved a more methodical evaluation, which had higher sensitivity for revealing neurobehavioural problems in comparison with the majority of prior studies conducted by investigators specializing in genetics or metabolic disease.

The LND variants provide an unusual window on the spectrum of dystonia. Dystonia is obvious when it is fully developed with twisting movements and odd postures, but its mildest expressions often are harder to recognize. By extrapolating from what is more clearly dystonia in more seriously affected classic LND cases, it seems likely that more mildly affected cases exemplify more

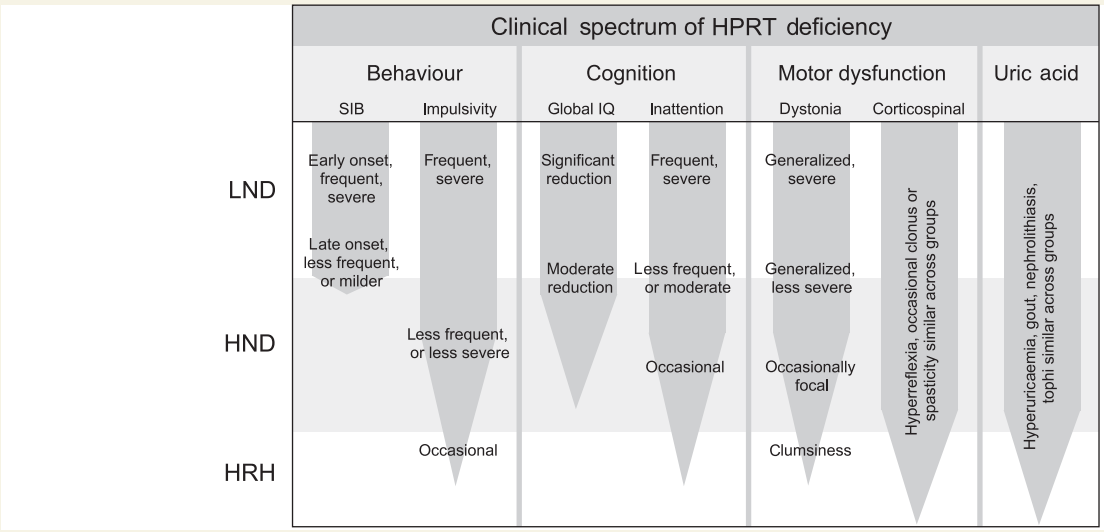

Figure 1 Schematic representation of the spectrum of clinical features in LND and its variants. Patients are divided into subgroups with the most severe being LND, the intermediate form being HPRT-related neurological dysfunction (HND), and the least severely affected being HPRT-related hyperuricaemia (HRH). The frequency or severity of each problem is depicted by the thickness of the tapering bar, with description of the spectrum of the problem across the groups.

subtle forms of dystonia. For example, the hyperlordotic postures seen in some variants may reflect milder expressions of the more severe truncal dystonia and opisthotonic postures common in classic LND (Jinnah *et al.,* 2006). Stuttering and hesitant speech may constitute an action dystonia, as previously suggested (Kiziltan and Akalin, 1996; Puig *et al.,* 2008). Clumsy hand movements or gaits with a 'stiff' or 'heavy' appearance may reflect the mildest expressions of dystonia. If this interpretation is correct, the implication is that the frequency of dystonia is much higher than current appreciated in the LND variants and perhaps other disorders too.

The spectrum of cognitive abnormalities

Our studies and others in the literature also call attention to cognitive dysfunction in the LND variants (Schretlen *et al.,* 2001). Our studies suggest that cognitive dysfunction is more frequent than previously appreciated. The difference again probably involves methods of assessment. Cognitive assessments frequently under-estimate disability when they rely only on clinical impressions without formal neuropsychological testing. Several of our patients thought to be cognitively normal based on global clinical impressions were found to have significant cognitive disability after formal neuropsychological testing. Others with broadly normal IQs showed more selective deficits in specific cognitive domains. However, cognitive dysfunction usually is not severe. Most patients had IQ scores in the borderline to low-average range (70–89).

The spectrum of behavioural abnormalities

Patients with classic LND display a characteristic behavioural phenotype that includes self-injurious behaviours, impulsive acts of aggression such as striking out or spitting, and use of foul or sexually charged language (Nyhan, 1976; Anderson and Ernst, 1994; Schretlen *et al.,* 2005). Self-injurious behaviour was an exclusionary criterion for defining a variant form of LND, so it was absent from the current series. However, our studies are consistent with the literature in implying that behaviour in the LND variants may not always be normal. Five LND variants exhibited behaviours potentially related to self-injury, such as habitual fingernail biting. It is tempting to speculate that this onychophagia is a *forme fruste* of more serious finger biting, which is the commonest expression of self-injury in classic LND (Anderson and Ernst, 1994; Schretlen *et al.,* 2005).

Other socially difficult behaviours, such as impulsivity, severe enough to warrant medical attention also were common in the LND variants. Similar problems have been described before, such as one case who was noted to act on impulses to jump from a moving vehicle or insert a nail into an electric outlet (Geerdink *et al.,* 1973). Another LND variant was noted to have precipitously pulled out a large patch of hair from his head for no apparent reason, and to have exhibited antisocial behaviour that led to incarceration (Nyhan, 1978). These cases may not reach strict definitions of self-injurious behaviour that involve tissue injury, but it is important to acknowledge that the criterion for tissue injury for definition of self-injury is somewhat arbitrary. Distinctions between the variant and LND cases are further blurred by classic cases of LND with very mild or late-onset of self-injury. One of our classic LND patients had very mild self-injury limited to a hypertrophic abrasion on one thumb due to repetitive hand-to-mouth behaviour, but without overt bleeding from biting (Jinnah *et al.,* 2006). A review of the literature discloses that self-injury typically arises before 4 years of age, but may be delayed until late teenage years, when it often is infrequent or mild (Fig. 2). These observations suggest a spectrum of maladaptive behaviour across classic and variant LND rather than an all-or-none phenomenon, a suggestion supported by a study with standardized behavioural rating

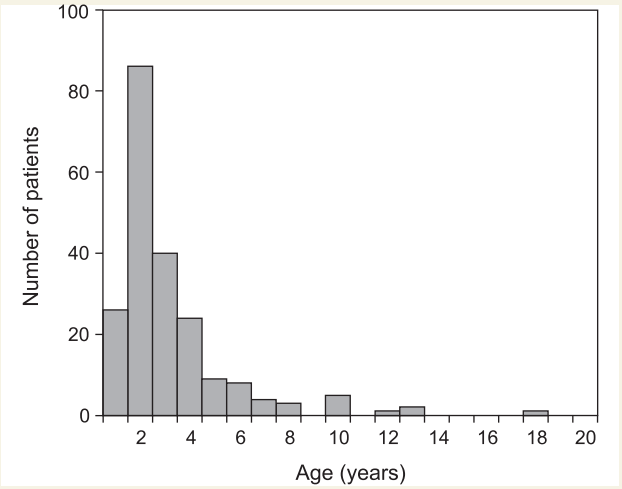

Figure 2 Histogram showing age at onset of self-injury in previously reported cases of classic LND. Among 349 classic LND cases described in 133 previous reports, the age at onset of self-injury was available for 212 cases. Cases were binned in yearly increments, with a mean age of 3.1 ± 2.5 and a median age of 2 years.

scales showing the LND variants score between those of normal and classic LND in nearly every problem behaviour category (Schretlen *et al.*, 2005).

The spectrum of uric acid abnormalities

There also are significant variations in the severity of problems due to uric acid, though these were not systematically evaluated in our patients. Efforts to address uric acid problems are challenging because its overproduction is treated with allopurinol as soon as it is recognized. As a result, uric acid complications reflect primarily the efficacy of treatment rather than variations in disease severity.

Prior studies have indicated that overproduction of uric acid does not differ between classic and variant cases (Mateos and Puig, 1994; Jinnah and Friedmann, 2001; Puig *et al.*, 2001). However, these studies were limited by relatively small numbers. When considering all available uric acid measures in untreated patients reported in the literature, a significant difference between the patient subgroups becomes evident (Table 5). Further studies are needed that control for age, renal function, and other variables known to affect uric acid measures independent of HPRT deficiency.

Despite the spectrum of problems related to uric acid, it seems unlikely that they are causally related to the neurological or behavioural problems in LND. Treatment of LND patients from birth with allopurinol does not influence the development of neurobehavioural problems, and there are other clinical disorders with excessive production of uric acid but without the neurobehavioural problems of LND (Jinnah and Friedmann, 2001).

Patterns of disease and nosology

The relatively large number of LND variants evaluated here combined with our prior study of classic LND (Jinnah *et al.*, 2006) facilitates the identification of patterns of disease rather than a random assortment of phenotypic abnormalities (Fig. 1). For example, self-injurious behaviour in classic LND typically is associated with the most severe motor dysfunction and the most prominent cognitive disability. Patients with little or no motor abnormalities appear to have less cognitive impairment, with a significant correlation of BFM scores with IQ (Fig. 3). Although exceptions exist, these observations suggest the overall clinical phenotype occurs as a continuously graded spectrum of severity.

Despite this spectrum, there is both heuristic and practical value for defining subgroups for clinical studies, treatment of specific features, and counselling. The spectrum of disease most commonly has been divided into three groups (Sege-Peterson *et al.*, 1992; Jinnah and Friedmann, 2001). The most severe phenotype is designated as classic LND, which encompasses overproduction of uric acid with all the neurological manifestations including self-injurious behaviours. An intermediate group includes uric acid overproduction with varying degrees of motor disability, but self-injury is absent. These patients have been designated HPRT-related neurological dysfunction. The least severely affected group has been designated HPRT-related hyperuricaemia, which includes patients with uric acid overproduction, but clinically insignificant neurological or behavioural deficits. Essentially, the occurrence of self-injurious behaviour distinguishes classic patients from variants, and clinically apparent motor disability distinguishes the variants into those with and without neurological impairment.

When dystonia is rated with the BFM scale and stratified according to these subgroups, there is considerable overlap but good correspondence between severity and clinical subgroup (Fig. 4). This result is expected because motor dysfunction falls on a continuous spectrum and is a criterion for distinguishing the LND variants. The BFM also discriminates LND from variants, even though it is not a criterion for separating these groups. Using IQ as an estimate of cognition, there again is significant overlap but a good correspondence between median scores and clinical subgroup (Fig. 5), even though IQ is not a criterion for

Table 5 Serum and urine uric acid in classic and variant LND

Patient group	Serum uric acid (mg/dl)	Urine uric acid (mg/kg per 24 h)	Urine uric acid/ creatinine ratio
Classic LND	11.7 ± 4.8	42.6 ± 17.3	3.2 ± 1.1
HPRT-related neurological dysfunction	13.0 ± 3.8	33.6 ± 13.1	1.6 ± 0.8
HPRT-related hyperuricaemia	12.4 ± 5.7	23.9 ± 9.8	1.0 ± 0.5

Uric acid measures for 349 classic and 125 variant cases of LND reported in the prior literature. To avoid skewing the results by over-representation of individual samples, multiple values or ranges of values reported for any one case were averaged to give a single value. When multiple values were reported over several years for one case, only the first value was used, since serum uric acid varies according to age and the values could not be averaged. We excluded values from patients who were receiving drugs known to alter uric acid. Statistical comparisons were conducted via the Kruskal–Wallis test for non-parametric data, which revealed significant group differences for 24 h urinary uric acid ($P = 0.003$) and uric acid/creatinine ratios ($P < 0.001$) but not for serum uric acid ($P = 0.13$).

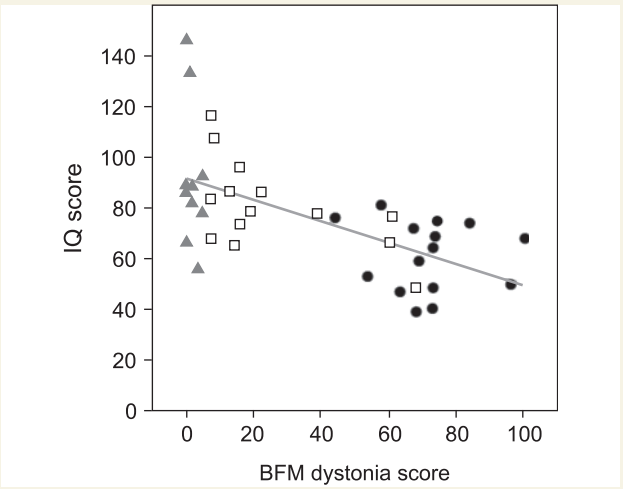

Figure 3 Correlations between dystonia and cognition. Dystonia was rated with the BFM dystonia rating scale, with mild motor deficits scored as mild expressions of dystonia. Scores for patients with LND come from our previous study (Jinnah *et al.*, 2006) while those for variants come from Tables 1 and 2. Cognition was assessed with IQ, which was taken from the results of clinical diagnostic testing or previous publications. Patient subgroups are LND (circles), HPRT-related neurological dysfunction (squares), and HPRT-related hyperuricaemia (triangles). Patients with LND and HPRT-related neurological dysfunction were distinguished by the presence of self-injurious behaviour. The HPRT-related hyperuricaemia group was defined as clinically insignificant motor dysfunction with a BFM score of 5 or less. There was a significant negative correlation between BFM and IQ scores (Spearman rho = −0.64, $P < 0.001$). This correlation remained after controlling for age (Spearman rho = −0.63, $P < 0.001$). There was no significant correlation between BFM and age (Spearman rho = 0.20, $P = 0.21$).

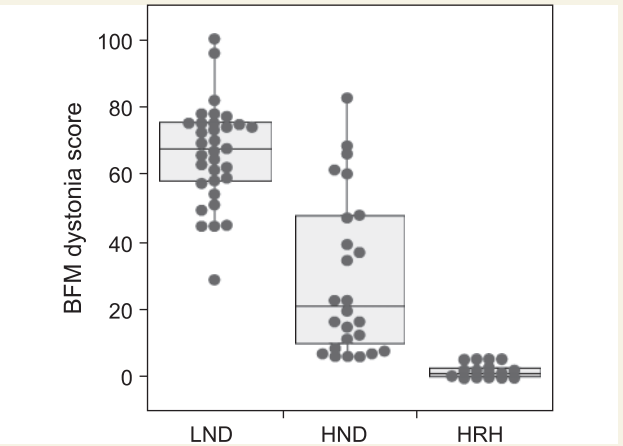

Figure 4 Severity of dystonia according to patient subgroup. Dystonia was rated with the BFM dystonia rating scale, with mild motor deficits scored as mild expressions of dystonia. Patient subgroups are LND, HPRT-related neurological dysfunction (HND), and HPRT-related hyperuricaemia (HRH). Patients with LND and HPRT-related neurological dysfunction were distinguished by the presence of self-injurious behaviour. The HPRT-related hyperuricaemia group was defined as clinically insignificant motor dysfunction with a BFM score of 5 or less. Scores for patients with LND come from our previous study (Jinnah *et al.*, 2006) while those for variants come from Tables 1 and 2. Individual scores are overlaid with a box-whisker plot, where the middle horizontal line in each box shows the median. The upper and lower limits of the box define the upper and lower quartiles. Whiskers span the entire data range excepting outliers, defined as values that fell outside the upper or lower quartile plus 1.5 times the inter-quartile distance. The groups were compared statistically using the Kruskal–Wallis H-statistic, which revealed overall significance at $P < 0.0001$. *Post hoc* Wilcoxin signed ranked tests revealed significant differences ($P < 0.001$) between each of the groups.

discriminating groups. Thus the clinically defined groups appear to be internally consistent in distinguishing grades of severity.

Some caveats regarding nosology

Despite the internal consistency of the proposed nosological classification, some caveats must be noted. First, BFM scores are not normally distributed, but instead suggest a bimodal population (Figs 3 and 4). This finding might support a two-group classification system as previously suggested (Kelley *et al.*, 1969). However, the lack of a normal distribution could reflect an artefact of insufficient numbers of patients with intermediate severity, non-linearity of the BFM scale, more frequent progression of patients with intermediate scores, or recurrent mutations that result in non-random clinical outcomes. For example, the C151T hotspot that encodes a null enzyme generates an overrepresentation of classic patients (Jinnah *et al.*, 2000, 2006), and the recurrent G143A mutation that encodes a partially dysfunctional enzyme creates an overrepresentation of very mildly affected patients (Tables 1 and 2).

The second caveat is that despite the overall correlation between BFM scores and IQ in our patients, significant discrepancies exist, suggesting the lack of exact correspondence between motor and cognitive function (Fig. 3). It is important to acknowledge that cognitive function was not methodically assessed with the same instruments across all patients due to differences in age and language, and IQ scores may not capture significant deficits in specific cognitive domains. Further studies of cognitive domains most affected, such as attention, may provide more useful measures than overall IQ for defining clinically relevant subgroups. However, since motor and cognitive dysfunction may be dissociable, it seems reasonable to consider significant cognitive dysfunction as a criterion for reclassifying a patient with HPRT-related hyperuricaemia to HPRT-related neurological dysfunction, regardless of any motor disability.

The third caveat is that corticospinal motor signs do no seem to show graded severity across the patient groups, since they are equally frequent and severe in both classic and variant LND (Fig. 6). This finding may suggest the pathogenesis of corticospinal problems is unrelated to the pathogenesis of the extrapyramidal features. However, corticospinal signs are minor compared to

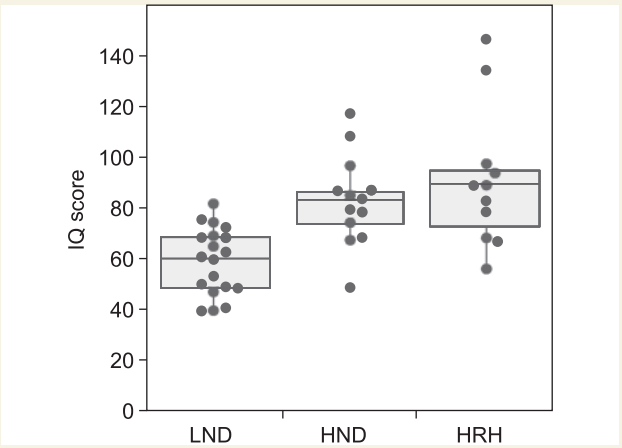

Figure 5 IQ scores according to patient subgroup. The IQ was not methodically assessed with a standardized instrument due to differences in age and language, but instead was taken from the results of clinical diagnostic testing or previous publications. Patient subgroups include LND, HPRT-related neurological dysfunction (HND), and HPRT-related hyperuricaemia (HRH). Patients with LND and HPRT-related neurological dysfunction were distinguished by the presence of self-injurious behaviour. The HPRT-related hyperuricaemia group was defined as clinically insignificant motor dysfunction with a BFM score of 5 or less. Scores for patients with LND come from our previous study (Jinnah *et al.,* 2006) while those for variants come from Tables 1 and 2. Individual scores are overlaid with a box-whisker plot, where the middle horizontal line in each box shows the median. The upper and lower limits of the box define the upper and lower quartiles. Whiskers span the entire data range excepting outliers, defined as values that fell outside the upper or lower quartile plus 1.5 times the inter-quartile distance. The groups were compared statistically using the Kruskal–Wallis H-statistic, which revealed overall significance at $P < 0.0001$. *Post hoc* Wilcoxin signed ranked tests revealed significant differences ($P < 0.001$) between the LND and each of the other two groups. The difference between HPRT-related neurological dysfunction and HPRT-related hyperuricaemia groups was not significant ($P = 0.56$).

extrapyramidal signs, and they may not warrant consideration in patient classification. There also are rare reports of patients with clinical features not found in our patients. Two cases from the literature were reported to have a spinocerebellar syndrome (Kelley *et al.,* 1969) and another was reported to have ataxia with dystonia (Adler and Wrabetz, 1996). However, the first two cases were re-evaluated by others who described an extrapyramidal syndrome rather than ataxia (Nyhan, 1978). The other case was re-evaluated here (case DM). Though he had dysmetric limb movements, they were considered secondary to his severe generalized dystonia rather than true cerebellar ataxia. This view is supported by the lack of other features supportive of cerebellar dysfunction in any of our variant or classic LND cases (Jinnah *et al.,* 2001, 2006). Thus there seems little evidence for true cerebellar ataxia in LND or its variants, and this feature seems sufficiently infrequent to be considered atypical. Although our studies focus on the use of clinical features alone for nosological classification, additional molecular and biochemical measures of the disease may be helpful for validating or refining the classification further.

Pathogenesis of phenotypic variation

LND and its variants are caused by different mutations in the *HPRT* gene (Table 6). Prior genotype–phenotype comparisons have suggested that the location and type of gene mutation are less relevant for predicting the clinical phenotype than the effect of the mutation on residual enzyme function (Jinnah *et al.,* 2000, 2004). Mutations resulting in little or no residual enzyme function typically cause classic LND, while mutations permitting residual activity more often lead to less severely affected LND variants. The mutations in the current series support this concept, with the majority resulting in single amino acid substitutions compatible with residual enzyme function (Table 1). There also were five patients with splicing mutations, which are known to be 'leaky' and permit variable residual activity (Hunter *et al.,* 1996; O'Neill *et al.,* 1998; Mak *et al.,* 2000; Gaigl *et al.,* 2001). Four others had low but detectable mRNA levels leading to low enzyme activity. One patient had a duplication involving exons 2–3, previously shown to undergo partial reversion leaving a small amount of residual enzyme activity (Yang *et al.,* 1988).

The concept that the severest phenotype occurs when HPRT activity is absent whereas the milder variants have residual enzyme function is supported by most studies in which enzyme activity was measured using assay conditions that mimic the natural state in cultured fibroblasts, lymphocytes, or intact erythrocytes (Page *et al.,* 1981; Fairbanks *et al.,* 1987; Page and Nyhan, 1989; Puig *et al.,* 2001). For most cases, there is a good correlation between clinical severity and residual enzyme activity. Rare case reports where enzyme activity lacks correlation with phenotypic severity sometimes are presented as evidence against this idea (Rijksen *et al.,* 1981; Cossu *et al.,* 2002). These apparent exceptions most often occur when the enzyme is measured via assays that do not replicate natural conditions (McDonald and Kelley, 1971; Dancis *et al.,* 1973; Holland *et al.,* 1976; Bakay *et al.,* 1979; Cameron *et al.,* 1984; Hersh *et al.,* 1986; Fairbanks *et al.,* 1987; Zoref-Shani *et al.,* 2000; Jinnah *et al.,* 2004). All of our LND variants who had enzyme activity measured in live cells displayed measurable residual activity, and discrepancies between assays from live cells versus lysates were evident for many cases that had both assays (Table 1). These observations highlight some problems associated with the lack of standardized biochemical testing. Though assays based on live cells are more accurate than those based on cell lysates, most diagnostic centres use lysate-based assays because they are technically simpler and less expensive.

The current studies also are consistent with prior studies of classic LND indicating that pathogenesis involves dysfunction of basal ganglia circuits (Visser *et al.,* 2000). These circuits have been divided into several parallel but segregated pathways serving motor function, cognition, oculomotor control, and behavioural or 'limbic' functions. The most prominent motor abnormality in LND and its variants is dystonia, which may be attributed to dysfunction of motor circuits involving the putamen and motor

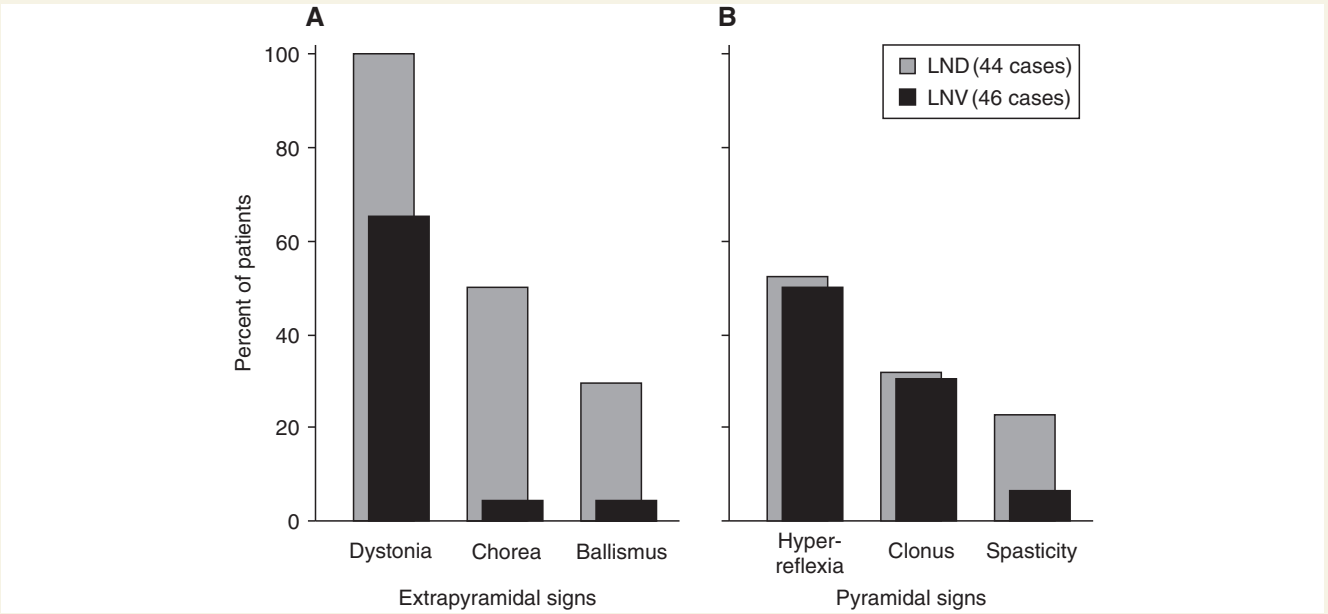

Figure 6 Motor features in classic versus variant LND. The percent of patients in the current series of LND variants (LNV; $n = 46$, black bars) is compared with the percent of patients with classic LND ($n = 44$, grey bars) from our prior studies (Jinnah *et al.*, 2006). Panel A depicts extrapyramidal features while Panel B depicts pyramidal features.

Table 6 Mutations of the *HPRT* gene in classic and variant LND

Mutation class	LND ($n = 280$)	LNV ($n = 101$)	NA ($n = 9$)	Total ($n = 390$)
Single base substitution				
Missense[a]	86	76	4	167
Nonsense[b]	29	1	1	31
Splice site[c]	44	11	0	55
Deletions				
Coding sequences	80	2	4	86
Splice site	5	0	0	5
Insertions				
Coding sequences	22	1	0	23
Splice site	1	0	0	1
Miscellaneous				
Duplications	3	3	0	6
Substitutions	4	1	0	5
Regulatory elements[d]	0	3	0	3
Female cases[e]	6	1	0	7
Double mutants	0	2	0	2

The genetic mutations in the *HPRT* gene for both classic cases (LND) and the less seriously affected variants (LNV). The clinical subtype for some patients could not be determined because of insufficient information in some of the reports (NA). A complete list of individual mutations and associated publications can be found at http://www.lesch-nyhan.org.

[a]Single base change leading to single amino acid subsitution.

[b]Single base change leading to premature termination of protein translation.

[c]Single base change leading to intron/exon splicing defect.

[d]Unidentified promoter or enhancer non-coding sequence change resulting in reduced mRNA.

[e]All females have had an identifiable mutation on one allele combined with non-random X-inactivation.

cortex (Jinnah *et al.*, 2006). Cognitive disability with prominent defects in attention may be attributed to dysfunction of circuits involving the caudate and frontal cortices (Schretlen *et al.*, 2001). The characteristic ocular motor apraxia with saccadic distractability in LND and its variants resembles the oculomotor defects of Huntington's disease, which have been linked with the caudate and frontal cortex eye fields (Jinnah *et al.*, 2001). Finally, self-injurious and other difficult behaviours can be attributed to pathways through the ventral striatum and mediobasal frontal cortex (Visser *et al.*, 2000).

Dysfunction of basal ganglia circuits in LND and its variants appears to be related to selective vulnerability of dopaminergic neurons. Although these constitute only small population of neurons, they have a profound modulatory influence on corticostriatal physiology. Post-mortem neurochemical studies have revealed 60–90% loss of dopamine in the basal ganglia (Lloyd *et al.*, 1981; Saito *et al.*, 1999), and PET studies have shown similar reductions in fluorodopa uptake or dopamine transporters in the basal ganglia (Ernst *et al.*, 1996; Wong *et al.*, 1996). A selective loss of dopamine also is seen in the basal ganglia in *HPRT* knockout mice (Jinnah *et al.*, 1992, 1994, 1999), and in cultured HPRT-deficient dopaminergic neurons (Bitler and Howard, 1986; Yeh *et al.*, 1998; Lewers *et al.*, 2008). Histopathological studies of autopsied brain tissue or the *HPRT* knockout mice do not show a loss of midbrain dopamine neurons, suggesting the loss of dopamine reflects a metabolic rather than a degenerative process (Del Bigio and Halliday, 2007; Egami *et al.*, 2007; Ceballos-Picot *et al.*, 2009). In this regard, LND resembles DOPA-responsive dystonia more than it resembles Parkinson's disease.

Although the most prominent clinical features in LND and its variants may be attributed to dysfunction of the basal ganglia,

other regions may not be spared entirely. For example, hyperreflexia and clonus provide evidence for dysfunction of corticospinal motor pathways. Cognitive limitations also may reflect involvement of the cerebral cortex. Contrary to a recent claim (Del Bigio and Halliday, 2007), there seems little evidence for clinically significant cerebellar ataxia.

Diagnosis

The diagnosis of classic LND is relatively straightforward when all the telltale clinical features, including self-injury, are apparent. Diagnosis is more challenging in variants with attenuated syndromes. The differential diagnosis of early-onset dystonia or clumsiness, with or without cognitive impairment, is broad. Ancillary neurological testing with neuroimaging or EEG has limited value. Instead, overproduction of uric acid, frequently evident as an elevated serum uric acid, is one of the most useful clues (Jinnah and Friedmann, 2001). Hyperuricaemia is uncommon below 40 years of age and should prompt further evaluation, especially if it is combined with evidence for motor or cognitive impairment. Patients for whom diagnoses are delayed ultimately develop one of the consequences of hyperuricaemia, such as nephrolithiasis or gout, both of which are uncommon before 40 years of age (Cameron *et al.,* 1993). The development of either problem in a young person with motor or cognitive abnormalities also should lead to further testing.

Hyperuricaemia provides a useful early clue, but it is not adequate for definitive diagnosis. Serum uric acid is highly dependent on many factors including hydration, diet, medications and renal efficiency. A few LND variants have persistently normal serum uric acid, and many have elevations that are sufficiently small to escape notice. Molecular testing for a mutation in the *HPRT* gene provides a reliable means of diagnosis (Jinnah *et al.,* 2000). The gene test also facilitates carrier diagnosis and prenatal testing. The main shortcoming of molecular testing is that mutations must be identified by sequencing the gene because they are heterogeneous. Since this process is time-consuming and expensive, it is offered by only a handful of centres worldwide (http://www.lesch-nyhan.org). Another shortcoming is that mutation screening will miss the unusual cases of *HPRT* deficiency that are due to non-coding reductions in HPRT mRNA expression (Dawson *et al.,* 2005; Garcia *et al.,* 2008). Finally, unique mutations have little prognostic value.

Another option for diagnostic testing is biochemical measurement of HPRT enzyme activity (Jinnah *et al.,* 2004). Since assays of live cells provide enzyme measures that correlate with disease severity, they may have predictive value for prognosis. However, they are technically demanding and offered by only a few centres worldwide. Nevertheless, further studies addressing the most appropriate biochemical assays could be valuable for counselling of cases diagnosed early.

Summary

These studies provide the largest summary to date for the spectrum of neurological manifestations that can occur in association with HPRT deficiency. The results are valuable for raising awareness of atypical presentations of this rare disease, where diagnosis is challenging. The LND variants may lack clinically apparent cognitive dysfunction or overtly abnormal behaviour characteristic of the classic phenotype. Motor function may range from normal to severe disability, with the most common problem being varying manifestations of dystonia. These studies also are valuable for pointing to clues for the diagnosis, as well as diagnostic methods and their limitations. Early diagnosis is important because some of the manifestations such as those related to uric acid are treatable, and because early recognition facilitates carrier identification for family counselling.

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