Attenuated variants of Lesch-Nyhan disease

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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
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., 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

Keywords: neurogenetics; genotype–phenotype correlation; metabolic disease; uric acid; dystonia; behaviour; Kelly–Seegmiller syndrome

Abbreviations: ADHD = attention-deficit hyperactivity disorder; BFM = Burke–Fahn–Marsden scale; HPRT = hypoxanthine–guanine phosphoribosyltransferase; LND = Lesch–Nyhan disease
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 (Naussieda 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 impairment during childhood or transient decompensation as adults during periods of stress or fatigue.

One patient had a high-pitched nasal voice suggestive of spasmodic dysphonia. 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 qualify for impulse control disorder), four with clinically apparent problems with...
Table 1 Case demographics

<table>
<thead>
<tr>
<th>Case-family</th>
<th>Other identifiers</th>
<th>HPRT mutation</th>
<th>Consequence</th>
<th>Residual functiona</th>
<th>Presenting problem</th>
<th>Presenting age (years)</th>
<th>Age last seen (years)</th>
<th>Non-neurologic problems</th>
<th>Medications</th>
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<td>239–240delGA insTT</td>
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<td>Infancy</td>
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<td>Renal insufficiency</td>
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<td><em>(Jinnah et al., 2000)</em></td>
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<td>Infancy</td>
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<td><em>(Hersh et al., 1986; Sege-Peterson et al., 1992; Jinnah et al., 2000)</em></td>
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<td>16</td>
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<td>NA</td>
<td><em>(Garcia et al., 2008)</em></td>
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<td>17</td>
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<td>Tophi, renal insufficiency, nephrolithiasis, dysphornism</td>
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<td><em>(Larovere et al., 2004, 2007)</em></td>
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(continued)
Table 1 Continued

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<th>Case-family</th>
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<th>Presenting problem</th>
<th>Presenting age (years)</th>
<th>Age last seen (years)</th>
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<th>Medications</th>
<th>Prior reports</th>
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<td>30</td>
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</tr>
<tr>
<td>32–26</td>
<td>DM; GM 1622</td>
<td>E2-3 duplication</td>
<td>Partial reversion</td>
<td>ND (EL), 1.6% (LF)</td>
<td>Motor delay</td>
<td>0.5</td>
<td>31</td>
<td>Multiple scars on all limbs</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>33–27</td>
<td>Sardinia</td>
<td>C463T</td>
<td>P155S</td>
<td>ND (EL or LE), 2–4% (LF)</td>
<td>Motor delay</td>
<td>1–2</td>
<td>32</td>
<td>Gout, nephrolithiasis, G6PD deficiency</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>34–28</td>
<td>LW</td>
<td>G148C</td>
<td>A50P</td>
<td>2.5 (LF)</td>
<td>Motor delay</td>
<td>0.6</td>
<td>34</td>
<td>Nephrolithiasis</td>
<td>Allopurinol, diazepam</td>
<td>(Sege-Peterson et al., 1992)</td>
</tr>
<tr>
<td>35–22</td>
<td>None</td>
<td>A584C</td>
<td>Y19SS</td>
<td>ND (EL)</td>
<td>Gout</td>
<td>19</td>
<td>35</td>
<td>NA</td>
<td>Allopurinol</td>
<td>(Larovere et al., 2004, 2007)</td>
</tr>
<tr>
<td>36–16</td>
<td>None</td>
<td>G148A presumed</td>
<td>R48H</td>
<td>AFM</td>
<td>Motor delay</td>
<td>1.5</td>
<td>37</td>
<td>Gout, recurrent tophi, nephrolithiasis</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>37–29</td>
<td>Salamanca</td>
<td>T128G, G130A</td>
<td>M34R, D44N</td>
<td>7.8% (LF)</td>
<td>Motor delay</td>
<td>1.5</td>
<td>42</td>
<td>NA</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>38–30</td>
<td>LP</td>
<td>T596G</td>
<td>F199C</td>
<td>8% (EL)</td>
<td>Motor delay</td>
<td>2.3</td>
<td>43</td>
<td>Nephrolithiasis, gout</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>39–29</td>
<td>Salamanca</td>
<td>T128G, G130A</td>
<td>M34R, D44N</td>
<td>7.8% (LF)</td>
<td>Motor delay</td>
<td>6</td>
<td>45</td>
<td>NA</td>
<td>Allopurinol</td>
<td>(Page et al., 1987; Sege-Peterson et al., 1992; Torres et al., 2000; Puig et al., 2001)</td>
</tr>
<tr>
<td>40–25</td>
<td>Tsou</td>
<td>G152A</td>
<td>R51Q</td>
<td>NA</td>
<td>Gout</td>
<td>30</td>
<td>45</td>
<td>Tophi</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>41–31</td>
<td>Arlington</td>
<td>A239T</td>
<td>D80V</td>
<td>ND (EL)</td>
<td>Motor delay</td>
<td>5</td>
<td>46</td>
<td>Hypertension, migraines</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>42–32</td>
<td>Cha-ji</td>
<td>T93G</td>
<td>D31E</td>
<td>5% (EL)</td>
<td>Gout</td>
<td>27</td>
<td>53</td>
<td>Nephrolacnosis</td>
<td>Allopurinol, glibencamid</td>
<td></td>
</tr>
<tr>
<td>43–16</td>
<td>None</td>
<td>G148A</td>
<td>R48H</td>
<td>AFM</td>
<td>Tophus on knee</td>
<td>28</td>
<td>56</td>
<td>Tophi, nephrolithiasis, renal insufficiency, diabetes mellitus</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>44–33</td>
<td>Moosejaw</td>
<td>C582G</td>
<td>D194E</td>
<td>10.8% (EL)</td>
<td>NA</td>
<td>58</td>
<td>NA</td>
<td>Severe gouty arthritis, urate nephropathy, scoliosis</td>
<td>Allopurinol</td>
<td>(Jinnah et al., 2000; Lightfoot et al., 1994; Snyder et al., 1984)</td>
</tr>
<tr>
<td>45–34</td>
<td>Marseille</td>
<td>T407C</td>
<td>I136T</td>
<td>1.4% (EL), 5.4% (L)</td>
<td>Gout</td>
<td>40</td>
<td>60</td>
<td>NA</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>46–33</td>
<td>Moosejaw</td>
<td>C582G</td>
<td>D194E</td>
<td>8.4% (EL)</td>
<td>Haematuria</td>
<td>22</td>
<td>65</td>
<td>Gout, tophi, macrocytic anaemia, renal insufficiency</td>
<td>Allopurinol</td>
<td></td>
</tr>
</tbody>
</table>

Some information was not available (NA) because knowledgeable informants or records could not be located. For nosological classification, a BFMI 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).

*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.

The test result varied according to phosphoribosyl pyrophosphate substrate applied.

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.

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

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

(continued)
<table>
<thead>
<tr>
<th>Case-family</th>
<th>Speech Gait</th>
<th>Extrapyramidal features</th>
<th>BFM</th>
<th>Other motor features</th>
<th>Cognition</th>
<th>Behaviour</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>23–14</td>
<td>Slightly slowed and indistinct, intermittent jaw dystonia, childhood stuttering Normal</td>
<td>Normal except overflow hand posturing</td>
<td>Slow/clumsy hand movements</td>
<td>7</td>
<td>None</td>
<td>IQ = 83</td>
<td>None</td>
</tr>
<tr>
<td>24–19</td>
<td>Reduced arm swing</td>
<td>Extreme leg spasms prevent standing or walking</td>
<td>Slow arm and hand movements</td>
<td>NA</td>
<td>None</td>
<td>IQ = 97</td>
<td>Normal</td>
</tr>
<tr>
<td>25–20</td>
<td>Severe dystonic dysarthria</td>
<td>Independent but very slow and laboured with very stiff appearance</td>
<td>Moderate generalized dystonia affecting face, neck, trunk, limbs; bradykinesia</td>
<td>12.5</td>
<td>Brisk arm and leg reflexes, ankle clonus</td>
<td>ADHD, IQ = 86</td>
<td>Anxiety disorder</td>
</tr>
<tr>
<td>26–21</td>
<td>Moderate dystonic dysarthria, childhood stuttering</td>
<td>Independent but very slow and laboured with very stiff appearance</td>
<td>Moderate generalized dystonia affecting face, neck, trunk, limbs; bradykinesia</td>
<td>39</td>
<td>None</td>
<td>ADHD, special education, IQ = 78</td>
<td>Incarcerated for inappropriate behaviour</td>
</tr>
<tr>
<td>27–22</td>
<td>Slightly indistinct</td>
<td>Independent but very slow and stiff appearance with rare skip-like postural adjustments</td>
<td>Mild generalized dystonia affecting face and limbs</td>
<td>6</td>
<td>Brisk arm and leg reflexes, ankle clonus</td>
<td>Marked cognitive impairment</td>
<td>Aggressive</td>
</tr>
<tr>
<td>28–23</td>
<td>Slight dystonic dysarthria</td>
<td>Independent but hyperlordotic</td>
<td>Hypomimia, mild generalized dystonia, affecting face, trunk, limbs</td>
<td>NA</td>
<td>Brisk leg reflexes</td>
<td>Special education</td>
<td>Normal</td>
</tr>
<tr>
<td>29–5</td>
<td>Moderate dystonic dysarthria with jaw dystonia</td>
<td>Independent but hyperlordotic</td>
<td>Moderate generalized dystonia affecting face, trunk, limbs with bradykinesia, rigidity</td>
<td>37</td>
<td>Brisk leg reflexes, ankle clonus</td>
<td>Special education</td>
<td>Normal</td>
</tr>
<tr>
<td>30–24</td>
<td>High-pitched nasal voice</td>
<td>Independent but hyperlordotic</td>
<td>Mild generalized dystonia affecting face and limbs</td>
<td>16</td>
<td>Brisk arm and leg reflexes, ankle clonus</td>
<td>IQ = 96</td>
<td>Onychophagia when stressed</td>
</tr>
<tr>
<td>31–25</td>
<td>Normal</td>
<td>Independent but hyperlordotic</td>
<td>Postural and kinetic tremor</td>
<td>NF</td>
<td>None</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>32–26</td>
<td>Severe dystonic dysarthria</td>
<td>Independent but very slow and stiff appearance with rare skip-like postural adjustments</td>
<td>Severe generalized dystonia affecting face, neck, trunk, limbs; occasional chorea and ballistic limb flailing</td>
<td>61</td>
<td>Reduced distal muscle bulk</td>
<td>IQ = 87, 77</td>
<td>None</td>
</tr>
<tr>
<td>33–27</td>
<td>Moderate dystonic dysarthria</td>
<td>Independent but very slow and stiff appearance with rare skip-like postural adjustments</td>
<td>Moderate generalized dystonia affecting face, trunk, limbs; bradykinesia</td>
<td>16</td>
<td>None</td>
<td>ADHD, IQ = 74</td>
<td>Normal</td>
</tr>
<tr>
<td>Case-family</td>
<td>Speech</td>
<td>Gait</td>
<td>Extrapyramidal features</td>
<td>BFM</td>
<td>Other motor features</td>
<td>Cognition</td>
<td>Behaviour</td>
</tr>
<tr>
<td>------------</td>
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</tr>
<tr>
<td>34–28 Severe dystonic dysarthria</td>
<td>Truncal hypotonia with dystonic leg posturing prevents standing or walking</td>
<td>Resting hypotonia, severe generalized dystonia affecting face, neck, trunk, limbs; occasional choreiform and ballistic limb flailing</td>
<td>68</td>
<td>Brisk arm reflexes</td>
<td>IQ = 49</td>
<td>Sits on arms to avoid hitting bystanders, story fabrication</td>
<td>Motor and speech delay with involuntary movements noted by 1 year; involuntary movements increasingly apparent through 30 years</td>
</tr>
<tr>
<td>35–22 Normal</td>
<td>Normal</td>
<td>Minor overflow posturing of one hand</td>
<td>1</td>
<td>None</td>
<td>Mild executive syndrome</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>36–16 Moderate dystonic dysarthria</td>
<td>Slightly slowed and heavy appearance</td>
<td>Slow/clumsy limb movements, stereotypical action-induced elevation of one shoulder</td>
<td>11</td>
<td>Brisk arm and leg reflexes, neuropathy</td>
<td>Poor school performance</td>
<td>Onychophagia</td>
<td></td>
</tr>
<tr>
<td>37–29 Mild dystonic dysarthria with slight stuttering</td>
<td>Independent but hyperlordotic and stiff appearance</td>
<td>Slow/clumsy hand movements with overflow posturing</td>
<td>14.5</td>
<td>None</td>
<td>ADHD, could not finish public school, IQ = 68</td>
<td>Onychophagia</td>
<td></td>
</tr>
<tr>
<td>38–30 Slightly slowed and indistinct</td>
<td>Slowed and stiff appearance; desires support at all times</td>
<td>Mild generalized dystonia with slow/clumsy hand movements</td>
<td>22.5</td>
<td>Brisk arm and leg reflexes</td>
<td>Frontal syndrome</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>39–29 Mild dystonic dysarthria with severe jaw dystonia and stuttering</td>
<td>Independent but hyperlordotic and stiff appearance</td>
<td>Blepharospasm</td>
<td>5</td>
<td>None</td>
<td>IQ = 68</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>40–25 Normal</td>
<td>Impaired by joint deformities from tophaceous gout</td>
<td>None</td>
<td>0</td>
<td>None</td>
<td>Normal</td>
<td>Progressive disability due to joint deformity</td>
<td></td>
</tr>
<tr>
<td>41–31 Slightly slowed and indistinct</td>
<td>Extreme leg spasms prevent standing or walking</td>
<td>Painful transient leg spasms, postural and kinetic tremor</td>
<td>6</td>
<td>None</td>
<td>Slow learner</td>
<td>Impulsive</td>
<td>Leg braces from 5 to 6 years, mild dystonic posturing until sudden decline at 40 years due to painful leg spasms</td>
</tr>
<tr>
<td>42–32 Normal</td>
<td>Slightly slowed, cannot toe or heel walk due to joint deformity from tophaceous gout</td>
<td>None</td>
<td>0</td>
<td>None</td>
<td>Brisk leg reflexes, peripheral neuropathy</td>
<td>Normal</td>
<td>Progressive hand disability due to joint deformity</td>
</tr>
<tr>
<td>43–16 Moderate dystonic dysarthria</td>
<td>Normal</td>
<td>None</td>
<td>NF</td>
<td>None</td>
<td>NA</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
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 recorded 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

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

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number (n = 47)</th>
<th>Percent of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal</td>
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<td>38.3</td>
</tr>
<tr>
<td>Choreoathetosis</td>
<td>9</td>
<td>19.1</td>
</tr>
<tr>
<td>Dystonia</td>
<td>9</td>
<td>19.1</td>
</tr>
<tr>
<td>Athetosis</td>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>19</td>
<td>40.4</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>14</td>
<td>29.8</td>
</tr>
<tr>
<td>Spasticity</td>
<td>11</td>
<td>23.4</td>
</tr>
<tr>
<td>Clonus</td>
<td>7</td>
<td>4.3</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>59.6</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>19</td>
<td>40.4</td>
</tr>
<tr>
<td>Seizures</td>
<td>7</td>
<td>14.9</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>4.3</td>
</tr>
</tbody>
</table>

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.

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 the 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...
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

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**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.
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
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 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).

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 not 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
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
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 corticos-
triatal 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 dopa-
mine 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,

table 6

<table>
<thead>
<tr>
<th>Mutation class</th>
<th>LND (n = 280)</th>
<th>LNV (n = 101)</th>
<th>NA (n = 9)</th>
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<td>167</td>
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<td>Double mutants</td>
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</table>

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

aSingle base change leading to single amino acid substitution.
bSingle base change leading to premature termination of protein translation.
cSingle base change leading to intron/exon splicing defect.
dUnidentified promoter or enhancer non-coding sequence change resulting in
reduced mRNA.
eAll females have had an identifiable mutation on one allele combined with
non-random X-inactivation.

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.
Lesch–Nyhan variants

other regions may not be spared entirely. For example, hypertonia 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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References


Kiziltan G, Akalin MA. Stuttering may be a type of action dystonia. Mov Disord 1996; 11: 278–82.


Lesch–Nyhan variants


