

# Behavioral aspects of Lesch–Nyhan disease and its variants

David J Schretlen\* PhD;

Julianna Ward PhD;

Stephen M Meyer MA;

Jonathan Yun MD, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, USA.

Juan G Puig MD, Division of Internal Medicine, 'La Paz' University Hospital, Madrid, Spain.

William L Nyhan MD, Department of Pediatrics, University of California San Diego School of Medicine, La Jolla, CA;

H A Jinnah MD PhD, Department of Neurology;

James C Harris MD, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA.

\*Correspondence to first author at Johns Hopkins Hospital, 600 N Wolfe Street, Meyer 218, Baltimore, MD 21287-7218, USA. E-mail: dschret@jhmi.edu

Self-injury is a defining feature of Lesch–Nyhan disease (LND) but does not occur in the less severely affected Lesch–Nyhan variants (LNV). The aim of this study was to quantify behavioral and emotional abnormalities in LND and LNV. Thirty-nine informants rated 22 patients with LND (21 males, 1 female), 11 males with LNV, and 11 healthy controls (HC; 10 males, 1 female) using two well-validated rating scales. The age of patients with LND ranged from 12 years 7 months to 38 years 3 months (mean 22y 11mo; SD 7y 8mo), whereas the age range of those with LNV was 12 years 9 months to 65 years (mean 30y 7mo; SD 15y 2mo), and the healthy controls were aged 12 years 4 months to 31 years 3 months (mean 17y 10mo; SD 5y 7mo). Behavioral ratings were based on the Child Behavior Checklist and the American Association on Mental Retardation's Adaptive Behavior Scale – Residential and Community, 2nd edition. Statistical analyses revealed that patients with LND showed severe self-injury together with problematic aggression, anxious-depressed symptoms, distractibility, motor stereotypes, and disturbing interpersonal behaviors. Patients with LNV were rated as being intermediate between the HC and LND groups on all behavior scales. Although the LNV group did not differ from HCs on most scales, their reported attention problems were as severe as those found in LND. We conclude that self-injurious and aggressive behaviors are nearly universal and that other behavioral abnormalities are common in LND. Although patients with LNV typically do not self-injure or display severe aggression, attention problems are common and a few patients demonstrate other behavioral anomalies.

Lesch–Nyhan disease (LND) is a rare, X-linked disorder of purine metabolism that is caused by a near absence of the enzyme hypoxanthine–guanine phosphoribosyltransferase (HPRT). Decreased HPRT activity has been associated with three basic phenotypes. Patients whose enzyme activity is less than 1.5% of normal demonstrate classic LND. In addition to having hyperuricemia, they demonstrate dystonia, dysarthria, mental retardation\*, and self-injury (Lesch and Nyhan 1964, Jinnah and Friedmann 2001). Self-injurious behaviors usually emerge by the age of 3 years, and most frequently include biting the lips, cheeks, or fingers, banging the head, and poking fingers into the eyes or the spokes of a wheelchair (Anderson and Ernst 1994, Robey et al. 2003). Persons whose HPRT enzyme activity ranges from 1.6% to 8% of normal generally present with hyperuricemia and some motor abnormalities but not intellectual disability or self-injury. Those whose residual HPRT enzyme activity levels exceed 8% to 10% of normal present only with hyperuricemia (Hersh et al. 1986). However, we found that eight of nine Lesch–Nyhan 'variants' produced IQ scores that were below average, and five produced IQs that were below 70 (Schretlen et al. 2001). As a group they showed selective but unambiguous impairments of attention, reasoning, and verbal learning/memory. Moreover, the pattern of their cognitive deficits was strikingly similar to that of 15 patients with LND. In this paper we refer to all patients whose residual HPRT activity exceeds 1.5% of normal and who do not self-injure as having Lesch–Nyhan variants (LNV).

Our previous finding that individuals with LNV suffer from cognitive deficits that are milder but qualitatively similar to those seen in LND raises the question of whether they might also show milder versions of the behavioral and emotional abnormalities that occur in patients with LND. Although two excellent investigations of the frequency, topography, and antecedents of self-injurious and aggressive behaviors in LND have been reported (Anderson and Ernst 1994, Robey et al. 2003), comparable abnormalities have not been studied in persons with LNV. Further, except for these two investigations, previous behavioral studies of LND have focused exclusively on self-injury. However, patients with LND have been described as engaging, curious, good-humored, manipulative, obstinate, irritable, apologetic, and distractible (Michener 1967, Nyhan 1976, Bull and LaVecchio 1978, Anderson et al. 1992, Matthews et al. 1999, Jinnah and Friedmann 2001). Such varied descriptions suggest that even detailed assessment of self-injury is not likely to capture the full behavioral picture of LND, or the presumably more subtle behavior anomalies that might characterize LNV.

The aim of this study was to assess a broad spectrum of emotional and behavioral characteristics of individuals with LND and LNV by using well-validated informant rating scales. On the basis of our earlier finding of the relationship between HPRT deficiency and cognitive functioning, our hypothesis was that individuals with LND would show more aberrant behaviors than those with LNV, but that both patient groups would demonstrate more problem behaviors than healthy controls.

## Method

### PARTICIPANTS

Study participants included 22 patients with LND, 11 patients with LNV, and 11 healthy controls (HC). Because LND is an

See end of paper for list of abbreviations.

\*US usage: mental retardation.

although females can manifest it owing to inactivation of a normal X chromosome (Aral et al. 1996, De Gregorio et al. 2000). Our sample included one 20-year-old female with LND and her unaffected identical twin sister whom we described in a separate paper (De Gregorio et al. 2005). All other participants were male. Altogether, 38 (86%) of the participants were Caucasian, and the remaining six (14%) were African-American.

Participants in the LND group ranged from 12 years 7 months to 38 years 3 months (mean 22y 11mo, SD 7y 8mo). They were diagnosed on the basis of having hyperuricemia, self-injurious behavior, disabling motor abnormalities, and cognitive impairment. The diagnoses of most were confirmed by evidence of residual HPRT enzyme activity levels of less than 1.6% in cultured fibroblasts or a mutation that predicted null enzyme activity (Jinnah et al. 2000). Our sole female patient had a residual HPRT activity level of about 15%, but she met all clinical criteria for LND. The LNV participants ranged in age from 12 years 9 months to 65 years (mean 30y 7mo, SD 15y 2mo). They were diagnosed on the basis of having hyperuricemia and at least mild motor abnormalities in the absence of self-injurious behaviors. These participants came to clinical attention because of hyperuricemia in most cases and delayed motor development in a few. The patients with LND and LNV were recruited through our clinics, other physicians, the Lesch–Nyhan Disease Patient Registry, and the Matheny School and Hospital in Peapack, New Jersey, USA. Although most patients were English-speaking US citizens, two patients were from Canada, two were from Spain, and one was from Germany. Lack of a knowledgeable informant was the only exclusion criterion for patients.

In addition to the 33 patients with LND or LNV, 11 HCs contributed data to the present study. The age of participants in the HC group ranged from 12 years 4 months to 31 years 3 months (mean 17y 10mo, SD 5y 7mo). These participants were recruited by word of mouth from the Bal-

timore metropolitan area. No participant reported a history of substance dependence, schizophrenia, affective illness, or neurological disorder.

Finally, 37 informants provided behavioral ratings of the study participants. They included 27 mothers, two fathers, four other family members, three professional caregivers, and one other rater. Seven informants (six mothers, one father) provided ratings for two participants; the remaining 30 informants rated just one participant.

This study was approved by the Johns Hopkins University School of Medicine's Institutional Review Board. All participants gave either (1) written informed consent or (2) oral assent in addition to the written informed consent provided by a parent or legal guardian before their participation in the present study.

#### PROCEDURE

Each participant underwent an assessment that included neuroimaging, neurological, and cognitive measures that is not reported here. In addition, a family member or caregiver rated each participant on the basis of several personality, symptom, and adaptive behavior questionnaires. Results from two of these, the Child Behavior Checklist (CBCL; Achenbach 1991) and the American Association on Mental Retardation's Adaptive Behavior Scale – Residential and Community, 2nd edition (ABS-RC2; Nihira et al. 1993) formed the basis of this report. Although both of these have been used to assess behavioral abnormalities in persons with mental retardation arising from other causes (Borthwick-Duffy et al. 1997, Hatton et al. 2001), neither has been reported in connection with LND. The CBCL consists of 118 items scored on a 3-point scale (from not true to often true). It was designed to assess behavior problems in children aged from 4 to 18 years, and its eight clinical scales measure Withdrawal, Somatic Complaints, Anxiety/depression, Social

**Table I: Informant ratings of participants on CBCL and ABS-RC2 scales**

<i>Instrument and scale</i>	<i>HC</i>	<i>LNV</i>	<i>LND</i>	<i>ES</i>
<b>CBCL</b>				
Withdrawn Behavior	1.0 (1.6)	2.3 (1.6)	2.6 (2.7)	0.083
Somatic Complaints	0.7 (0.8)	1.7 (2.1)	2.9 (2.9)	0.142
Anxious/depressed	1.5 (1.7) <sup>a</sup>	4.2 (3.3)	7.0 (4.0) <sup>b</sup>	0.324
Social Problems	1.1 (2.5) <sup>a</sup>	3.5 (2.1)	5.0 (2.1) <sup>b</sup>	0.353
Thought Problems	0.4 (1.0) <sup>a</sup>	0.6 (1.3) <sup>a</sup>	2.8 (2.3) <sup>b</sup>	0.315
Attention Problems	1.8 (1.5) <sup>a</sup>	6.7 (3.1) <sup>b</sup>	8.1 (3.7) <sup>b</sup>	0.392
Delinquent Behavior	1.2 (1.2)	1.8 (1.9)	3.7 (3.0)	0.200
Aggressive Behavior	2.8 (2.6) <sup>a</sup>	6.5 (5.5) <sup>a</sup>	13.4 (8.3) <sup>b</sup>	0.337
<b>ABS-RC2</b>				
Social Behavior	2.8 (2.8) <sup>a</sup>	3.9 (4.9) <sup>a</sup>	21.7 (13.5) <sup>b</sup>	0.485
Conformity	2.2 (3.5)	3.0 (3.5)	6.9 (7.0)	0.145
Trustworthiness	0.6 (1.8) <sup>a</sup>	1.5 (1.6)	5.7 (5.1) <sup>b</sup>	0.299
Stereotyped/hyperactive behavior	0.2 (0.4) <sup>a</sup>	5.1 (7.0)	9.4 (8.3) <sup>b</sup>	0.269
Sexual Behavior	0.0 (0.0)	0.4 (1.3)	1.0 (1.9)	0.097
Self-abusive Behavior	0.0 (0.0) <sup>a</sup>	1.1 (1.3) <sup>a</sup>	8.4 (5.7) <sup>b</sup>	0.515
Social Engagement	0.6 (1.5) <sup>a</sup>	1.2 (1.4)	4.7 (4.2) <sup>b</sup>	0.297
Disturbing Interpersonal Behavior	1.3 (2.7) <sup>a</sup>	3.3 (4.4) <sup>a</sup>	13.0 (9.1) <sup>b</sup>	0.402

Results are mean (SD). Different superscript letters denote significantly different ( $p < 0.05$ , with Bonferroni correction) group means. ABS-RC2, Adaptive Behavior Scale – Residential and Community, 2nd edn. (Nihira et al. 1993); CBCL, Child Behavior Checklist (Achenbach 1991); HC, healthy controls; LNV, Lesch–Nyhan variants; LND, Lesch–Nyhan disease; ES, effect size estimates based on partial eta-squared.

Problems, Thought Problems, Attention Problems, Delinquent Behaviors, and Aggressive Behaviors. Although the ABS-RC2 has two parts, for the present analysis we used only Part 2, which assesses social behaviors. Each of the 41 items that comprise Part 2 consists of four to 12 behaviors that the examinee is rated as doing 'never', 'occasionally', or 'frequently' (scored 0, 1, or 2 respectively). The scores for these individual behaviors are summed for each item, and the sums of selected items comprise eight scales. These eight scales assess Social (mostly aggressive) Behaviors, Conformity, Trustworthiness, Stereotyped/hyperactive Behaviors, Sexual Behaviors, Self-abusive Behaviors, Social Engagement, and Disturbing Interpersonal Behaviors. Raw scores were used for all statistical analyses.

#### DATA ANALYSIS

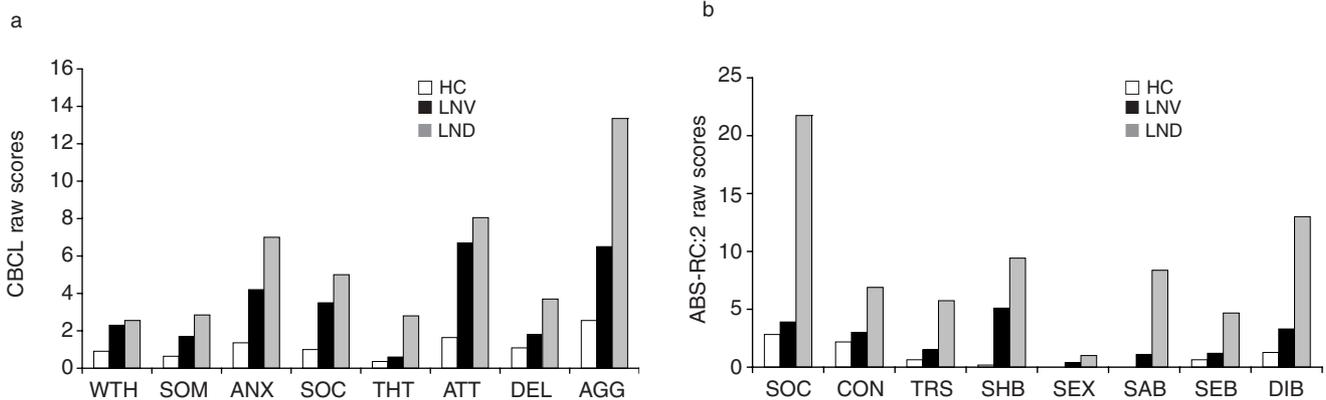
A multivariate analysis of covariance (MANCOVA), with age as the covariate, was used to test the effects of diagnostic group (LND, LNV, and HC) on informant ratings of behaviors assessed by the CBCL and ABS-RC2. Univariate and pairwise comparisons (with Bonferroni correction) were then used to determine which scales and groups contributed to the overall differences.

#### Results

A one-way analysis of variance revealed significant group differences in age ( $F_{(2,41)}=4.86; p=0.013$ ). Post-hoc comparisons showed that the LNV group was significantly older than the HC group but not the LND group, and that the LND and HC groups did not differ in age.  $\chi^2$  analyses revealed no significant association between diagnostic group and race ( $\chi^2_{(2)}=0.39; p=0.82$ ). Because the LNV and HC groups differed in age, we entered age as a covariate in a MANCOVA with diagnostic group as the between-participants factor and raw scores on the eight Achenbach CBCL scales as the dependent variables. This analysis yielded a highly significant overall effect of diagnosis, ( $F_{(16,56)}=3.59; p<0.001$ ) but no significant overall effect of age

( $p=0.60$ ). Univariate  $F$  tests revealed significant effects of diagnostic group on all but two CBCL scales (Withdrawal, Somatic Complaints). As shown in Table I, the LNV group's behavior ratings were intermediate between those of the HC and LND groups on every CBCL scale. Although the patients with LNV did not differ significantly from either the HC or LND group on most scales, they were rated as having significantly more problems with attention than the HCs and significantly fewer Aggressive Behaviors than patients with LND. The patients with LND were rated as having significantly more anxious and depressed behaviors, Social Problems, disrupted thinking, inattention, and aggressive behaviors than HC participants. Thus, patients with LND showed significant behavioral disruption in most CBCL domains, whereas patients with LNV differed significantly from HCs in just one dimension (Attention), in which they showed as much disruption as patients with LND.

In a second MANCOVA, ratings on Part 2 of the ABS-RC2 were examined as a function of diagnostic group after controlling for age. This analysis yielded a Hotelling's trace of 3.15 ( $F_{(16,56)}=5.50; p<0.0001$ ) for the overall effect of diagnostic group, but again revealed no significant effect for age ( $p=0.43$ ). Univariate  $F$  tests revealed significant group effects on all but two ABS-RC2 scales (Conformity, Sexual Behavior). The LNV group's ABS-RC2 behavior ratings again were intermediate between those of the HC and LND groups on every scale. The patients with LNV did not differ significantly from the HC group on any ABS-RC2 scale. However, they were rated as showing significantly fewer behavior problems than the LND group on three scales: Social Behavior, Self-abusive Behavior, and Disturbing Interpersonal Behavior. On the ABS-RC2, the Social Behavior scale consists primarily of items that assess aggression. For example, Item 1 is 'Threatens or does physical violence', and specific behaviors include 'spits on others', 'bites others', and 'throws objects at others'. Other items on this scale include specific behaviors that assess violent temper tantrums, teasing, bossing, using angry language, etc. The Self-abusive Behavior scale comprises three items that include such specific



**Figure 1:** Mean informant behavior ratings of patients with Lesch–Nyhan disease (LND), Lesch–Nyhan variant (LNV), and healthy controls (HC). (a) Child Behavior Checklist (CBCL; Achenbach 1991) scales: WTH, Withdrawn; SOM, Somatic Complaints; ANX, Anxiety/depression; THT, Thought Problems; ATT, Attention Problems; DEL, Delinquent Behaviors; AGG, Aggressive Behaviors. (b) Adaptive Behavior Scale – Residential and Community, 2nd edition (ABS-RC2; Nibira 1993) scales: SOC, Social Behavior; CON, Conformity; TRS, Trustworthiness; SHB, Stereotyped/hyperactive Behavior; SEX, Sexual Behavior; SAB, Self-abusive Behavior; SEB, Social Engagement; DIB, Disturbing Interpersonal Behavior.

behaviors as 'bites or cuts self', 'bangs head or other body parts against objects', 'slaps or strikes self', 'pulls own hair, ears, etc.', and 'purposely provokes abuse by others'. The Disturbing Interpersonal Behavior scale includes a heterogeneous mixture of items that assess tendencies to overestimate one's abilities, react poorly to criticism, demand excessive attention, feel persecuted, feign illness, and display heightened emotionality. The patients with LND were rated as showing significantly more of these behaviors than both the HC and LNV groups. Group ratings on the CBCL and ABS-RC2 scales are depicted in Figure 1.

Finally, to determine whether some patients with LNV demonstrate behavioral abnormalities in domains other than attention, we derived cumulative frequency distributions for their CBCL and ABS-RC2 scale scores and compared these with the mean scores of patients with LND. This revealed that six patients with LNV showed behavioral abnormalities that equalled or exceeded the LND group mean on at least one CBCL scale, and three patients with LNV showed behavioral abnormalities that equalled or exceeded the LND group mean on at least one ABS-RC2 scale. All of the CBCL scales and four of the ABS-RC2 scales (Conformity, Stereotyped/hyperactive Behavior, Sexual Behavior, and Disturbing interpersonal behavior) were represented among those on which the patients with LNV produced abnormal scores. None of the patients with LNV had a behavioral abnormality that was as severe as those of the average patient with LND on the other four ABS-RC2 scales (Self-abusive Behavior, Social [aggressive] Behavior, Trustworthiness, and Social Engagement). Thus, even though the LNV group's mean scores did not differ significantly from those of the HC group on most CBCL and ABS-RC2 scales, a few patients with LNV had behavioral abnormalities that were as severe as the average patient with LND.

### Discussion

Four main findings emerged from the present study. First, group differences clearly validated the use of the ABS-RC2 to quantify the self-injurious behaviors that characterize LND. Second, informant ratings suggest that the LND behavioral phenotype extends beyond self-injury to include aggression and other behavioral abnormalities. Third, on informant ratings, patients with LNV were generally more similar to HCs than to patients with LND. Fourth, patients with LNV were more similar to those with LND in terms of attentional problems, and a few LNV patients showed other behavioral abnormalities that were as severe as those seen in LND.

The antecedents, frequency, nature, and severity of self-injurious behaviors shown by patients with LND have been described by two excellent surveys of family members and other caregivers (Anderson and Ernst 1994, Robey et al. 2003). Although the CBCL and ABS-RC2 do not provide such detailed descriptions of these behaviors, both have been used extensively to assess behavior problems in other developmentally disabled populations (Borthwick-Duffy et al. 1997, Hatton et al. 2001), and our findings validate their usefulness for clinical assessment of LND. Specifically, as shown in Table I, the largest group difference was observed on the ABS-RC2 Self-abusive Behavior scale. Significant group differences also were observed on several other ABS-RC2 and CBCL scales, especially those designed to assess aggression.

Anecdotal reports indicate that patients with LND can manifest a broad array of maladaptive (and adaptive) behaviors. Yet

we know of no systematic investigation of behavioral anomalies other than aggression and self-injury, which is traditionally thought to define the behavioral phenotype (Nyhan 1972, Harris 2001). However, in this connection, the present findings were striking. Patients with LND showed more aggressive, inattentive, distractible, anxious/depressed, stereotyped, hyperactive, attention-seeking, and disturbing interpersonal behaviors. Conversely, they did not demonstrate more social withdrawal, somatic complaints, delinquency, problems with conformity, or aberrant sexual behaviors than the HCs. Thus, these findings clearly suggest that the LND behavioral phenotype extends beyond self-injury to include aggressive behavior in virtually all cases, inattention or distractibility in most cases, and other behavioral anomalies in many cases.

To our knowledge, this is the first behavioral study of LNV. The behavior ratings of the LNV group consistently fell between those of the HC and LND groups. Although they did not differ significantly from HCs on most clinical scales, this was probably due to limited statistical power, as the LNV group's mean scores on several CBCL and ABS-RC2 scales (Anxious/depressed, Social Problems, Withdrawn, and Stereotyped/hyperactive Behaviors) were closer to the HC than the LND group. In contrast, we previously found that patients with LNV performed significantly worse than HCs in IQ and other cognitive tests (Schretlen et al. 2001). These findings suggest that individuals with LNV are cognitively more similar to patients with LND than to HCs, but are behaviorally more similar to healthy controls than to patients with LND. This could reflect differential involvement of dopaminergic frontal-striatal circuits that primarily subserve cognitive versus emotional information processing (Visser et al. 2000).

In this study, patients with LNV were rated as significantly different from healthy controls and indistinguishable from patients with classic LND on the CBCL Attention scale. Not only is this consistent with anecdotal reports by other investigators (Matthews et al. 1999), it also provides independent support for our previous finding that patients with LNV showed their greatest cognitive impairment on the Brief Test of Attention (Schretlen et al. 2001). This auditory divided-attention task is sensitive to distractibility and has been shown to distinguish patients without dementia with Huntington disease from healthy adults who were matched to the patients in terms of age, education, race, and Mini-Mental State Examination scores (Schretlen et al. 1996). Given that Huntington disease is characterized by motor abnormalities, cognitive decline, and behavioral changes, primarily involves striatal pathology, and probably involves dopaminergic abnormalities (Visser et al. 2000), these findings could imply that more extensive dopamine depletion is required to produce the behavioral phenotype seen in LND than the cognitive deficits that appear in partial HPRT deficiency, Huntington disease, and other diseases of the basal ganglia.

Persons with LND wear restraints and other protective devices most of the time, invariably suffer from severe motor abnormalities, and sometimes receive anxiolytic or other medications to reduce their risk of self-injury. All of these could inhibit their expression of the very behaviors we sought to assess. We did not give informants any specific instructions to take these factors into account when rating patients' behaviors. As a result, their ratings could underestimate the severity of abnormalities that some patients with LND might demonstrate if they were unrestrained, were free of all medications,

and had sufficient motor control to execute a broader range of aberrant behaviors. However, we believe this design limitation had relatively little impact on our essential findings because patients with LND differed most from the other two groups in terms of the very behaviors (self-injury and aggression) that restraints, medications, and poor motor control are most likely to inhibit.

Although this study is one of the largest clinical studies of individuals with HPRT-deficiency spectrum disorders, it nonetheless includes a relatively small number of variants. Consequently, we hesitate to draw firm conclusions about the behavioral manifestations of LNV on the basis of these data. This is especially true because varying degrees of HPRT deficiency have been associated with widely differing neurological and neurocognitive manifestations (Hersh et al. 1986, Page and Nyhan 1989, Puig et al. 2001). Nevertheless, our findings suggest that some behavioral aspects of the LND phenotype occur in persons with LNV. These especially involve distractibility and other cognitive impairments, but also can include other behavioral anomalies.

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#### List of abbreviations

ABS-RC2	Adaptive Behavior Scale - Residential and Community, 2nd edn
CBCL	Child Behavior Checklist
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
LND	Lesch-Nyhan disease
LNV	Lesch-Nyhan variants
HC	Healthy controls