Brain white matter volume abnormalities in Lesch-Nyhan disease and its variants

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ABSTRACT

Objective: We sought to examine brain white matter abnormalities based on MRI in adults with Lesch-Nyhan disease (LND) or an attenuated variant (LNV) of this rare, X-linked neurodevelopmental disorder of purine metabolism.

Methods: In this observational study, we compared 21 adults with LND, 17 with LNV, and 33 age-, sex-, and race-matched healthy controls using voxel-based morphometry and analysis of covariance to identify white matter volume abnormalities in both patient groups.

Results: Patients with classic LND showed larger reductions of white (26%) than gray (17%) matter volume relative to healthy controls. Those with LNV showed comparable reductions of white (14%) and gray (15%) matter volume. Both patient groups demonstrated reduced volume in medial inferior white matter regions. Compared with LNV, the LND group showed larger reductions in inferior frontal white matter adjoining limbic and temporal regions and the motor cortex. These regions likely include such long association fibers as the superior longitudinal and uncinate fasciculi.

Conclusions: Despite earlier reports that LND primarily involves the basal ganglia, this study reveals substantial white matter volume abnormalities. Moreover, white matter deficits are more severe than gray matter deficits in classic LND, and also characterize persons with LNV. The brain images acquired for these analyses cannot precisely localize white matter abnormalities or determine whether they involve changes in tract orientation or anisotropy. However, clusters of reduced white matter volume identified here affect regions that are consistent with the neurobehavioral phenotype. **Neurology® 2015;84:190-196**

GLOSSARY

HC = healthy control; **HPRT** = hypoxanthine-guanine phosphoribosyltransferase; **LND** = Lesch-Nyhan disease; **LNV** = Lesch-Nyhan variant; **MNI** = Montreal Neurological Institute; **VBM** = voxel-based morphometry.

Lesch-Nyhan disease (LND) is a rare, X-linked disorder caused by mutations of the gene that encodes the purine salvage enzyme, hypoxanthine-guanine phosphoribosyltransferase (HPRT).¹ Residual HPRT enzyme activity that is less than 1.5% of normal typically produces classic LND, which is characterized by hyperuricemia, severe dystonia, recurrent self-injury, and cognitive impairment.²⁻⁴ Mutations that lead to enzyme activity between 1.5% and 20% of normal (i.e., partial HPRT deficiency) yield variant phenotypes (LNV) in which motor and cognitive deficits vary with enzyme activity, self-injury is absent, and other aberrant behaviors are attenuated.⁵

The neural substrates of neurobehavioral abnormalities in LND are unclear. Most investigators have focused on basal ganglia circuits because cardinal features of the phenotype point to dysfunction of these regions. While structural brain abnormalities are rarely seen on routine clinical neuroimaging, we recently found widespread gray matter volume reductions using voxel-based morphometry (VBM).⁶ These were most prominent in the caudate and putamen, followed by their downstream targets: the thalamus, limbic brain, and cerebral cortex, including

Supplemental data
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the dorsolateral, inferior frontal, cingulate, insula, hippocampal/parahippocampal, amygdala, and middle temporal regions.

The aim of this investigation was to identify regional white matter abnormalities in LND and LNV. Lacking diffusion-weighted imaging data, we used VBM with analysis of covariance to assess white matter abnormalities in LND and LNV and localize them to anatomical regions and white matter tracts to the extent possible. We hypothesized that both patient subgroups would show volumetric white matter abnormalities compared with healthy adults, and we compared LND and LNV patient subgroups to identify possible substrates of the characteristic that most distinguishes them: self-injurious behavior.

METHOD Participants. Twenty-one adults with LND, 17 with LNV, and 33 healthy controls (HCs) contributed to this analysis. The same participants contributed data to a previous report of regional gray matter volume abnormalities.⁶ Clinical diagnoses were made by a neurologist (H.A.J.) with expertise in LND. The diagnosis of LND was based on the presence of hyperuricemia, motor neurologic abnormalities, self-injurious behavior, cognitive impairment, and either residual HPRT enzyme activity less than 1.5% of normal or a mutation in the *HPRT1* gene predicting null enzyme activity. Participants with LNV displayed similar but milder clinical characteristics, no history of self-injurious behavior, and reduced HPRT enzyme activity or a mutation in the *HPRT1* gene. Patients were recruited through clinics and physician referral, the Lesch-Nyhan Syndrome Registry, and the Matheny School and Hospital. HCs were recruited from the Baltimore area and had no reported history of substance abuse, mental illness, or neurologic disorder.

Standard protocol approvals, registrations, and patient consents. Each participant gave written informed consent if competent to do so or oral informed assent with written informed consent by a guardian. This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Johns Hopkins and Emory University institutional review boards.

Procedure. Each participant underwent neurologic examination by a neurologist (H.A.J.) who specializes in movement disorders and LND and cognitive testing supervised by a neuropsychologist (D.J.S.) with experience in LND. Each participant received a T1-weighted brain scan. Scans conducted before 2009 were acquired on a 1.5T GE Genesis Signa machine (GE Healthcare, Waukesha, WI) (repetition time 35 milliseconds, echo time 2 milliseconds, field of view 256 mm, flip angle 45°, 1.0 × 1.0 × 1.5 mm). Those conducted after 2009 were acquired on a 3T Siemens Trio machine (Siemens AG, Erlangen, Germany) (repetition time 2,300 milliseconds, echo time 2.9 milliseconds, field of view 256 mm, flip angle 9°, 1.0 × 1.0 × 1.2 mm). All patients with LND and some with LNV were given alprazolam before scanning to help them lie still in the scanner, and then were monitored thereafter until they awoke fully.

Imaging and statistical analysis. VBM was conducted using the VBM8 toolbox within the SPM8 software package to obtain

white matter volumes for each participant. Following the methods described earlier,⁶ before automated segmentation and alignment, all images were manually aligned to the anterior commissure–posterior commissure line to prevent errors during the automation process that could arise from the reduced intracranial volumes of patients. Segmentation and normalization were performed using Jacobian modulation to account for differences in overall brain size, because entering intracranial volume as a covariate would confound the results given the large group differences in head size. Resulting white matter volumes were smoothed using a 6-mm isotropic gaussian kernel and compared using analysis of covariance within SPM8, controlling for white matter volume variations due to age and the scanner on which images were acquired. In addition, scanner effects were modeled to ensure that false positives did not arise as a result of the differing acquisition parameters. These methods are described more fully elsewhere.⁶

Regionally specific white matter abnormalities were identified by a 3-group analysis of covariance with a stringent cluster-level family-wise error correction of $p < 0.01$ and a cluster-forming threshold of $p < 0.0005$. Masks for each cluster that remained significant after family-wise correction were then created with the xjView (version 8.11) viewing program for qualitative comparison. We next conducted 6 post hoc t test analyses within SPM8 (HC > LND, HC > LNV, LNV > LND, HC < LND, HC < LNV, and LNV < LND) to identify regions of white matter volume that distinguished the groups in each pairwise comparison. More typical significance levels (family-wise error correction of $p < 0.05$ and cluster-forming threshold of $p < 0.0005$) were used for these analyses.

Group differences in sex and race were assessed using the χ^2 test. Group differences in years of schooling were tested with a 2-group t test that compared only persons with LNV and healthy adults because persons with LND typically require special education. Finally, between-group analyses of variance with pairwise, Bonferroni-corrected post hoc comparisons were used to examine group differences in segmented volumes and ratios derived from the brain MRI scans (table 1).

RESULTS As shown in table 1, the 3 participant groups did not differ significantly in age or sex. Patients with LNV completed fewer years of education than healthy adults. Those with LND were excluded from this comparison because their educational experience was so specialized and unlike that of the other groups. Both patient groups showed significantly reduced global gray and white matter volumes relative to HCs. However, while patients with LND showed greater reduction of white (26%) than gray (17%) matter volume, those with LNV showed nearly equal reductions of white (14%) and gray (15%) matter. Neither patient group differed from healthy adults in their total brain-to-intracranial volume ratios. This suggests that age-related atrophy is not accelerated among patients.

Based on analyses of covariance, the LND group showed 2 clusters of white matter voxels with significantly smaller volumes than those of the HC group (table 2). One large cluster (87,596 voxels) showed contiguous white matter deficits throughout the brain with local maxima identified bilaterally in the insular,

Table 1 Demographic characteristics and brain volumes (in cm³) by group

Characteristic	LND	LNV	HC	Statistic	p
Age, y	25.0 ± 9.2	35.2 ± 16.8	28.9 ± 12.9	$F_{2,68} = 3.01$	0.06
Sex, M/F, n	20/1	17/0	33/0	$\chi^2_{2,68} = 2.42$	0.30
Education, y	NA	11.1 ± 3.4 _a	14.0 ± 2.2 _b	$t_{34} = 2.41$	0.05
Race, white/black, n	19/2	15/1	28/6	$\chi^2_{2,68} = 1.80$	0.41
Intracranial volume ^a	1,197 ± 178 _a	1,286 ± 106 _a	1,495 ± 130 _b	$F_{2,68} = 31.1$	0.001
TBV ^b	1,003 ± 155 _a	1,077 ± 107 _a	1,267 ± 120 _b	$F_{2,68} = 29.9$	0.001
Gray matter volume	601 ± 106 _a	611 ± 78 _a	724 ± 71 _b	$F_{2,68} = 17.4$	0.001
White matter volume	402 ± 63 _a	466 ± 40 _b	543 ± 68 _c	$F_{2,68} = 34.7$	0.001
TBV/TICV ratio	0.84 ± 0.03	0.84 ± 0.03	0.85 ± 0.03	$F_{2,68} = 1.29$	0.282

Abbreviations: HC = healthy control; LND = Lesch-Nyhan disease; LNV = Lesch-Nyhan variant; NA = not applicable; TBV = total brain volume; TICV = total intracranial volume.

All values except for sex and race are expressed as means ± SD. Years of schooling are not shown for patients with LND because of their atypical educational histories. Different subscripts (a–c) indicate that the corresponding groups differ ($p < 0.05$) based on pairwise post hoc comparisons with Bonferroni correction. Identical and absent subscripts denote the lack of a significant group difference.

^a Sum of gray matter, white matter, and CSF volumes (TICV).

^b Sum of gray matter and white matter volumes (TBV).

inferior frontal, and striatal regions. A second smaller cluster (187 voxels) contained local maxima in the lingual region, extending into the cerebellar white matter. As depicted in figure 1A, these abnormalities encroached on white matter tracts in many regions. The LNV group showed less widespread volumetric deficits relative to HCs. These include 5 significant clusters that range from 261 to 11,716 voxels, with local maxima adjacent to the caudate nuclei bilaterally,

and the calcarine sulcus extending into cerebellar white matter (figure 1B). Based on Montreal Neurological Institute (MNI) coordinates, the local maxima of these clusters all fell within regions of decreased white matter volume observed in the LND group. Thus, the regions of reduced white matter volume seen in adults with LNV represent a subset of those seen in adults with classic LND. Finally, figure 1C depicts regions in which persons with classic LND showed significantly smaller white matter volumes than those with LNV. Local maxima within these clusters localized to the striatum bilaterally, anterior/middle cingulum, inferior and middle frontal regions, and both primary and supplementary motor areas. There were no white matter clusters in LND or LNV that were significantly larger than in HCs.

The MNI coordinates for local maxima of VBM-defined clusters of decreased white matter volume cannot be localized reliably to specific white matter tracts, but one can infer their proximity to known tracts by visual inspection in combination with published white matter atlases.^{7,8} Qualitatively, both patient groups displayed reduced volume in brainstem and striatal white matter tracts relative to healthy adults. Patients with LNV showed relative sparing of right white matter volumes in the subcortical regions and bilaterally in superior neural regions. In addition, white matter volumes in the corticospinal tract region were reduced in LND but not in LNV. Direct pairwise comparison of the patient groups revealed that adults with classic LND showed decreased volume of white matter tracts near the supplementary motor area and the junction of the inferior frontal lobe adjoining

Table 2 Significant clusters of reduced white matter volume based on post hoc group comparisons

Cluster	Size, voxels	p Value ^a	MNI coordinates (x, y, z) of local maxima ^b
HC > LND			
1	87,596	<0.001	34.5, -7.5, 25.5; -27, -9, 24; 28.5, -22.5, 31.5
2	187	0.001	-15, -73, -5
HC > LNV			
1	11,716	<0.001	12, -12, 16.5; 12, -1.5, -1.5
2	674	<0.001	-12, -51, -31.5
3	10,443	<0.001	-3, -4.5, 1.5; -8, -24, 6
4	261	0.01	34.5, -81, 12
5	1,814	<0.001	-1.5, -22.5, -36
LNV > LND			
1	779	0.004	-20, -15, 51
2	3,484	<0.001	20, 8, 25; -23, 3, 43
3	376	0.042	-17, 20, 12
4	766	0.002	-23, 3, 43

Abbreviations: HC = healthy control; LND = Lesch-Nyhan disease; LNV = Lesch-Nyhan variant; MNI = Montreal Neurological Institute.

^a Values reflect imposition of family-wise error correction.

^b Local maxima shown in MNI space (x, y, z).

Figure 1 Axial slice view showing group differences in white matter volume

Statistical parametric maps showing clusters of reduced white matter volume in adults with LND compared to healthy adults (A), adults with LNV compared to healthy adults (B), and adults with LND compared to those with LNV (C). Images are shown following neurologic convention (left hemisphere appears on the left side), with a cluster-forming threshold of $p < 0.0005$ and a cluster-level family-wise error correction of $p < 0.05$. Areas of significance are overlaid on the average fractional anisotropy maps from the Illinois Institute of Technology human brain atlas.⁹ LND = Lesch-Nyhan disease; LNV = Lesch-Nyhan variant.

temporal and limbic regions. Despite the imprecise spatial resolution of white matter tract localization in VBM, the regions that distinguish patients with LND from those with LNV primarily involve long association fibers, likely including subsections 1 and 2 of the superior longitudinal fasciculus, the uncinate fasciculus, and the cingulum. Additional volumetric deficits appeared near the corticospinal tract adjacent to the supplementary motor area.

Scanner effects. Potential confounding effects of using 2 different scanners on white matter volume were tested using a liberal threshold ($p < 0.001$, uncorrected). This comparison yielded 11 clusters that ranged in size from 1 to 19 voxels. However, when the statistical thresholds used in previous analyses were applied, no voxel of white matter remained significantly associated with the machine used. A glass brain image of the uncorrected significant voxels is shown in figure e-1 on the *Neurology*[®] Web site at Neurology.org.

DISCUSSION This study sheds new light on the biological bases of the neurobehavioral abnormalities in LND and its attenuated variants. Most previous research has focused on the basal ganglia and their dopaminergic pathways.^{9–12} However, the present study reveals marked and widespread reductions of brain white matter volume too. These findings could reflect abnormalities of brain connectivity. If so, then they clearly show that pathways beyond the basal ganglia also are affected.

The white matter results found here amplify the findings of recent VBM studies of gray matter, which showed that volumetric decreases extend beyond the basal ganglia to involve cortical targets in the frontal and temporal lobes, with relative sparing of the occipital regions and cerebellum.⁶ They also are compatible with the clinical phenotype. For example, dystonia often is associated with defects of the putamen, but also with the primary and supplementary motor cortex.^{13,14} Decreased white matter volumes adjacent to the supplementary motor cortex could indicate

dysfunction of this region, or fibers of passage between the primary motor cortex and basal ganglia. Spasticity and hyperreflexia also are common in LND, and might relate to abnormalities in the corticospinal white matter.^{15,16} The cognitive impairments that characterize both LND and LNV⁴ similarly could result from disruption of subcortical white matter containing cortical association and commissural connections. One prior study linked self-injurious behaviors in adults with borderline personality disorder to abnormalities in frontal white matter.¹⁷ The authors stated that the observed abnormalities included inferior white matter in both frontal lobes, but their regions of interest clearly included the superior longitudinal fasciculus, which appears to be considerably more abnormal in LND than in LNV, as shown in figure 1C. Self-injurious behaviors also are associated with dysfunction of nigrostriatal dopamine pathways, which are not myelinated and, therefore, unlikely to be specifically identified by VBM.

One limitation of cross-sectional VBM studies is that it can be challenging to discriminate primary defects related to HPRT deficiency from secondary downstream consequences. Both gray and white matter volumes can change in response to practice effects for both motor and cognitive functions^{18,19} Thus, reduced volumes in LND and LNV could partly reflect the consequences of a chronic illness. For example, all patients with LND and many with LNV have generalized dystonia, limiting their ability to walk. Thus, one might argue that chronic disuse of the legs could lead to reduced volumes in the corticospinal pathways. Other cortical regions could be affected by educational or other experiential limitations. However, the term “disuse” is not entirely appropriate for the LND neurobehavioral phenotype. Dystonia and chorea are hyperkinetic disorders. This strains the argument that they might cause secondary brain changes due to “disuse.” Likewise, self-injury is an active process, rather than one that involves disuse. A related concept is regional target atrophy due to lack of projections and synaptic connectivity that leads to relative underactivity of the target regions. Perhaps also worth emphasizing here is that white matter was not globally affected. The anterior and posterior commissures were spared, and the cerebral peduncles were largely unaffected. This suggests that corticocortical connectivity across the hemisphere is normal, and corticofugal connectivity with brainstem and spinal cord targets is relatively normal. These aspects are quite different from the disuse atrophy that results from cortical disconnection in multiple sclerosis, or from the changes associated with disuse in cerebral palsy.

Alternatively, surrogate experimental models in which experiential factors can be controlled indicate that white matter loss might result directly from HPRT

deficiency. For example, while Nissl and immunohistochemical stains have shown no neuronal loss in any brain region in the HPRT-deficient knockout mouse, Golgi histochemistry studies have revealed dendrites to be shorter with less complex branching patterns in the basal ganglia and cerebral cortex.²⁰ Because these mice are behaviorally normal, the dendritic abnormalities are not likely to be a secondary result of chronic illness. In addition, several HPRT-deficient neuron-like cell models also have shown impoverished outgrowth of neurites in culture,^{21–26} suggesting that the defect is intrinsic, and does not result from interactions with other brain cells or activity-dependent experience. Taken together, these findings imply that a defect in neurite outgrowth is a direct effect of HPRT deficiency. Such a defect in the human brain is likely to be accompanied by reduced associated myelin and total white matter, as found in the current study.

While these VBM results point to specific regions of brain volume abnormalities, they do not address the underlying pathologic substrates. If the previously observed decreases in gray matter volume denote smaller neuron counts, rather than a reduction in soma size,²⁷ this could explain our findings of decreased white matter volume. More likely, decreased white matter volume reflects dysmyelination of local axons or dendrites, loss or atrophy of axons or dendrites, or combined loss of fibers and associated myelin. Several prior histopathologic studies of LND brains collected at autopsy have failed to reveal any obvious abnormalities in random white matter samples, arguing for combined loss of myelin and associated fibers rather than a selective defect in myelination. Further imaging studies with diffusion-weighted imaging will be required to delineate the underlying actual fiber tracts most involved, and more targeted histologic studies of these tracts in autopsy material may be required to delineate the underlying pathologic substrates.

Finally, the results obtained here underscore the need to examine diffusion-weighted imaging in patients with LND and LNV. Analysis of fractional anisotropy could provide insight into the integrity of white matter tracts with reduced volume identified by the current VBM studies. Similarly, measures derived from tractography could elucidate abnormalities of the organization, length, and width of fiber bundles in specific white matter tracts that connect basal ganglia structures to cortical regions in circuits that might account for specific features of LND and LNV phenotypes.¹¹ In any case, the finding that persons with LND showed substantially larger reductions of white than gray matter raises the intriguing possibility that gray matter abnormalities might result from a “chronic disconnection,” rather than cause the white matter changes found in this study.

AUTHOR CONTRIBUTIONS

David J. Schretlen: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision, obtaining funding. Mark Varvaris: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, acquisition of data, statistical analysis, study supervision. Tracy D. Vannorsdall: drafting/revising the manuscript, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. Barry Gordon: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, obtaining funding. James C. Harris: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, acquisition of data, study supervision. H.A. Jinnah: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval, study supervision.

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REFERENCES

1. Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 1964;36:561–570.
2. Jinnah HA, Visser JE, Harris JC, et al. Delineation of the motor disorder of Lesch-Nyhan disease. *Brain* 2006;129:1201–1217.
3. Schretlen DJ, Ward J, Meyer SM, et al. Behavioral aspects of Lesch-Nyhan disease and its variants. *Dev Med Child Neurol* 2005;47:673–677.
4. Schretlen DJ, Harris JC, Park KS, Jinnah HA, Del Pozo NO. Neurocognitive functioning in Lesch-Nyhan disease and partial hypoxanthine-guanine phosphoribosyl-transferase deficiency. *J Int Neuropsychol Soc* 2001;7:805–812.
5. Jinnah HA, Ceballos-Picot I, Torres RJ, et al. Attenuated variants of Lesch-Nyhan disease. *Brain* 2010;133:671–689.
6. Schretlen DJ, Varvaris M, Ho TE, et al. Regional brain volume abnormalities in Lesch-Nyhan disease and its variants: a cross-sectional study. *Lancet Neurol* 2013;12:1151–1158.
7. Zhang S, Peng H, Dawe RJ, Arfanakis K. Enhanced ICBM diffusion tensor template of the human brain. *Neuroimage* 2011;54:974–984.
8. Oishi K, Faria AV, van Zijl PCM, Mori S. *MRI Atlas of Human White Matter*, 2nd ed. London: Elsevier Academic Press; 2011.
9. Wong DF, Harris JC, Naidu S, et al. Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo. *Proc Natl Acad Sci USA* 1996;93:5539–5543.
10. Ernst M, Zametkin AJ, Matochik JA, et al. Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *N Engl J Med* 1996;334:1568–1572.
11. Visser JE, Baer PR, Jinnah HA. Lesch-Nyhan disease and the basal ganglia. *Brain Res Rev* 2000;32:449–475.
12. Baumeister AA, Frye GD. The biochemical basis of the behavioral disorder in the Lesch-Nyhan syndrome. *Neurosci Biobehav Rev* 1985;9:169–178.
13. Neychev VK, Gross RE, Lehericy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. *Neurobiol Dis* 2011;42:185–201.
14. Lehericy S, Tijssen MA, Vidailhet M, Kaji R, Meunier S. The anatomical basis of dystonia: current view using neuroimaging. *Mov Disord* 2013;28:944–957.
15. Hoon AH Jr, Stashinko EE, Nagae LM, et al. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. *Dev Med Child Neurol* 2009;51:697–704.
16. Lee SK, Kim DI, Kim J, et al. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. *Radiographics* 2005;25:53–65; discussion 66–68.
17. Grant JE, Correia S, Brennan-Krohn T, Malloy PF, Laidlaw DH, Schulz SC. Frontal white matter integrity in borderline personality disorder with self-injurious behavior. *J Neuropsychiatry Clin Neurosci* 2007;19:383–390.

18. Draganski B, May A. Training-induced structural changes in the adult human brain. *Behav Brain Res* 2008;192: 137–142.
19. May A. Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci* 2011;15:475–482.
20. Mikolaenko I, Rao LM, Roberts RC, Kolb B, Jinnah HAA. Golgi study of neuronal architecture in a genetic mouse model for Lesch-Nyhan disease. *Neurobiol Dis* 2005;20: 479–490.
21. Bitler CM, Howard BD. Dopamine metabolism in hypoxanthine-guanine phosphoribosyltransferase-deficient variants of PC12 cells. *J Neurochem* 1986;47:107–112.
22. Yeh J, Zheng S, Howard BD. Impaired differentiation of HPRT-deficient dopaminergic neurons: a possible mechanism underlying neuronal dysfunction in Lesch-Nyhan syndrome. *J Neurosci Res* 1998;53:78–85.
23. Smith DW, Friedmann T. Characterization of the dopamine defect in primary cultures of dopaminergic neurons from hypoxanthine phosphoribosyltransferase knockout mice. *Mol Ther* 2000;1:486–491.
24. Ceballos-Picot I, Mockel L, Potier MC, et al. Hypoxanthine-guanine phosphoribosyl transferase regulates early developmental programming of dopamine neurons: implications for Lesch-Nyhan disease pathogenesis. *Hum Mol Genet* 2009;18:2317–2327.
25. Cristini S, Navone S, Canzi L, et al. Human neural stem cells: a model system for the study of Lesch-Nyhan disease neurological aspects. *Hum Mol Genet* 2010;19:1939–1950.
26. Mekhoubad S, Bock C, de Boer AS, Kiskinis E, Meissner A, Eggan K. Erosion of dosage compensation impacts human iPSC disease modeling. *Cell Stem Cell* 2012;10:595–609.
27. Shirley TL, Lewers JC, Egami K, et al. A human neuronal tissue culture model for Lesch-Nyhan disease. *J Neurochem* 2007;101:841–853.

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