Pediatric Leigh Syndrome: Neuroimaging Features and Genetic Correlations

Sarah L. Stenton,[1,2] Ying Zou,[3] Hua Cheng,[4] Holger Prokisch,[1,2,3] and Fang Fang[3]

We read with interest the article by Alves et al[1] identifying associations between the genetic etiology of Leigh syndrome and the location of lesions on brain magnetic resonance imaging (MRI) in 53 patients. In light of these data, and to provide a replication cohort to confirm the clinical value of these associations, we independently analyzed 139 patients with Leigh syndrome and molecular confirmation at the Beijing Children's Hospital.

Replicating the mitochondrial DNA (mtDNA) encoded (64/139, 46.0%) and nuclear DNA (nDNA) encoded (75/139, 54.0%) gene enrichment analysis in our patients with Leigh syndrome, we were unable to demonstrate significant enrichment for lesions in any discrete brain areas. Similarly, in the analysis of OXPHOS subunit and assembly factor encoding genes (85/139, 61.2%) and all other genes (54/139, 38.8%), we were unable to recapitulate enrichment for lesions in the basal ganglia, and were likewise unable to demonstrate enrichment for cerebellar atrophy, which was reported in just one patient with variants in *MT-ATP6*. We were nonetheless able to demonstrate enrichment for involvement of the brainstem (odds ratio = 3.42, Cramer's V = 0.28, p value = 0.001), likely driven by the substantial fraction of patients with *SURF1* in our cohort (16/139, 11.5%; Table S1). A clear limitation of this analysis, therefore, is the high dependency on the underlying genetic composition of the cohort, which may differ considerably between clinical centers. This is further exemplified by a scarcity of patients with *MT-ATP6* in the

TABLE. Enrichment Analysis for MRI Features in Specific Molecular Diagnoses in Our Leigh Syndrome Cohort

SURF1					
Brain area	***SURF1* patients**	**Other patients**	**OR**	***p***	**Combined SE, SP**
Medulla oblongata[a]	16/16 (100%)	36/123 (29.3%)	Inf	2.74e-8[b]	12.5%, 99.2%
Brainstem[a]	16/16 (100%)	79/123 (64.2%)	Inf	2.83e-3[b]	
Cerebellum	8/16 (50%)	17/123 (13.8%)	6.12	1.82e-3[b]	
Lenticular nucleus[a]	7/16 (43.8%)	93/123 (75.6%)	0.25	1.49e-2[b]	
Basal ganglia[a]	7/16 (43.8%)	97/123 (78.9%)	0.21	4.81e-3[b]	
Thalamus	2/16 (12.5%)	54/123 (43.9%)	0.18	1.59e-2[b]	
MT-ND5					
Brain area	***MT-ND5* patients**	**Other patients**	**OR**	***p***	**Combined SE, SP**
Thalamus	8/9 (88.9%)	48/130 (36.9%)	13.44	3.06e-3[b]	55.6%, 96.2%
Medulla oblongata[a]	7/9 (77.8%)	45/130 (34.6%)	6.52	1.39e-2[b]	
Basal ganglia[a]	2/9 (22.2%)	102/130 (78.5%)	0.08	9.40e-4[b]	
Lenticular nucleus[a]	1/9 (11.1%)	99/130 (76.2%)	0.04	1.55e-4[b]	
PDHA1					
Brain area	***PDHA1* patients**	**Other patients**	**OR**	***p***	**Combined SE, SP**
Lenticular nucleus[a]	13/13 (100%)	87/126 (69%)	Inf	1.95e-2[b]	92.3%, 73.8%
Basal ganglia[a]	13/13 (100%)	91/126 (72.2%)	Inf	3.83e-2[b]	
Caudate[a]	1/13 (7.7%)	57/126 (45.2%)	0.10	8.13e-3[b]	

MRI = magnetic resonance imaging; OR = odds ratio; SE = sensitivity; SP = specificity.
[a]Confirms association reported by Alves et al[1].
[b]Cramer's V ≥ 0.25.

Alves et al cohort (3/53, 5.7%), whereas *MT-ATP6* is one of the most frequent diagnoses among the Beijing cohort (23/139, 16.5%), among patients with Leigh syndrome with molecular confirmation in the European Network of Mitochondrial Disease (GENOMIT) patient registry (42/476, 8.8%), and in the literature.[2–4] These data should be cautiously interpreted by clinicians in guiding a molecular diagnostic approach and family counseling.

In our analysis of single disease gene associations, we leveraged increased patient numbers per genetic diagnosis to confirm and expand a number of MRI associations demonstrated by Alves et al in *SURF1*, *MT-ND5*, and *PDHA1* (Table). In *SURF1*, enrichment for brainstem involvement with sparing of the basal ganglia was confirmed. We additionally demonstrate enrichment for cerebellar lesions and sparing of the thalamus. In *MT-ND5*, enrichment for brainstem lesions, more specifically within the medulla oblongata, with sparing of the basal ganglia was confirmed. We additionally demonstrate enrichment for thalamic lesions. In *PDHA1*, enrichment for basal ganglia lesions with sparing of the caudate was confirmed. Nevertheless, given the variable sensitivity and specificity of such MRI feature combinations (Table), their clinical value in pinpointing the definitive molecular diagnosis remains limited.

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Potential Conflicts of Interest

The authors declared no conflict of interest.

[1]*Institute of Human Genetics, School of Medicine, Technische Universität München, Munich, Germany*
[2]*Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany*
[3]*Department of Neurology, Beijing Children's Hospital, Capital Medical University, Beijing, China*
[4]*Image Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China*

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