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Heteroplasmy - A mixture of wild-type and mutant mitochondrial DNA. The proportion of mutant and wild-type molecules is often referred to as the heteroplasmy percentage, heteroplasmy frequency or heteroplasmy burden

>80% => disease ~1 in 8,000

Heteroplasmy present ~1 in 25 – with no disease

Stewart&Chinnery, 2020, Nat.Gen



































Deletions of mitochondrial DNA in muscle biopsies from individuals with Kearns-Sayre syndrome. DNA was digested with restrictase, which cuts the mitochondrial genome at one site, resulting in a 16.5-kb fragments that is detected on a gel. Each individual with the syndrome has two populations of mitochondrial DNA: one of normal size and one of smaller size form

Zeiani M, Moraes CT DiMauro S et al. Deletions of mitochondrial DNA in Kearns-Sayre syndrome. Neurology 1988; 38: 1339-1346)





























































Autistic spectum disorder and mitochondrial dysfunction Brain weight = ~1.4 kilograms= 2% of total body weight, but it demands 20% of energy (resting metabolic rate) Brain development is extremely sensitive to energy level/demand/supply => mitochondria should be involved somehow **Autism and Lactic Acidosis** Mary Coleman¹ John P. Blass Georgetown University School of Medicine Cornell University Medical College Journal of Autism and Developmental Disorders, Vol. 15, No. 1, 1985 Table | Serum lactic acid (5-20 mg/dl) ref. range Serum pyruvic acid (.3-.9 mg/dl) ref. range Age at time of work-up Sex Patient 10, 18, 27, 33 27.5, 29 23, 27 1.9, 1.1, 1.1, 1.8 .8, 1.5 1.14, 1.2 A B C F M M 3 Ď 15 30, 37 .96, 2.6 4 out of 80 patients with autism had higher lactate It was linked to PHD complex altered metabolism





Autistic spectum disorder and mitochondrial dysfunction

Autism and Intellectual Disability Associated with Mitochondrial Disease and Hyperlactacidemia

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Enzyme Activity or Metabolite Concentration	Patient 1	Patient 2	Patient 3	Control Values
NADH: Cit C oxidoreductase (Complex I + III) (mU/U CS)	156	310	253	107-560
Succinate: Cit C oxidoreductase (Complex II + III) (<u>mU/U CS</u>)	<u>49</u>	111	<u>35</u>	75–149
Succinate: DCPIP oxidoreductase (Complex II) (<u>mU/U CS</u>)	<u>29</u>	48	<u>27</u>	33–69
Succinate Dehydrogenase (mU/U CS)	74	119	79	57-239
Decylubiquinone: Cytochrome C oxidoreductase (Complex III) (mU/U CS)	<u>498</u>	<u>597</u>	615	610–1760
Cytochrome C oxidase (Complex IV) (mU/U CS)	<u>287</u>	<u>501</u>	<u>291</u>	590-1300
Coenzyme Q10 (nmol/U CS)	2.3	2.6	2.9	2.6-8.4
Citrate Synthase (nmol/min/mg)	243.7	125.7	<u>350</u>	71-200
Fasting Lactate (mM)	2.96	2.64	4.56	<2.30
Postprandial Lactate (mM)	3.84	2.82	5.15	<3
Fasting lactate/pyruvate ratio	<u>29.6</u>	<u>47.7</u>	14.2	10-15
Postprandial lactate/pyruvate ratio	25.6	42.2	24.5	10-15













Recommend de	Table 2 oses of vitamin supplements
Vitamin	Dose
Electron Transport Chain Support Co-enzyme Q10: Ubiquinol Co-enzyme Q10: Ubiquinone	5–30 mg/kg/day divided in 2 doses per day 10–30 mg/kg/day divided in 2 doses per day
Energy Storage and Transportation Creatine monohydrate	0.1 g/kg/day divided in 1-2 doses per day
Fatty Acid Oxidation Support L-carnitine Acetyl-L-carnitine Biotin (B7)	30–100 mg/kg/day divided in 2–3 doses per day 250–1000 mg/day divided in 2 doses per day 5–10 mg/day given once per day
B-Vitamins Thiamine (B1) Riboflavin (B2) Niacin (B3) Pyridoxine (B6)	50-100 mg/day given once per day 100-400 mg/day given once per day 50-100 mg/day given once per day 200 mg/day given once per day
Antioxidants Acetyl-L-carnitine Vitamin E Vitamin C alpha-lipoic acid	250–1000 mg/day divided in 2 doses per day 200–400 IU/day given once per day 100–500 mg/day given once per day 50–200 mg/day given once per day
Oxidative Stress Support Methylcobalamin (B12) Folinic Acid / leucovorin (B9) 5-methytetrahydrofolate (B9) N-acetvl-L-cysteine (NAC)	5–1000 mcg/day given once per day 400–800 ug/day given once per day 400–800 ug/day given once per day 10–70 mc/kg/day divided in 1–3 doses





















Table II. Spatial para	meters of PD	patients and	control s	ubjects.				
	Right limb patients	Right limb Control subjects	p	Confidence interval	Left limb patients	Left limb Control subjects	p	Confidence interval
Step lenght (m)	0.48 ± 0.13	0.619 ± 0.04	0.0001*	From -0.170 to -0.089	0.49 ± 0.13	0.74 ± 0.19	0.0001*	From -3.319 to -0.189
Velocity (m/s)	0.84 ± 0.28	1.33 ± 0.06	0.0001*	From -0.575 to -0.402	0.83 ± 0.28	1.33 ± 0.06	0.0001*	From -0.573 to -0.402
Swing velocity (m/s)	2.17 ± 0.63	3.29 ± 1.37	0.0001*	From -1.573 to -0.668	2.13 ± 0.61	3.27 ± 0.184	0.0001*	From -1.330 to -0.946
Stride lenght (m)	0.98 ± 0.27	1.40 ± 0.74	0.0007*	From -0.656 to -0.183	0.95 ± 0.28	1.40 ± 0.62	0.0001*	From -0.687 to -0.212
Sten width (m)	0 10 + 0 10	140 ± 0.07	0.0001*	From -1 333 to -1-262	0.11 ± 0.09	140 ± 0.6	0.0001*	From -1.332 to -1.267
otop mour (m)	0.10 ± 0.10	1110 2 0101		110111 11000 10 1 1000	0.11 2 0.00	1110 2.010		
Average velocity (m/s) Values are expressed	0.082 ± 0.29	0.11 ± 0.26 andard deviatio	0.63 n (mediar	From 0.144 to 0.088	0.082 ± 0.29 dicated (*p<0.0	0.12 ± 0.01	0.38	From -0.124 to -0.048
Average velocity (m/s) Values are expressed Table III. Temporal p	0.082 ± 0.29 as mean ± sta arameters of	0.11 ± 0.26 andard deviation PD patients a	0.63 in (mediar and contro	From 0.144 to 0.088 i); results of t-test are in of subjects.	0.082 ± 0.29 dicated (*p<0.0	0.12 ± 0.01	0.38	From -0.124 to -0.048
Average velocity (m/s) Values are expressed Table III. Temporal p	0.082±0.29 as mean ± sta arameters of Right limb patients	0.11 ± 0.26 andard deviation PD patients a Right limb Control subjects	0.63 on (mediar und contro	From 0.144 to 0.088 p); results of t-test are in ol subjects. Confidence interval	0.082 ± 0.29 dicated (*p<0.0	Left limb Control subjects	0.38 p	From -0.124 to -0.048 Confidence interval
Average velocity (m/s) Values are expressed Table III. Temporal p	0.082 ± 0.29 as mean ± sta arameters of Right limb patients 60.57 ± 9.97	0.11 ± 0.26 andard deviation PD patients a Right limb Control subjects 59.6 ± 1.2	0.63 in (mediar and contro p 0.523	From 0.144 to 0.088)); results of t-test are in of subjects. Confidence interval From -2.03 to 3.979	0.082 ± 0.29 dicated (*p<0.0 Left limb patients 61.24 ± 3.99	Left limb Control subjects 59.3 ± 1.8	0.38 p	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039
Average velocity (m/s) Values are expressed Table III. Temporal p Stance phase (%) Swing phase (%)	0.082 ± 0.29 as mean ± sta arameters of Right limb patients 60.57 ± 9.97 37.9 ± 3.49	0.11 ± 0.26 andard deviation PD patients a Right limb Control subjects 59.6 ± 1.2 40.4 ± 1.2	0.63 in (mediar and contro p 0.523 0.0001*	From 0.144 to 0.088 (i); results of t-lest are in of subjects. Confidence interval From -2.03 to 3.979 From -3.606 to -1.394	0.082 ± 0.29 dicated (*p<0.0 Left limb patients 61.24 ± 3.99 38.7 ± 3.99	0.12 ± 0.01 0.12 ± 0.01 0.5) Left limb Control subjects 59.3 ± 1.8 40.7 ± 1.8	0.38 p 0.01* 0.001	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039 * From -7.746 to -7.373
Average velocity (m/s) Average velocity (m/s) Values are expressed Table III. Temporal p Stance phase (%) Swing phase (%) Stance duration (s)	0.082 ± 0.29 a mean ± sta arameters of Right limb patients 60.57 ± 9.97 37.9 ± 3.49 0.74 ± 0.14	0.11 \pm 0.26 andard deviation PD patients a Right limb Control subjects 59.6 \pm 1.2 40.4 \pm 1.2 13.4 \pm 1.1	0.63 on (median on contro p 0.523 0.0001* 0.0001*	From 0.144 to 0.088 i); results of t-test are in al subjects. Confidence interval From -2.03 to 3.979 From -3.606 to -1.384 From -12.99 to -12.32	0.082 ± 0.29 dicated (*p<0.0 Left limb patients 61.24 ± 3.99 38.7 ± 3.99 0.74 ± 0.16	0.12 ± 0.01 0.12 ± 0.01 0.5) Left limb Control subjects 59.3 ± 1.8 40.7 ± 1.8 8.3 ± 0.6	0.38 p 0.01* 0.001 0.003*	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039 * From -7.746 to -7.373 From -3.34 to -0.688
Values are expressed Table III. Temporal p Stance phase (%) Stance dutation (s) Swing dutation (s)	0.082 ± 0.29 0.082 ± 0.29 I as mean ± sta arameters of Right limb patients 60.57 ± 9.97 37.9 ± 3.49 0.74 ± 0.14 0.44 ± 0.04	0.11 ± 0.26 andard deviation PD patients a Right limb Control Subjects 59.6 ± 1.2 40.4 ± 1.2 13.4 ± 1.1 0.63 ± 0.21	0.63 In (median Ind contro p 0.523 0.0001* 0.0001*	From 0.144 to 0.088 i); results of t-test are in ol subjects. Confidence interval From -2.03 to 3.979 From -3.606 to -1.334 From -12.99 to -12.32 From -2.24 to -0.125	0.082 ± 0.29 dicated (*p<0.0 Left limb patients 61.24 ± 3.99 38.7 ± 3.99 0.74 ± 0.16 0.46 ± 0.05	Left limb Control subjects 59.3 ± 1.8 40.7 ± 1.8 8.3 ± 0.6 0.626 ± 0.42	0.38 p 0.01* 0.001 0.003* 0.004*	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039 From -7.746 to -7.374 From -3.34 to -0.688 From 0.628 to 3.251
Values are expressed Table III. Temporal p Stance phase (%) Swing phase (%) Swing duration (s) Swing duration(s)	0.082 ± 0.29 0.082 ± 0.29 I as mean ± stu arameters of Right limb patients 60.57 ± 9.97 37.9 ± 3.49 0.74 ± 0.14 0.44 ± 0.04 1.19 ± 0.18	0.11 ± 0.26 andard deviation PD patients a Right limb Control subjects 59.6 ± 1.2 40.4 ± 1.2 13.4 ± 1.1 0.63 ± 0.21 0.426 ± 0.16	0.63 In (median Ind contro p 0.523 0.0001* 0.0001* 0.0001*	From 0.144 to 0.088 i); results of t-test are in ol subjects. Confidence interval From -2.03 to 3.979 From -3.606 to -1.394 From -12.99 to -12.32 From -0.254 to -0.125 From 0.675 to .802	0.082 ± 0.29 0.082 ± 0.29 dicated (*p<0.0 61.24 ± 3.99 38.7 ± 3.99 0.74 ± 0.16 0.46 ± 0.05 1.19 ± 0.19	0.12 ± 0.01 0.12 ± 0.01 0.55 Left limb Control subjects 59.3 ± 1.8 40.7 ± 1.8 8.3 ± 0.6 0.626 ± 0.42 0.429 ± 0.23	0.38 p 0.01* 0.0001 0.003* 0.004*	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039 * From -0.7746 to -7.373 From -3.34 to -0.688 From 0.628 to 3.251
Varrage velocity (m/s). Values are expressed Table III. Temporal p Stance phase (%) Stance duration (s) Swing duration(s) Cadene (stephini) [H2]	0.08 ± 0.18 0.082 ± 0.29 as mean ± str arameters of Fight limb patients 60.57 ± 9.97 37.9 ± 3.49 0.74 ± 0.14 1.19 ± 0.18 102.4 ± 13.17	Right limb Right limb PD patients a Right limb Control subjects 59.6 ± 1.2 40.4 ± 1.2 13.4 ± 1.1 0.63 ± 0.21 0.426 ± 0.16 113.84 ± 4.3	0.63 In (median and contro p 0.523 0.0001* 0.0001* 0.0001* 0.0001*	From 0.144 to 0.088 i); results of t-test are in ol subjects. Confidence interval From -2.03 to 3.979 From -3.606 to -1.394 From -0.254 to -0.125 From -0.254 to -0.025 From -15.55 to -7.24	0.082 ± 0.29 0.082 ± 0.29 dicated (*p<0.0 Left limb patients 61.24 ± 3.99 0.74 ± 0.16 0.74 ± 0.16 1.19 ± 0.19 102.4 ± 13.17	Left limb Control Subjects 59.3 ± 1.8 40.7 ± 1.8 8.3 ± 0.6 0.626 ± 0.42 0.626 ± 0.42	0.38 p 0.01* 0.0001 0.003* 0.004* 0.0001	From -0.124 to -0.048 Confidence interval From -0.292 to -0.039 * From -7.746 to -7.373 From -3.34 to -0.688 From 0.628 to 3.251 * From 0.675 to 0.802 * From -15.55 to -7.24















