Oxidative Stress Induced Mitochondrial Dysfunction in Children with Autism Spectrum Disorder

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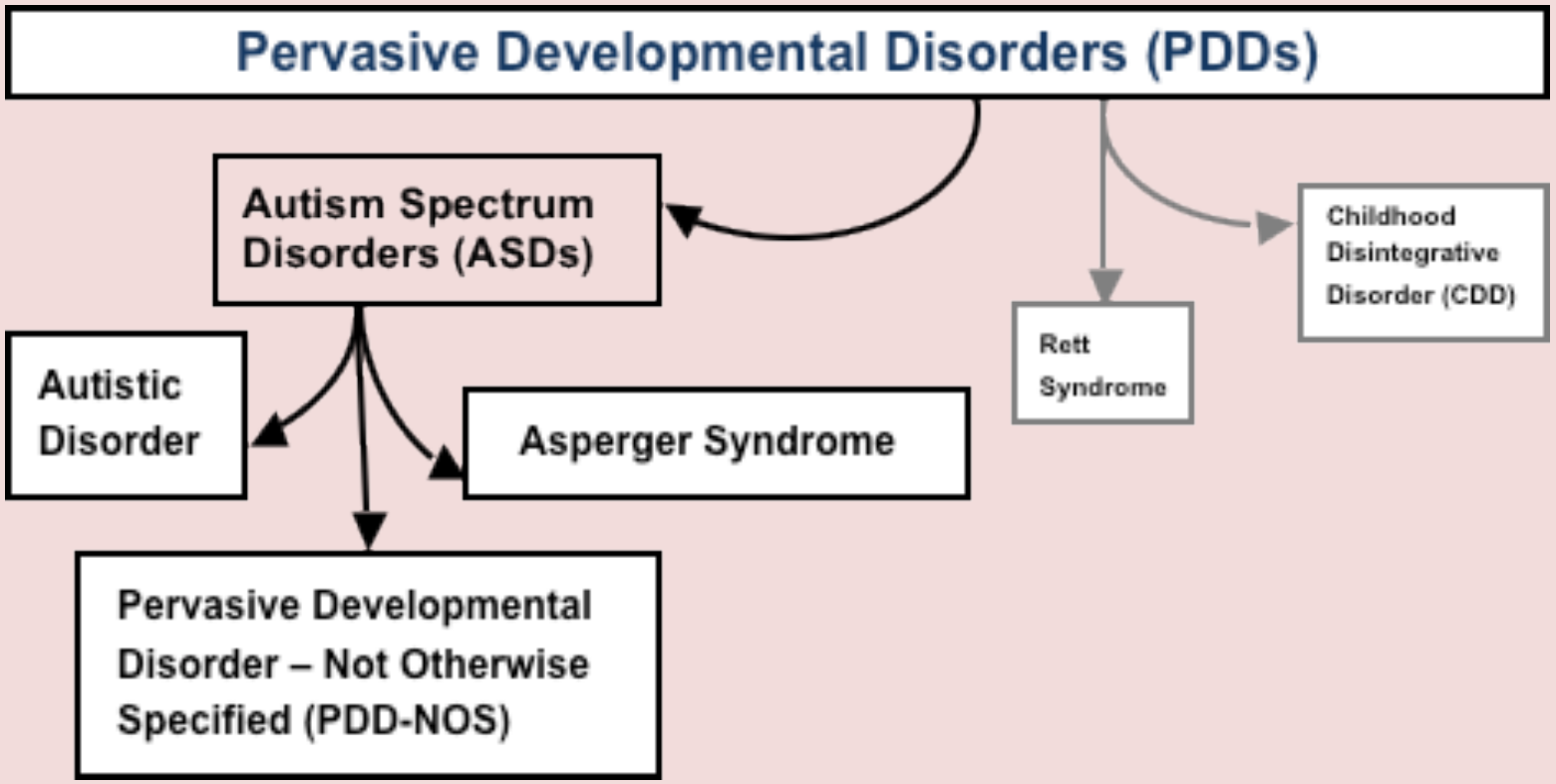
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



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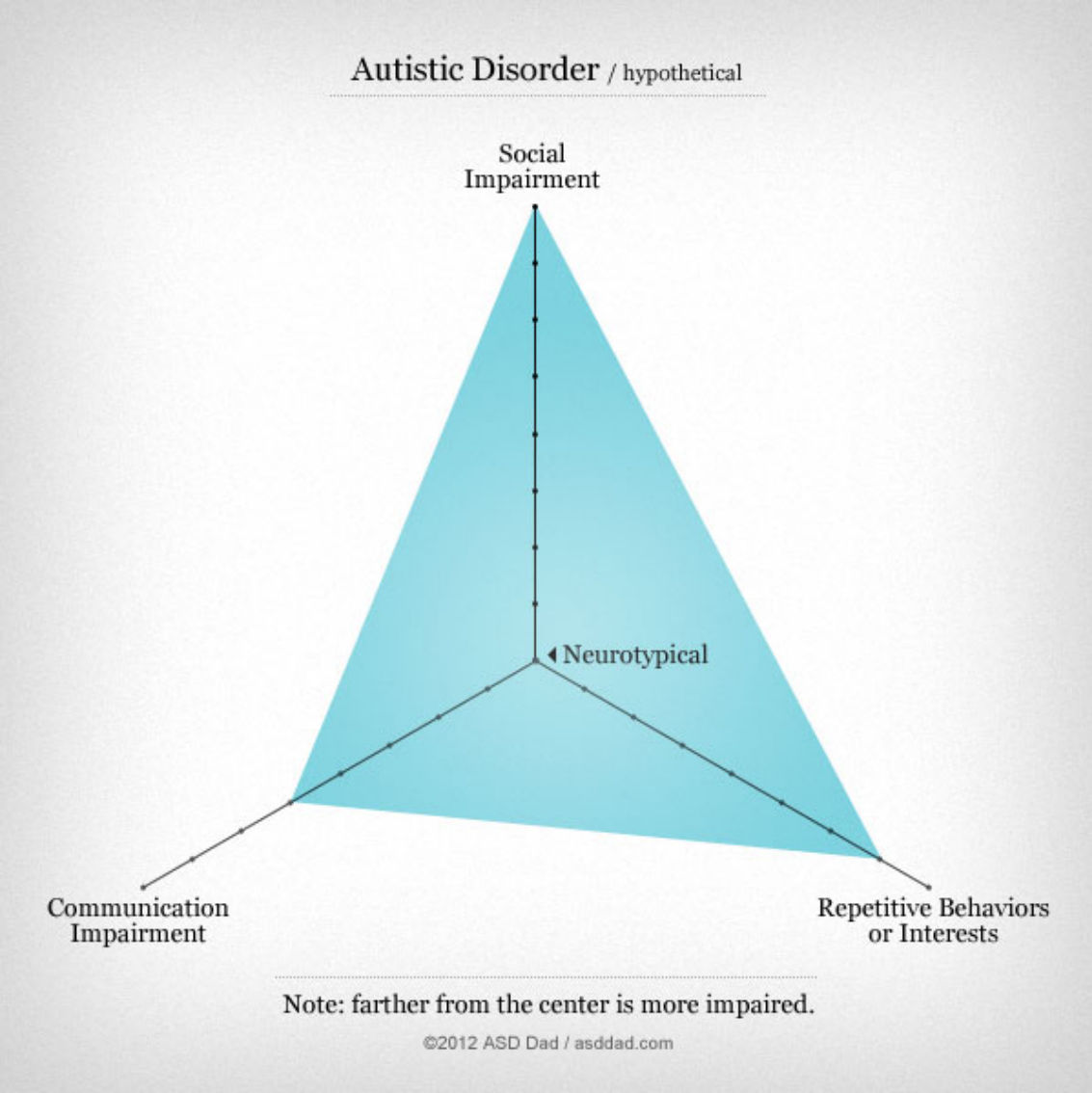

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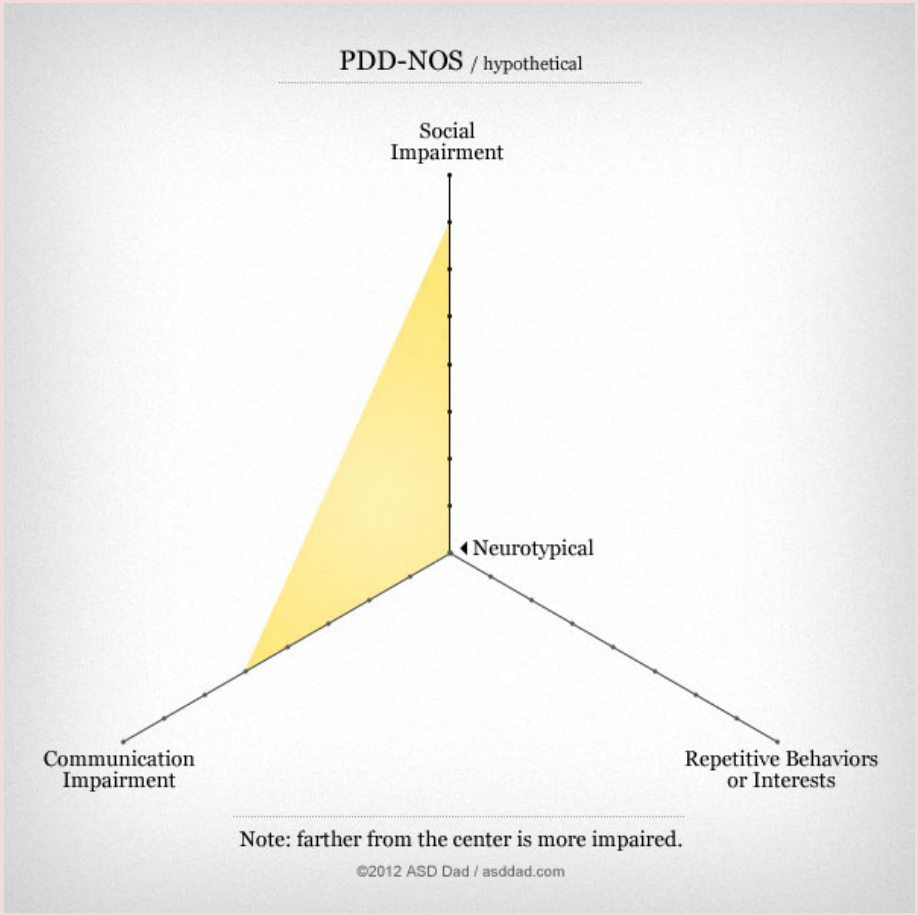

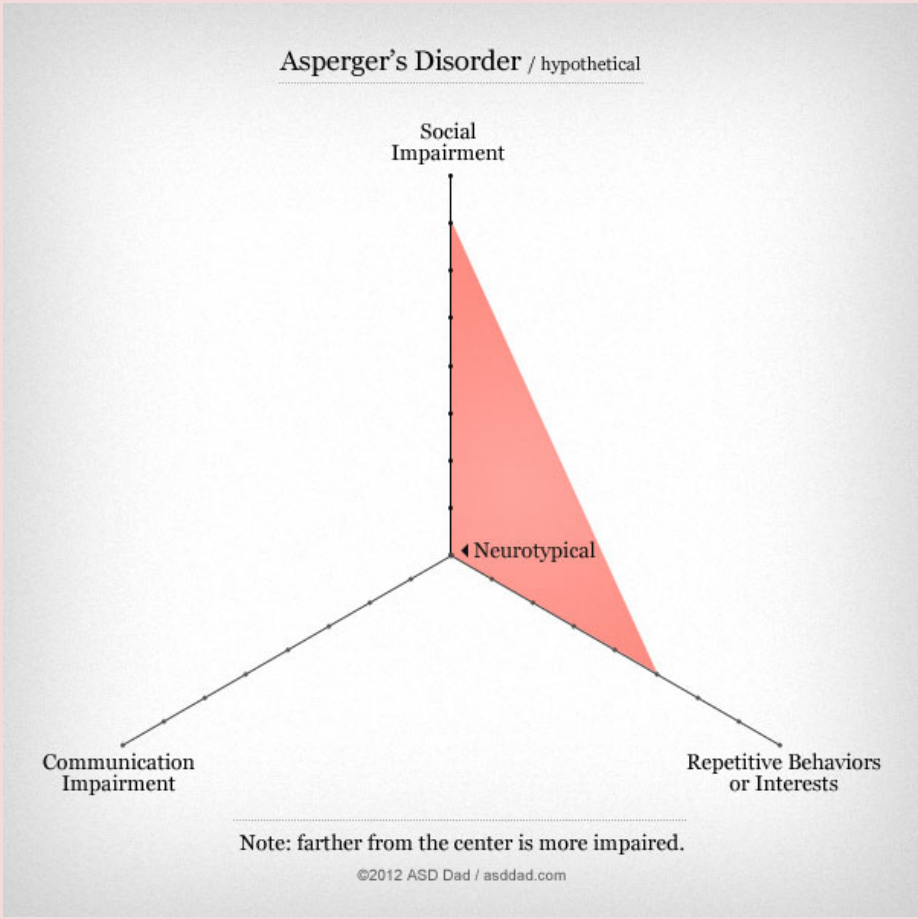

Age of Onset

Autistic Disorder and **Pervasive Development Disorder**

- By Definition (DSM-IV/ICD-10) – Before 36 Months – Three patterns
  - 33% Regression from normal development
    - Usually Between 12 and 24 months
  - 33% Symptoms from Early Infancy
  - 33% Symptoms obvious after 1 year old – developmental plateau
- Onset after 36 months – other diagnosis
- Regression after 36 months Childhood Disintegrative Disorder

Asperger's Syndrome

- No Age Criteria for diagnosis
- Typically not diagnosed until later childhood because less obvious when language development is normal.

Early Behavior in Children who Later Developed Autism

•Abnormalities the differentiate autism from both developmental delay and typically developing children are primarily considered social behaviors and include

- Responding to Name
- Looking at other people
- Showing objects
- Joint Attention (Pointing and Following a Point)
- Decreased Social Interactions – Playing Peek-a-boo
- Looking at others – looking for parents

Pointing

- Starts Around 8-10 Months
- Majority of Gestures at 12 Months

Protoimperative

- Desired Object
- Impaired in younger ASD
- May develop in older ASD

Protodeclarative

- Deficient in ASD
- Shared Experience
- Joint Attention

Protodeclarative Gestures

- Start Around 8-10 Months
- Pointing
- Showing: Extending arms holding object towards someone's face to share interest
- Giving: Placing an object in someone's hand to share object of interest with them (should not be confused with giving object in order for someone to do something necessary to fulfill child's need)

Causes of Autism

The Etiology of Autism: More than Genetic Disorders

Estimated Prevalence of Genetic Abnormalities	
Cytogenetic Abnormalities	5%
Fragile X	5%
Rett Syndrome (Females only)	5% (~1% overall)
Chromosomal Microarray	10%
Total	21%

This leaves about 79%+ children with ASD without an identified genetic diagnosis.

(Schaefer and Mendelson, Genetics in Medicine, 2008)

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

Inherited Metabolic Disorders – Mostly Case Reports

Mitochondrial Disease Cases (~25%)

Pyrimidine and Purine metabolism: Dihydropyrimidinase deficiency,
Phosphoribosylpyrophosphate synthetase superactivity,
Adenylosuccinate lyase deficiency

Disorders of γ-aminobutyric acid metabolism:
Succinic semialdehyde dehydrogenase deficiency

Carnitine Biosynthesis: 6-*N*-trimethyllysine dioxygenase deficiency

Disorders of amino acid metabolism: Phenylketonuria, Histidinemia
Branched Chain Ketoacid Dehydrogenase Kinase Deficiency

Disorders of Cholesterol Metabolism: Smith–Lemli–Opitz Syndrome

Disorders of creatine metabolism

Sulfation defects

Biotinidase deficiency

Urea Cycle Defects: Ornithine transcarbamylase deficiency, Citrullinemia,
Argininosuccinic aciduria, Carbamoyl phosphate synthetase deficiency

Lysosomal Storage Disease: Sanfilippo syndrome, Infantile ceroid lipofuscinosis

Zecavati and Spence, 2009 Curr Neurol Neurosci Rep 9(2):129-36
Schaefer and Mendelson, Genetics in Medicine, 2013

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Non-inherited Metabolic Conditions Associated with Autism

Mitochondrial Disorders	Redox Abnormalities	Folate Abnormalities
Mitochondrial Disease with no genetic abnormalities (75%) Electron Transport Chain Deficiencies in Immune Cells and Brain Tissue ETC Complex I and IV overactivity Acyl-carnitine Elevations	Decreased reduced Glutathione & Cysteine Reduced Glutathione Peroxidase function Increased oxidized Glutathione, DNA, Proteins and Lipids	Cerebral Folate Insufficiency Autoantibodies to Folate Receptor α Mitochondrial Disease/Dysfunction

Genetics Disorders Associated with ASD & Metabolic Abnormalities

Mitochondrial Disorders	Redox-Folate Metabolism
Rett syndrome Down syndrome PTEN mutations 15q11-q13 duplication Angelman syndrome Septo-optic dysplasia	Rett syndrome Down syndrome Phenylketonuria

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Open

Molecular Psychiatry (2011), 1–13

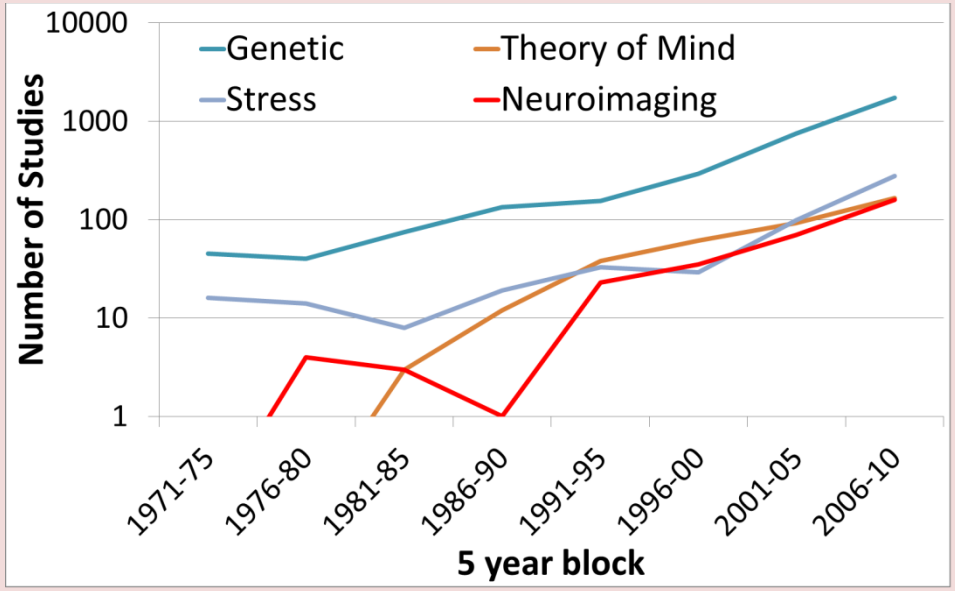
www.nature.com/mp

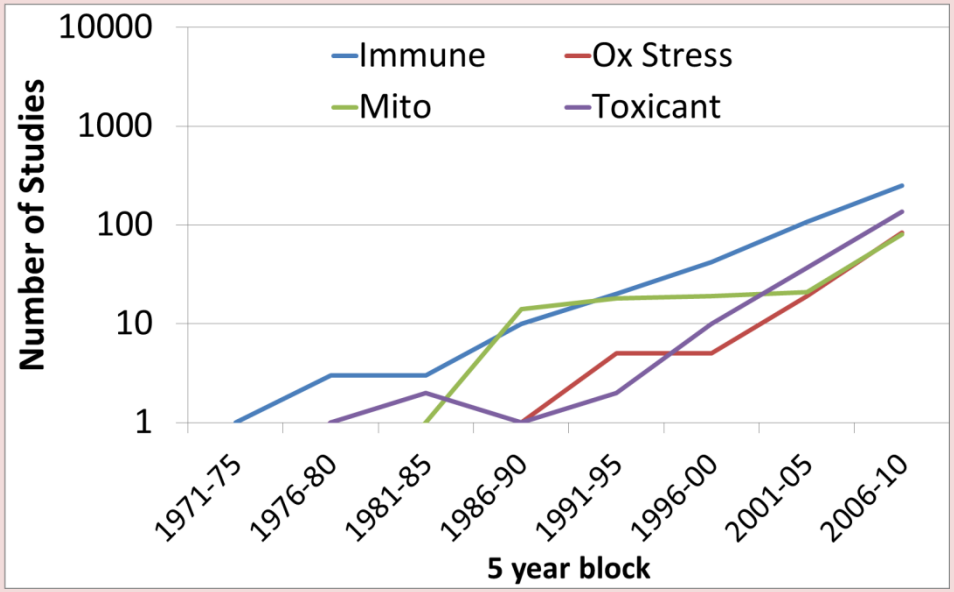
REVIEW

A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures

DA Rossignol[1] and RE Frye[2]

[1]*International Child Development Resource Center, Melbourne, FL, USA and* [2]*Arkansas Children's Hospital Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA*





ARCHIVES OF
GENERAL PSYCHIATRY

ONLINE FIRST July 2011

Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism

Joachim Hallmayer, MD; Sue Cleveland, BS; Andrea Torres, MA; Jennifer Phillips, PhD; Brianne Cohen, BA; Tiffany Torigoe, BA; Janet Miller, PhD; Angie Fedele, BA; Jack Collins, MBA; Karen Smith, BS; Linda Lotspeich, MD; Lisa A. Croen, PhD; Sally Ozonoff, PhD; Clara Lajonchere, PhD; Judith K. Grether, PhD; Neil Risch, PhD

Objective: To provide rigorous quantitative estimates of genetic heritability and effects of shared environment

Conclusion: Susceptibility to ASD has moderate genetic heritability (38%) and a substantial shared twin environmental component (58%)

New Understanding of Autism

- Autism is defined as a collection of symptoms
- Symptoms of autism are associated with underlying medical disorders in may cases
- In many cases, autism is a multisystemic disorder with primary neurological manifestations.
- The rise in Autism cases is probably due to complex interactions between genetics, environment and the dynamics of physiological development.

The Mitochondria And Autism

Mitochondrial disease

- Relatively new field
- First disease described in 1988
  - Wallace, Leber's hereditary optic neuropathy, published in Science
  - Holt, Mitochondrial Myopathy, published in Nature
- Usually defined by extremely clinical symptoms with a progressive course
  - High energy dependent tissues
  - Neurological Disease
  - Gastrointestinal Disease
  - Immune Dysfunction
- Not just powerhouse, also important in
  - programmed (apoptotic) cell death
  - Oxygen Radical Regulation

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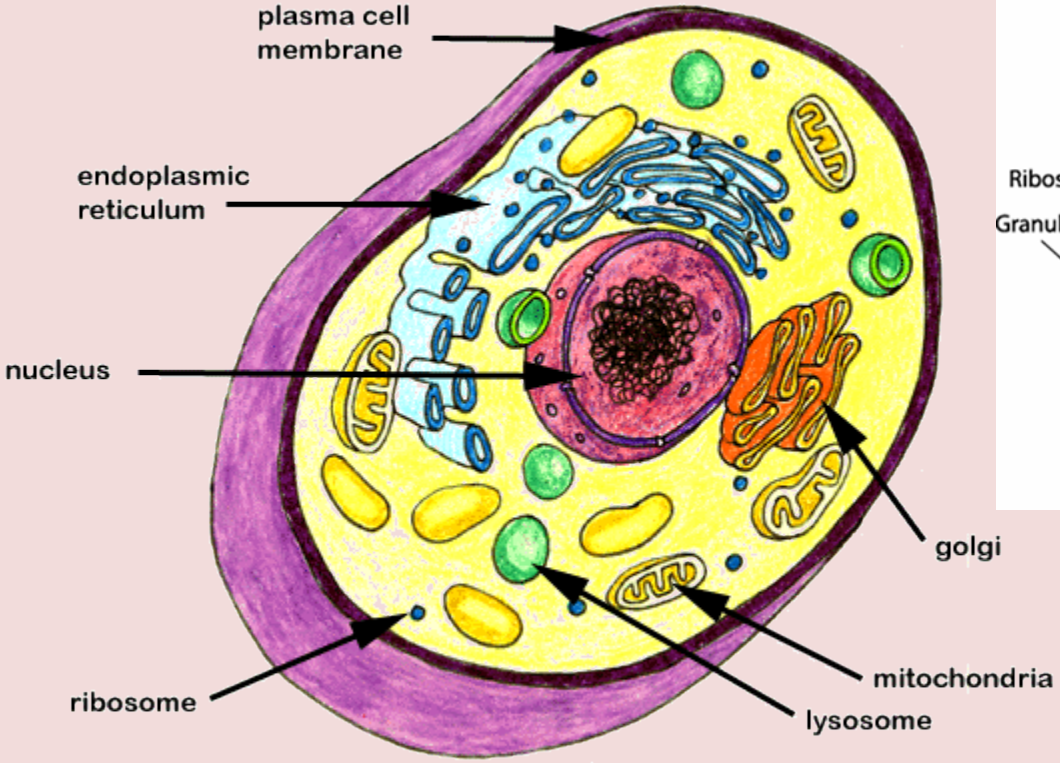

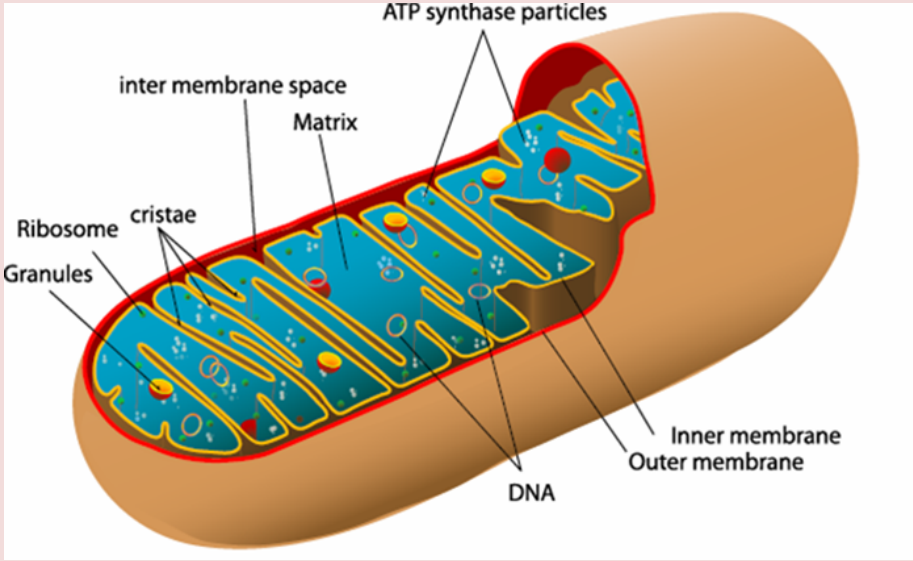

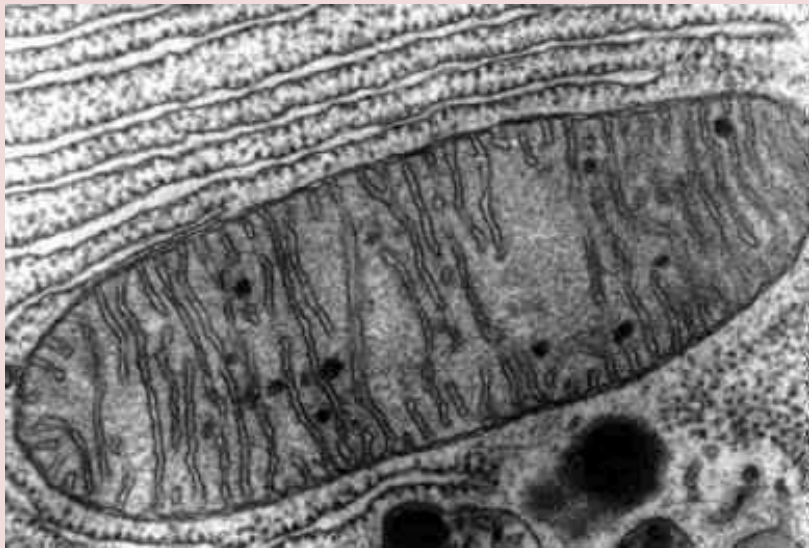

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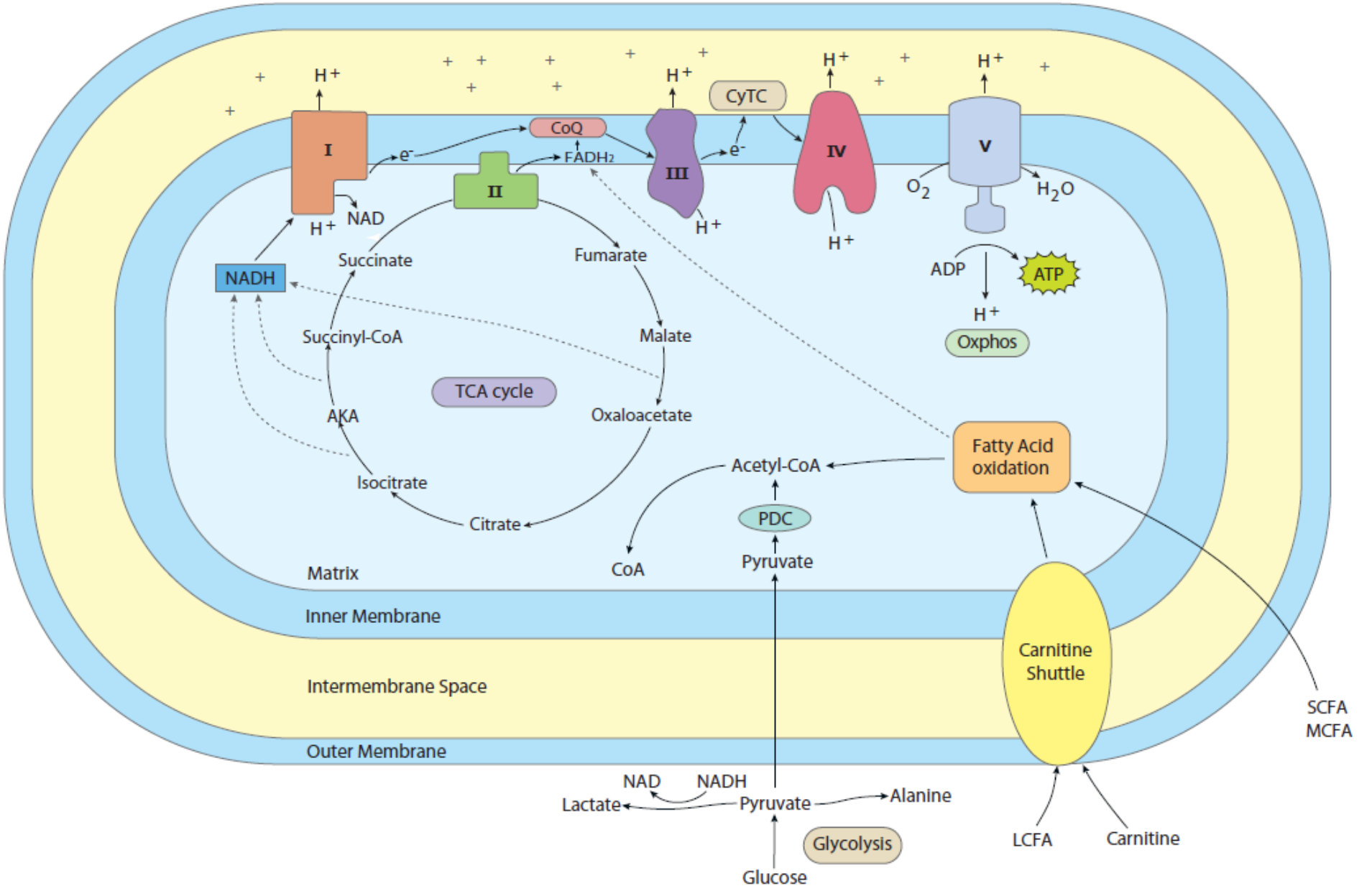
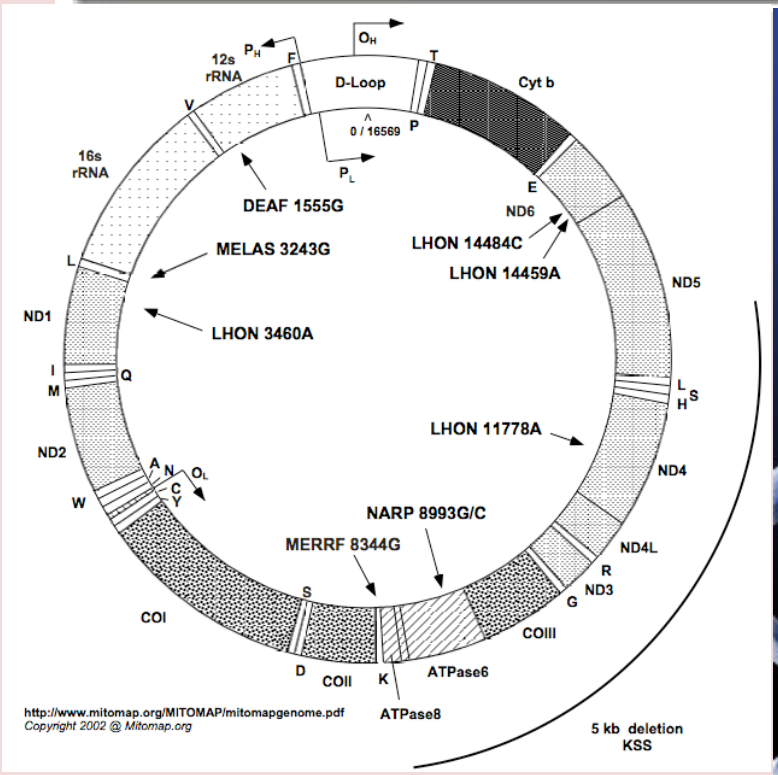
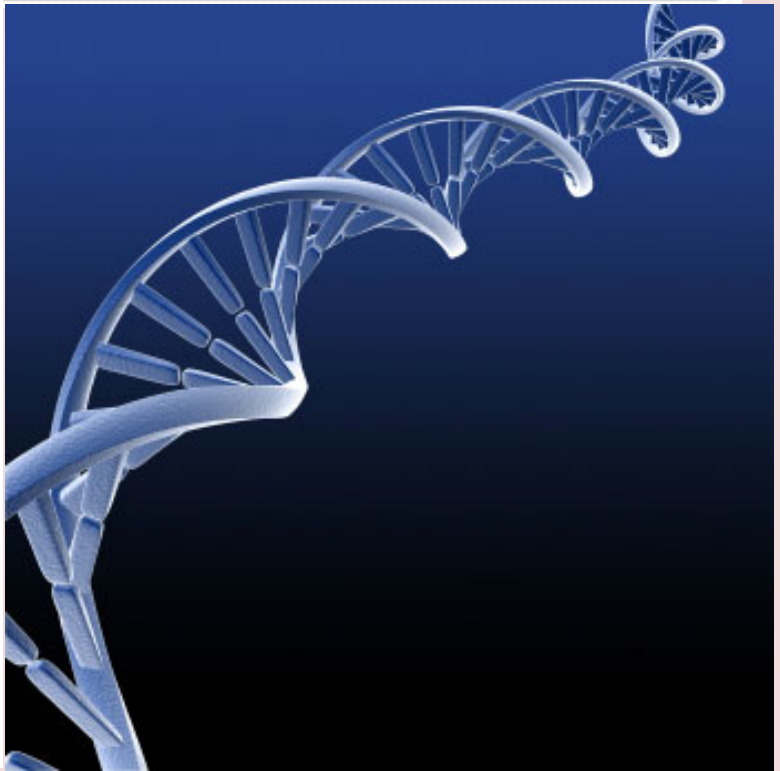


Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

Respiratory chain complex	nDNA subunits	mtDNA subunits	Redox cofactors
I (EC 1.6.6.3)	38	7	FMN, [Fe–S] centres, ubiquinones
II (EC 1.3.5.1)	0	4	FAD, [Fe–S] centres, cytochrome b_{560}
III (EC 1.10.2.2)	10	1	Cytochromes *b* and *c*1, Rieske protein
IV (EC 1.9.3.1)	10	3	[Cu_a] centre, [Cu_b-haem *a*3] centre
V (EC 3.6.1.34)	14	2	None





Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

Open

Molecular Psychiatry (2011), 1–25

www.nature.com/mp

ORIGINAL ARTICLE

Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis

DA Rossignol[1] and RE Frye[2]

Table 1 Pooled prevalence estimates for MD in ASD and for abnormal biomarkers of mitochondrial dysfunction in ASD

	Studies	*Total N*	*Overall prevalence*	*Minimum (%)*	*Maximum (%)*
General ASD population					
Mitochondrial disease in ASD	3	536	5.0% (3.2%, 6.9%)	3.6	9.1
Elevated lactate	6	479	31.1% (27.0%, 35.3%)	17	77
Elevated pyruvate	2	110	13.6% (7.2%, 20.1%)	8	30
Elevated lactate/pyruvate ratio	1	192	27.6% (21.2%, 33.9%)		
Elevated alanine	1	36	8.3% (0.0%, 20.1%)		
Low total carnitine	1	30	90.0% (81.0%, 99.0%)		
Elevated creatine kinase	1	47	46.8% (32.4%, 61.2%)		
Elevated ammonia	1	80	35.0% (24.5%, 45.5%)		
Elevated AST	1	147	45.6% (37.5%, 53.7%)[a]		
Elevated ALT	1	87	7.0% (0.5%, 13.5%)		

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Table 2 Pooled statistics and meta-analysis of group differences for mitochondrial biomarkers in ASD compared with controls

Biomarker	*Number of studies*	*ASD*		*Control*		*F-value*	*Hedge's g (CI)*	*Q for g*	*Glass's Δ (CI)*	*Q for Δ*
		Total N	*Mean (95% CI)*	*Total N*	*Mean (95% CI)*					
Lactate ($mM\,l^{-1}$)	5	114	1.73 (1.61, 1.88)	114	0.91 (0.87, 0.96)	8.72†	1.42 (0.92, 1.92)†	3.64	3.22 (2.66, 3.78)†	45.89†
Pyruvate ($nM\,l^{-1}$)	1	24	0.12 (0.11, 0.14)	24	0.06 (0.06, 0.06)	20.25†	1.96 (0.85, 3.08)†		6.40 (5.04, 7.76)†	
Carnitine ($mg\,ml^{-1}$)	1	30	3.83 (3.44, 4.31)	30	6.40 (6.22, 6.62)	4.61†	2.51 (1.61, 3.42)†		4.21 (3.01, 5.41)†	
Ubiquinone	1	15	91.4 (81.9, 103.0)	15	144.2 (130.4,161.1)	2.13	1.90 (0.79, 3.01)†		1.63 (0.62, 2.64)†	
Creatine kinase	2	55	178.8 (139.6, 226.9)	59	92.2 (89.9, 121.9)	6.93†	0.57 (–0.15, 1.30)	0.05	0.94 (0.19, 1.69)	0.69
AST	1	147	36.3 (34.4, 38.6)	98	29.7 (28.1, 31.7)[a]	2.34†	0.49 (–0.22, 1.32)		0.67 (–0.07, 1.41)	
ALT	1	87	24.6 (19.77, 30.52)	70	20.6 (18.7, 23.1)	7.37†	0.18 (–0.61, 0.97)		0.38 (–0.42, 1.19)	

Abbreviations: ALT, alanine aminotransferase; ASD, autism spectrum disorder; AST, aspartate aminotransferase; CI, confidence interval.

[a]Standard error of AST was misstated in the publication as 3.0 but in actuality it is 1.0.

†$P < 0.0001$.

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

North American Journal of Medicine and Science Jul 2012 Vol 5 No.3 141

Original Research

Biomarkers of Abnormal Energy Metabolism in Children with Autism Spectrum Disorder

Richard E. Frye, MD, PhD*

Division of Autism Research, Department of Pediatrics Arkansas Children's Hospital Research Institute, Little Rock, AR

A review of metabolic studies from 133 consecutive patients evaluated in a medically-based autism clinic

Examined a wide range of metabolic markers in children with autism including markers of fatty-acid oxidation disorders

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

6 Biomarkers Reviewed

3 Groups with high prevalence Identified

Lactate, Alanine-to-Lysine & Acyl-Carnitine 55.6%

Biomarker	Total Tested	Abnormal at Least Once	Patients with Abnormalities Tested Twice	Abnormal Twice	Prevalence
Lactate	96	34 (35%)	20 (59%)	9 (45%)	15.9%
Alanine	94	8 (9%)	5 (63%)	1 (20%)	1.7%
AST	113	20 (18%)	14 (70%)	8 (57%)	10.1%
CK	81	11 (14%)	4 (36%)	2 (50%)	6.8%
Alanine-to-Lysine Ratio	98	39 (40%)	20 (51%)	8 (40%)	15.9%
Acyl-carnitine	58	23 (40%)	10 (44%)	6 (60%)	23.8%

Acyl-Carnitine Group Had Rate of Regression of 67% VERY HIGH

	Regression	Epilepsy
Lactate (n=9)	2 (22%)	3 (33%)
AST (n=8)	3 (38%)	1 (13%)
Alanine-to-Lysine Ratio (n=8)	2 (25%)	6 (75%)
Acyl-carnitine (n=6)	4 (67%)	1 (17%)
ASD Control (n=9)	5 (55%)	3 (33%)

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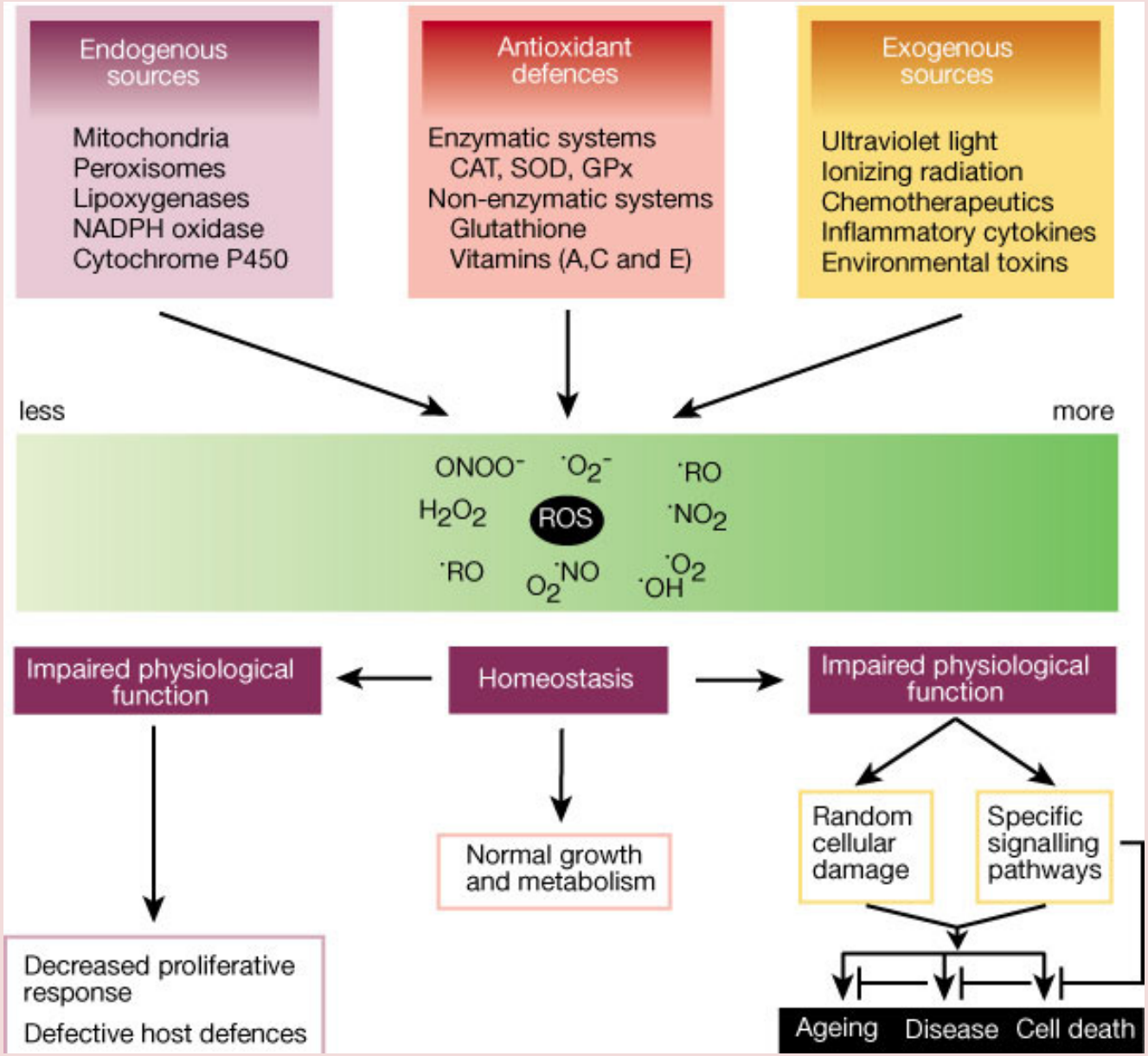
The Oxidative Stress And Autism

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



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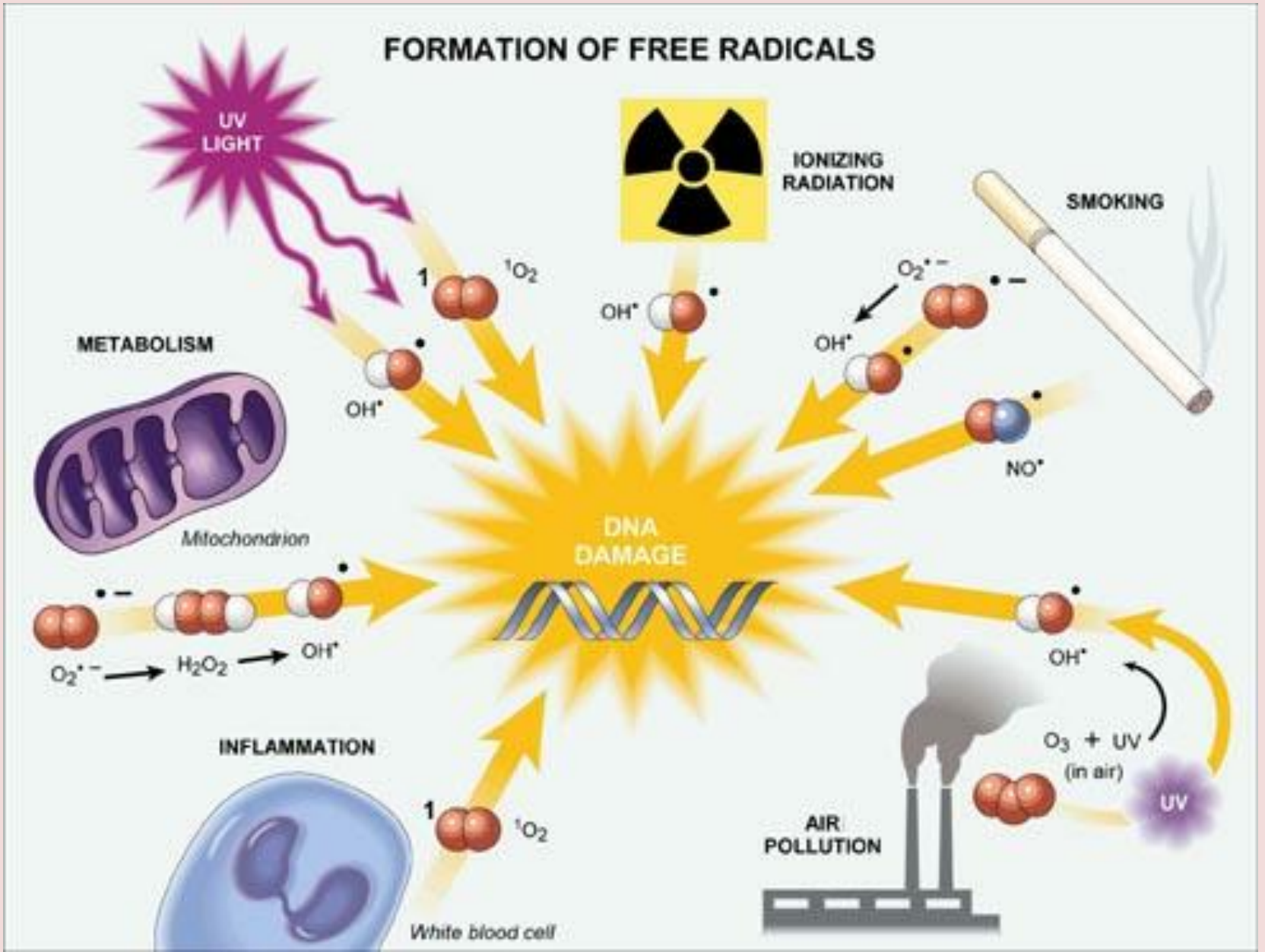
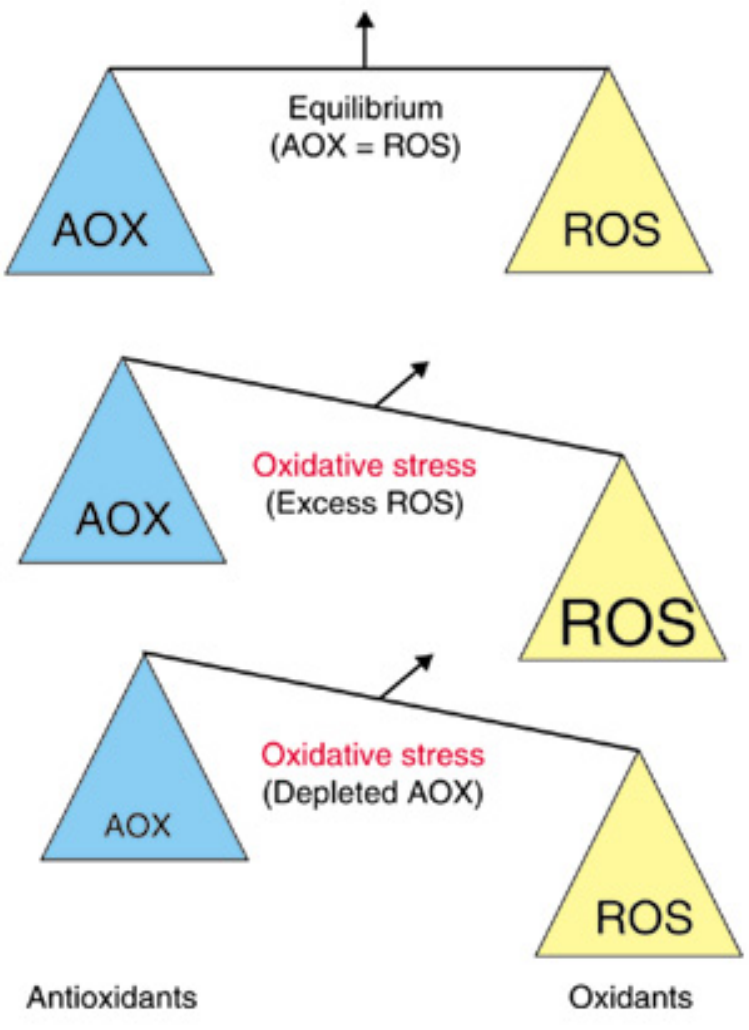


Imbalance in the Equilibrium



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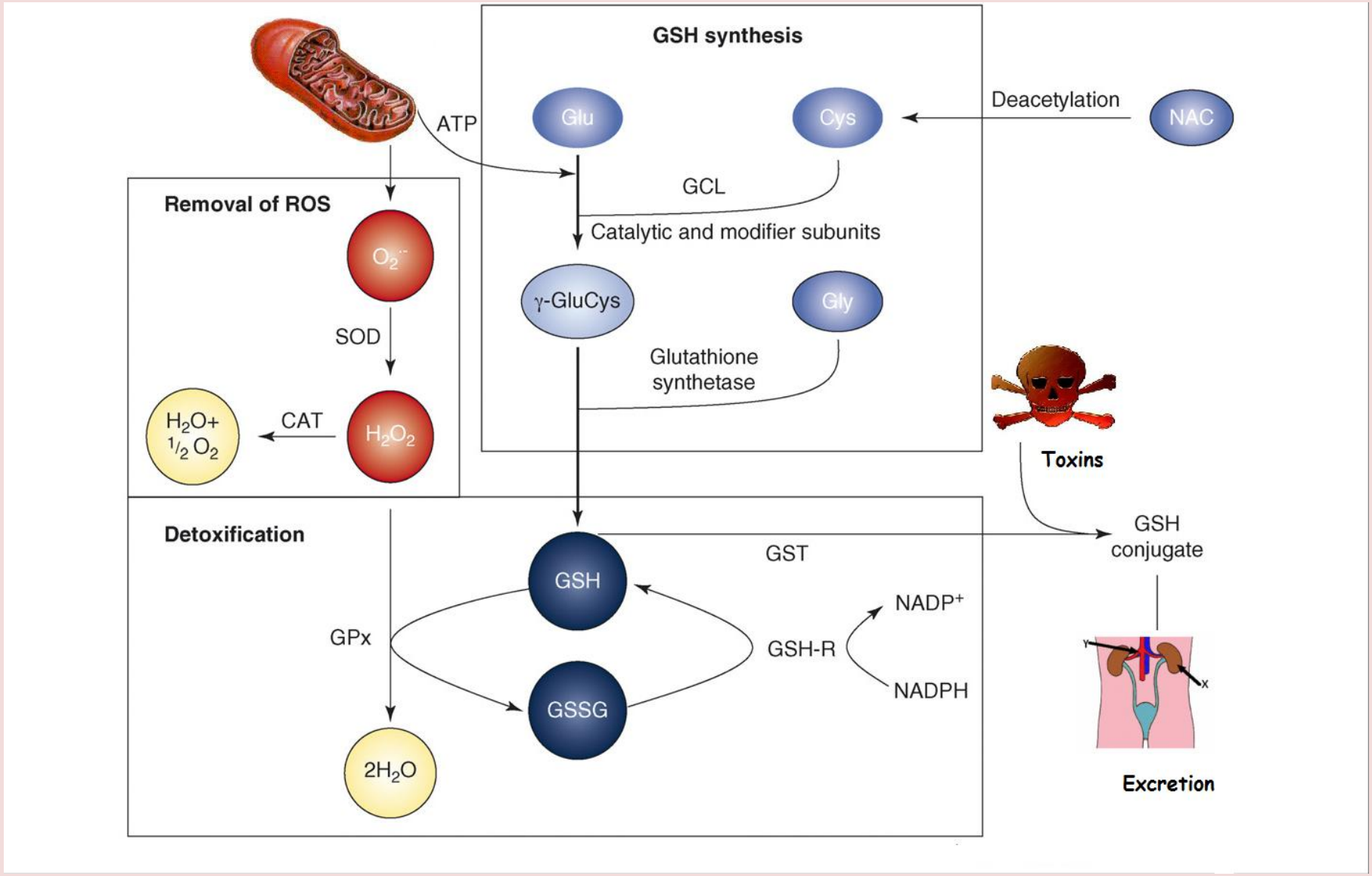
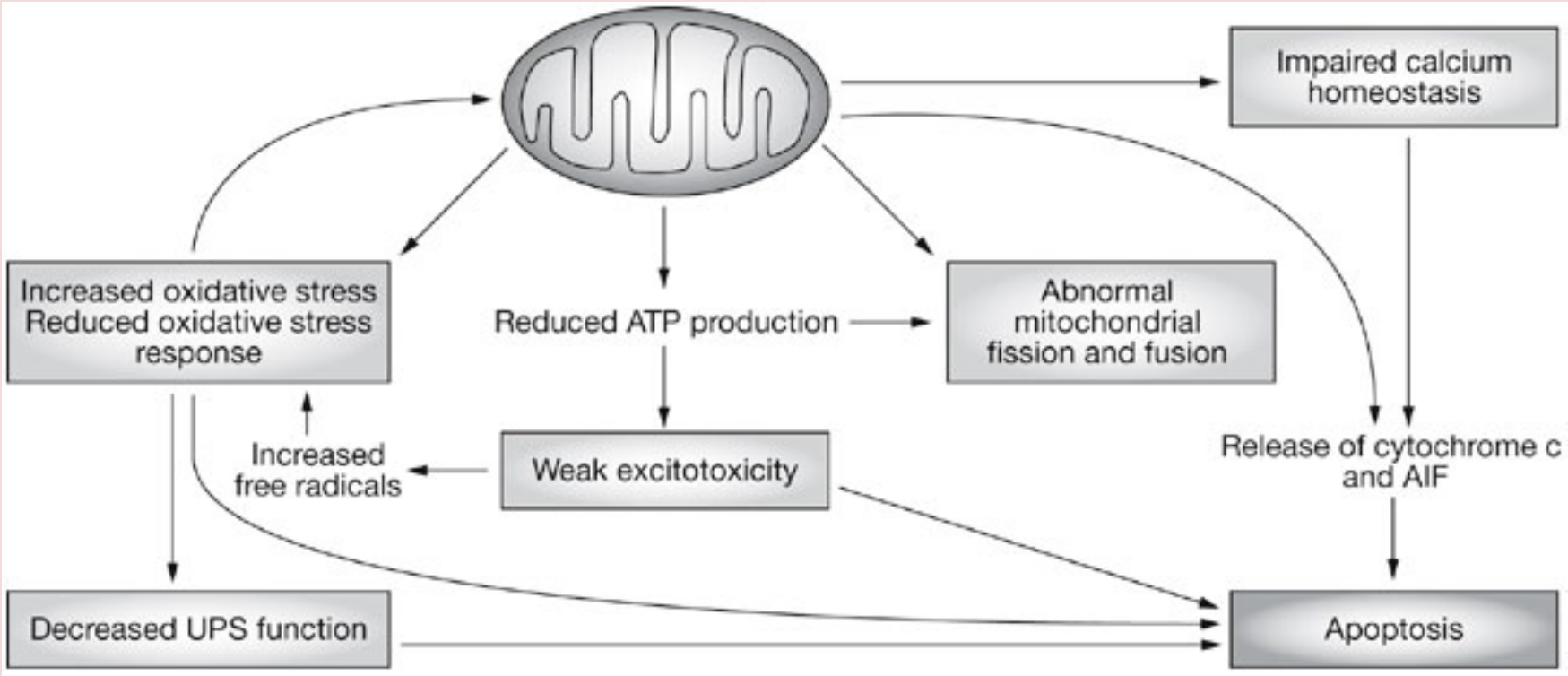


Oxidative Stress can weaken mitochondrial Function and cause programmed cell death



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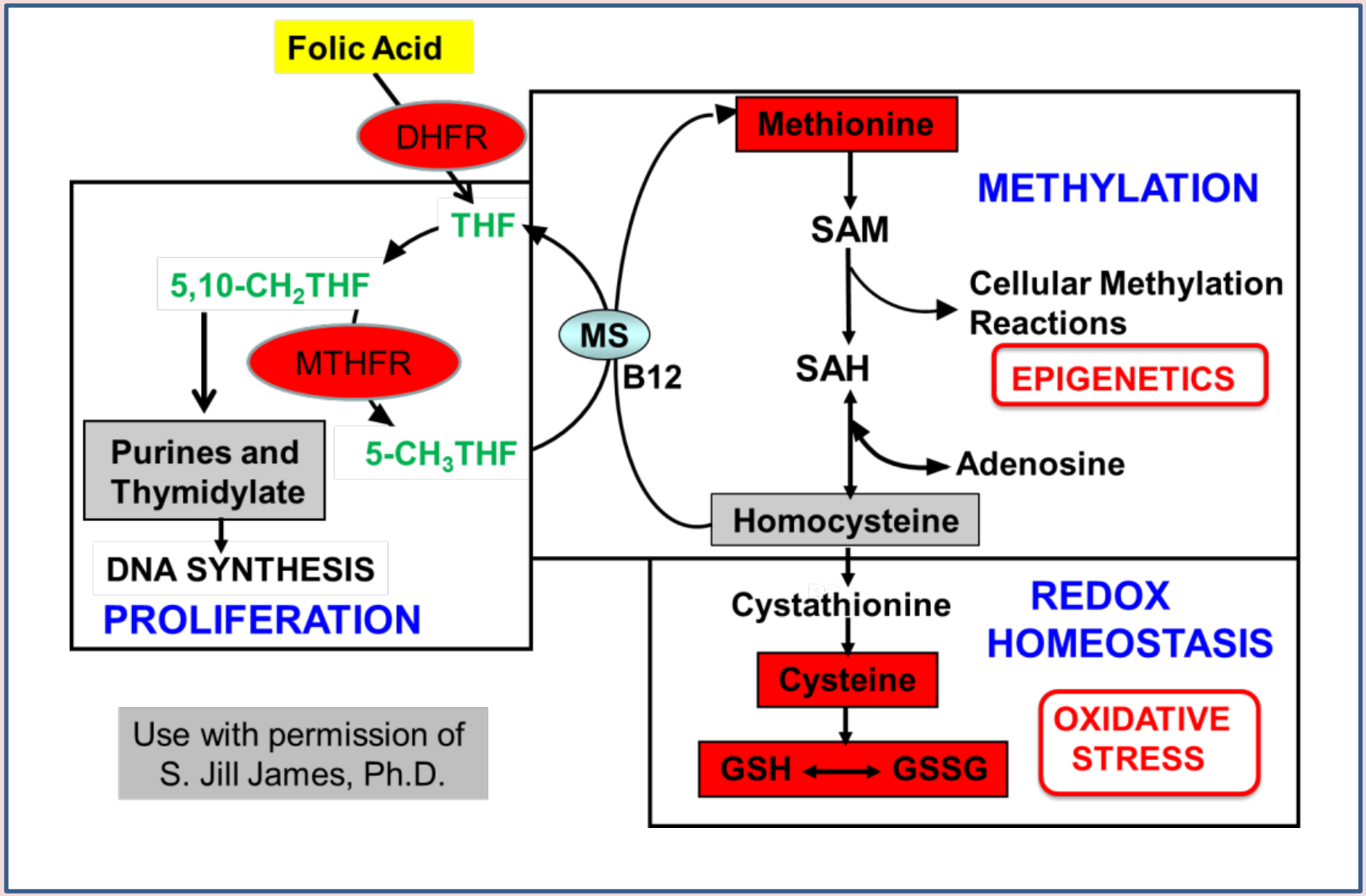
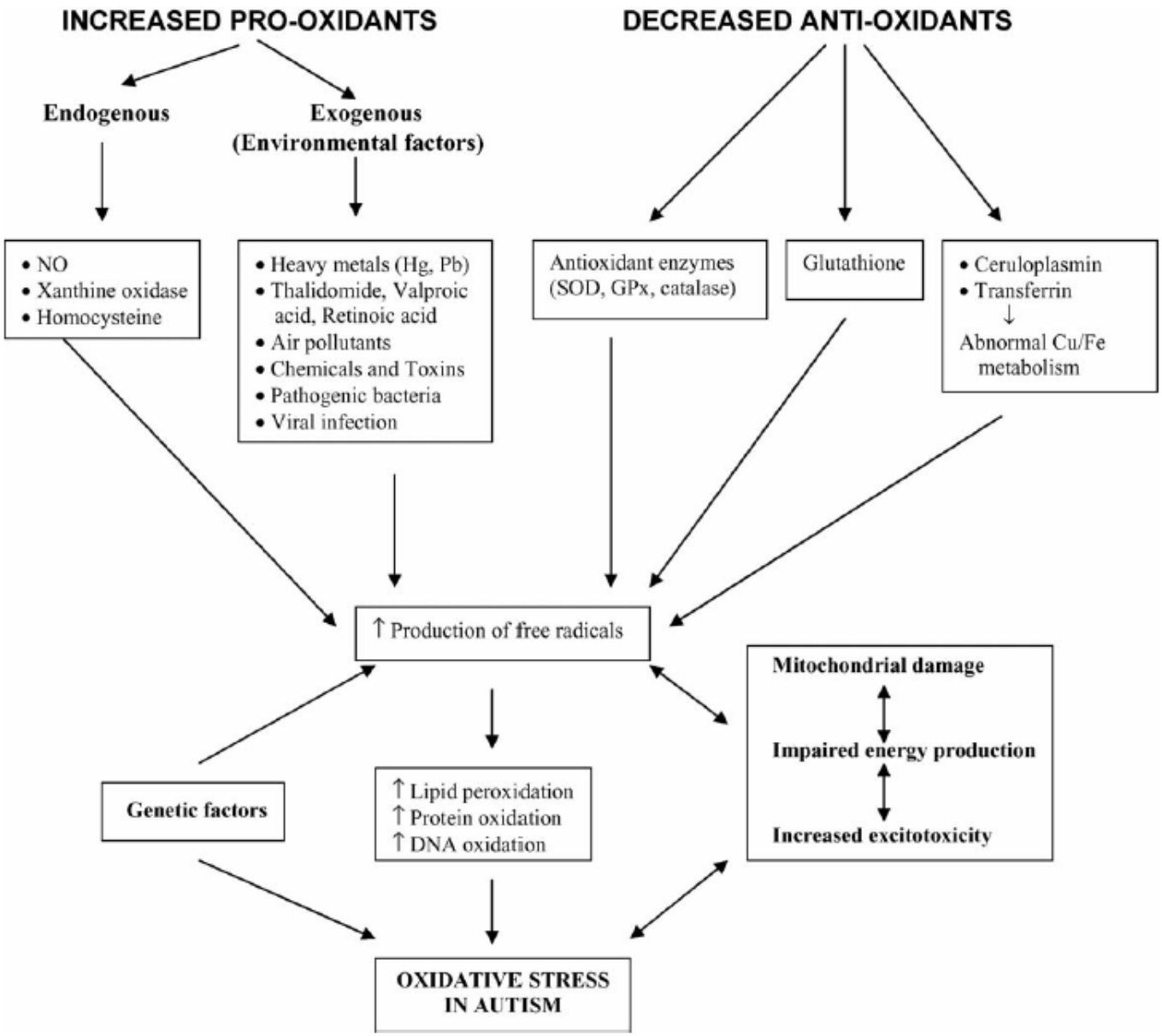


Metabolic Imbalance Associated with Methylation Dysregulation and Oxidative Damage in Children with Autism

Stepan Melnyk · George J. Fuchs · Eldon Schulz · Maya Lopez · Stephen G. Kahler · Jill J. Fussell · Jayne Bellando · Oleksandra Pavliv · Shannon Rose · Lisa Seidel · David W. Gaylor · S. Jill James

Plasma metabolites	Cases (n = 40)	Paired sibling (n = 40)	*p* Value*	Controls (n = 54)	*p* Value**
Methionine (μmol/L)	19.8 ± 2.6[a]	22.3 ± 4.3	<0.001	23.3 ± 3.9	ns
SAM (nmol/L)	61.6 ± 8.9[a]	70.7 ± 19.4	<0.006	71.0 ± 15.6	ns
SAH (nmol/L)	20.0 ± 4.6[a]	16.9 ± 3.9	<0.001	14.8 ± 4.1	0.05
Adenosine (μmol/L)	0.16 ± 0.07	0.11 ± 0.05	<0.001	0.14 ± 0.07	ns
Homocysteine (μmol/L)	4.86 ± 1.5	4.69 ± 1.0	ns	4.68 ± 1.0	ns
Folate (ng/ml)	19.9 ± 5.1	21.6 ± 4.1	ns	19.4 ± 4.2	ns
B12 (pg/ml)	872 ± 528	719 ± 288	ns	864 ± 552	ns
SAM/SAH	3.29 ± 1.1[a]	4.4 ± 1.7	<0.001	5.08 ± 1.8	ns
DNA methylation (%5mC)	3.03 ± 0.8[a]	3.9 ± 0.7	<0.001	4.13 ± 1.0	ns
Total Cysteine (μmol/L)	189 ± 21[a]	203 ± 26	<0.002	212 ± 18	ns
Free Cysteine (μmol/L)	21.6 ± 6.45	22.5 ± 5.0	ns	23.6 ± 5.3	ns
Free Cystine (μmol/L)	34.1 ± 7.5a[a]	27.1 ± 8.7	<0.001	26.4 ± 5.7	ns
Free Cysteine/Cystine	0.68 ± 0.25[a]	0.89 ± 0.25	<0.001	0.93 ± 0.27	ns
GSH (μmol/L)	1.84 ± 0.40[a]	2.06 ± 0.41	<0.001	2.58 ± 0.79	<0.001
GSSG (μmol/L)	0.23 ± 0.10[a]	0.15 ± 0.08	<0.001	0.16 ± 0.07	ns
GSH/GSSG	9.45 ± 4.08[a]	17.4 ± 10.3	<0.001	18.3 ± 8.6	ns
% Oxidized GSH (2GSSG/(GSH + 2GSSG))	22 ± 8.1[a]	12.7 ± 5.9	<0.001	11.4 ± 4.1	ns
3-Nitrotyrosine (nmol/L)	143 ± 74[a]	80 ± 43	<0.001	72 ± 27	ns
3-Chlorotyrosine (nmol/L)	51 ± 18[a]	34 ± 17	<0.001	26 ± 11	0.01
8-Oxo- deoxyguanosine (pmol/mg DNA)	95 ± 35[a]	65 ± 13	<0.001	63 ± 24	ns

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



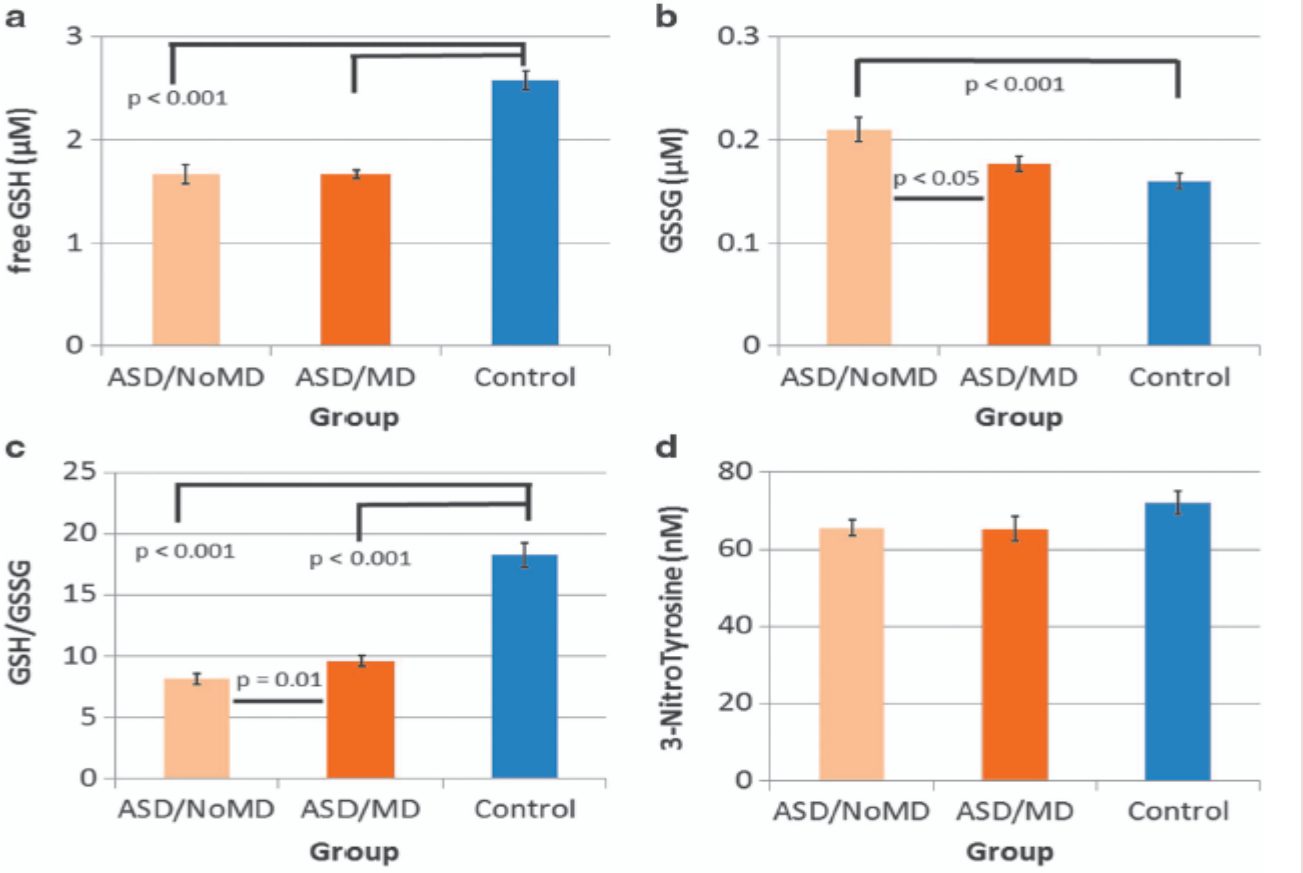
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

Citation: Transl Psychiatry (2013) 3, e273; doi:10.1038/tp.2013.51

www.nature.com/tp

Redox metabolism abnormalities in autistic children associated with mitochondrial disease

RE Frye[1,2], R DeLaTorre[3], H Taylor[4], J Slattery[1,2], S Melnyk[1,2], N Chowdhury[1] and SJ James[1,2]



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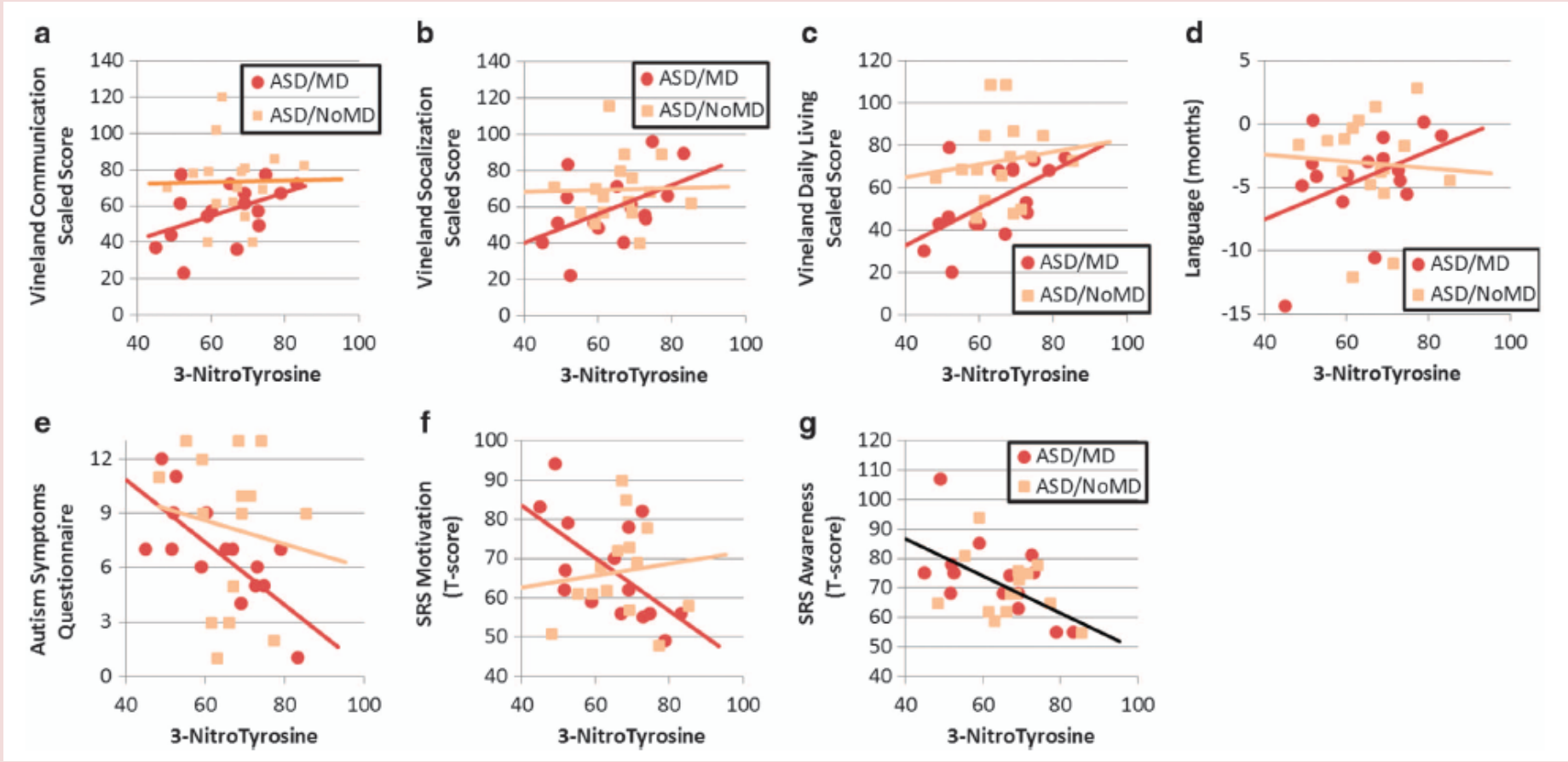


Acquired Mitochondrial Dysfunction In Autism

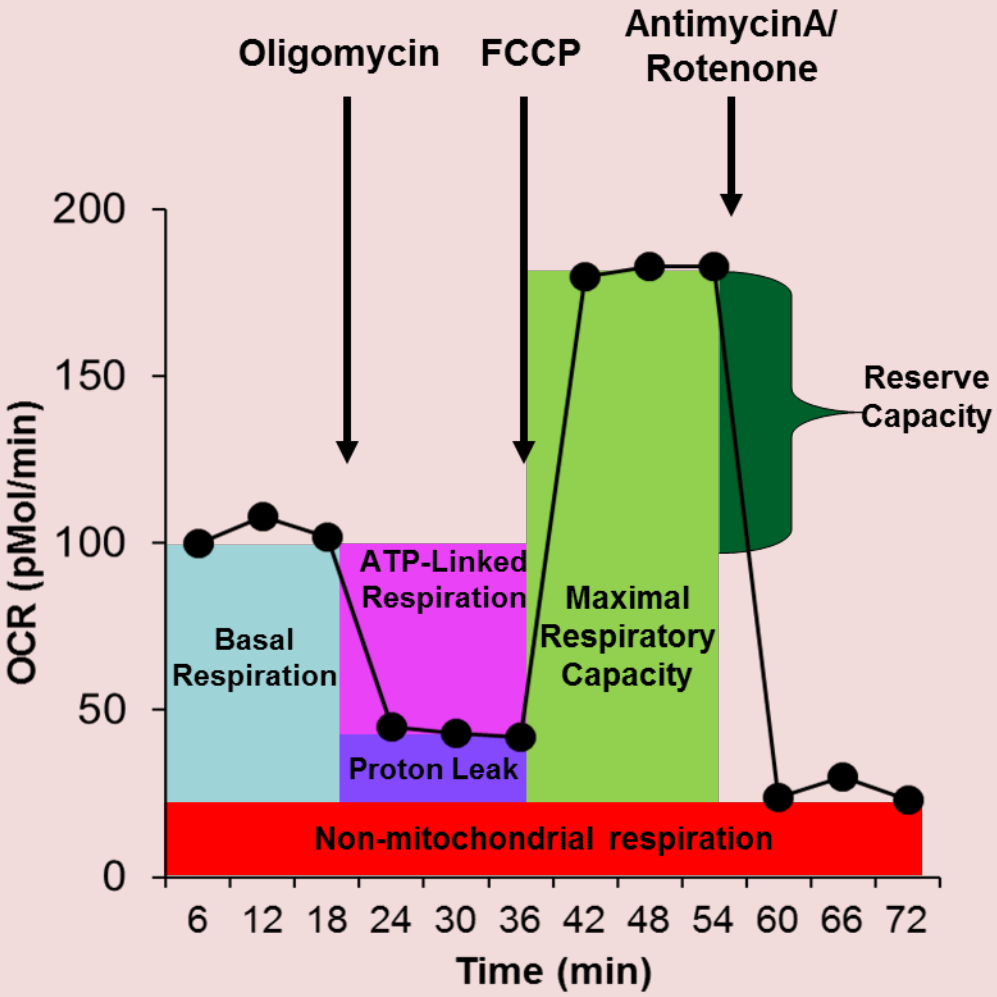
Seahorse Bioscience XF96 Extracellular Flux Analyzer for 96-well microplate assays

Seahorse Extracellular Flux Analysis

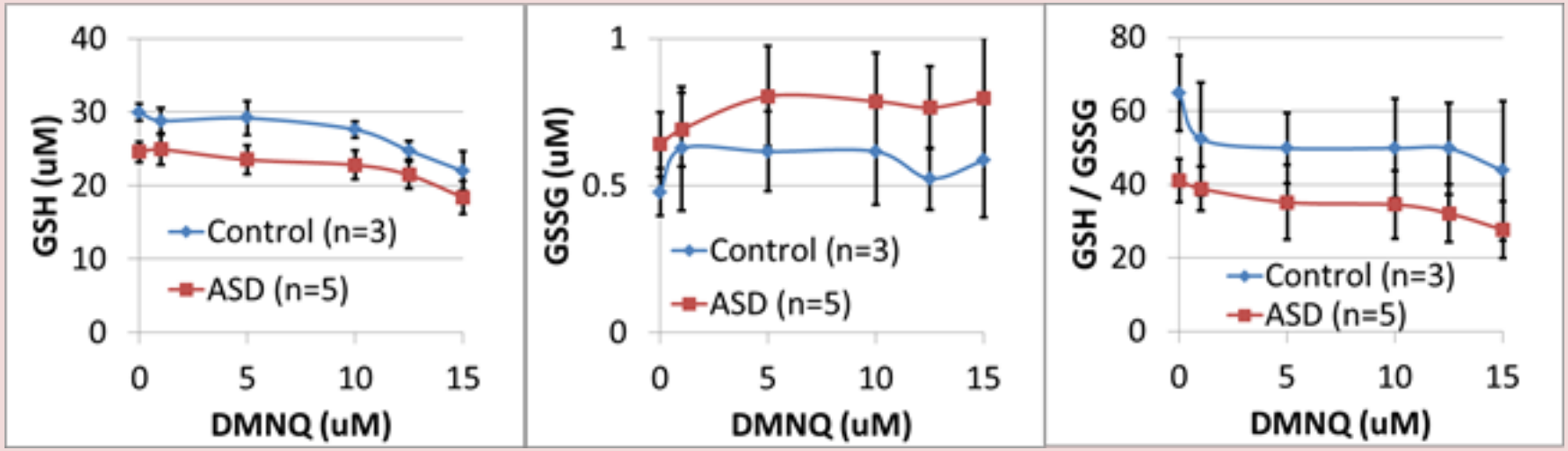
- Simultaneously quantify mitochondrial respiration and glycolysis in real time
- Bioenergetic Profile
  - Measure the basal respiration rate of cells
  - Compounds modulating mitochondrial function are added sequentially
  - The effect on oxygen consumption rate (OCR) measured after each compound addition
  - Reveals the four fundamental parameters of mitochondrial function: basal respiration, ATP turnover, proton leak, and maximal respiratory capacity

- Oligomycin (ATP coupler)
  - Inhibits ATP synthesis by blocking Complex V
  - Reveals the % OCR devoted ATP synthesis vs the % OCR to overcome proton leak
- FCCP (ETC accelerator)
  - Uncoupler: collapses mito membrane potential
  - Results in maximal uncontrolled OCR
  - Allows calculation of spare respiratory capacity (Max-Basal)
- Rotenone: Complex I inhibitor and
- Antimycin A: Complex III inhibitor
  - Combo shuts down mito respiration and enables mitochondrial and non-mitochondrial factors contributing to respiration to be calculated

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



OPEN ACCESS Freely available online

PLOS ONE

Oxidative Stress Induces Mitochondrial Dysfunction in a Subset of Autism Lymphoblastoid Cell Lines in a Well-Matched Case Control Cohort

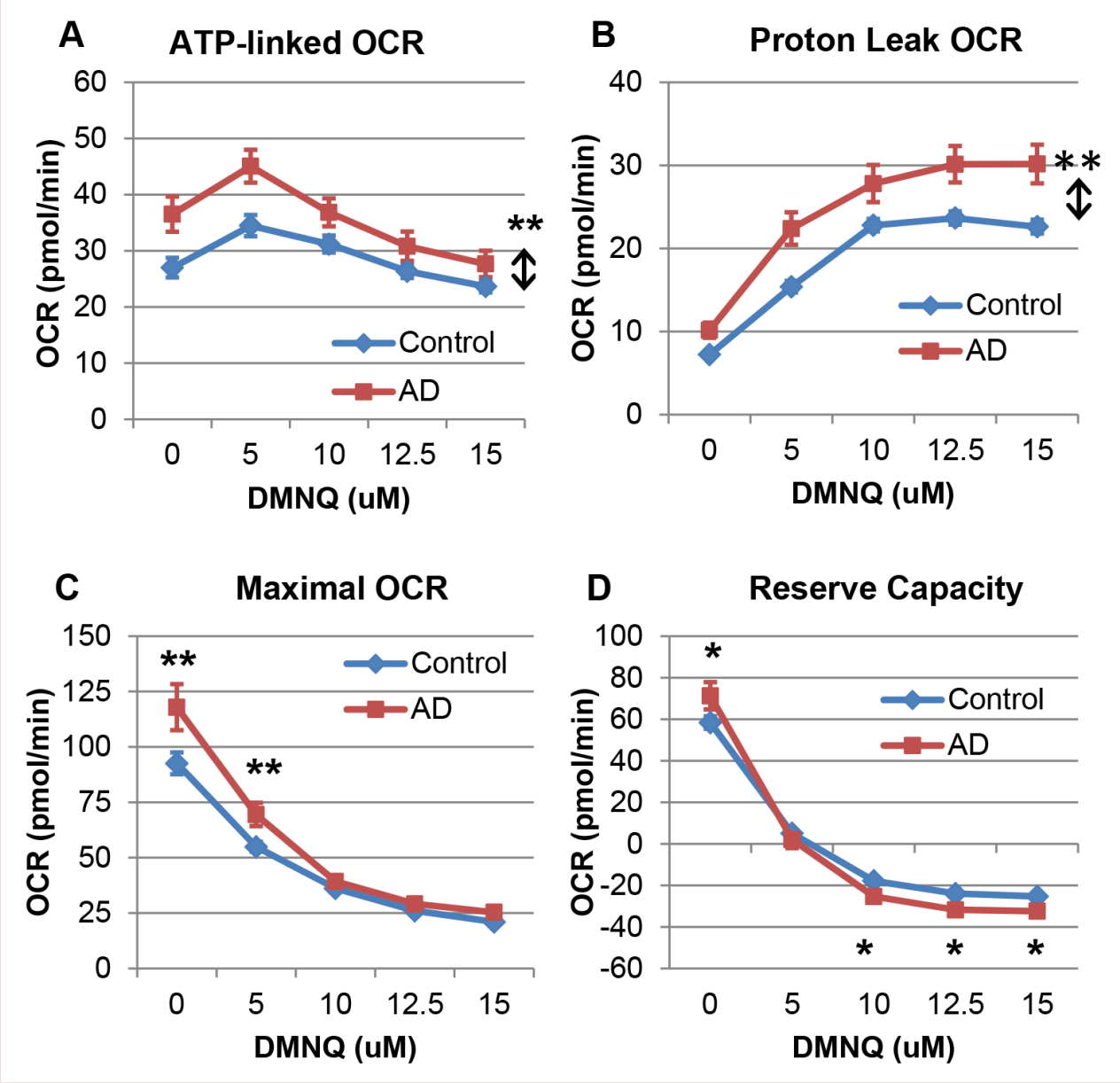
Shannon Rose, Richard E. Frye*, John Slattery, Rebecca Wynne, Marie Tippett, Oleksandra Pavliv, Stepan Melnyk, S. Jill James

Department of Pediatrics, Arkansas Children's Hospital Research Institute, Little Rock, Arkansas, United States of America

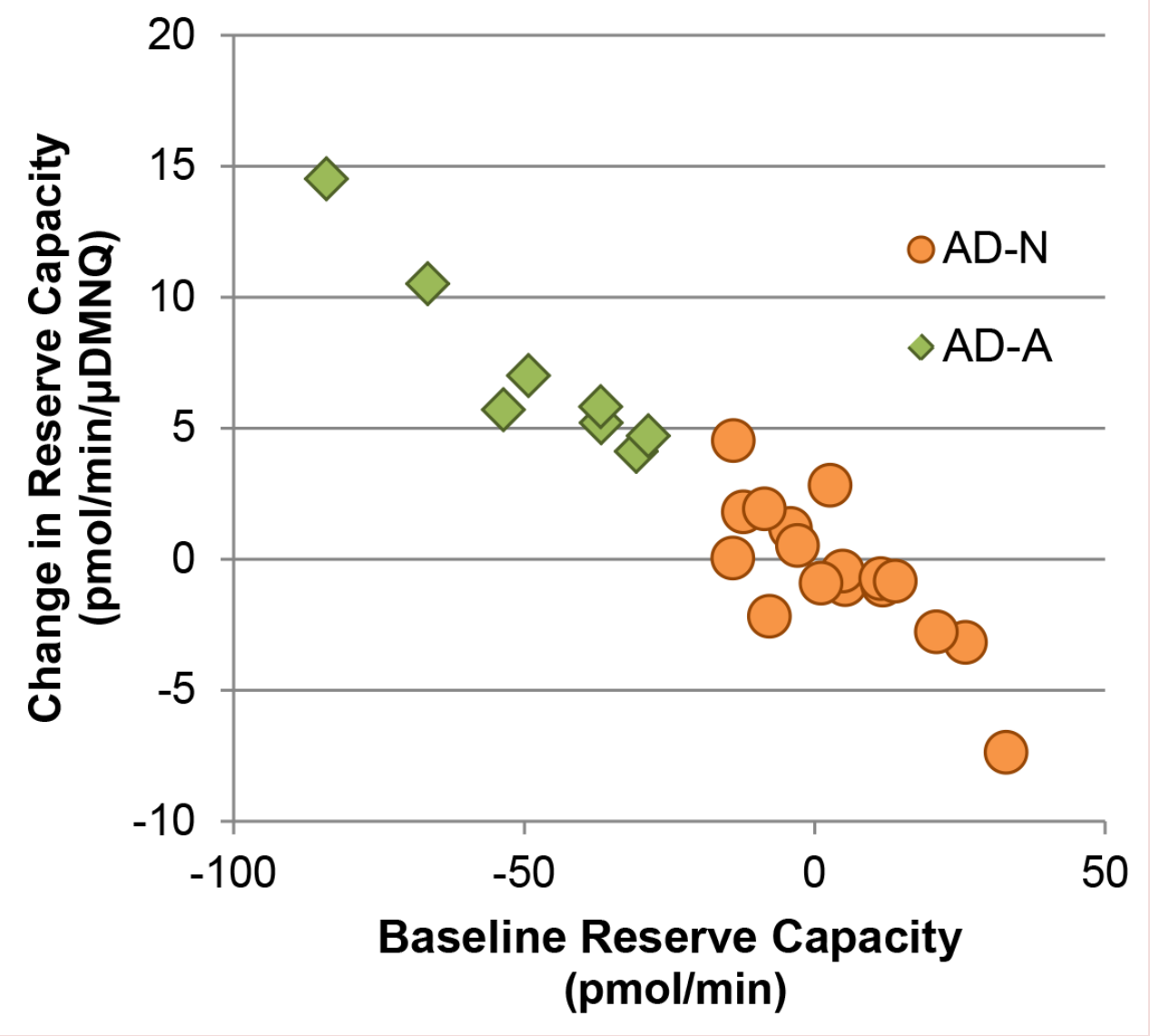
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

	Autism				Control		
Pair #	Cell ID	Source	Age (y)	Subgroup	Cell ID	Source	Age (y)
1	03C14441	NIMH	7	AD-A	GM17255	Coriell	6
2	03C16499	NIMH	11	AD-A	GM15862	Coriell	11
3	1393306	AGRE	3	AD-A	GM09659	Coriell	4
4	0939303	AGRE	11	AD-A	GM15862	Coriell	11
5	1165302	AGRE	13	AD-A	GM11626	Coriell	13
6	01C08594	NIMH	7	AD-A	GM17255	Coriell	6
7	01C08495	NIMH	4	AD-A	GM09659	Coriell	4
8	02C09713	NIMH	7	AD-A	GM11973	Coriell	7
9	02C10054	NIMH	6	AD-N	GM09380	Coriell	6
10	04C26296	NIMH	10	AD-N	GM11599	Coriell	9
11	00C04757	NIMH	10	AD-N	GM10153	Coriell	10
12	05C38988	NIMH	12	AD-N	GM16007	Coriell	12
13	03C15992	NIMH	5	AD-N	GM18054	Coriell	5
14	038804	AGRE	8	AD-N	GM11599	Coriell	9
15	1267302	AGRE	10	AD-N	GM10153	Coriell	10
16	1215301	AGRE	12	AD-N	GM16007	Coriell	12
17	008404	AGRE	13	AD-N	GM11626	Coriell	13
18	02C10618	NIMH	7	AD-N	GM09622	Coriell	7
19	02C09650	NIMH	7	AD-N	GM09622	Coriell	7
20	01C08367	NIMH	7	AD-N	GM09642	Coriell	7
21	04C27439	NIMH	7	AD-N	GM09642	Coriell	7
22	03C14349	NIMH	17	AD-N	GM17272	Coriell	17
23	04C24363	NIMH	4	AD-N	GM18054	Coriell	5
24	01C08022	NIMH	5	AD-N	GM09380	Coriell	6
25	03C17237	NIMH	10	AD-N	GM10153	Coriell	10

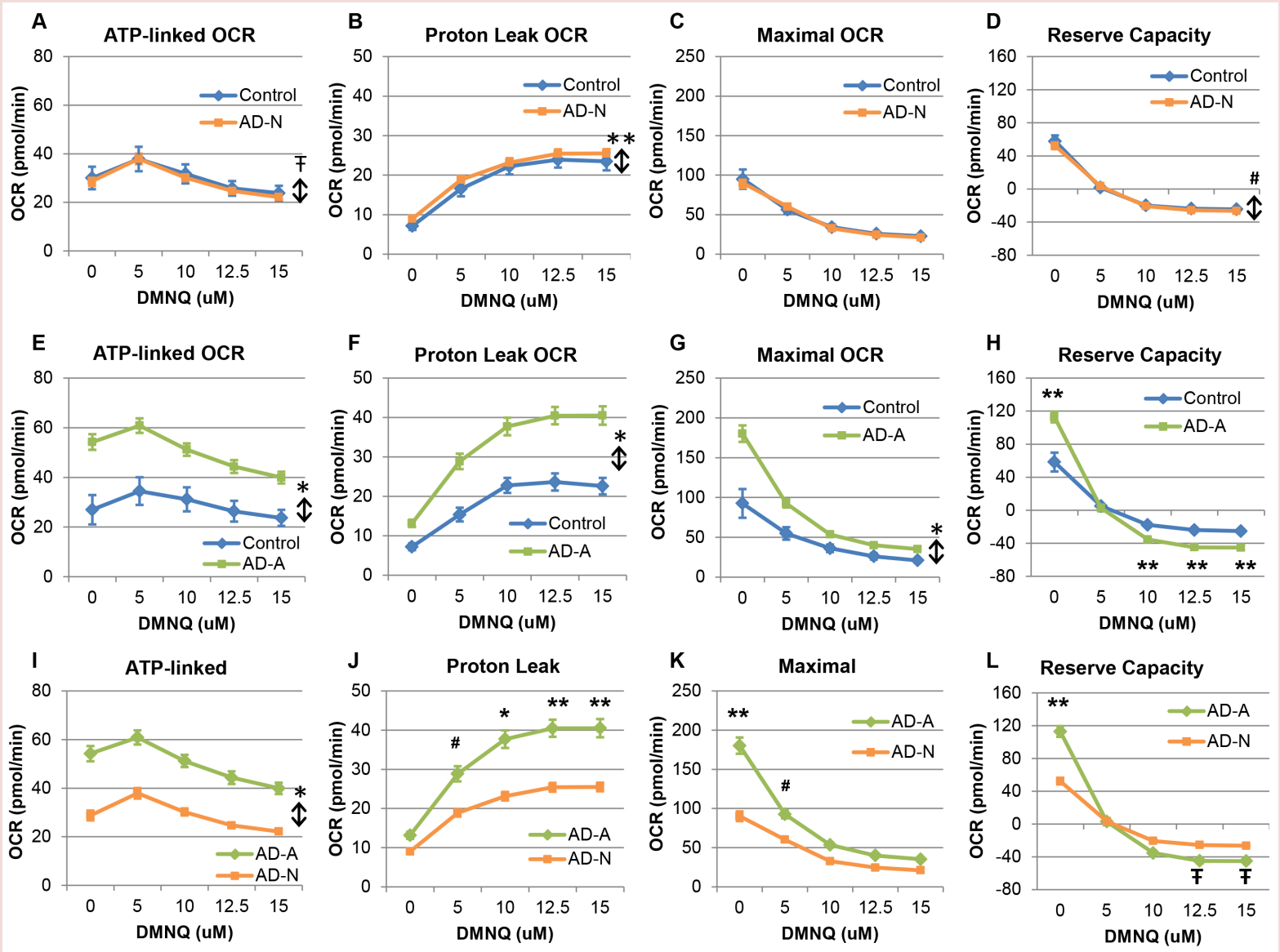
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



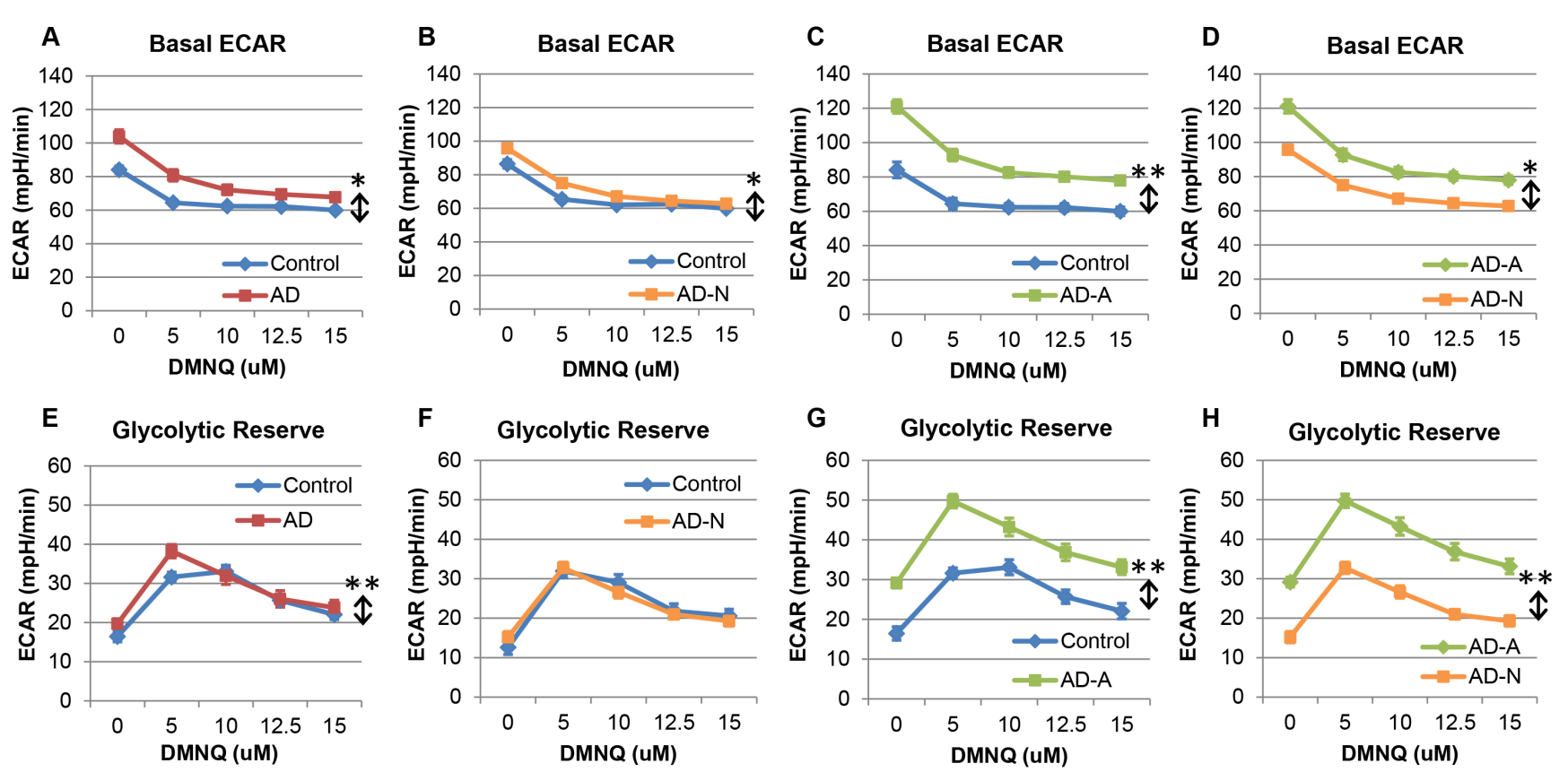
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



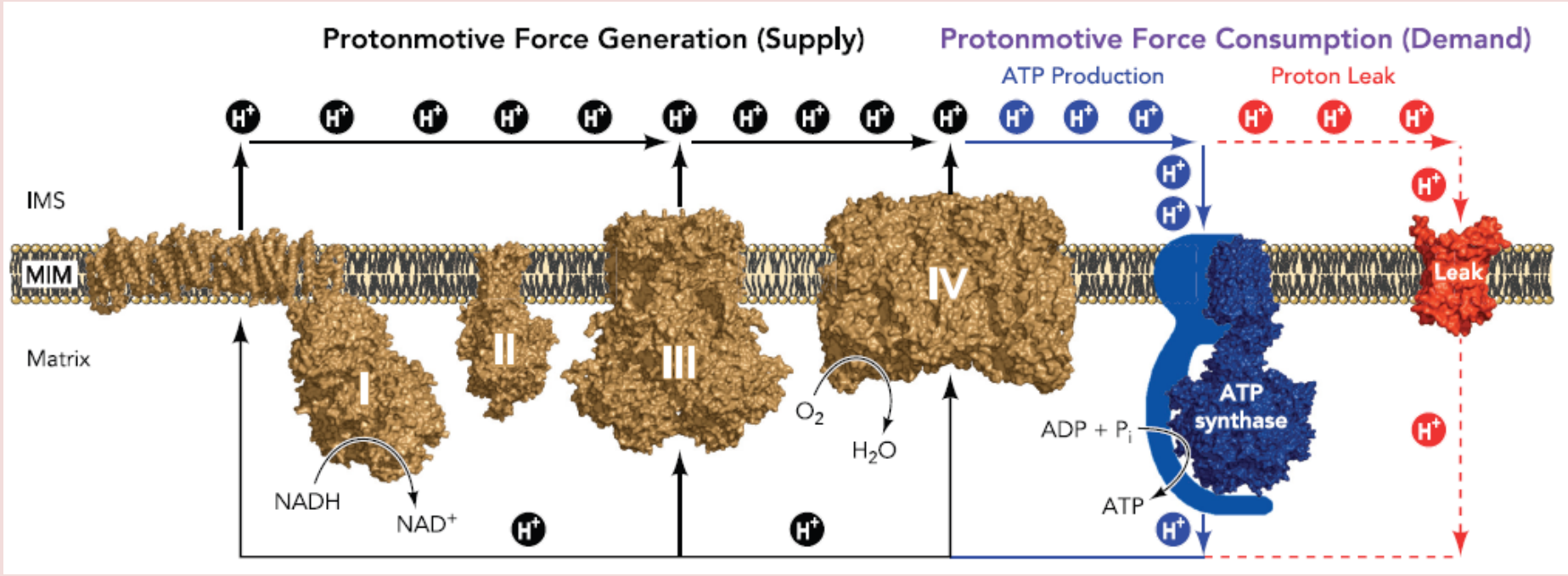
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



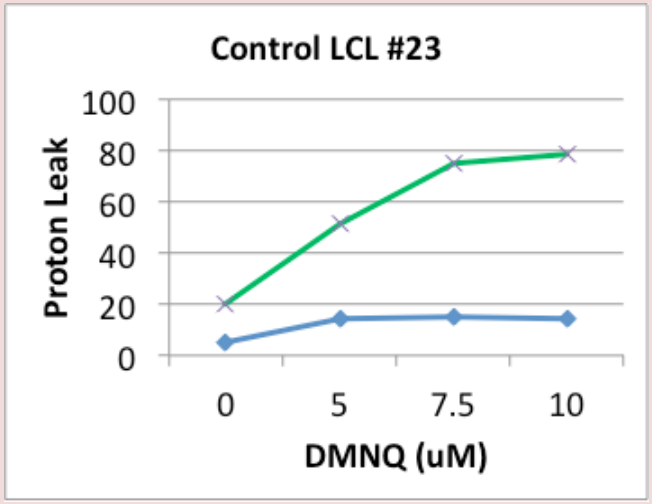
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

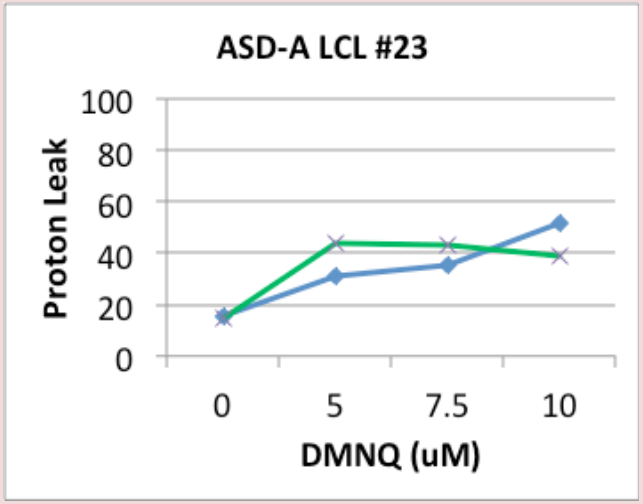


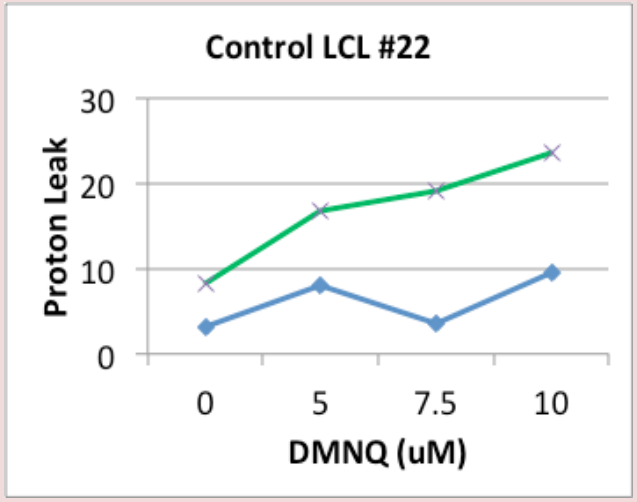
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

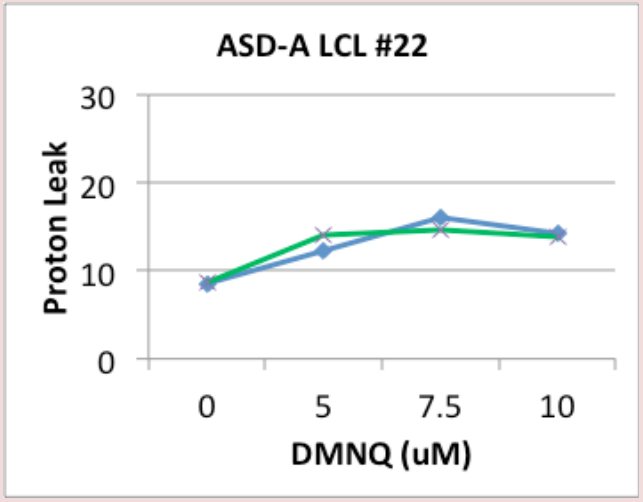


24 hour pretreatment with 50 uM Genipin, a UCP2 inhibitory

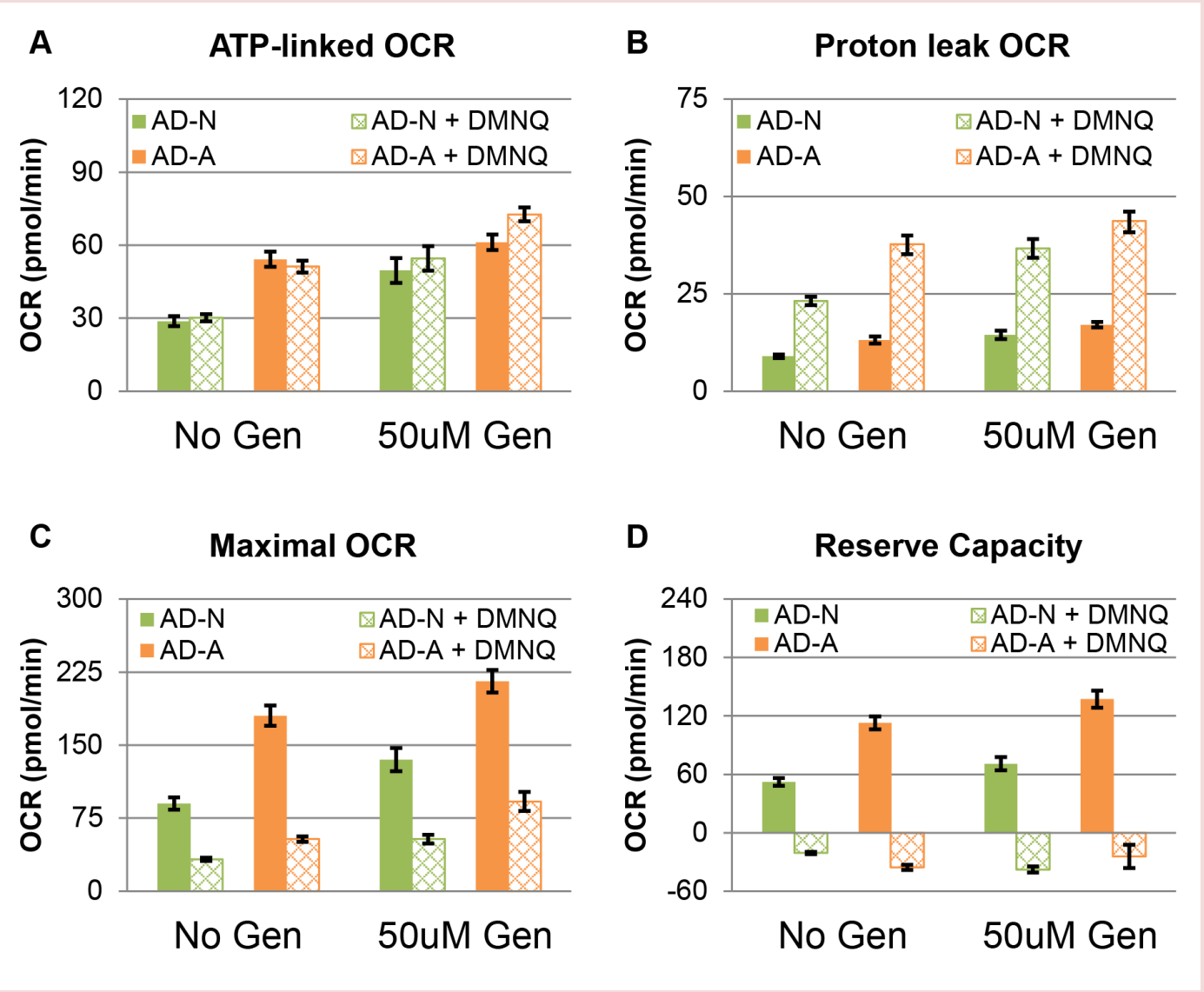




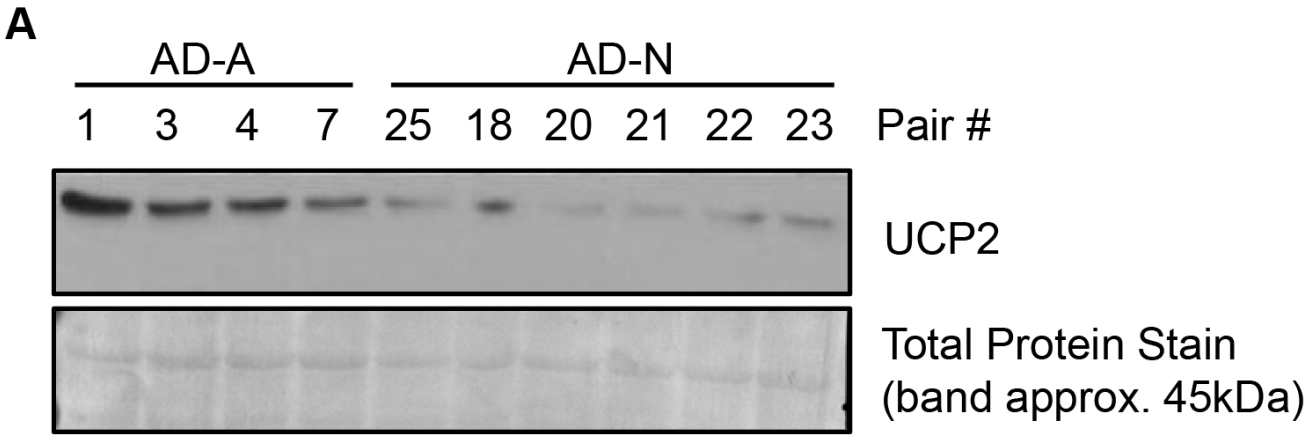


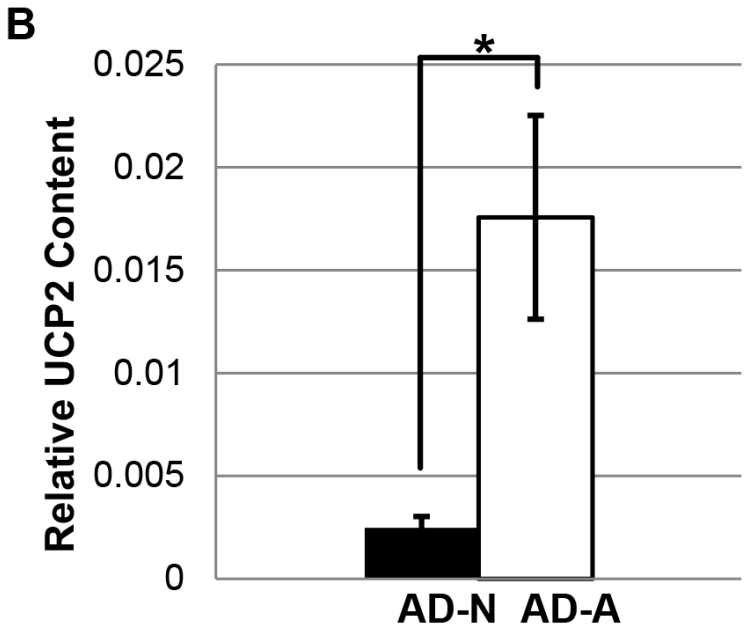


Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

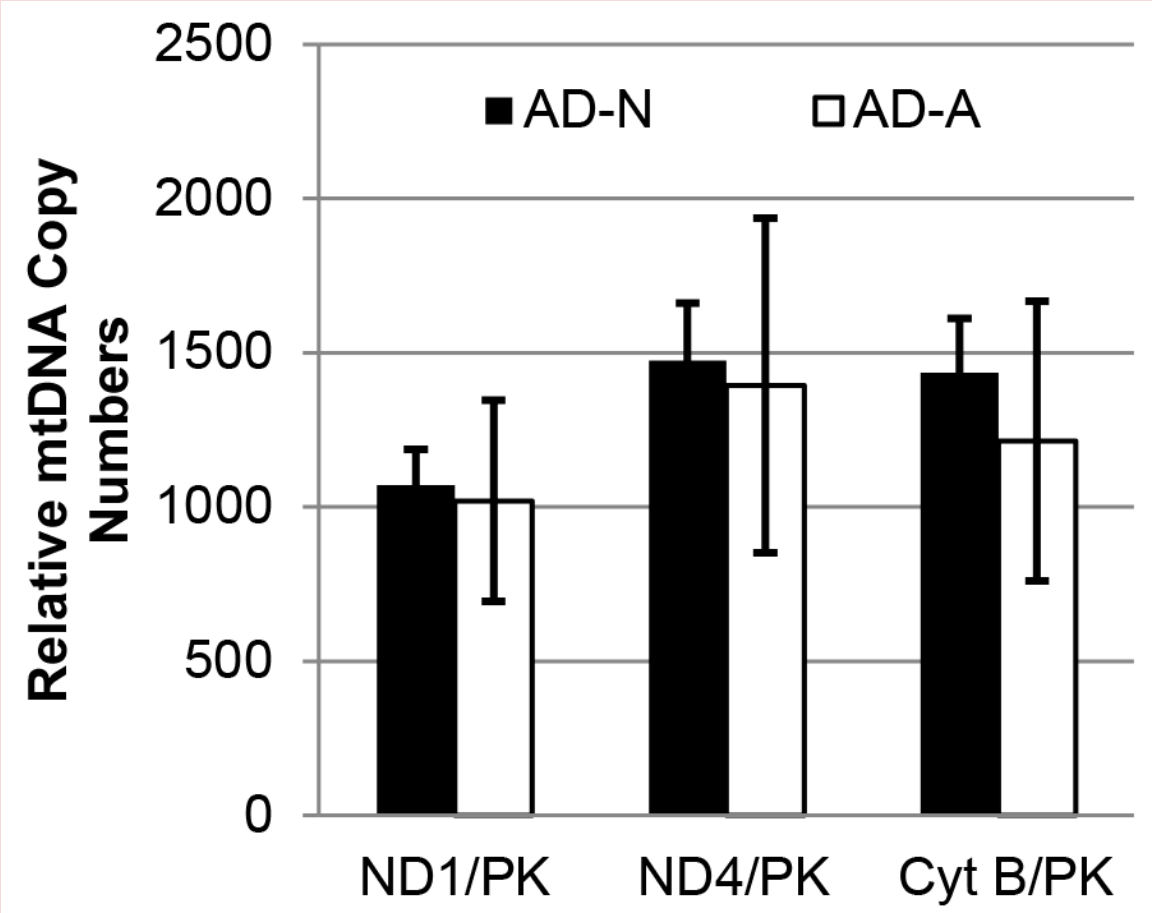


Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

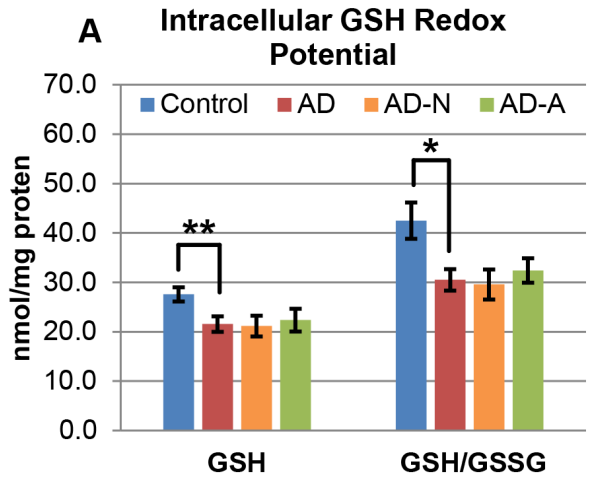


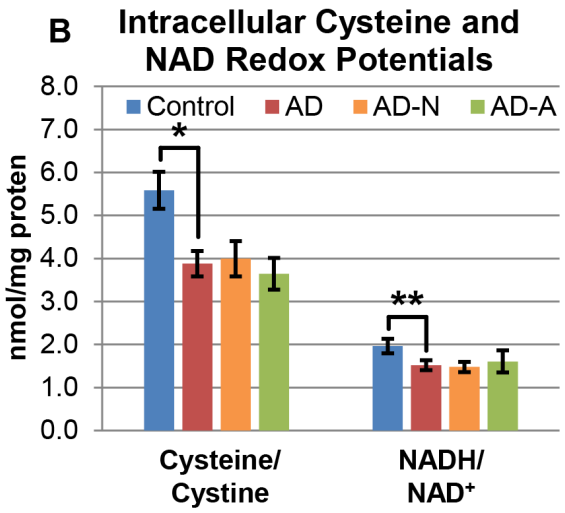


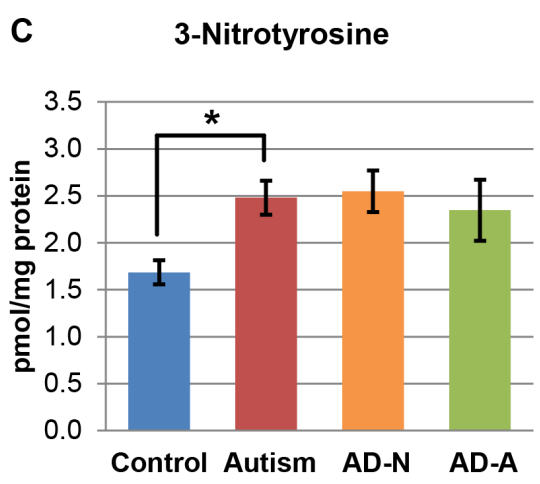
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

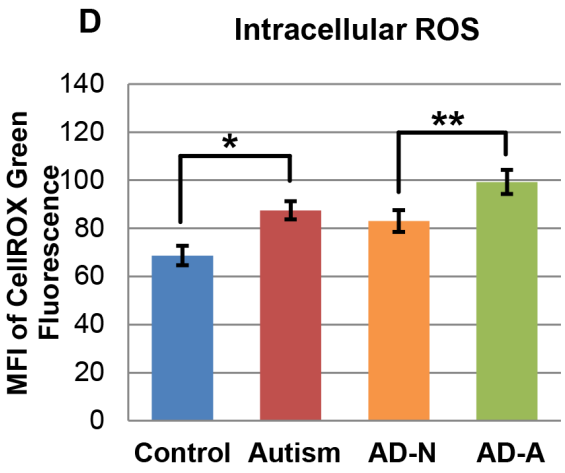


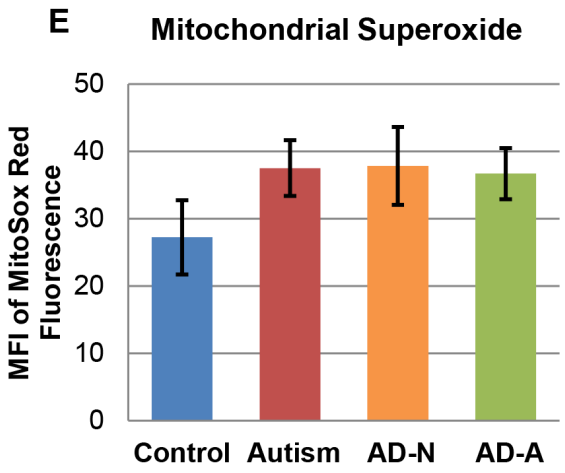
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

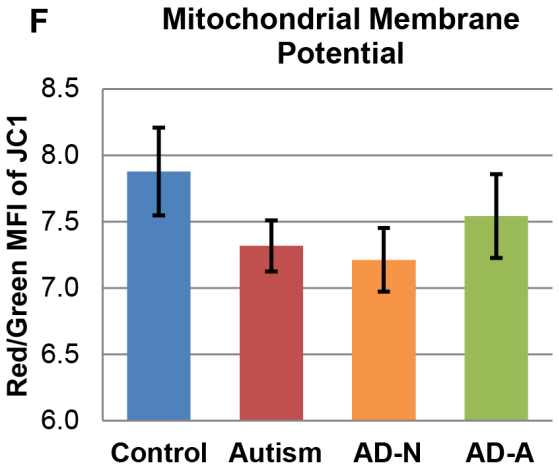




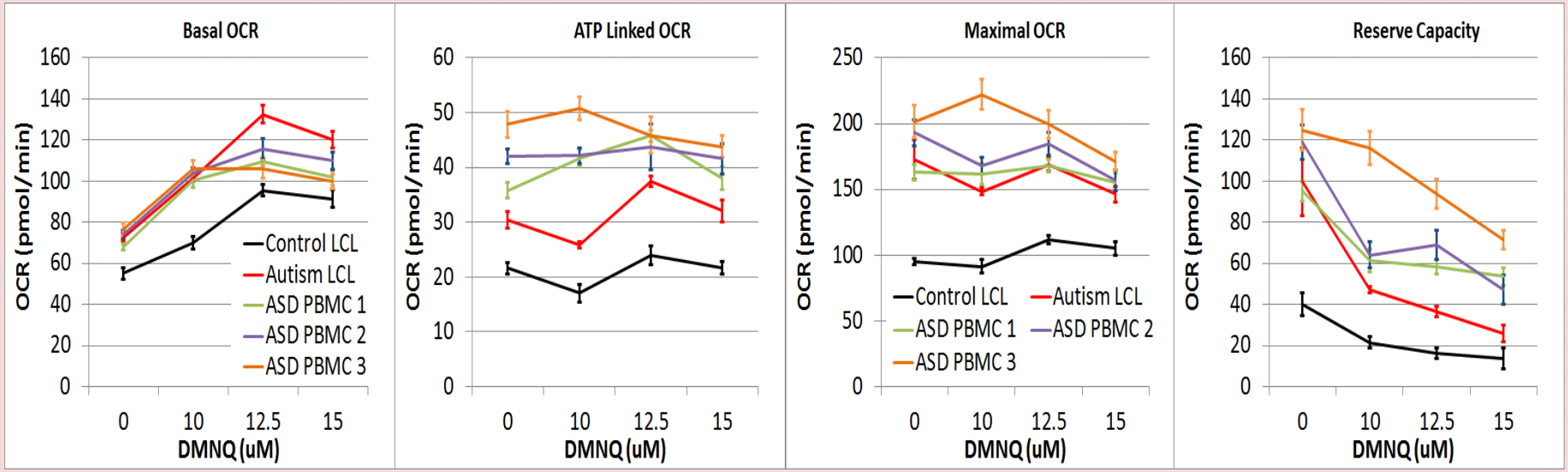




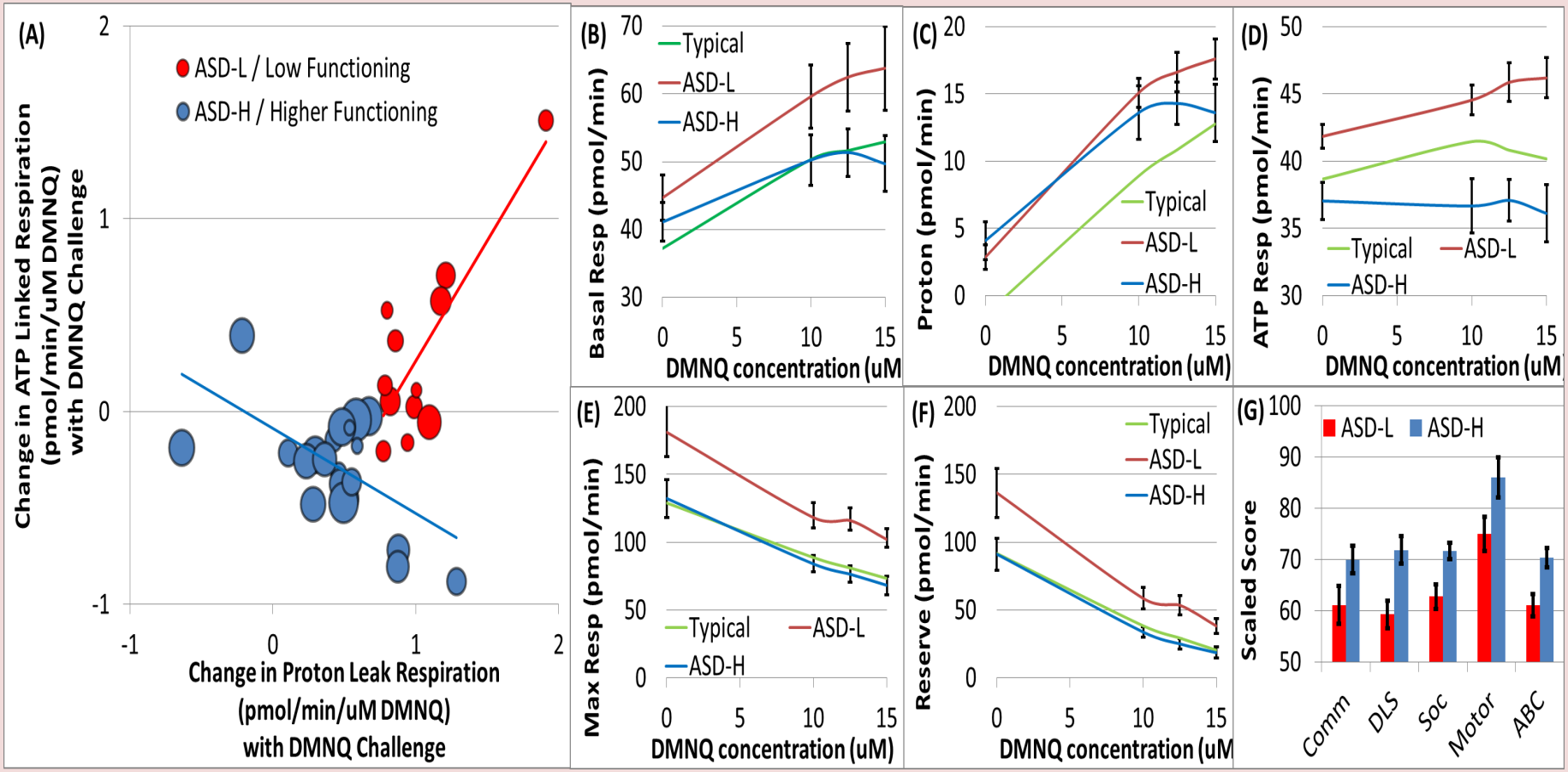




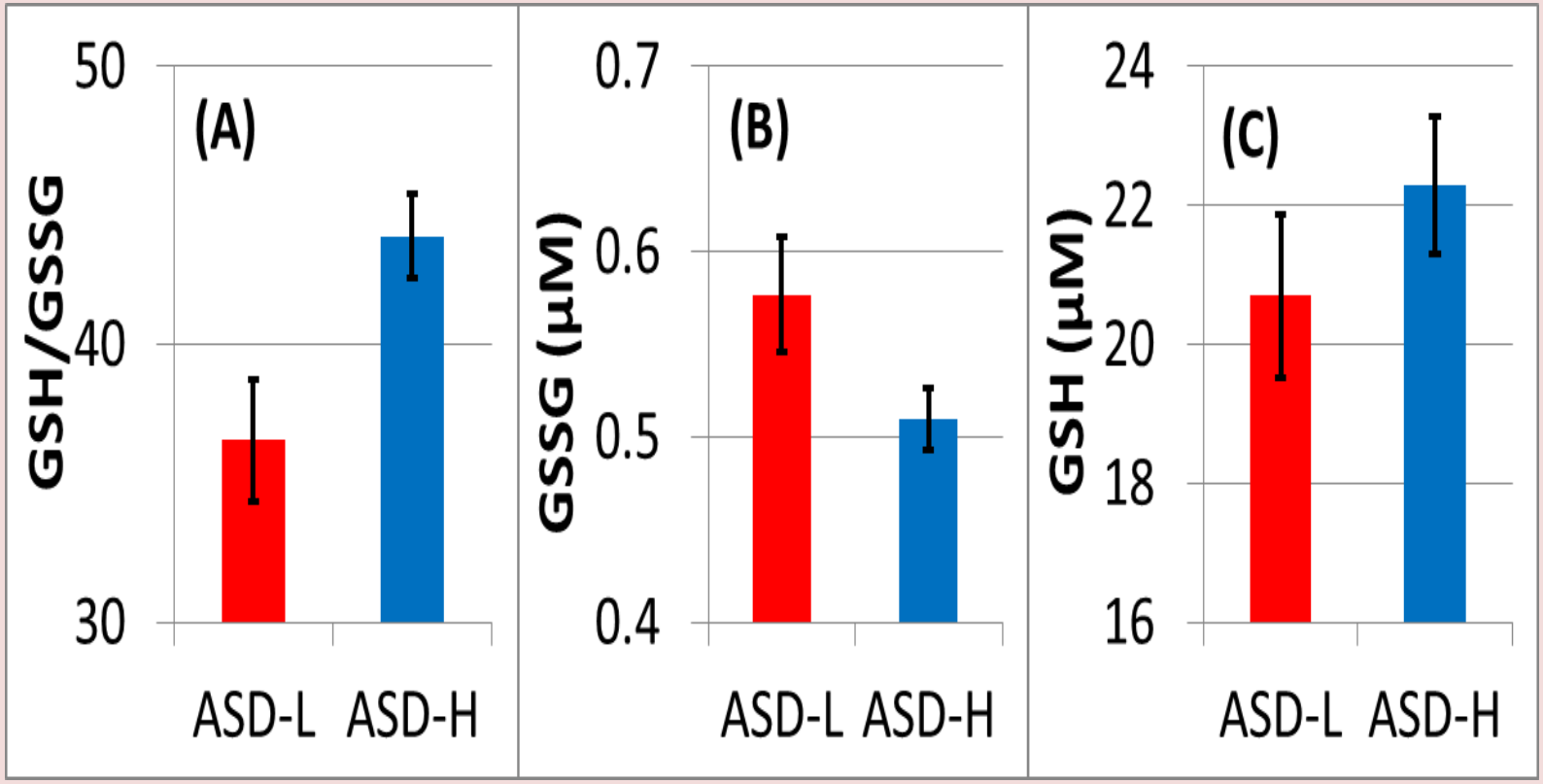
Mitochondrial Function in the PMBCs of 35 ASD children



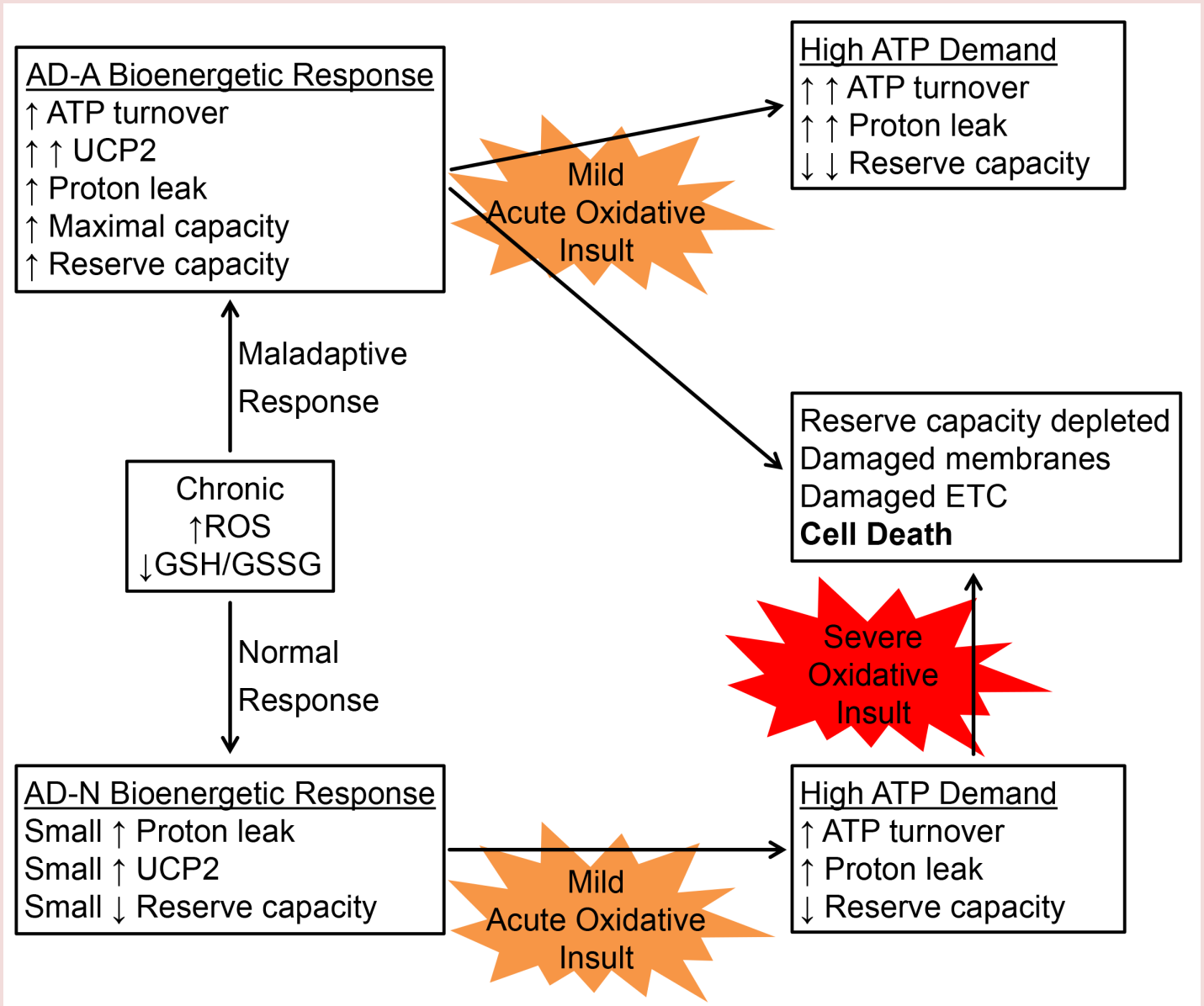
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

OPEN

Citation: Transl Psychiatry (2014) **4**, e377; doi:10.1038/tp.2014.15

www.nature.com/tp

ORIGINAL ARTICLE

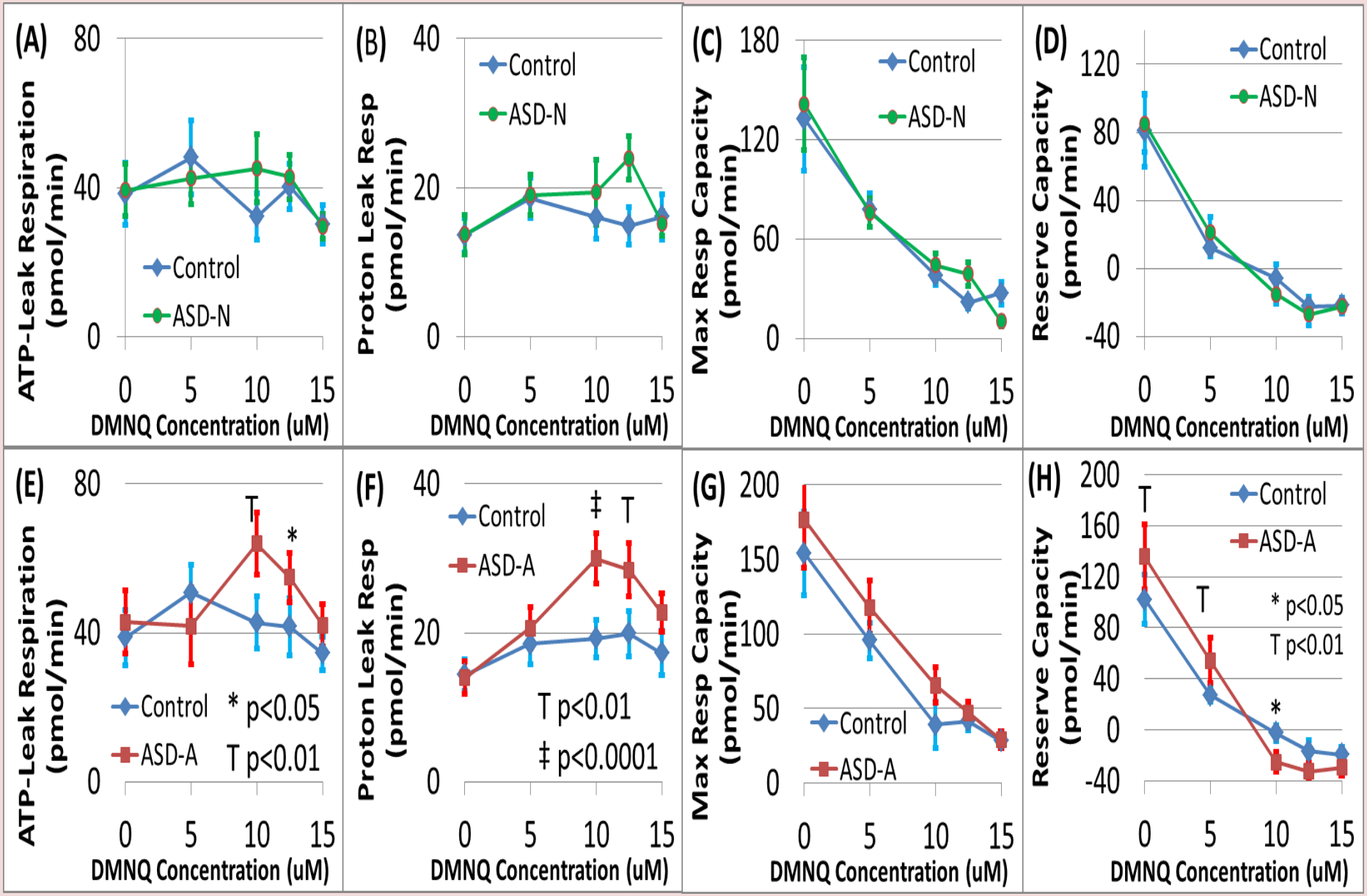
Oxidative stress induces mitochondrial dysfunction in a subset of autistic lymphoblastoid cell lines

S Rose, RE Frye, J Slattery, R Wynne, M Tippett, S Melnyk and SJ James

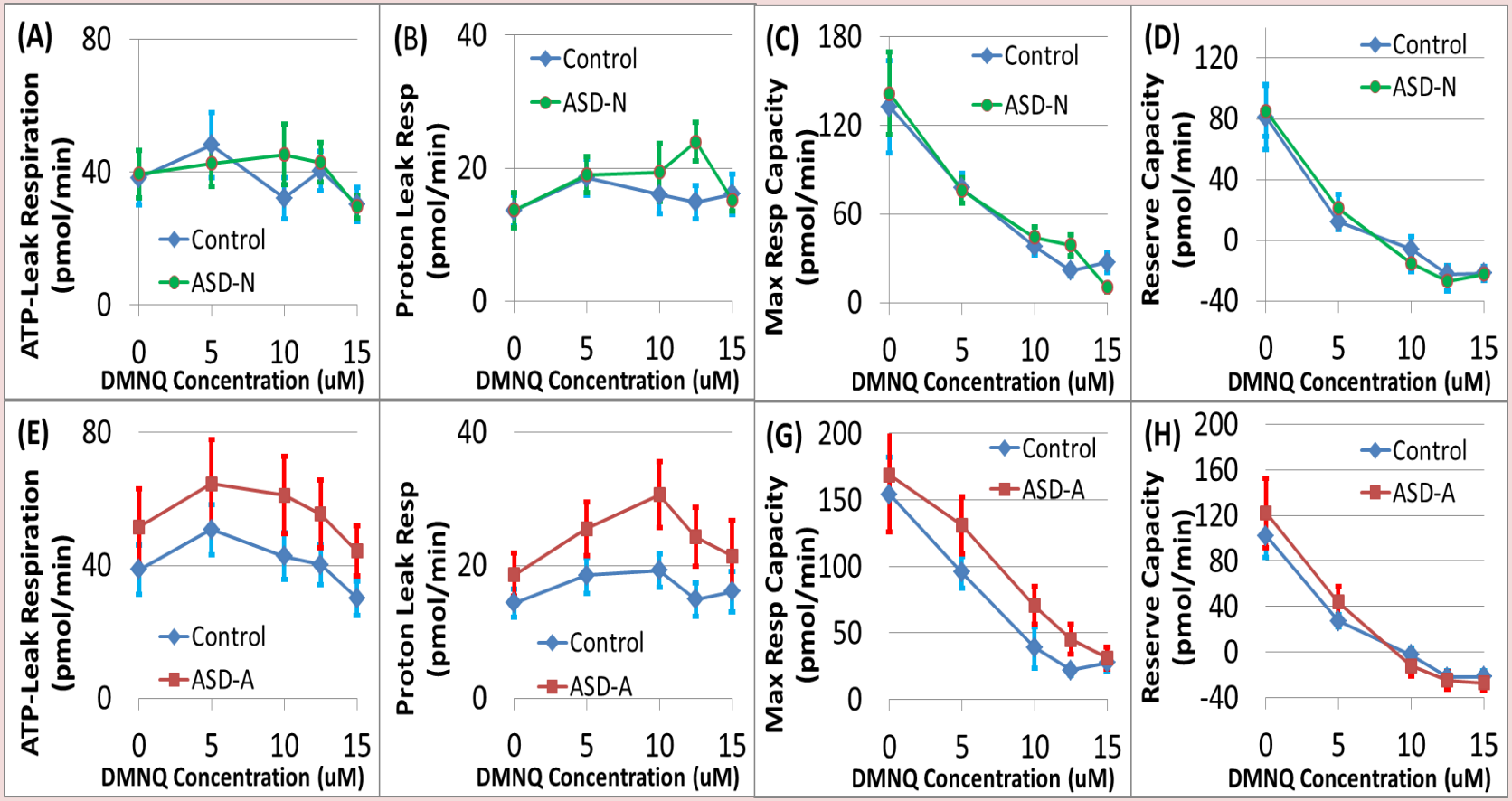
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

	ASD LCLs				Paired Control LCLs			
Pair	Cell ID	Source	Age	Gender	Cell ID	Source	Age	Gender
1	02C10054	NIMH	6y	Male	53370C	NIMH	37y	Male
2	05C38988	NIMH	12y	Male	47437C	NIMH	31y	Male
3	038804	AGRE	9y	Male	16118C	Corelle	21y	Male
4	0939303	AGRE	11y	Male	14782C	Corelle	44y	Male
5	1393306	AGRE	3y	Male	05048C	Corelle	22y	Male
6	03C15992	NIMH	5y	Male	27915C	NIMH	30y	Male
7	03C16499	NIMH	11y	Male	14547C	Corelle	44y	Male
8	01C08367	NIMH	7y	Male	05051C	Corelle	25y	Male
9	03C14349	NIMH	17y	Male	14811C	Corelle	37y	Male
10	03C14363	NIMH	3y	Male	14811C	Corelle	37y	Male
11	01C08022	NIMH	5y	Male	30231C	NIMH	44y	Male
12	02C09713	NIMH	7y	Male	49729C	NIMH	36y	Male
13	04C26296	NIMH	10y	Male	49729C	NIMH	36y	Male
14	008404	AGRE	13y	Male	14926C	Corelle	38y	Male
15	1267302	AGRE	11y	Male	14907C	Corelle	28y	Male
16	03C14441	NIMH	7y	Male	14811C	Corelle	37y	Male
17	02C09650	NIMH	7y	Male	53370C	NIMH	37y	Male
18	02C10618	NIMH	7y	Male	05049C	Corelle	22y	Male
19	04C27439	NIMH	7y	Male	27915C	NIMH	30y	Male
20	01C08495	NIMH	4y	Male	27915C	NIMH	30y	Male
21	03C17237	NIMH	10y	Male	49729C	NIMH	36y	Male
22	01C08594	NIMH	7y	Male	27915C	NIMH	30y	Male

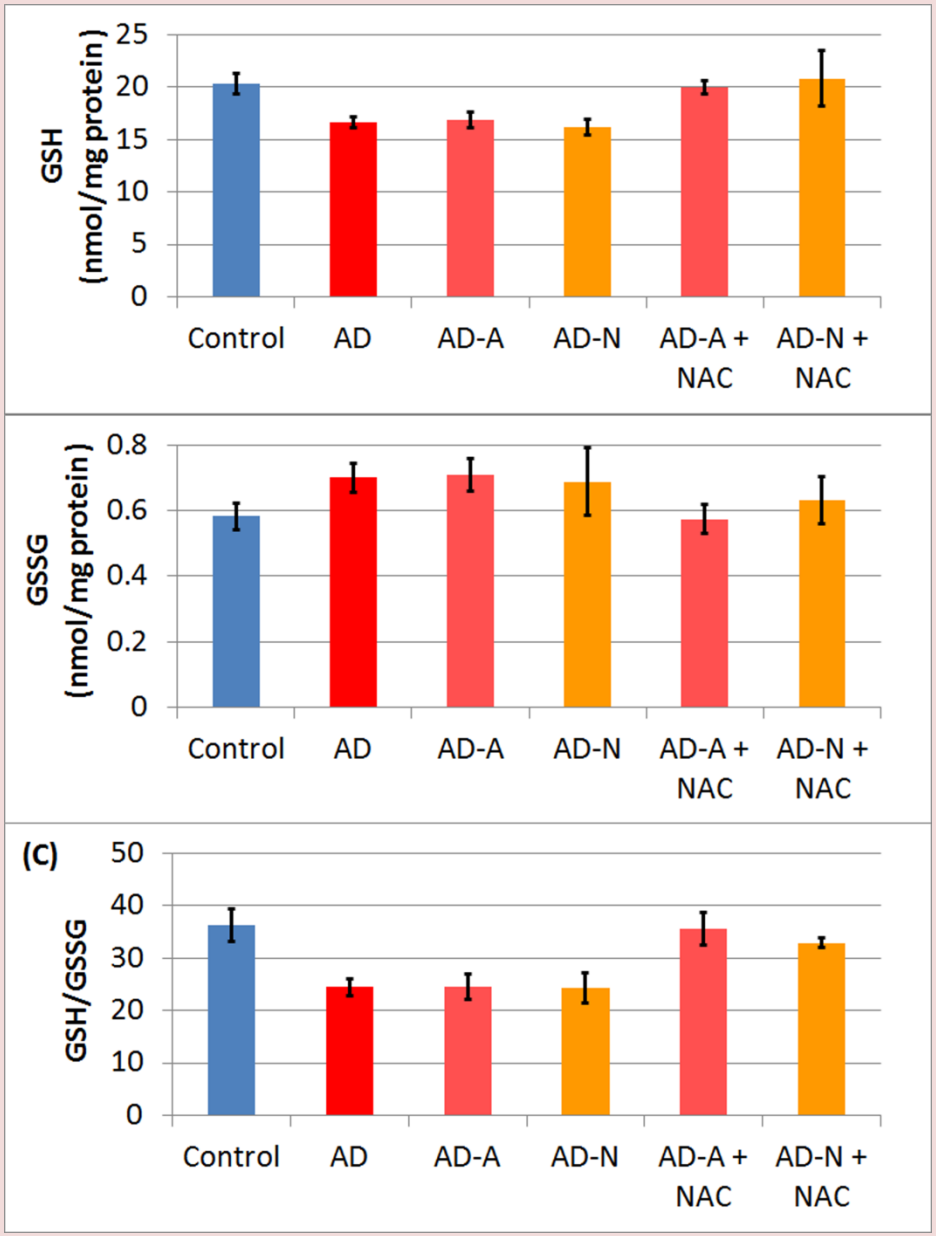
Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



- LCLs and PMBCs from children with autism demonstrate mitochondrial function abnormalities when challenged to increased level of oxidative stress.

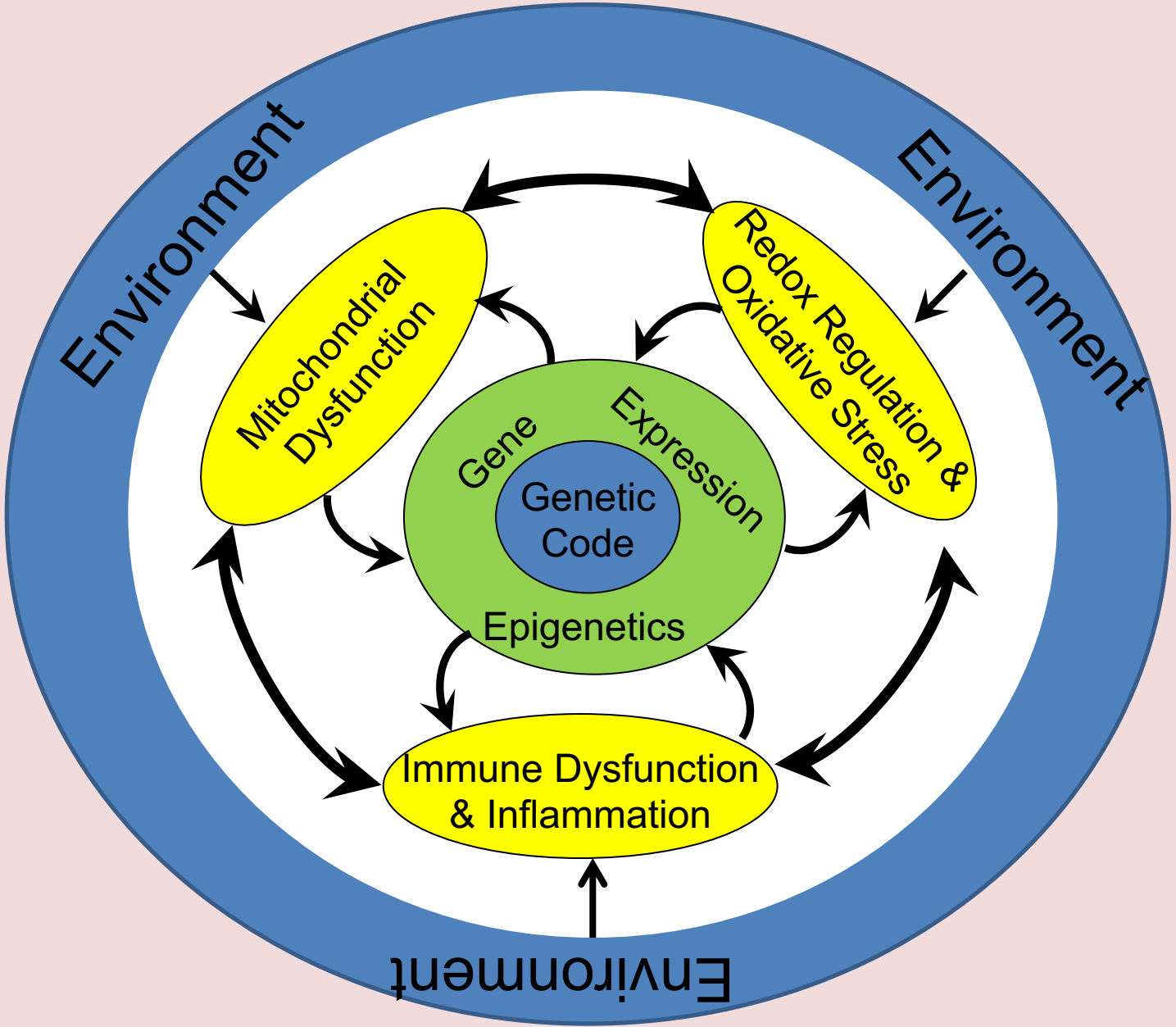
- There are subgroups of autistic children with abnormal mitochondrial function and others with normal mitochondrial function.

- Mitochondrial function in PMBCs from children with autism spectrum disorder is related to development and behavior

- N-acetyl-L-Cysteine normalizes mitochondrial function in those with abnormal mitochondrial function

Pulling it Together

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder



Studies in Our Center

Defining subgroups of mitochondrial disease and dysfunction in autism spectrum disorder

Aim: This research aims to better understand abnormalities in mitochondrial energy metabolism, and consequences of such abnormalities, in autism spectrum disorder (ASD).

Protocol: 1 to 5 visits to ACH with blood draws and cognitive and behavior evaluations. Primary measures are oxidative stress and mitochondrial function

Participants : Between the ages of 3-14 years.
Four Groups Matched on Age and Gender

- 50 Children with ASD who have mitochondrial disease (ASD/MD)
- 50 Children with ASD who do not have mitochondrial disease (ASD/NoMD)
- 50 Children with no ASD but have mitochondrial disease (NoASD/MD)
- 50 Children with developmental delays but no ASD or no MD (NoASD/NoMD)

150 children with general ASD
50 TD controls (ASD ruled out using SCQ)

Contact: John Slattery, jcslattery@uams.edu
Funding: Jane Johnson Foundation (partial)

A Folinic acid intervention for ASD

Specific Aim 1: To determine whether an intervention of folinic acid over a 12-week period is a safe and effective treatment for ASD and improves mitochondrial function

Specific Aim 2: To determine whether the metabolic, immune and genetic biomarkers can predict individual participant response to folinic acid treatment.

1. ***Folate Receptor alpha autoantibody***
2. ***Glutathione Metabolism***
3. ***Mitochondrial Function***
4. ***Genetic Polymorphisms:***

    Methylenetetrahydrofolate Reductase (MTHFR): 677C>T & 1298A>C
    Reduced folate carrier: 80G>A

Inclusion: ASD, 3-14 years of age, Language Impairment, No major changes in therapy
Exclusion: Antipsychotic medication, Severe Irritability, Severe Prematurity, GERD

Contact: John Slattery, jcslattery@uams.edu
Funding: Lee Silsby Compounding Pharmacy / BHARE Foundation / Fraternal Order of Eagles

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

1st International Symposium on the Microbiome in Health and Disease with a Special Focus on Autism

June 26th, 2014 Arkansas Children's Hospital

A collaborative effort between the Arkansas Autism Alliance and the N of One: Autism Research Foundation focusing on mechanisms of action in Autism Research.

The microbiome is the next frontier in medicine and research groups are investigating its contribution to certain diseases, along with its role in maintaining health. This unique cutting-edge conference will review the evidence for the role of the microbiome in health and disease with a special focus on how alterations in the microbiome may influence behavioral manifestations of autism.

Invited Speakers include:

- Dr. Susan Swedo, National Institute of Health
- Dr. William Parker, Duke University
- Dr. Tore Midtvedt, Karolinska Institute
- Dr. Jim Adams, Arizona State
- Dr. Carl Cerniglia, NCTR
- Dr. Derrick MacFabe, University of Western Ontario
- Dr. Rosa Krajmalnik-Brown, Arizona State
- Dr. Richard Frye, UAMS
- Dr. Emma Allen-Vercoe, University of Guelph

Register Here: http://www.microbiome-autism.com/

Lunch Provided to 1st 50 Registered

Free Admission

Media Contact: John Slattery jcslattery@uams.edu

N of One AUTISM RESEARCH FOUNDATION

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder

Autism Seahorse Laboratory
Shannon Rose
Rebecca Wynne

Autism Translational Research Center
John Slattery
Marie Tippet

Autism Metabolic Laboratory
Jill James
Stepan Melnyk
Teresa Evans
Oleksandra Pavliv

Funding
Jane Botsford Johnson Foundation
Arkansas Biomedical Institute

Acquired Mitochondrial Disorders in Children with Autism Spectrum Disorder