Suplementació nutracèutica en els trastorns psiquiàtrics

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REVIEWS

Impaired mitochondrial function in psychiatric disorders

Husseini Manji[1], Tadafumi Kato[2], Nicholas A. Di Prospero[1], Seth Ness[1], M. Flint Beal[3], Michael Krams[1] and Guang Chen[1]

Nat Rev Neurosci. 2012 Apr 18;13(5):293-307.

Role of mitochondria and energy metabolism in schizophrenia and psychotic disorders

C. Konradi [a,b,*], D. Öngür [c,d]

Schizophr Res. 2017 Sep;187:1-2.

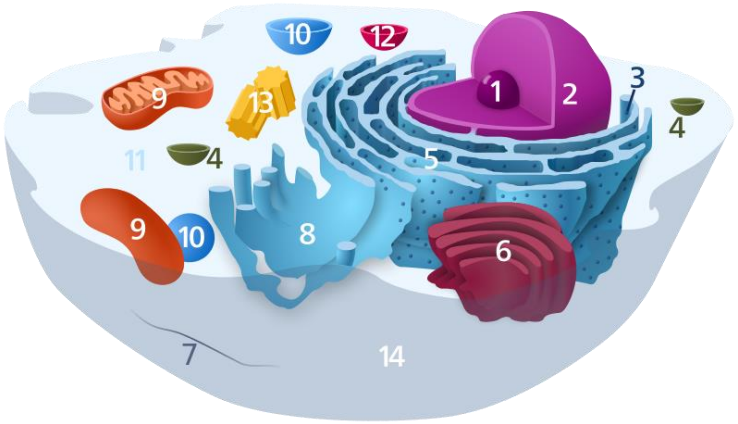
Mitochondrial Etiology of Neuropsychiatric Disorders

Pei L[1], Wallace DC[2].

Biol Psychiatry. 2018 May 1;83(9):722-730.

La **disfunció mitocondrial**

1) Pot afectar **processos cel·lulars claus**, alterant el funcionament sinàptic i contribuint als canvis tròfics en el cervell associats al deteriorament a llarg termini de las malalties psiquiàtriques.
2) Pot afectar **diversos òrgans** i explicar part de l'elevada comorbilitat present en diverses malalties psiquiàtriques.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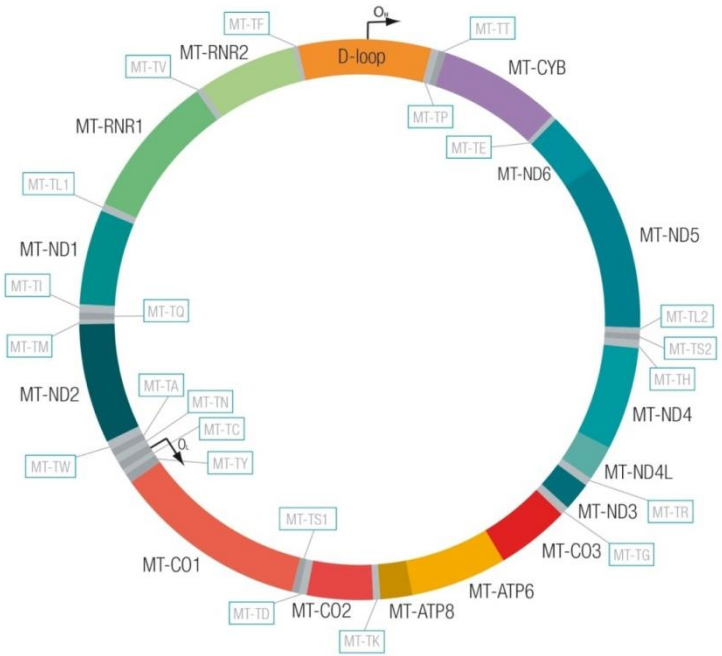
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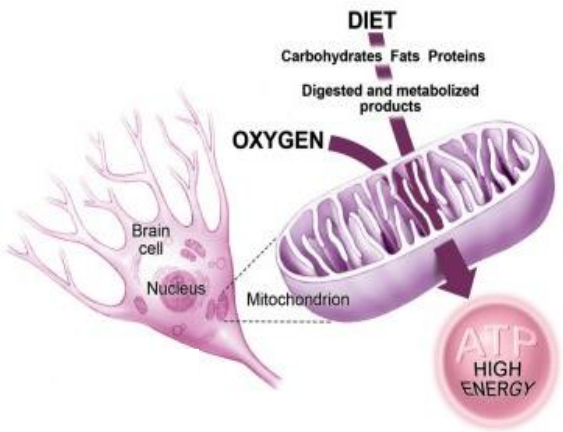
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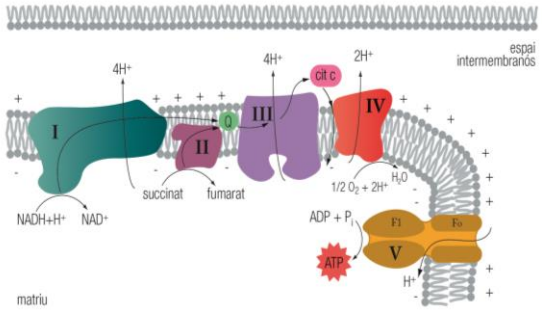
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Autisme i discapacitat intel·lectual

OXFORD

Human Molecular Genetics, 2018, Vol. 0, No. 0 1–10

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Original Article

ORIGINAL ARTICLE

Genetic and clinical evidence of mitochondrial dysfunction in autism spectrum disorder and intellectual disability

Alba Valiente-Pallejà[1,2,3,†], Helena Torrell[4,†], Gerard Muntané[1,5,†], Maria J. Cortés[2,3,6,7], Rafael Martínez-Leal[2,3,6,7], Nerea Abasolo[4], Yolanda Alonso[1,2,3,7], Elisabet Vilella[1,2,3,7] and Lourdes Martorell[1,2,3,7,*]

Table 1. Percentage of subjects in the three study groups presenting conditions commonly associated with mitochondrial disorders (CAMDs)

Conditions	HC $n = 112$	ASD $n = 122$	ID $n = 115$	Statistics		
				Compared groups	χ^2	P
Specific conditions with frequency >5% in the study groups						
Constipation	17.0	73.8	57.4	HC vs. ASD	75.403	**<0.001**
				HC vs. ID	38.496	**<0.001**
				ASD vs. ID	7.060	**0.008**
Edema	3.6	15.6	27.8	HC vs. ASD	9.357	**0.002**
				HC vs. ID	24.478	**<0.001**
				ASD vs. ID	5.262	**0.021**
Seizures	0	63.9	42.6	HC vs. ASD	107.059	**<0.001**
				HC vs. ID	59.918	**<0.001**
				ASD vs. ID	10.820	**0.001**
Vision alterations	5.4	18.0	33.9	HC vs. ASD	8.762	**0.003**
				HC vs. ID	28.458	**<0.001**
				ASD vs. ID	7.810	**0.005**
Strabismus	1.8	10.7	13.0	HC vs. ASD	7.647	**0.006**
				HC vs. ID	10.268	**0.001**
				ASD vs. ID	0.328	0.567
Sphincters incontinence	0	66.4	31.3	HC vs. ASD	113.400	**<0.001**
				HC vs. ID	40.994	**<0.001**
				ASD vs. ID	29.160	**<0.001**

HC: healthy controls; ASD: autism spectrum disorder; ID: intellectual disability.

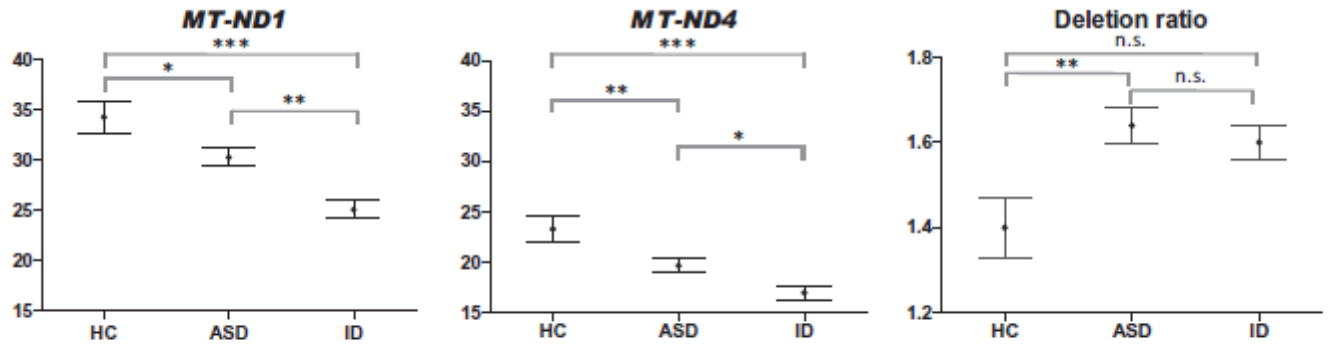


Figure 1. Estimated marginal means of the *MT-ND1* and *MT-ND4* genes and the deletion ratio in the three study groups. HC: healthy controls; ASD: autism spectrum disorder; ID: intellectual disability; n.s.: not significant; *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 2. Putatively pathogenic variants present in the study sample

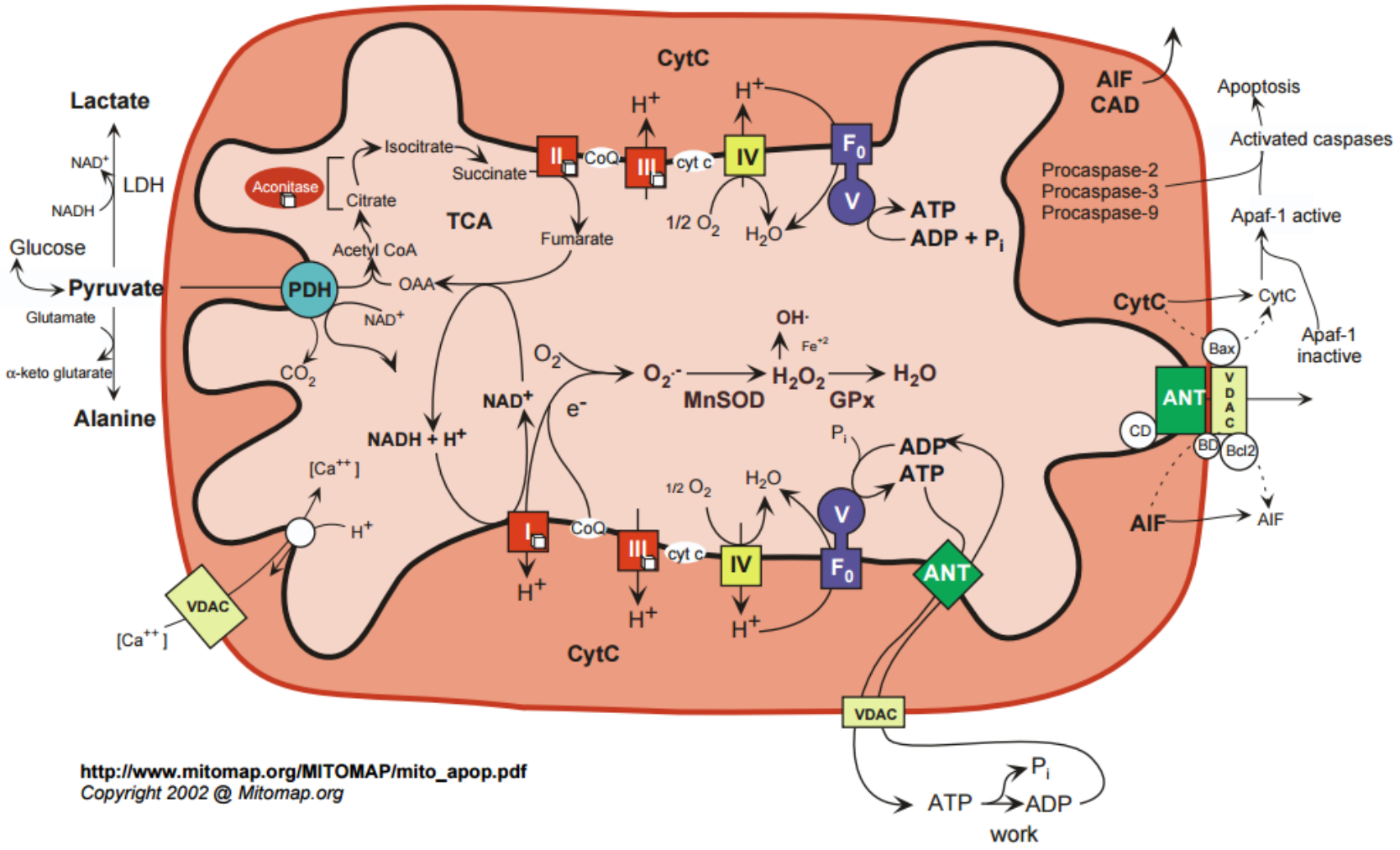
N	Variant	AA change	Freq.	dbSNP ID	Samples	Locus	Homo/ heteroplasmy	Disease score
Non-synonymous variants								
1	m.8663A>C	Q46P	0		ID074	MT-ATP6	0.79	0.889
2	m.8936T>A	L137H	0		A003, ID009, ID036, ID055, ID069, ID073, ID074, ID104, ID112		0.60–0.97	0.855
3	m.11039C>T	L94F	0		ID071	MT-ND4	0.99	0.702
4	m.11268C>T	T170I	0.0010		A095, ID015		1	0.739
5	m.13855C>A	L507M	0		ID070	MT-ND5	1	0.686
6	m.15132T>C	M129T	0.0002		A117	MT-CYB	1	0.821
7	m.15482T>C	S246P	0		ID038		1	0.559
8	m.15597T>C	V284A	0		A059		1	0.581
rRNA variants								
1	m.680T>C		0.0006		A099	MT-RNR1	1	
2	m.720T>C		0		A070		0.99	
3	m.736C>T		0		ID057		1	
4	m.851A>G		0	rs28502491	A092, ID011		0.96–1	
5	m.870C>T		0.0005		ID116		1	
6	m.1007G>A		0.0010	rs111033213	A051		0.99	
7	m.1120C>T		0.0005	rs727505171	ID007		1	
8	m.1211G>A		0.0010	rs397515725	A063, A095, ID015, ID042		1	
9	m.1303G>A		0.0023		A021		1	
10	m.1537C>T		0.0003		ID108		1	
11	m.1555A>G[a]		0.0032	rs267606617	A043, A054, ID018		0.99–1	
12	m.1717T>C[a]		0.0007		ID076	MT-RNR2	1	
13	m.1821A>G		0.0008		ID105		1	
14	m.1834T>C		0.0007		A078, A089, A156		1	
15	m.2141T>C		0.0031		ID112		1	
16	m.2222T>C		0		ID061, ID087		1	
17	m.2223A>G		0		ID038		1	
18	m.2234C>T		0		ID017		1	
19	m.2244T>G		0		ID011		1	
20	m.2398A>G		0		A068		1	
21	m.2407T>C		0		ID024		1	
22	m.2524A>C		0.0001		A096		1	
23	m.2702G>A		0.0020		A067		1	
24	m.2746T>C		0.0005	rs28663331	A090		1	
25	m.2775A>G		0		ID061, ID087		1	
26	m.2792A>C		0.0001		A057		1	
27	m.2969A>G		0.0002		ID065		1	
28	m.3203A>G		0.0009		ID055		1	
29	m.3213A>G[a]		0.0003		A098		1	
tRNA variants								
1	m.4310A>G		0.0008		ID085	MT-TI	1	
2	m.4336T>C		0.0220	rs41456348	A059, ID004	MT-TQ	0.98–1	0.4
3	m.4388A>G		0.0002	rs375986475	ID036	MT-TQ	1	
4	m.4435A>G[a]		0.0010		A079, ID037	MT-TM	0.95–1	0.35
5	m.5605A>G		0.0003		A152	MT-TA	1	
6	m.10007T>C		0.0010	rs201906571	A009	MT-TG	1	
7	m.12142A>G[a]		0.0001		A125	MT-TH	1	
8	m.12193A>G		0		A084		1	
9	m.14684C>T		0.0009		A003	MT-TE	1	
10	m.14687A>G		0.0098	rs200189658	ID112		1	0.65
11	m.15913C>T		0.0003		ID065	MT-TT	0.99	
12	m.15946C>T		0.0032	rs202014122	A014, A045		0.99–1	

Table 3. Clinical characteristics reported to be associated with mtDNA variants present in the study sample

Variant	Locus	Heteroplasmy	Subjects	Age	Gender	Deafness	Migraine	AD/PD	Hypertension	Visual loss	MMRF
m.1537C>T	*MT-RNR1*	1	ID108	60	M	+	NE	–	–	–	–
m.1555A>G	*MT-RNR1*	1	ID018	33	M	–	NE	–	–	+	–
		1	A043	43	F	–	NE	–	–	–	–
		1	A054	54	F	+	NE	–	–	–	–
m.4336T>C	*MT-TQ*	0.98	A059	38	M	–	NE	–	+	–	–
		1	ID004	63	F	–	NE	+	–	–	–
m.4388A>G	*MT-TQ*	1	ID036	36	F	–	NE	–	+	–	–
m.4435A>G	*MT-TM*	1	ID037	40	F	–	NE	–	+	–	–
		0.96	A079	39	M	–	NE	–	+	–	–
m.14687A>G	*MT-TE*	1	ID112	21	M	–	NE	–	+	+	–

In summary, our study identified 1) a high frequency of conditions commonly associated with mitochondrial disorders that occurred concomitantly with 2) low mtDNA content and 3) the presence putative pathogenic mtDNA mutations in subjects with ASD and ID. Based on these findings, subjects with ASD and ID may present mitochondrial dysfunction. Future research will elucidate whether the screening for mtDNA alterations in ASD and ID can be as appropriate as the screening for nuclear DNA alterations.

Mitochondrial Energetics



http://www.mitomap.org/MITOMAP/mito_apop.pdf

Diagram of the mammalian mitochondrion showing the relationship between energy production, ROS generation, and regulation of apoptosis.

Esquizofrènia

Analysis of mitochondrial dysfunction in schizophrenia through clinical, biochemical and genetic analyses

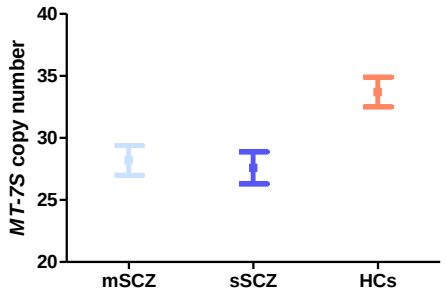
Alba Valiente[1,2] (MD, Mres), Gerard Muntané[1,2,3] (Bsc, PhD), Helena Torrell[4] (Bsc, PhD); Yolanda Alonso[1,2] (MD, PhD); David Mulet[1] (BNurs, Mres); Elena Montaña[1] (MD, Mres); Elisabet Vilella[1,2] (BSc, PhD); Lourdes Martorell[1,2*] (BSc, PhD)

Table 1. Sample characteristics in the three study groups.

	mSCZ N=29	**sSCZ** N=28	**HCs** N=33	Statistical tests
Epidemiological and biological data				
Gender, M/F, N	23/6	21/7	21/12	X^2=2.047; p=0.359
Age, m ± SD, y	43.9 ± 12.9	44.6 ± 11.8	41.7 ± 12.0	F=0.433; p=0.650
BMI, m ± SD, kg/m^2	27.2 ± 5.2	28.7 ± 4.9	24.5 ± 3.8	F=5.684; p=0.005
Systolic pressure	125.7 ± 14.7	125.5 ± 14.7	125.0 ± 16.7	F=0.017; p=0.983
Diastolic pressure	77.8 ± 10.8	75.6 ± 11.0	76.7 ± 11.6	F=0.247; p=0.782
PANSS score				
PANSS positive, m ± SD	17.2 ± 6.7	16.0 ± 7.3	-	F=0.113; p=0.738
PANSS negative, m ± SD	25.3 ± 7.0	25.0 ± 4.2	-	F=3.399; p=0.071
PANSS general, m ± SD	28.1 ± 12.6	26.7 ± 7.7	-	F=1.208; p=0.277
PANSS total, m ± SD	70.7 ± 21.9	67.6 ± 15.3	-	F=0.328; p=0.569
Illness progress				
Age at onset, m ± SD, y	20.1 ± 4.7	19.6 ± 2.9	-	t=0.449; p=0.655
Years of evolution	22.1 ± 12.1	25.8 ± 11.2	-	t=1.192; p=0.238
Pharmacological treatment				
Benzodiazepines, N (%)	16 (55.1)	12 (42.9)	-	X^2=0.864; p=0.352
Anticholinergics, N (%)	7 (24.1)	5 (17.9)	-	X^2=0.338; p=0.561
Antidepressants, N (%)	6 (20.7)	5 (28.6)	-	X^2=0.073; p=0.786
Mood stabilizers, N (%)	11 (37.9)	8 (28.6)	-	X^2=0.562; p=0.454
Antipsychotics[a], m ± SD, mg/day	337 ± 281	506 ± 324	-	t=2.158; p=0.035
Drug use				
Alcohol, m ± SD, standard drink/day	0.04 ± 0.2	0	0.7 ± 0.7	F=22.635; p<0.001
Smoking, m ± SD, cigarettes/day	12.8 ± 12.3	11.9 ± 11.2	1.3 ± 4.3	F=11.197; p<0.001
Physical Activity				
IPAQ-total[b], m ± SD, MET-min/week	3724 ± 4382	2137 ± 2245	3211 ± 3236	F=1.907; p=0.155

Table 2. Number of subjects presenting CAMDs in the three study groups.

CAMDs	**mSCZ** N=29	**sSCZ** N=28	**HCs** N=33	Statistical tests
Headaches, N (%)	8 (28)	6 (21)	5 (15)	X^2=1.436; p=0.488
Bowel function, N (%)	15 (51)	13 (46)	7 (21)	X^2=7.019; p=0.030
Soft tissues and fatigue, N (%)	8 (28)	10 (36)	6 (18)	X^2=2.399; p=0.301
Nervous system, N (%)	20 (69)	14 (50)	6 (18)	X^2=16.630; p<0.001
Ears and eyes, N (%)	9 (31)	8 (29)	8 (24)	X^2=0.368; p=0.832
Endocrine, N (%)	3 (10)	3 (11)	3 (9)	X^2=0.050; p=0.975
Heart and blood vessels, N (%)	13 (45)	13 (46)	7 (21)	X^2=5.375; p=0.068
Number of conditions/individual, mean ± SD	3.4 ± 2.3	3.4 ± 3.3	1.4 ± 1.5	F=8.153; p=0.001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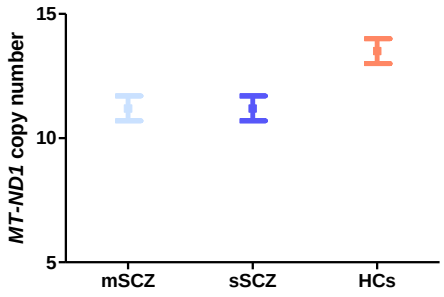
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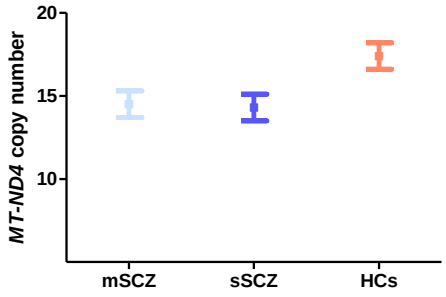
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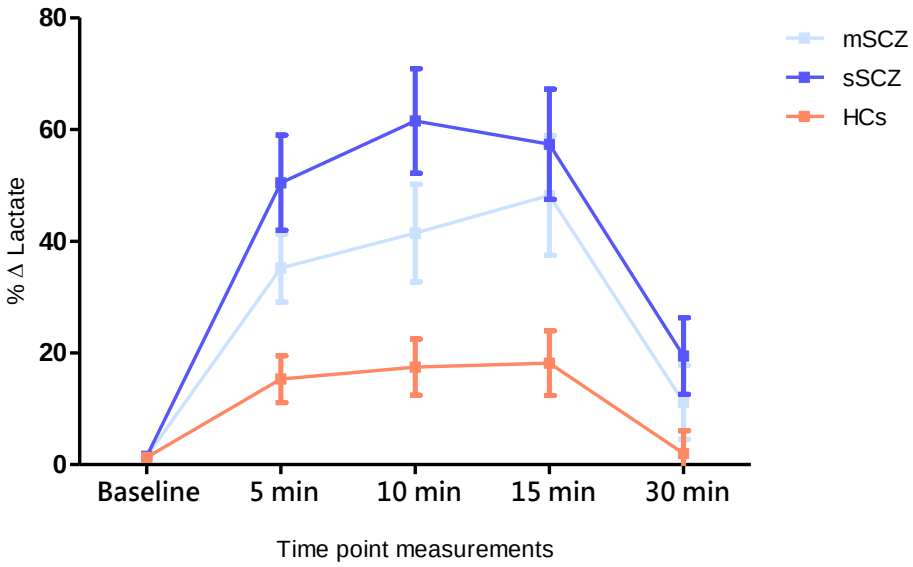
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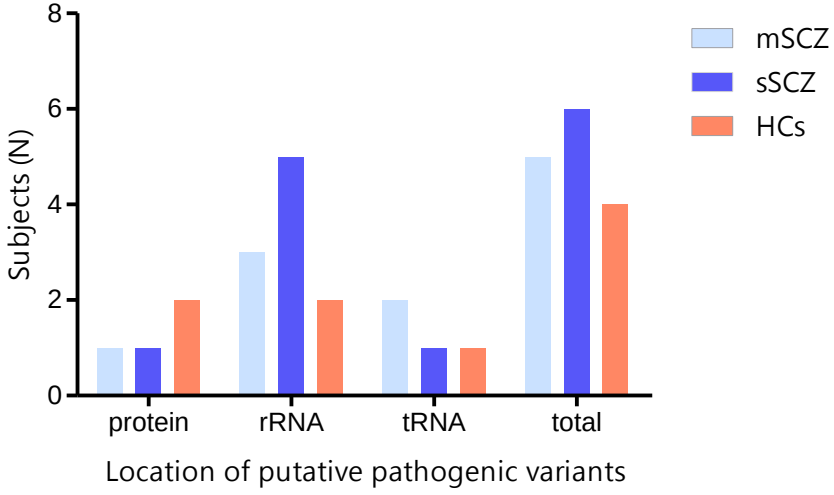
Subjects (N)
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protein
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total
Location of putative pathogenic variants
mSCZ
sSCZ
HCs

La millora de la **funció mitocondrial** podria representar una via per al desenvolupament de **noves teràpies** i també una oportunitat per a què els tractaments psicofarmacològics siguin més eficients.

En pacients amb trastorns mitocondrials i patologia psiquiàtrica s'ha observat una **millora de la simptomatologia psiquiàtrica** amb la suplementació nutracèutica.

CoQ (200-400 mg/d, VitE (400 UI/d, carnitina (2g/d) i Mg (250-500 mg/dia). *Anglin et al. Psychosomatics 2011*.

Hipòtesi: La suplementació nutracèutica millora la sintomatologia dels pacients amb malalties psiquiàtriques.

- Estudis *in vivo*: Avaluar l'efecte dels suplements nutracèutics en les característiques clíniques dels pacients psiquiàtrics.

  Assaig clínic, aleatoritzat, doble cec, de 3-6 mesos de tractament

  - Esquizofrènia, primers episodis psicòtics
    - Antipsicòtics + nutracèutics vs. Antipsicòtics
  - Pacients d'alt risc per psicosi
    - Antipsicòtics + nutracèutics vs. Antipsicòtics
    - Nutracèutics vs. placebo

  (*Avaluació de la funció cognitiva (MATRICS) y símptomes (PANSS) basal, 3 i 6 meses)

  - Autisme

- Estudis *in vivo*: Avaluar l'efecte dels suplements nutracèutics en la funció mitocondrial


Gràcies