How are cyclic vomiting syndrome, depression, autism, migraine, chronic pain and more related to mitochondrial function?

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Richard G. Boles, M.D.

Medical Genetics

Childrens Hospital Los Angeles

Associate Professor of Pediatrics

Keck School of Medicine at USC

Potential Conflict of Interest

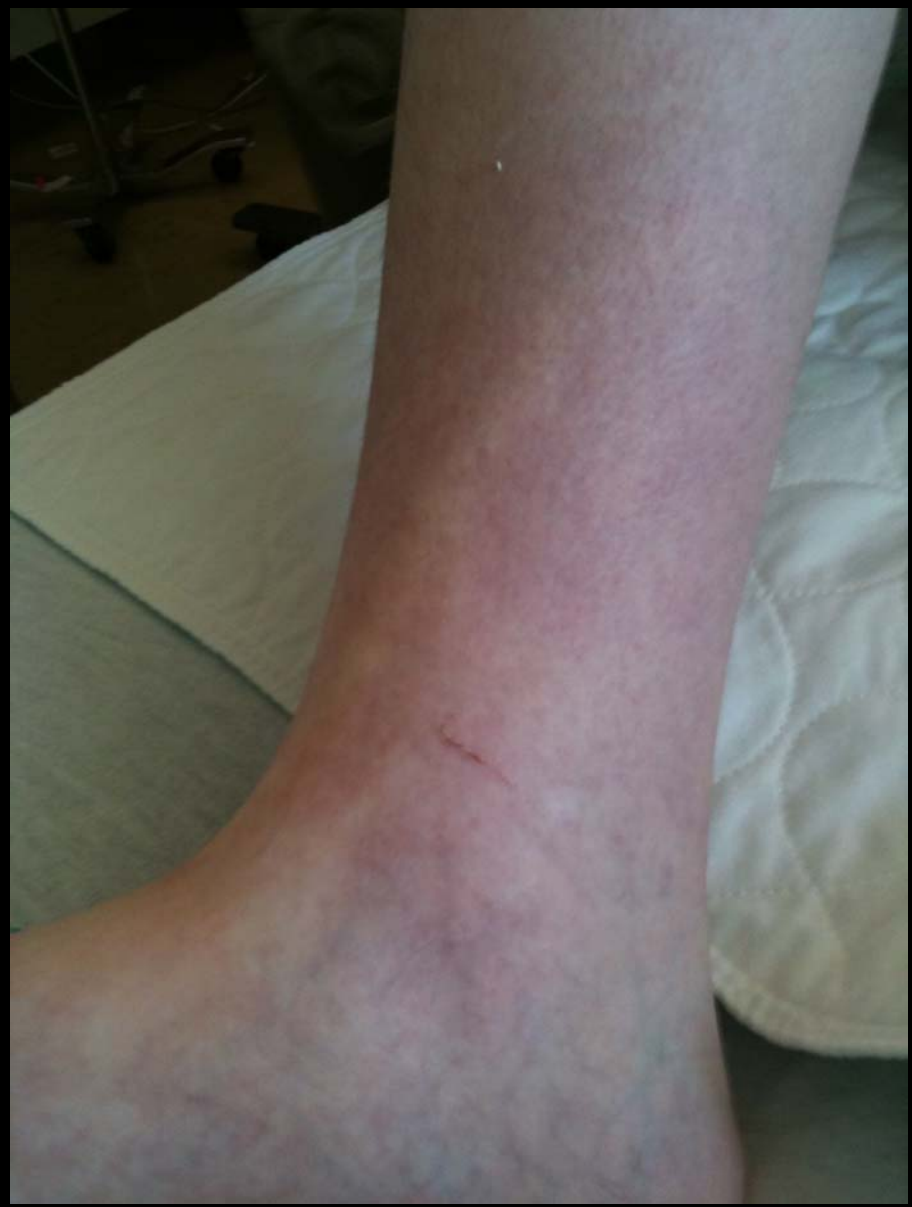
- CHLA and Dr. Boles have filed a PCT (international patent application) on molecular diagnostics of the mtDNA polymorphisms that will be presented.

Case Report - Zachary

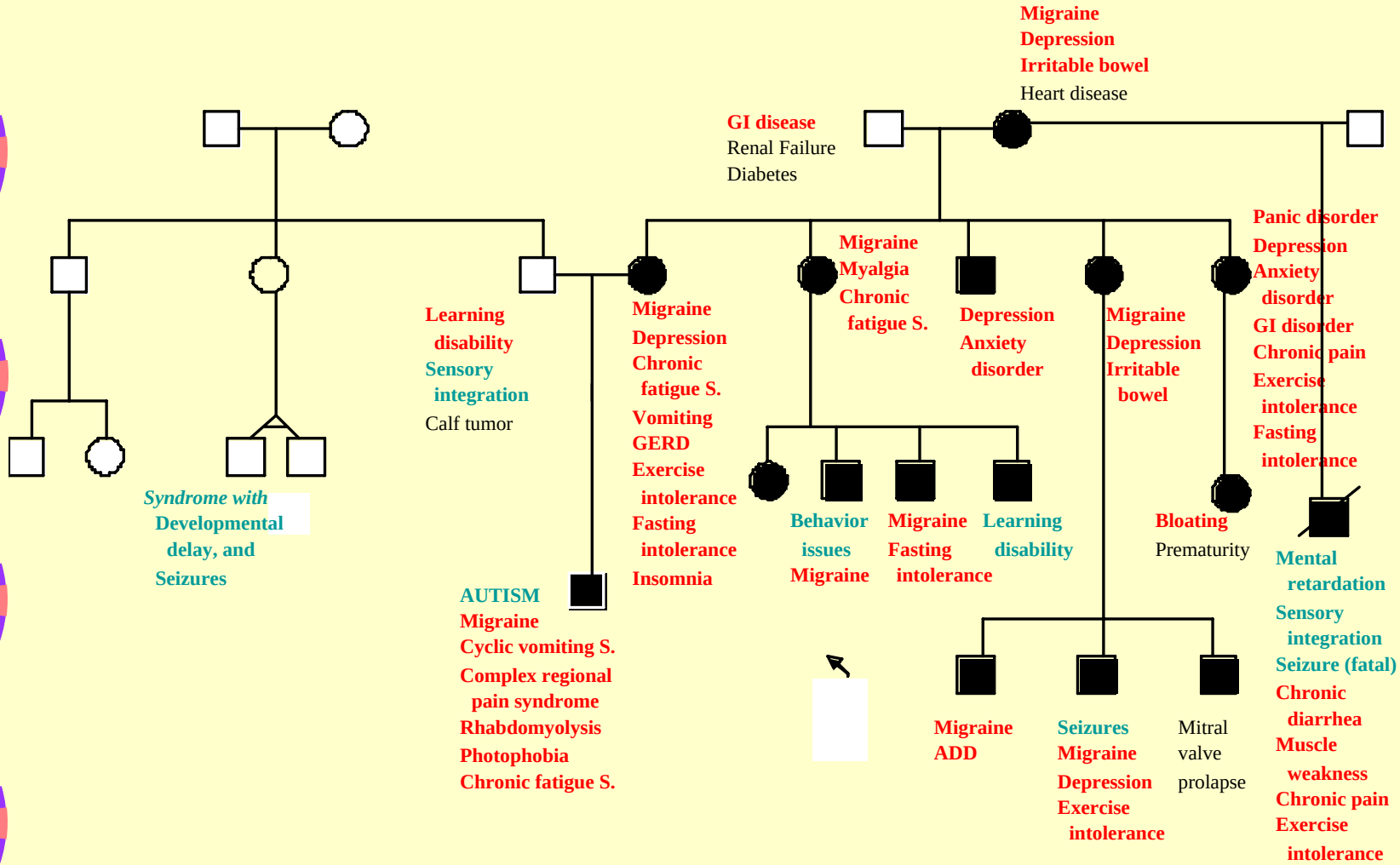
Zachary – Clinical

- Autism – early infancy, dx at age 2 years
  - Lost early language skills acquired at 18 mos.
- Diagnosed with “autism” at age 2 yrs
- Cyclic vomiting syndrome – age 6 yrs
  - episodes of nausea, vomiting and lethargy lasting from a few days to a week or more
- Rhabdomyolysis – age 11 years
  - Hospitalized twice, max CK = 100K; precipitated by anesthesia (dental) and influenza B
- Complex regional pain syndrome – age 12 yrs
  - episodes in which right foot becomes cold, purple, tender, allodynia, unable to bear wt, wheelchair bound for months
- Other chronic intermittent symptoms
  - headache, muscle pain, constipation, photophobia, ptosis, tics, hours-long episodes of hiccups.
- Tanner I at age 15 years
- Severe exercise intolerance
- Nijmegen criteria: 10 pts c/w definite mitochondrial disorder

Complex Regional Pain Syndrome-I: allodynia, painful, edematous, cold, purple, unable to stand or walk



Zachary, Pedigree



Zachary - Medications

- Methadone 15 mg q four to six hours
- MiraLax one capful twice a day
- Amitriptyline 75 mg per day
- Propranolol 10 mg BID
- Co-enzyme Q10 gel capsules 200 mg TID
- L-carnitor 3 tablets (330 mg each) BID
- B100 once per day
- Vitamin C 500 mg once per day

On mito-cocktail:

no vomiting episodes, or rhabdomyolysis
able to walk, including moderate distances
improved expressive speech
fewer temper tantrums

Somatic Complaints:

pain, cramping, itching, tingling, urgency, fatigue
It's What's Bothering You

- Are the leading cause of outpatient medical visits.
- Are the leading cause why patients with common mental disorders such as depression initially present to primary care.
- Are medically unexplained in at least one-third of patients.

"Functional" Disorders List:

- Anxiety disorder
- Autistic spectrum disorders
- Chronic fatigue syndrome
- Complex regional pain syndrome
- Cyclic vomiting syndrome
- Major depressive disorder
- Fibromyalgia
- Functional abdominal pain
- Ketotic hypoglycemia
- Interstitial cystitis
- Irritable bowel syndrome
- Migraine
- Post-traumatic stress disorder
- Restless legs syndrome
- Tinnitus

A population prevalence of 10-15% has been reported.

High Levels of Co-morbidity Among the Functional Disorders

- Migraine and Depression
  - Migraine: 5.8–fold higher risk for depression
  - Depression: 3.4–fold higher risk for migraine
- Migraine and Restless Leg Syndrome
  - 82% of restless legs syndrome patients have migraine.
- Migraine and Chronic Fatigue Syndrome
  - 67% of chronic migraine patients fulfilled the 1994 CDC criteria for CFS.
- Chronic Fatigue Syndrome and Fibromyalgia
  - Most patients have chronic pain, and several sources consider CFS and fibromyalgia to be the same condition.
- Irritable Bowel Syndrome and Fibromyalgia
  - 30% to 70% of fibromyalagia patients have IBS.

Functional Disorders

- Genetic components
- High degree of co-morbidity in individuals
- High degree of co-morbidity in families
- Respond to the same medications

Functional Disorders

- Genetic components
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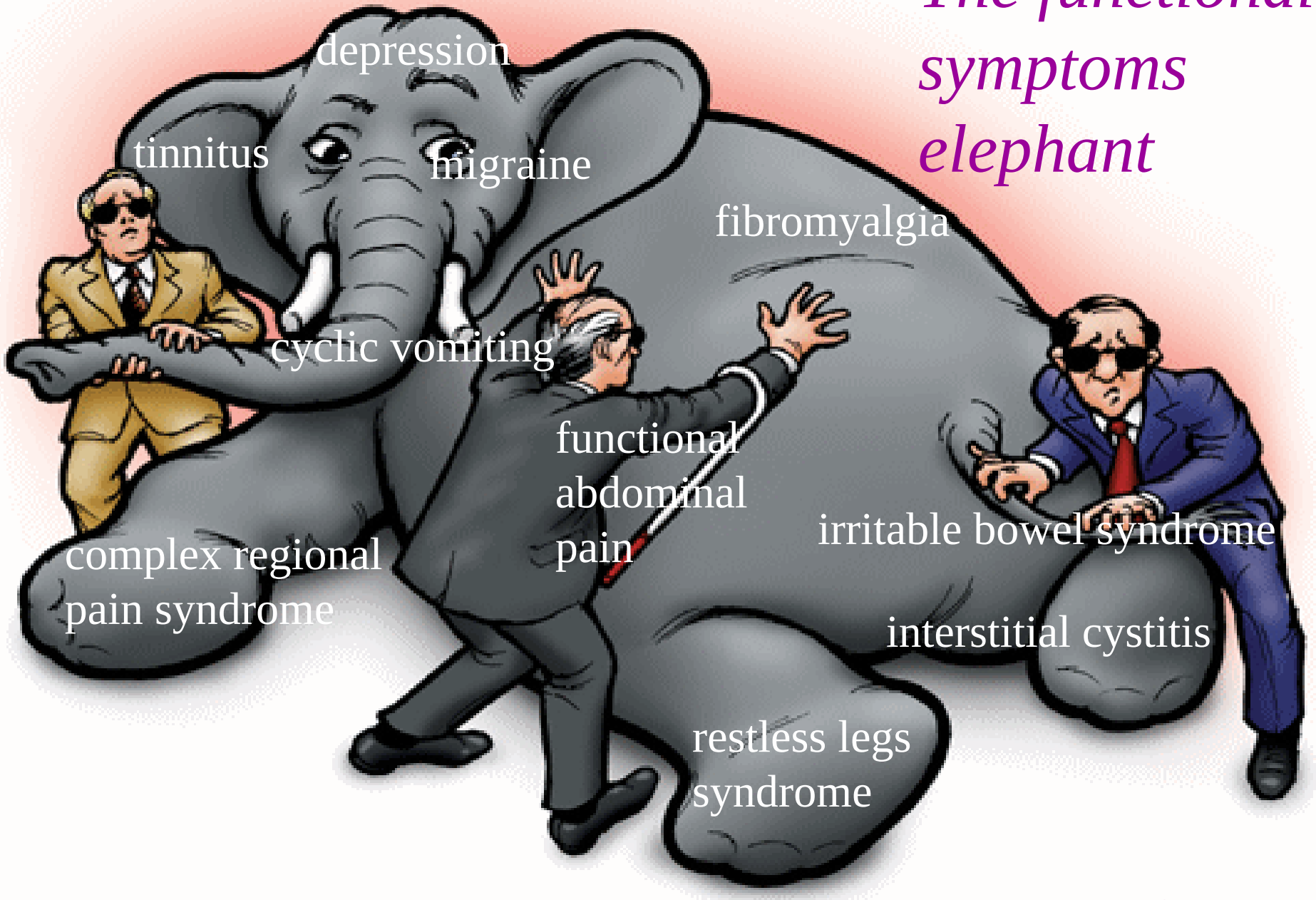
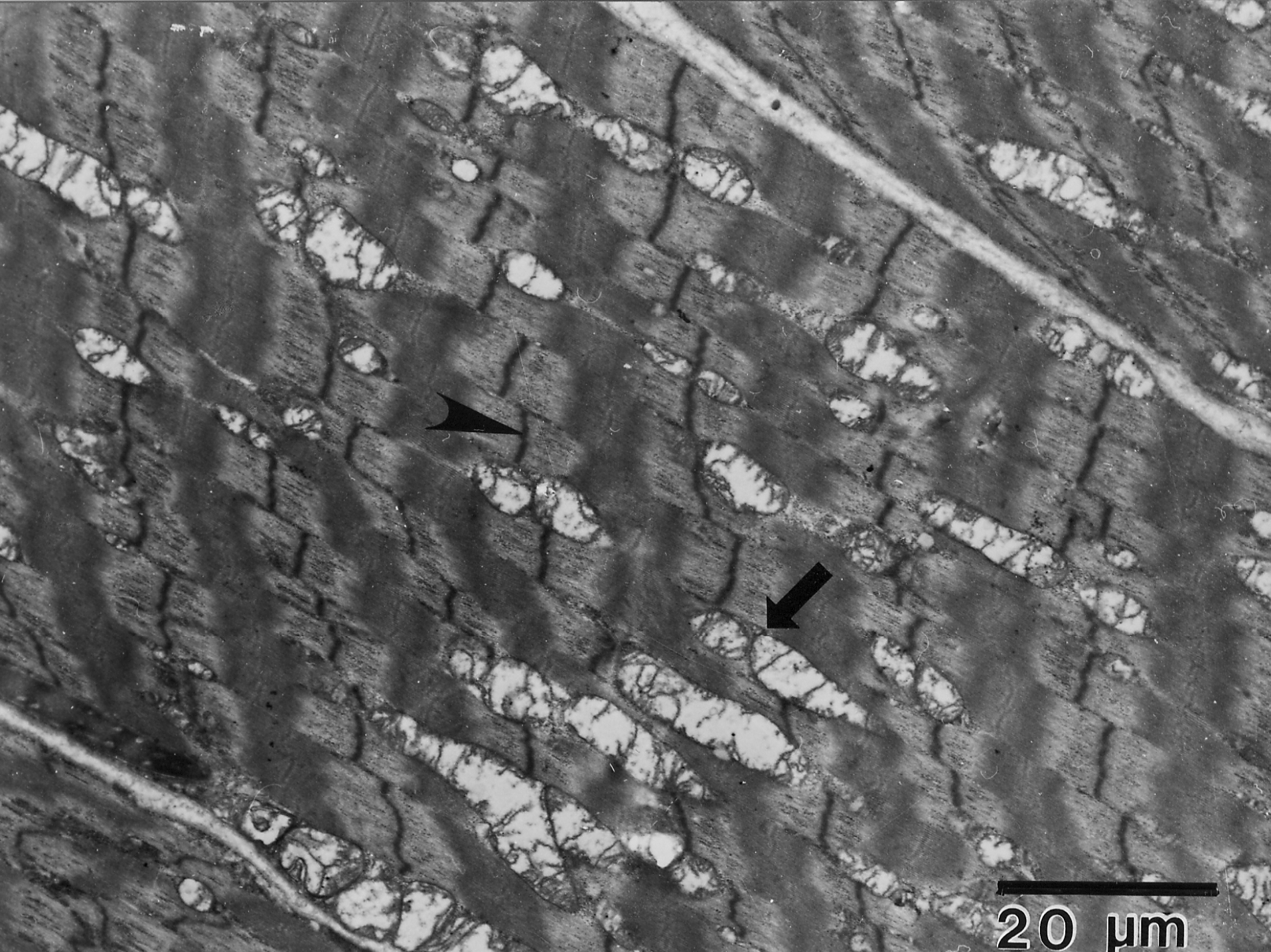
- Respond to the same medications

Could some of the genetic component for these conditions be shared?

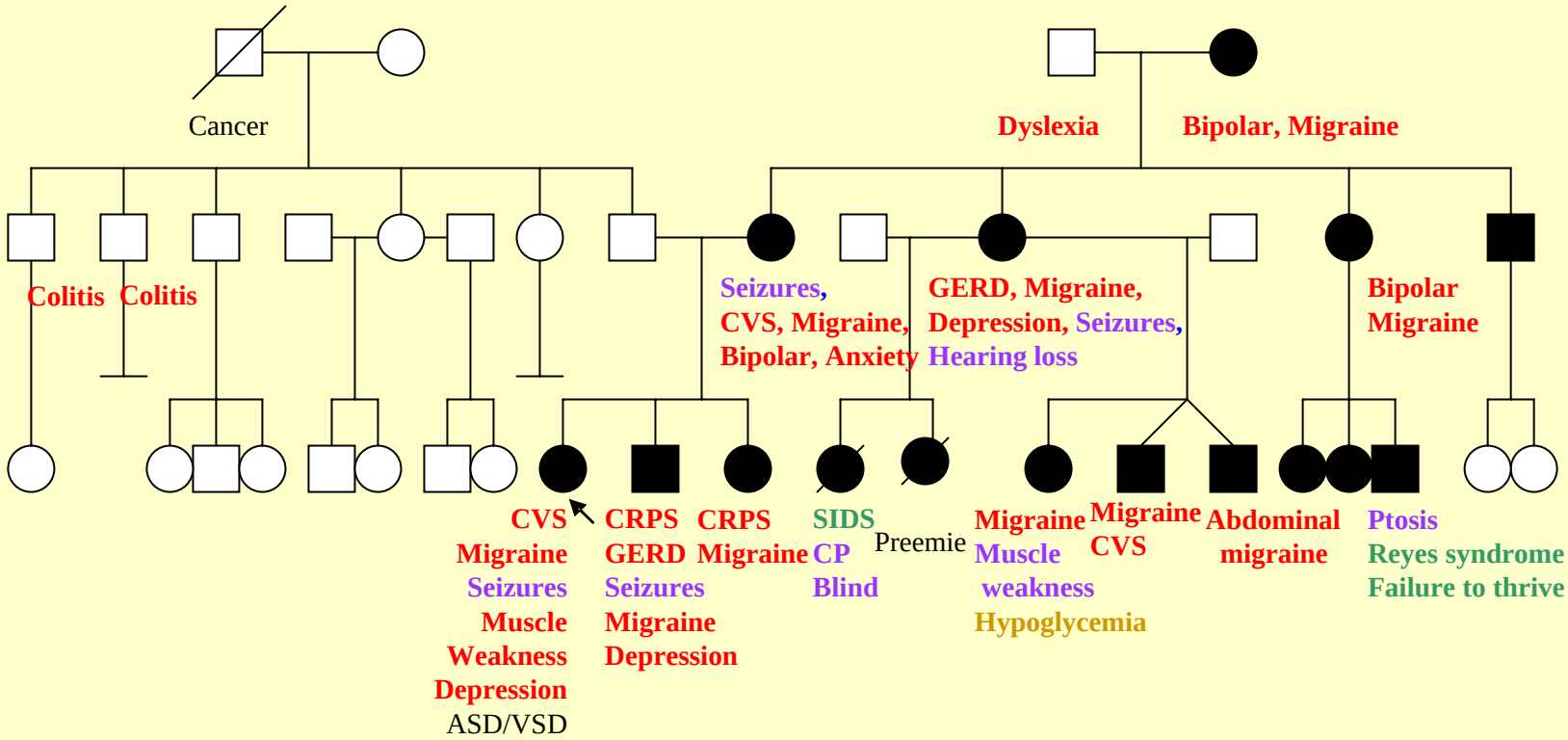
The functional symptoms elephant



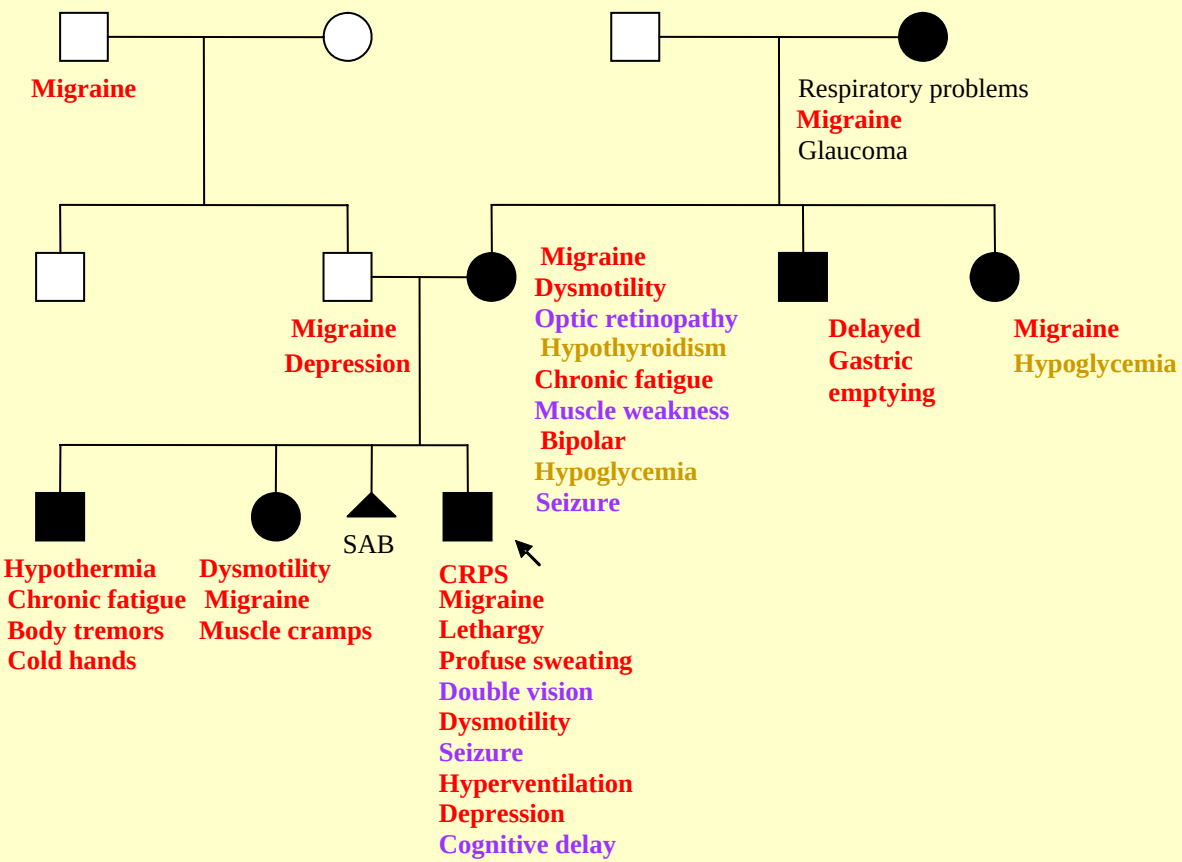
The elephant is lying down due to chronic fatigue


20 µm

Maternal Inheritance of Functional Disorders



Maternal Inheritance of Functional Disorders



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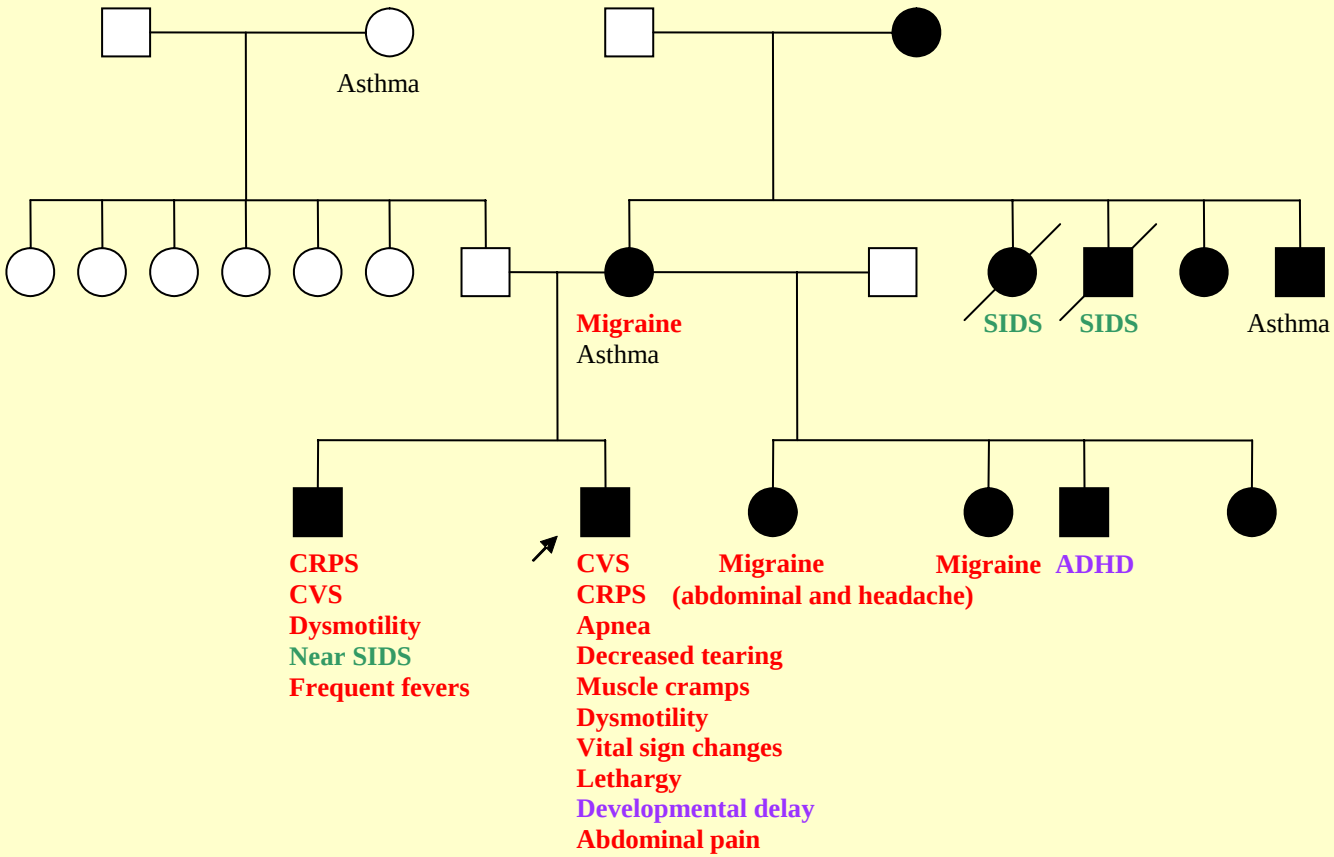

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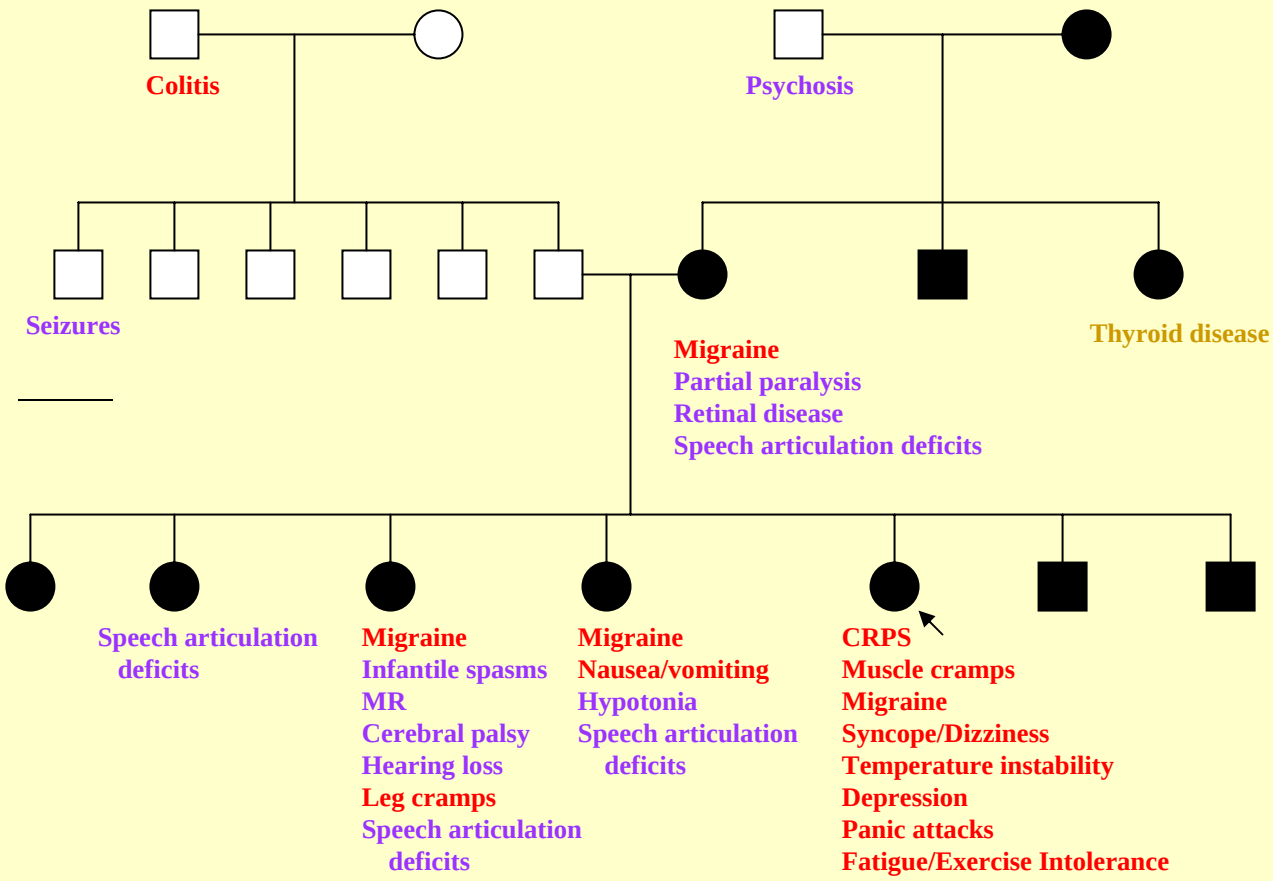

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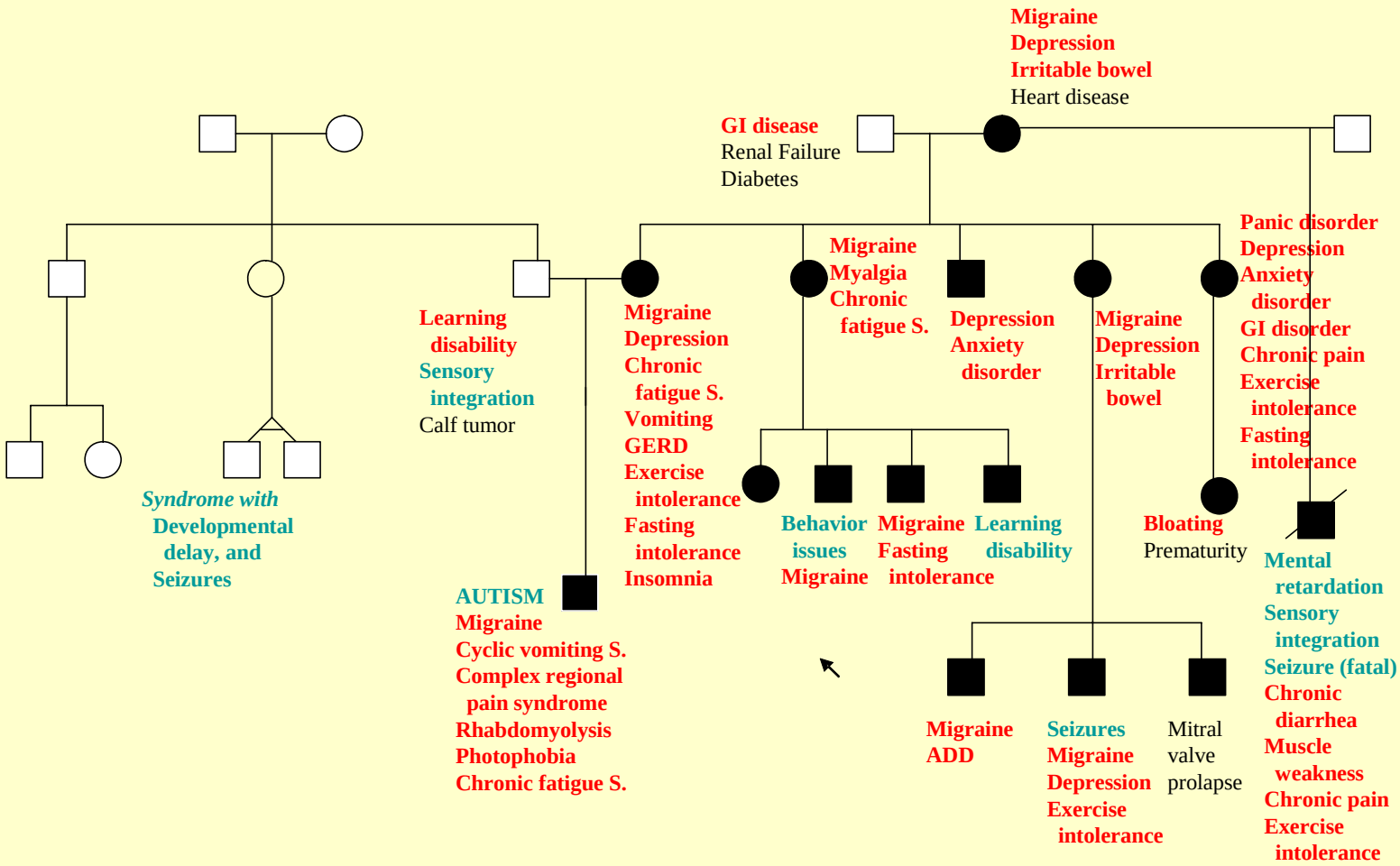
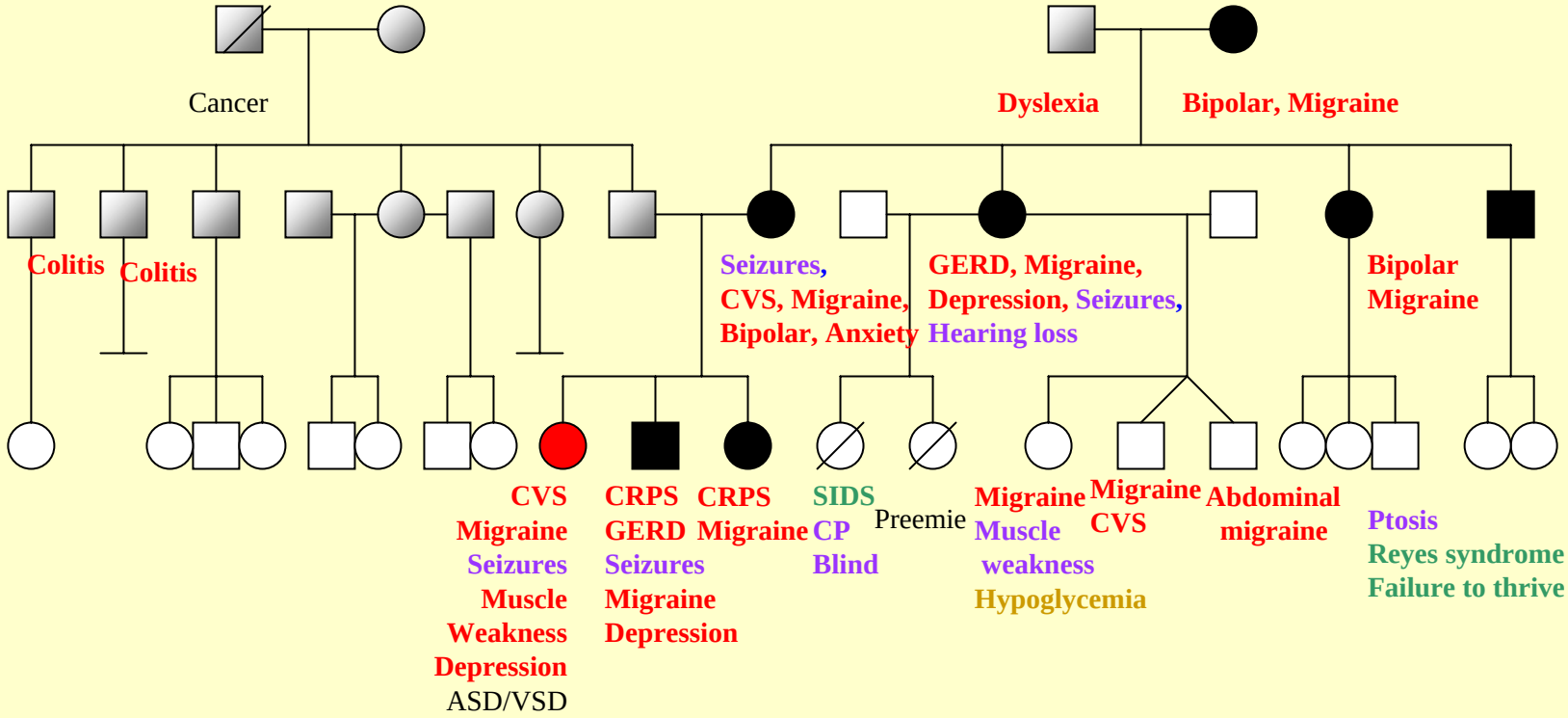


Quantitative Pedigree Analysis for Maternal Inheritance

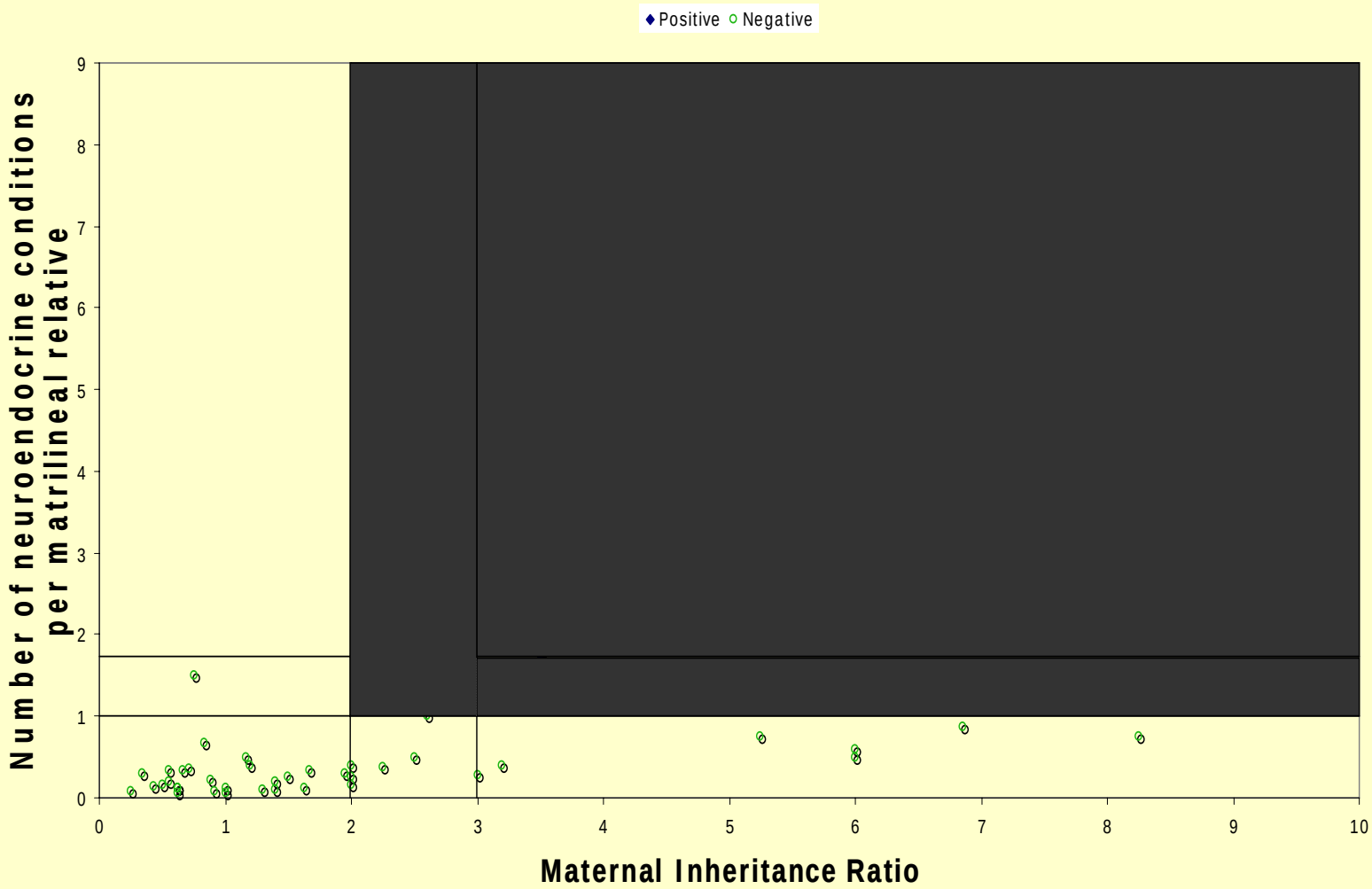


Matrilineage: 21 neurological/endocrine conditions in 7 first and second degree relatives = <u>3 conditions/relative</u>

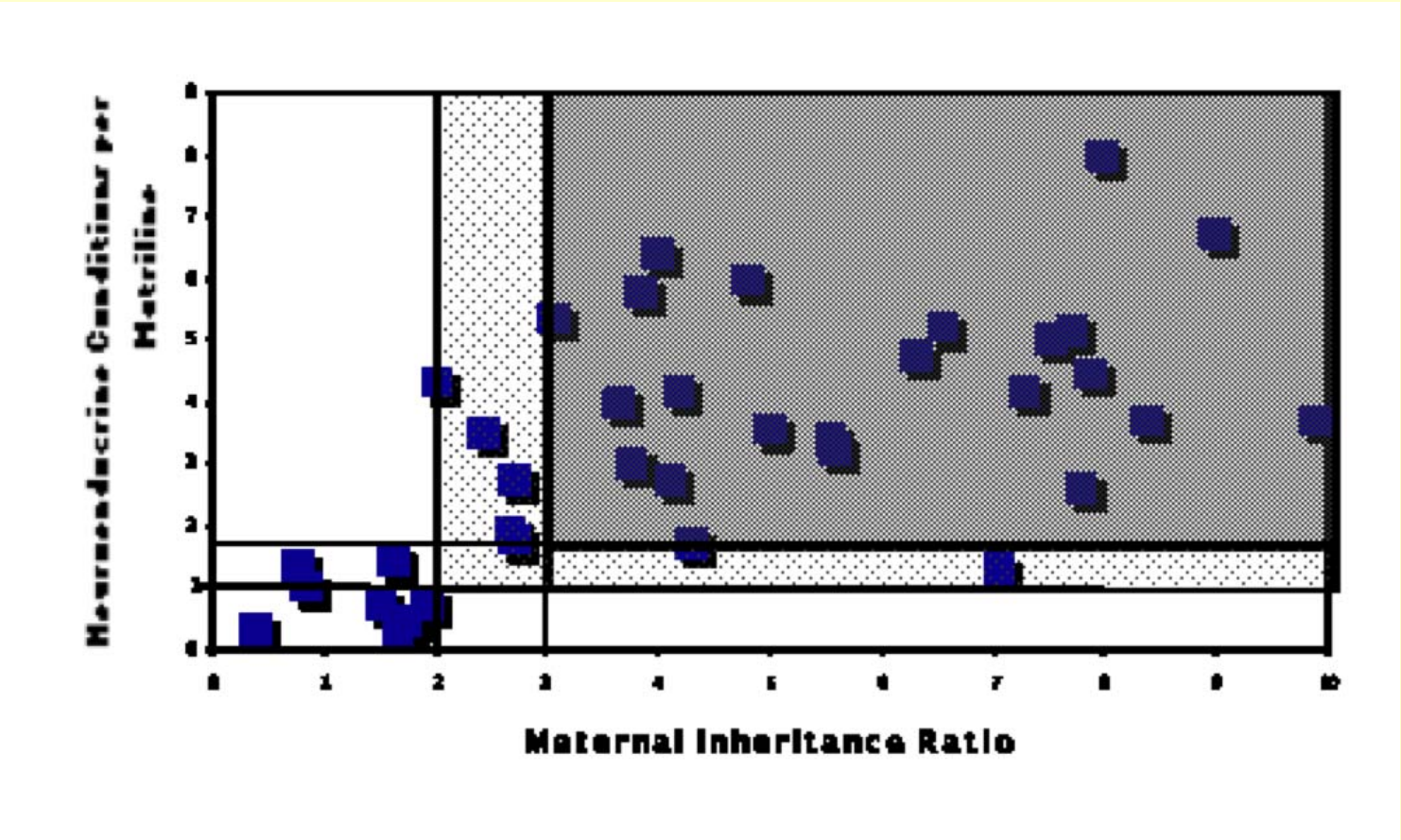
Control: 3 neurological/endocrine conditions in 9 first and second degree relatives = <u>0.33 conditions/relative</u>

3/0.33 = a **<u>Maternal Inheritance Ratio of 9.0</u>**

Quantitative Pedigree Analysis
Positive and Negative Controls



Quantitative Pedigree Analysis
Cyclic Vomiting Syndrome



Functional Disease

Could maternally inherited mtDNA sequences be the shared genetic component?Lee et al., Submitted

	CFS	Migraine	IBS	Depression	CVS	CRPS-I
Mitochondrial Group	19/25 76%	18/25 72%	13/25 52%	12/25 48%	9/25 36%	15/25 60%
Control Group	2/102 2%	15/103 15%	9/101 9%	13/101 13%	2/103 2%	7/101 7%
Odds Ratio (95% C.I.)	120 23-640	14 5-40	11 4-30	6.1 2.3-16	23 5-120	19 6-36

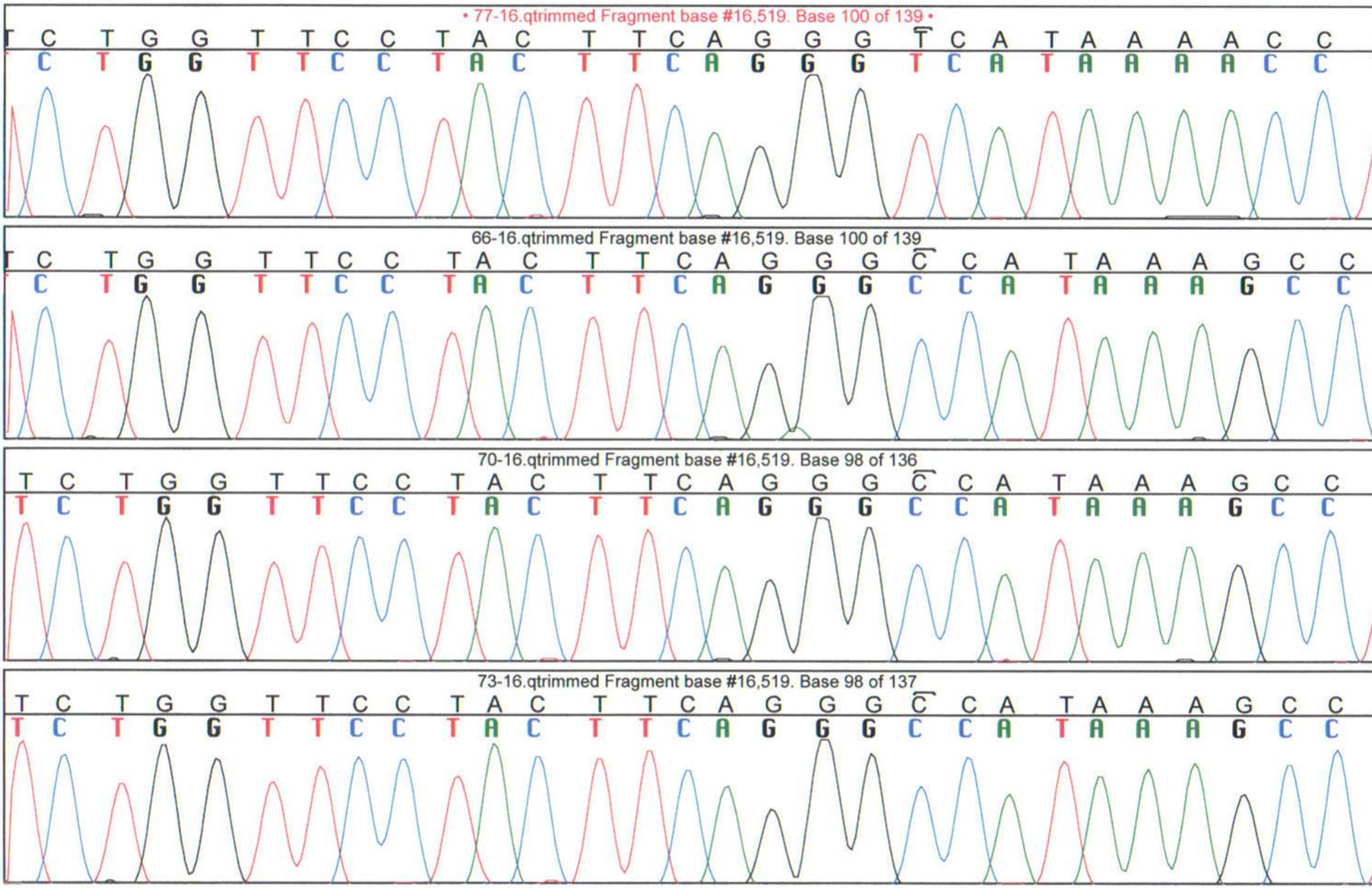
Mitochondrial Group: 18 mothers and 7 maternal aunts of children with maternally inherited mitochondrial disorders.

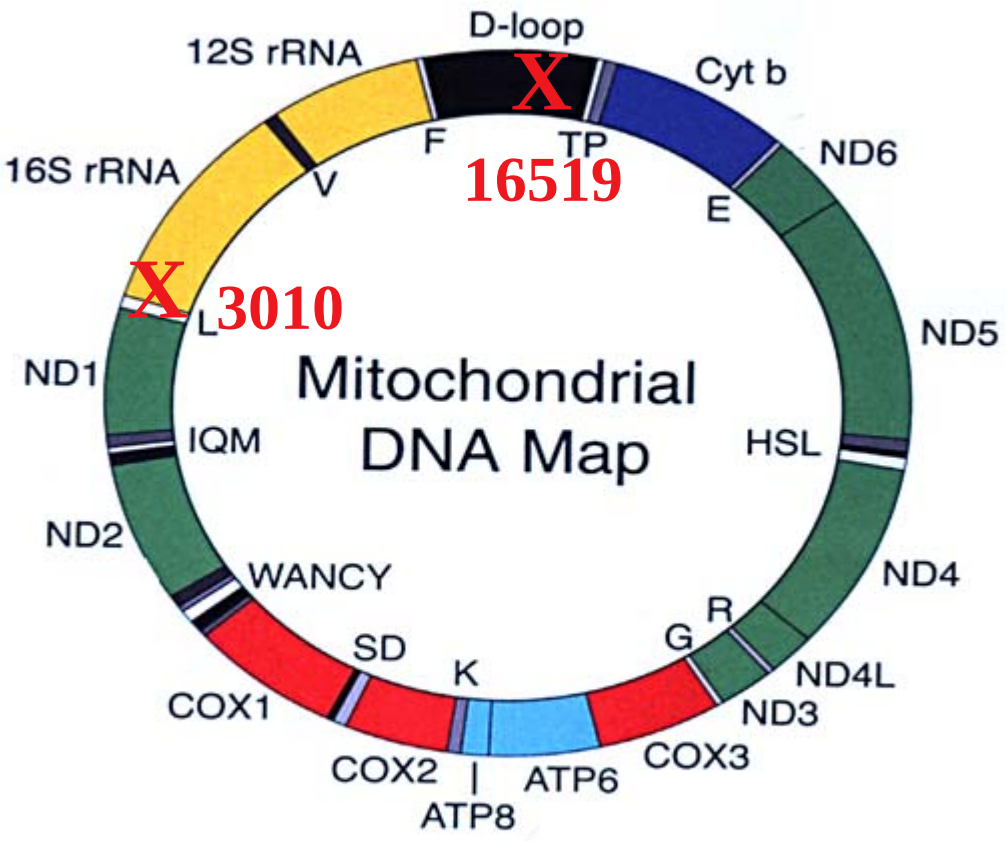
Control Group: 5 paternal aunts and 5 aunts-in-law of the same children above, 18 mothers of children with autosomal recessive metabolic disorders, and 75 mothers of high school students.

Cyclic Vomiting Syndrome (CVS) Definition:

- 1. Recurrent, identical episodes of nausea, vomiting and lethargy
- 2. Absence of these symptoms between episodes
- 3. Lack of a causal diagnosis following a work-up (except migraine)

Chromatograms from 16 3.21.07
Sequencher(tm) "3.21.07.SPF"





Functional Disorder-Associated mtDNA Polymorphisms

16519 C>T
mtDNA control region

3010 G>A
16S-ribosomal RNA gene

Cyclic Vomiting, Migraine & Chronic Fatigue

Prevalence of Two mtDNA Common Polymorphisms in Haplogroup H Individuals With Functional Disorders

	Cyclic Vomit Syndr.	Odds Ratio (95% C.I.)	Migraine w/o Aura	Odds Ratio (95% C.I.)	Chronic Fatigue Syndr.	Odds Ratio (95% C.I.)	Ctrl
16519T	21/30 70%	6.2 (2.7-14)	58/112 52%	3.6 (2.2-5.9)	22/58 38%	2.0 (1.1-3.7)	63/231 27%
3010A	9/30 30%	N/A	37/112 33%	N/A	Pending	Pending	143/444 32%
3010A among pts with 16519T	6/24 29%	**17** (2-156)	15/58 26%	**15** (1.9-117)	Pending	Pending	1/63 1.6%

Chronic Fatigue Syndrome

The 3010A mtDNA polymorphism predicts a several-fold increase in somatic symptoms.

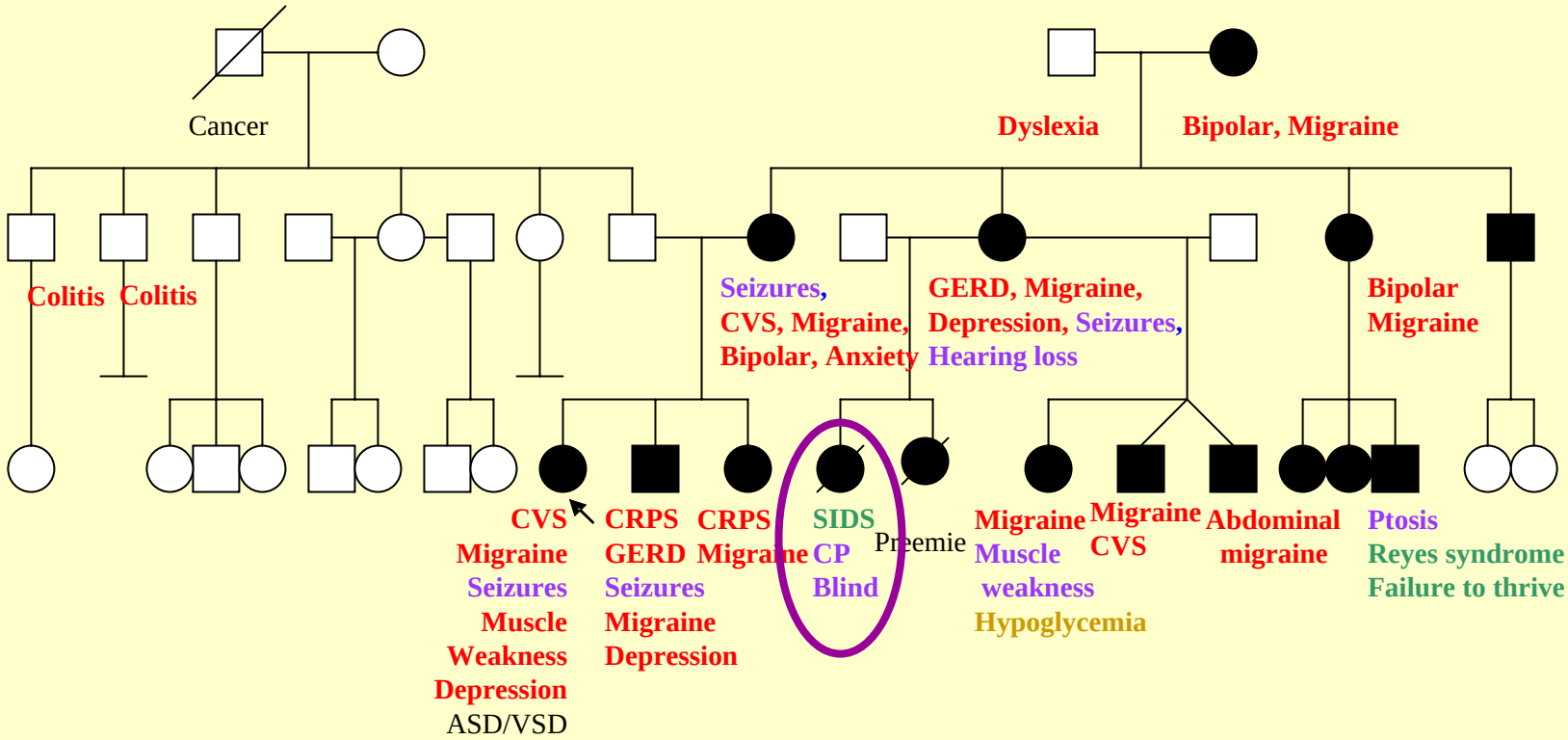
	Headache	Fainting or Dizziness	Muscle Pain	Muscle Weakness	Sleep Problems	Numbness or Tingling
3010A	14/21 67%	11/21 52%	19/21 90%	17/21 81%	19/22 86%	12/21 57%
3010G	8/25 32%	5/28 18%	16/28 57%	17/28 61%	13/27 48%	6/24 25%
Chi Square	P = 0.04	P = 0.02	P = 0.03	*P = 0.22*	P = 0.01	*P = 0.06*
Odds Ratio (95% C.I.)	**4.0** (1.1-18)	**4.7** (1.2-23)	**5.9** (1.2-54)	NA	**6.0** (1.4-38)	**3.7** (0.95-18)
T-test	P = 0.004	*P = 0.06*	P = 0.005	P = 0.03	P = 0.046	P = 0.03

Functional GI Disorders

700 adult patients evaluated at Mayo, in collaboration with Dr. Camilleri

- 7028C (defines haplogroup H)
  - IBS-C: OR 0.6 (0.4-0.9), P = 0.006
  - IBS-alt: P = 0.035
  - Satiation: higher max tol volume, P = 0.037
  - Gas sensation: lower, P = 0.031, 0.032
- 3010A (defines sub-haplogroup H1)
  - Chronic abd pain: OR 3.2 (1.2-8.0), P = 0.02
  - *Any FGID: OR 1.6 (1.0-2.8), P = 0.06*
  - *IBS-D: OR 1.7 (0.9-3.2), P = 0.09*
  - Gastric emptying: faster P = 0.043

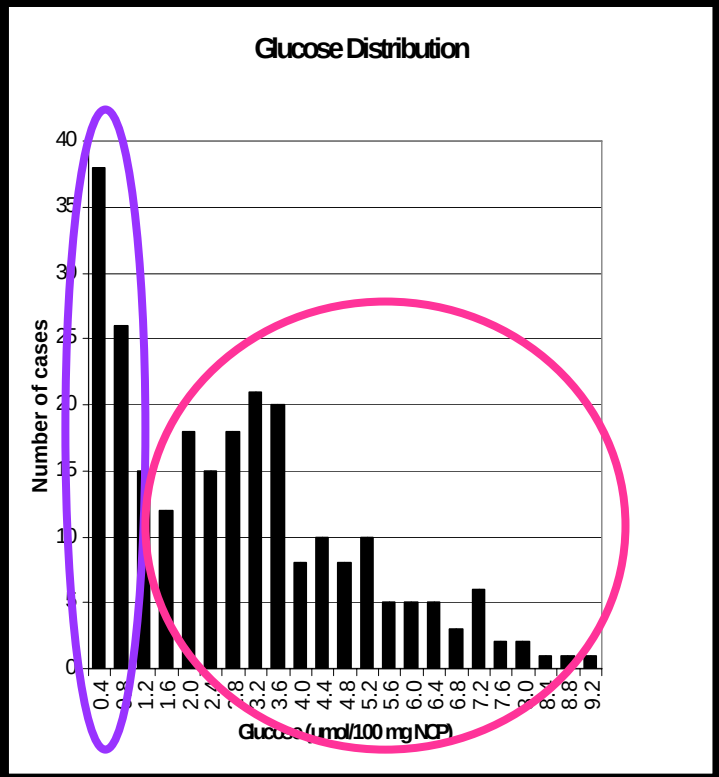
Maternal Inheritance of Functional Disorders-1



Hypoglycemia is common among matrilineal relatives in these families. Could nocturnal hypoglycemia in infants be the mechanism of SIDS?

Sudden Infant Death Syndrome

Glucose measurement in autopsied liver by GC/MS suggests heterogeneity, in which 20% of SIDS is associated with substrate depletion.



HAPLOTYPES

Glucose-depleted versus glucose-normal

P = 0.002; odds ratio (GT v. AC) = 40

95% confidence interval = 2.1 – 738

Glucose depleted v. controls: P = 0.06

Glucose normal v. controls: P = 0.0001

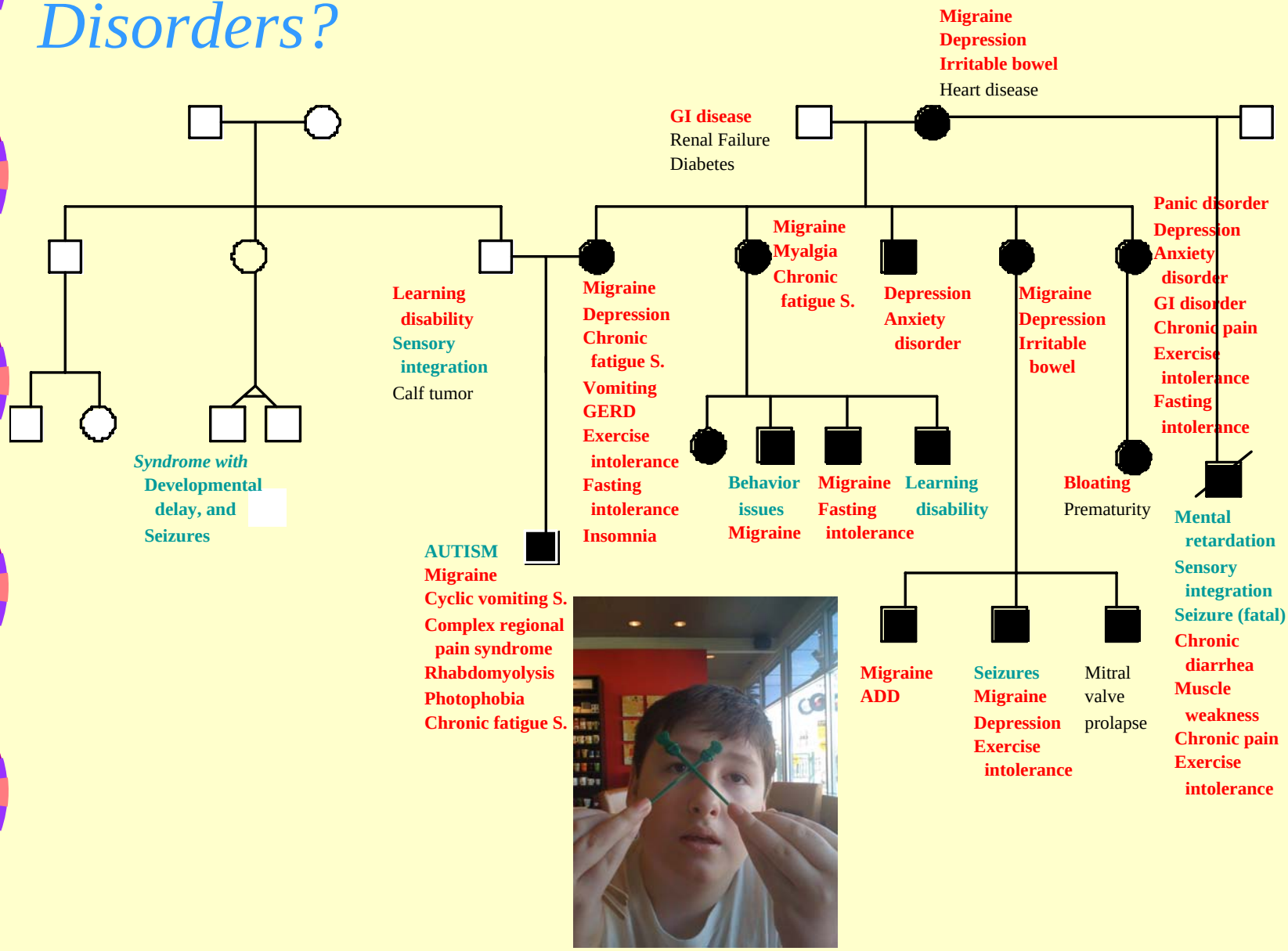
3010A

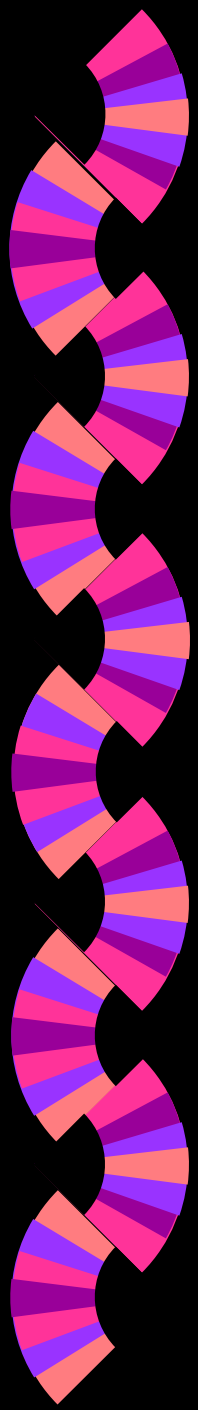
Glucose-normal versus controls:

P = 0.007

odds ratio 3.5, 95% C.I. 1.3-9.1

Is Autism Related To These Other Functional Disorders?





DSM-IV-TR Diagnosis	16519T	3010A
Autistic Disorder (AD) "Infantile Autism"	18/81 (22%)	27/81 (33%)
Pervasive Developmental Disorder NOS (PDD-NOS) "Atypical Autism"	24/49 (49%)	6/49 (12%)
All Other Autistic Disorders	9/30 (30%)	10/30 (33%)
Non PDD-NOS ASD Cases (AD + Others)	27/111 (24%) *P* = 0.002 O.R. 3.0 (1.5-6.0)	37/111 (33%) *P* = 0.006 O.R. 0.30 (0.1-0.8)
Population Controls From USA, UK, Italy and Finland (Prevalence rates are the same in these four nations)	63/231 (27%) *P* = 0.003 O.R. 2.5 (1.4-4.8)	143/444 (32%) *P* = 0.04 O.R. 0.31 (0.1-0.8)

Do Maternally Inherited mtDNA polymorphisms constitute a "Unified Theory" of Functional Disease?

- 16519T is statistically associated with:
  - Migraine headache *(odds ratio 4)*
  - Cyclic vomiting syndrome *(odds ratio 6)*
  - Chronic fatigue syndrome *(odds ratio 2)*
  - Complex regional pain syndrome *(odds ratio 2)*
  - Atypical autism *(odds ratio 2.5)*
  - SIDS subset with low hepatic glucose
- 3010A is statistically associated with:
  - Migraine headache in patients with 16519T *(odds ratio 15)*
  - Cyclic vomiting syndrome in patients with 16519T *(odds ratio 17)*
  - Constipation-type irritable bowel syndrome
  - Non-specific abdominal pain *(odds ratio 3)*
  - Functional co-morbidity in chronic fatigue syndrome *(OR 4-6)*
  - SIDS (common glucose-normal type) *(odds ratio 3)*
- 3010G is statistically associated with:
  - Atypical autism *(odds ratio 3)*
  - GI co-morbidity in major depressive disorder
  - Total functional symptomatology in high school students

Potential Applications:
Clinical Diagnostics: Urine Organic Acids

- Must be quantitative and collected during physiological stress:
  - At the beginning of an “episode”
  - With intercurrent illness causing fever or vomiting
- Elevations in:
  - Ketones
  - Krebs cycle intermediates (fumarate, malate, aconitate)
  - Dicarboxylic acids (including ethylmalonate and glutarate derivatives)
  - Lactate (occasional)

Potential Applications:
Therapy: General Principles

- Combine mitochondrial-directed treatment together with symptom-directed treatment.
- Mitochondrial-directed treatment is to:
  - Decrease energy demand
  - Increase energy supply

Potential Applications:
Therapy: Agents

- Fasting avoidance
  - "3+3 diet"
  - Special caution during viral illnesses, may need IVF
  - D10 with lytes at 1.5 times maintenance
- Exercise
- Co-enzyme Q10 (10 mg/kg/day; adult dose 300 mg/day; divided BID)
- L-carnitine (100 mg/kg/day; adult dose 2-3 grams/day; divided BID)
- Riboflavin 100-400 mg/day (or "B100")
- Amitriptyline (0.5 to 1 mg/kg/day; all qhs)

Co-enzyme Q10 Versus Amitriptyline in Cyclic Vomiting Syndrome Prophylaxis

	Amitriptyline	Co-enzyme Q10	P Odds Ratio
Episode Improvement	127/177 72%	17/25 68%	NS
Side Effects Reported	102/202 50%	0/28 0%	0.0000005
Stopped Therapy Due to Side Effects	42/198 21%	0/28 0%	0.007
Subjects' Statement Risks V. Benefits	63/134 47%	17/22 77%	0.009 3.6 (1.2-10)

Cyclic Vomiting Syndrome (CVS) Practice Review - Demographics

- Gender

Male	13	31%
Female	29	69%

- Race/Ethnicity

Caucasian	28	67%
Hispanic	11	26%
African-American	2	5%
Native-American	1	2%

- Inheritance Pattern

Probable maternal	21	60%
Indeterminate	4	11%
Probable non-maternal	10	29%

Cyclic Vomiting Syndrome (CVS) Practice Review - Protocol

- Dietary: “3+3 diet” and the avoidance of fasting.
- Co-Q: Ubiquinone in liquid or gel capsule form (from a variety of brands) at a starting dose of 10 mg/kg/day, or 200 mg, divided twice a day, whichever is smaller.
- L-carnitine: Starting dose of 100 mg/kg/day divided BID, or 2 grams twice a day, whichever is smaller. A small minority of families, all with untreated blood levels >30 μM, were not treated.
- Amitriptyline: Subjects < 5 years with continued vomiting episodes despite the above therapies were treated at a starting dose of 0.5 mg/kg/day given at night.
- Cyproheptadine: Subjects < age 5 years and over with continued vomiting episodes despite the above therapies were treated at a starting dose of 0.25 mg/kg/day divided twice a day.
- Topiramate: Two participants who were refractory to all of the above measures were started on 25 mg of topiramate twice a day.

Cyclic Vomiting Syndrome (CVS) Practice Review - Protocol

- Dosages were increased every one to a few months until one of the following occurred:
  - Resolution of vomiting episodes
  - Intolerable side effects that failed a reduction in dosage followed by a slow dosage increase
  - The following maximum was reached (empirically-derived):
    - Co-Q: blood level > 3.0 mg/L
    - L-carnitine: free carnitine blood level > 40 μM
    - Amitriptyline*: amitriptyline + nortriptyline blood level > 150 ng/ml
    - Cyproheptadine: Dosage of 0.5 mg/kg/day
    - Topiramate: Dosage of 200 mg BID (adolescents and adults)

*Blood levels were not routinely monitored for dosages < 1 mg/kg/day as they were uniformly low in the authors' prior experience.

Cyclic Vomiting Syndrome (CVS) Practice Review - Treatment

Clinical Success	27/30	90%
Episodes essentially resolved on therapy	23	
Episodes greatly improved (>75% improvement)	2	
Episodes improved (50-75%), then lost-to-follow-up	2	
Clinical Failure	3/30	10%
Episodes unchanged on therapy	1	
Episodes resolved, but could not tolerate tx, then returned	1	
Episodes continue, not able to tolerate amitriptyline	1	
Not Judged	12/42	29%
Lost to follow-up after 1 or 2 visits, results unknown	9	
Episodes self-resolved	2	
Episodes improved, still not therapeutic level of amitript.	1	
Side Effects	8/30	27%
Amitriptyline	6	
Cyproheptadine	1	
Co-enzyme Q10	1	
Unclear (non-specific on high doses of multiple agents)	2	

Conclusions - 1

- 1. There is increasing evidence of a shared genetic predisposition towards multiple (possibly most) functional disorders.
- 2. Some families have mtDNA sequences that confer a several-fold increased risk for the development of at least some functional disorders.
- 3. 16519T and 3010A constitute a substantial proportion of the increased risk in these families, at least within haplogroup H.

Conclusions - 2

- 4. The data suggest that energy metabolism is involved in the etiology of at least some cases of migraine, depression, chronic fatigue syndrome, CRPS, IBS, abdominal pain, CVS, SIDS and possibly other functional disorders as well.
- 5. These cases can be screened for in a primary care setting by the application of a few questions, followed by referral for pedigree analysis and “stressed” urine organic acid determination.
- 6. Anecdotal clinical experience and some pilot data suggests that “mito-somatic disorders” are somewhat treatable.

Kathleen Adams
Erin Baldwin
Sawona Biswas
Michael Camilleri
Kingshuk Das
Martin Dichgans
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