GASTROINTESTINAL MANIFESTATIONS OF MITOCHONDRIAL DISORDERS

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Objectives

- Understanding of Mitochondrial diseases associated with gastrointestinal (GI) symptoms
- Understanding of clinical clues and GI symptoms that may lead to correct diagnosis
- Approach to diagnosis including genetic classification
- Discussion of therapeutic options

Mitochondrial disorders

- Inherited heterogeneous group of disorders that can affect multiple organ systems with varying intensity
- Symptoms maybe acute or chronic with intermittent decompensation
- In childhood onset disease, there is often history of developmental delay
- In adulthood the past history maybe unremarkable
- Estimated to be 1 in 5000 children
- Inheritance may be both maternal and autosomal, making genetic counselling challenging

Mattman A,Sirrs, S, Mezei M et al: Mitochondrial disease clinical manifestations: An overview
www.bcmj.org vol. 53 No.4, May 2011 BC medical journal

Mitochondria

- Intracellular organelles with complex roles in intermediary metabolism and cell signaling
- Function include ATP generation via the oxidative phosphorylation system
- Primary mitochondrial dysfunction is recognized to be responsible for a rapidly increasing number of monogenic diseases
- Secondary mitochondrial disturbance has been implicated in a large number of common disease processes i.e. diabetes, cancer Parkinson's disease etc.

Rahman S. Gastrointestinal and hepatic manifestations of mitochondrial disorders.
J Inherit Metab Dis. 2013 Jul;36(4):659-73. doi: 10.1007/s10545-013-9614-2. **Review**.
PMID: 23674168

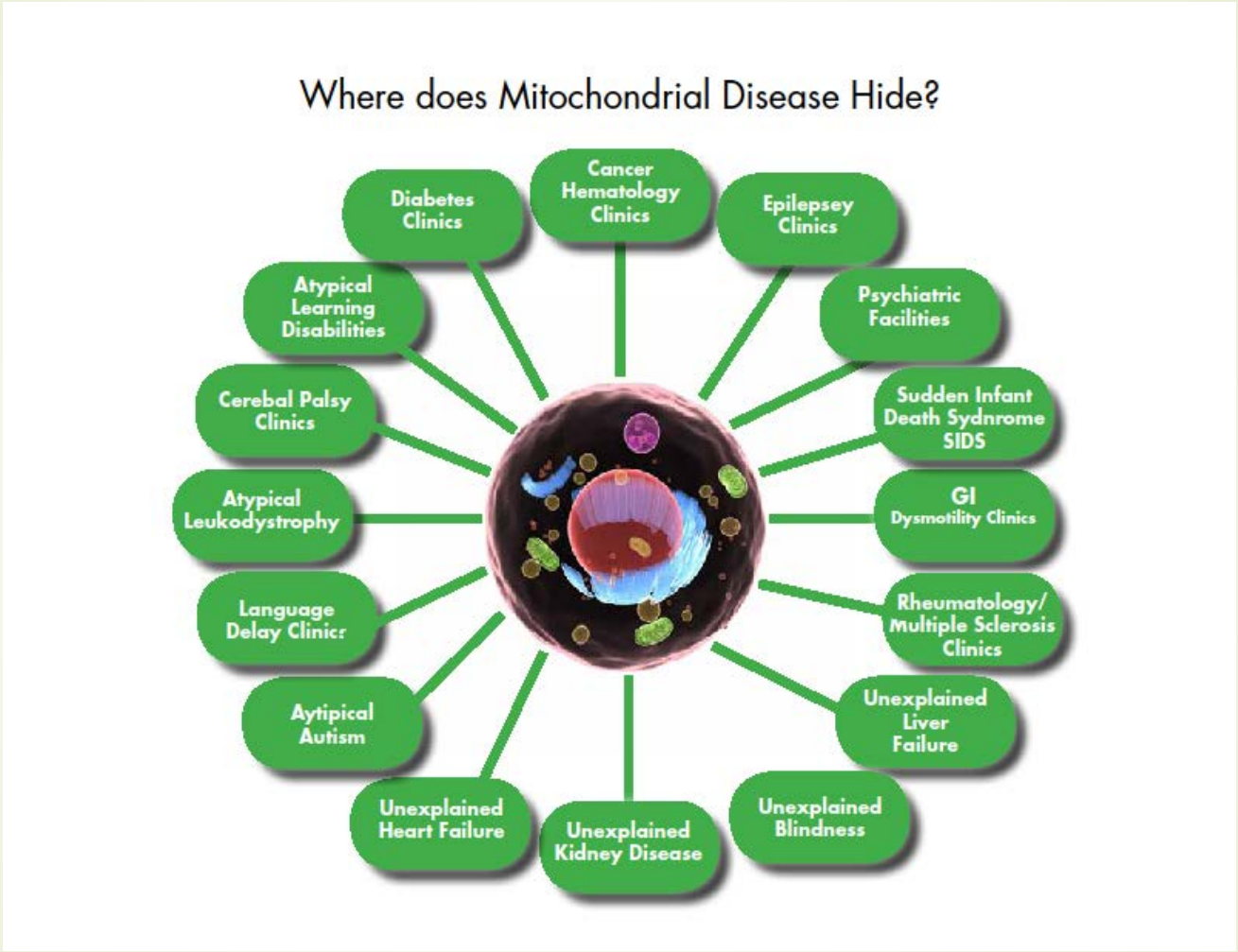
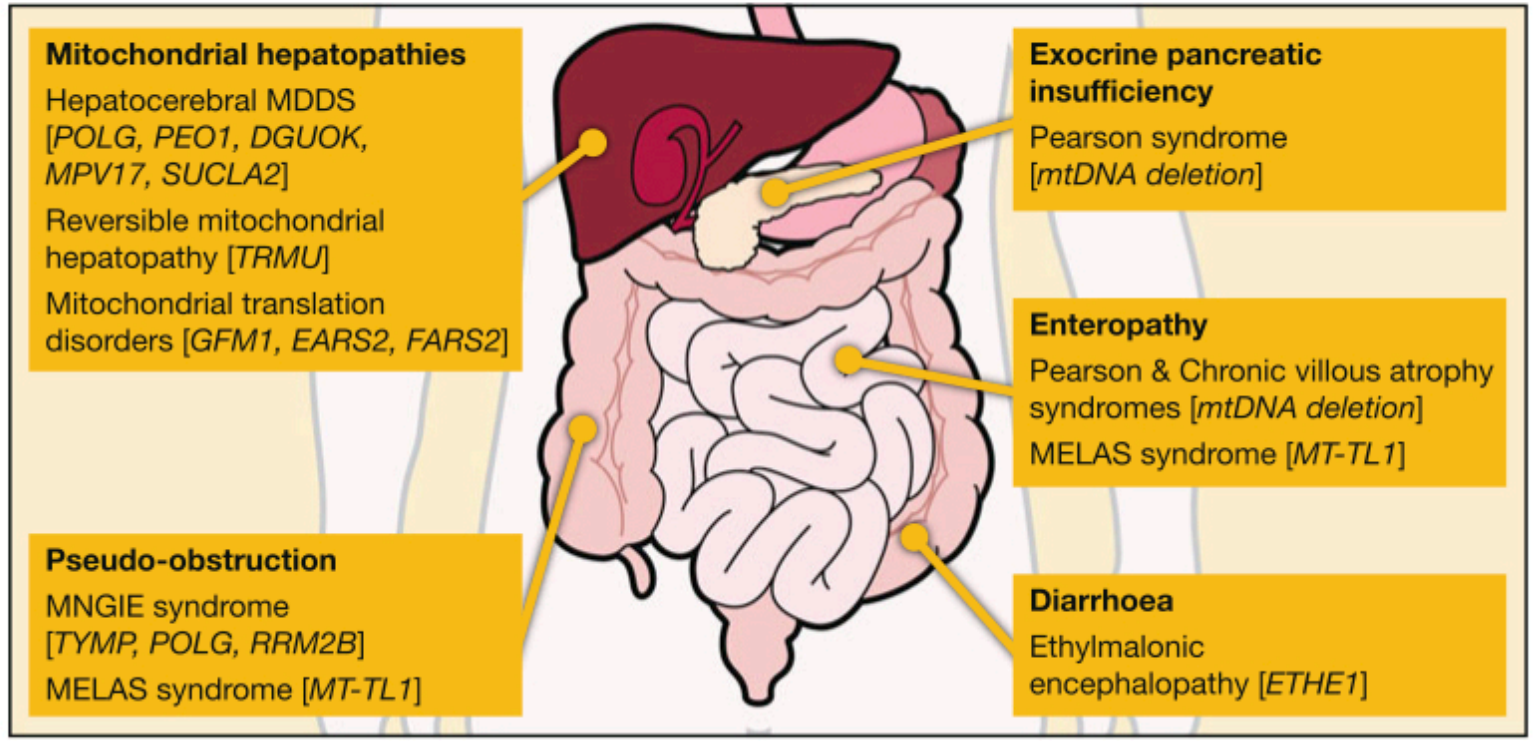

Where does Mitochondrial Disease Hide?
Diabetes Clinics
Cancer Hematology Clinics
Epilepsey Clinics
Atypical Learning Disabilities
Psychiatric Facilities
Cerebal Palsy Clinics
Sudden Infant Death Sydnrome SIDS
Atypical Leukodystrophy
GI Dysmotility Clinics
Language Delay Clinic
Rheumatology/ Multiple Sclerosis Clinics
Aytipical Autism
Unexplained Liver Failure
Unexplained Heart Failure
Unexplained Kidney Disease
Unexplained Blindness

Fig. 1 Mitochondrial syndromes associated with prominent gastrointestinal and hepatic involvement. Names given in square brackets refer to genes known to be mutated in patients with these phenotypes



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Clinical features	Disorder	Gene(s)
Anorexia and stroke-like episode, +/− SNHL	MELAS	*MT-TL1*
Exocrine pancreatic insufficiency and sideroblastic anaemia	Pearson marrow-pancreas syndrome	Large-scale mtDNA rearrangement
Feeding difficulties, vomiting and (stepwise) neurodevelopmental regression	Leigh syndrome	>40 genes (mtDNA and nuclear)
Pseudo-obstruction and peripheral neuropathy (+/− PEO and leukoencephalopathy)	MNGIE	*TYMP*
Diarrhoea, acrocyanosis and petechiae (+ characteristic organic aciduria)	Ethylmalonic encephalopathy	*ETHE1*

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Primary disorders with predominant GI symptoms

1. Mitochondrial neurogastrointestinal encephalopathy (MNGIE)
2. Ethylmalonic encephalopathy (EME)

Mitochondrial neurogastrointestinal encephalopathy (MNGIE)

- Rare autosomal recessive disorder caused by thymidine phosphorylase deficiency.
- More than 100 cases reported to date
- GI symptoms are usually presenting symptoms and 100% develop GI symptoms during course of disease
- Clinical syndrome comprises:
  1. GI dysmotility
  2. Cachexia
  3. Peripheral neuropathy
  4. Ptosis
  5. Ophthalmoparesis
  6. Hearing loss in >50% cases

Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Bain 2011 Nov;134(Pt q11):3326-32. PMID 21933806

MNGIE

- Typically presents between first and third decades (avg. age 18).
- GI symptoms have been reported as early as infancy
- GI dysmotility symptoms:
  1. Dysphagia
  2. Early satiety
  3. Nausea/vomiting
  4. Abdominal cramps
  5. Borborygmi
  6. Intestinal psuedoobstruction
  7. Bloating
  8. Diarrhea

Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. Neurologist. 2004 Jan;10(1):8-17. Review. PMID: 14720311

MNGIE Diagnosis

- May reveal lactic acidemia and raised CSF lactate and protein
- MRI brain reveals florid leukoencephalopathy
- Diagnosis made by elevated thymidine and deoxyuridine in plasma and/or urine
- Also severe reduction in thymidine phosphorylase activity which can be assayed in platelets or white cells

MNGIE Diagnosis

- Muscle biopsy no longer required for diagnosis
- Defect in mtDNA which is believed to be secondary to impaired mtDNA replication as a result of imbalanced nucleoside pools
- Almost all cases due to TYMP mutations (autosomal recessive)
- In rare instances very similar phenotypes have been reported with mutations in other genes involved in mtDNA maintenance i.e. *POLG* and *RRM2B*

Van Goethem G, Schwartz M, Löfgren A, Dermaut B, Van Broeckhoven C, Vissing J. Novel POLG mutations in progressive external ophthalmoplegia mimicking mitochondrial neurogastrointestinal encephalomyopathy. Eur J Hum Genet. 2003 Jul;11(7):547-9. PMID: 12825077

Ethylmalonic encephalopathy (EME)

- Rare autosomal recessive disorder
- Prevalent in Mediterranean and Middle eastern populations
- More than 70 cases known worldwide
- EME presents usually in infancy
- Clinical syndrome comprises
  1. Persistent diarrhea
  2. Neurological symptoms
  3. Recurrent petechiae
  4. Orthostatic acrocyanosis

Tiranti V, Zeviani M. Altered sulfide (H(2)S) metabolism in ethylmalonic encephalopathy. Cold Spring Harb Perspect Biol 2013 Jan 1;5(1):a011437. Review. PMID: 23284046

EME diagnosis

- Lactic acidemia, elevated urinary excretion of ethymalonic and methyl succinic acids and increased C4 and C5 acyl carnitines in blood
- Muscle biopsy shows reduced cytochrome oxidase (COX) activity
- Defect in *ETHE1 gene*
- ETHE1 encodes mitochondrial sulfur dioxygenase which detoxifies hydrogen sulfide produced by intestinal anaerobes
- Defective ETHE1 leads to accumulation of hydrogen sulfide which is a potent inhibitor of COX and also blocks mitochondrial short chain fatty acid oxidation

Tiranti V, D'Adamo P, Briem E, Ferrari G, Mineri R, Lamantea E, Mandel H, Balestri P, Gacia-Silva MT, Vollmer B, Rinaldo P, Hahn SH, Leonard J, Rahman S, Dionisi-Vici C, Garavaglia B, Gasparini P, Zeviani M. Ethylmalonic encephalopathy is caused by mutations in ETHE1, a gene encoding a mitochondrial matrix protein. Am J Hum Genet 2004 Feb;74(2):239-52.

Gastrointestinal problems in other mitochondrial disorders:

- **PEARSON SYNDROME:**
  - Exocrine pancreatic insufficiency
  - Transfusion dependent macrocytic (sideroblastic) anemia (presenting in infancy and resolving by age 2y)
  - Neutropenia and thrombocytopenia may also occur
  - Lactic acidosis and renal tubulopathy
  - Diarrhea present by 18 months of age
  - Bone marrow biopsy reveals ringed sideroblasts and vacuolated myeloid precursors
  - Prognosis very poor. Half patients die of overwhelming acidosis or acute liver failure in early childhood
  - Defect in large-scale mtDNA rearrangment

Rotig A, Colonna M, Bonnefont JP, Blanche S, Fischer A, Saudubray JM, Munnich A.
Mitochondrial DNA deletion in Pearson's marrow/pancreas syndrome. Lancet. **1989** Apr 22;1(8643):902-3.
No abstract available. PMID: 2564980

- **CHRONIC VILLOUS ATROPHY SYNDROME:**
  - Associated with single large scale mtDNA rearrangement
  - Young children present with watery diarrhea associated with villous atrophy without features of Pearson's disease, i.e., exocrine pancreatic insufficiency

Cormier-Daire V1, Bonnefont JP, Rustin P, Maurage C, Ogler H, Schmitz J, Ricour C, Saudubray JM, Munnich A, Rotig A. Mitochondrial DNA rearrangements with onset as chronic diarrhea with villous atrophy. J Pediatr. 1994 Jan;124(1):63-70.

- **LEIGH SYNDROME:**
  - Non-specific GI symptoms, i.e., vomiting, poor feeding, failure to thrive
  - Symptoms can be mistaken for GERD, but are CNS-mediated resulting from focal brainstem lesions
  - Causes include defects in any of the Oxydative phosphorylation complexes
  - Mutations in >40 mtDNA and nuclear-coded gene linked

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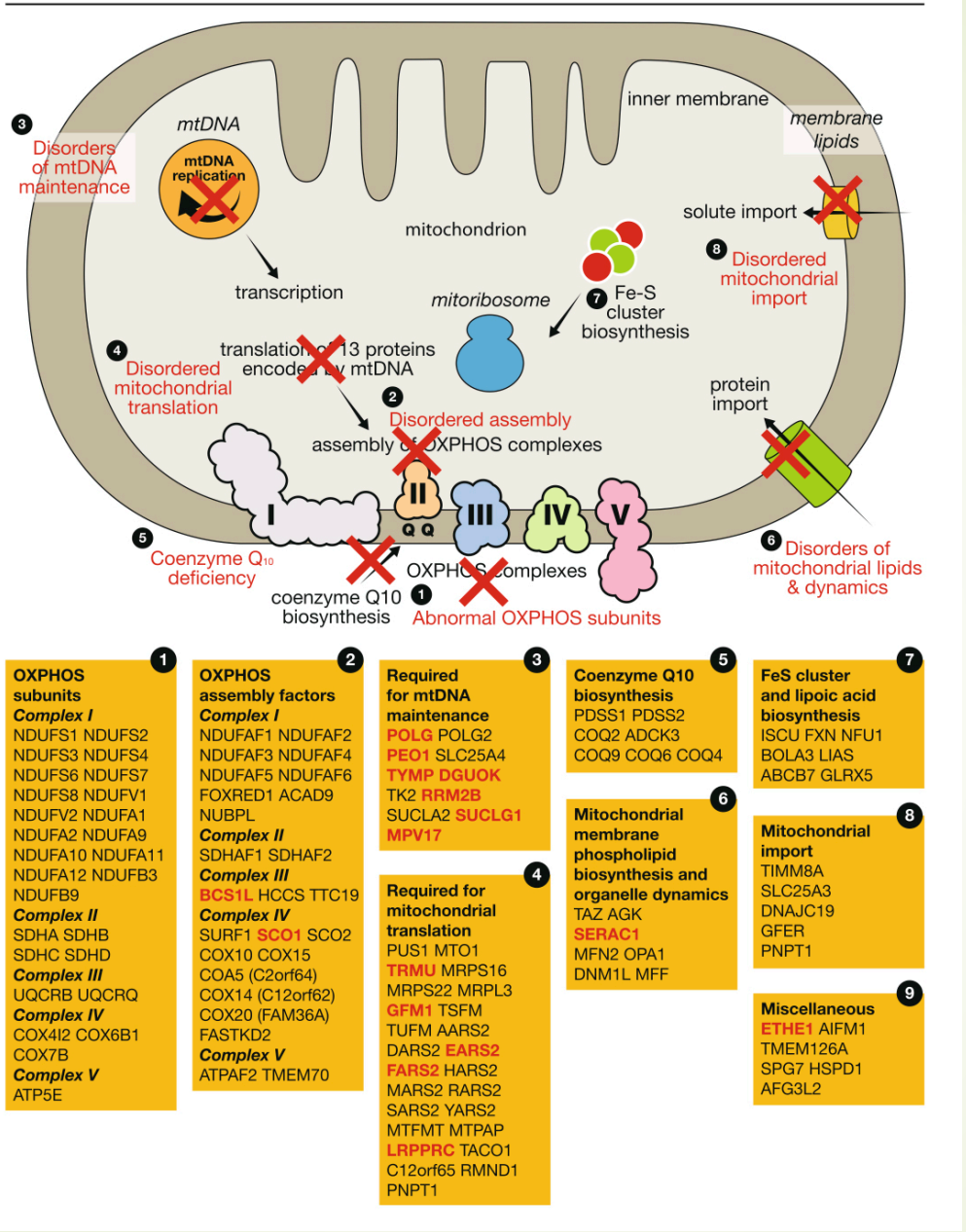
- **MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS AND STROKELIKE EPISODES (MELAS):**
  - Diagnostic criteria defined as stroke-like episode occurring before age 40y
  - Neurologic symptoms:
    1. Seizures
    2. Progressive dementia
    3. Lactic acidosis
    4. Myopathy
    5. Severe migraines
    6. Sensorineural hearing loss
    7. Peripheral neuropathy
    8. Psychiatric problems

Hirano M, Ricci E, Koenigsberger MR, Defendini R, Pavlakis SG, DeVivo DC, DiMauro S, Rowland LP. Melas: an original case and clinical criteria for diagnosis. Neuromuscul Disord. 1992;2(2):125-35. Review.

- GI disturbance reported in 64% patients
  - GI symptoms:
    1. Abdominal discomfort
    2. Vomiting
    3. Constipation
    4. Diarrhea
    5. Gastroparesis
    6. Intestinal pseudo-obstruction
    7. Recurrent pancreatitis
  - Extra-neurological manifestations include cardiomyopathy and renal disease
  - Defect in mtDNA mutations (MT-TL1)



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Approach to diagnosis

- Multidisciplinary approach needs to be taken
- A full systems assessment:
  1. Cardiological: Echo, EKG
  2. Ophthalmological
  3. Audiological
  4. Neurological: Brain MRI, nerve conduction studies, EMG, EEG
  5. Renal function to evaluate extent of disease involvement
  6. Gastrointestinal: CT, Xrays, UGI, EGD, Flex sig, Scintigraphy,Antroduodenal manometry
  7. Pulmonary: PFT's for respiratory insufficiency
  8. Nutritional evaluation and swallowing assessment

El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013 Apr;10(2):186-98. doi: 10.1007/s13311-013-0177-6. Review. PMID: 23385875

Approach to diagnosis

- Metabolite tests, i.e., urine analysis, lactate level, plasma acylcarnitine, urine organic acids, thymidine and deoxyuridine analysis can be done for screening
- Muscle biopsy may reveal abnormalities on:
  1. Histo-chemical testing
  2. Electron microscopy may show abnormal mitochondrial morphology or crystalline inclusions
  3. Biochemical testing may demonstrate deficiency of single or multiple OXPHOS enzymes
- Direct genetic testing may be the most appropriate first line investigation for some phenotypes associated with specific genetic diagnosis

Therapeutic options:

- Currently incurable disorders with mostly poor prognosis in majority of patients
- **GENERAL SUPPORTIVE MEASURES:**
  - Regular blood transfusions in Pearson syndrome
  - Gastrostomy feeding
  - Parenteral feeding
  - Cofactor replacement i.e. folinic acid, levocarnitine, creatine, coenzyme Q10, B vitamins, antioxidants such as alpha lipoic acid, vitamin E, vitamin C

El-Hattab AW, Scaglia F. Mitochondrial DNA depletion syndromes: review and updates of genetic basis, manifestations, and therapeutic options. Neurotherapeutics. 2013 Apr;10(2):186-98. doi: 10.1007/s13311-013-0177-6. Review. PMID: 23385875

- **LIVER TRANSPLANT FOR MITOCHONDRIAL HEPATOPATHIES**
- **ALLOGENIC STEM CELL TRANSPLANTATION FOR MNGIE**
- **OTHER EXPERIMENTAL THERAPIES:**

1. *Combined treatment with metronidazole and N-acetylcysteine in patients with EME to:
   a) reduce sulfide production by decreasing colonization of intestinal anaerobes
   b) replenish glutathione levels to buffer sulfide in patients
2. **Development of carrier erythrocyte entrapped enzyme replacement for MNGIE
3. **Adeno-associated viral and lentiviral-mediated gene replacements have been reported for mouse models of EME and MNGIE

*Viscomi C1, Burlina AB, Dweikat I, Savoiado M, Lamperti C, Hildebrandt T, Tiranti V, Zeviani M. Combined treatment with oral metronidazole and N-acetylcysteine is effective in ethylmalonic encephalopathy. Nat Med. 2010 Aug;16(8):869-71. doi: 10.1038/nm.2188. Epub 2010 Jul 25.

**Di Meo I, Auricchio A, Lamperti C, Burlina A, Viscomi C, Zeviani M. Effective AAV-mediated gene therapy in a mouse model of ethylmalonic encephalopathy. EMBO Mol Med. 2012 Sep;4(9):1008-14. doi: 10.1002/emmm.201201433. PMID: 22903887

Conclusion

- Mitochondrial disorders are highly heterogeneous disorders with pleomorphic clinical features
- Gastrointestinal and hepatic disturbance is a feature of >10% of human mitochondrial disease
- There are some discrete syndromes with clear genotype-phenotype correlations
- Careful observation may expedite genetic diagnosis although detailed histological and biochemical analysis of tissue is essential for diagnosing majority of cases
- Not very many therapeutic advances made to date, but experimental approaches on the horizon.