# # 56. Identification of candidate genetic susceptibility variants in the carnitine (Cn) transporter (*SLC22A4*, *SLC22A5*, *SLC6A14*) and carnitine biosynthesis (*TMLHE*, *BBOX1*) gene families in Autism Spectrum Disorder (ASD): A novel precision medicine target.

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## INTRODUCTION

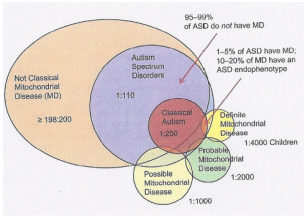
That brain carnitine (Cn) deficiency might lead to ASD has been suggested by reports of severe Cn deficiency in ASD and by evidence that TMLHE deficiency is a risk factor for ASD supporting a mixed, common gene variant-environment hypothesis; male predominance may relate to X-linked *SLC6A14* whose inactivation could limit transport of Cn across the blood-brain barrier. It has been proposed that 10-20 % of nonsyndromic ASD involving extreme male bias may develop due to early brain Cn deficiency that may be amenable to early reversal and prevention.

## AIM

To identify predicted loss-of function variants and copy number variations in the Cn transporter (*SLC22A4, SLC22A5, SLC6A14*) and Cn biosynthesis (*TMLHE, BBOX1*) genes that are enriched in individuals with ASD.

## METHOD

Using GWAS, we surveyed for variants in our target genes that were enriched in ASD cases in the Autism Speaks MSSNG and Simons Simplex Cohort genomes (n= 7,642) compared to typically developed, healthy controls (n=7,000)



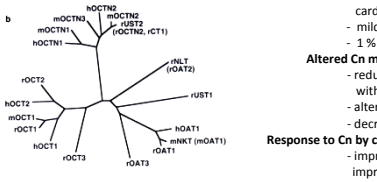

## RESULTS

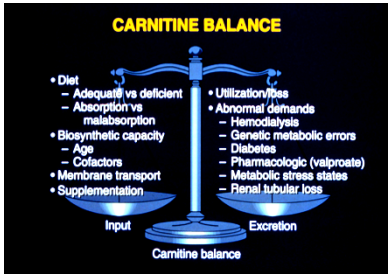
We identified:

20 deletions ranging from 6.4 kb to 189 kb in *TMLHE*, which are heterozygous in 7 females (one a triplication; 3 paternally inherited) and hemizygous in males (all maternally inherited)

One deletion of 10kb in *SLC22A5* in a male (paternal inherited)

There were 17 rare heterozygous, inherited loss-of-function mutations impacting the *SLC22A4, SLC22A5*, and *BBOX1* genes.




**OCTN2 deficiency**

- lethal infantile AR disorder with recurrent coma, progressive cardiomyopathy and myopathy reversed by lifelong oral L-Cn
- milder phenotypes with ADHD and ID improved with L-Cn
- 1 % carrier prevalence

**Altered Cn metabolism in ASD subgroup**

- reduced serum Cn in 100 children with non-syndromic ASD with elevations in lactate and ammonia
- alteration of mitochondrial redox function in ASD
- decreased serum free Cn and abnormal SC and LC acylcarnitines

**Response to Cn by children with ASD in preliminary RCTs and open label studies**

- improvement in childhood autism rating scale and clinical global impression scales in non-syndromic ASD
- preliminary evidence of benefit for ID and ASD in respiratory chain, OCTN2 and TMLHE deficiencies

| Cn transporters | Affinity | Localization | Gene | Inheritance |
|---|---|---|---|---|
| OCTN1 | low | mitochondrial | *SLC22A4* | AR 5q31 |
| OCTN2 | high | plasmalemmal | *SLC22A5* | AR 5q31 |
| Cationic AA neurotransmitters | | blood-brain barrier | *SLC6A14* | XL Xq23 |
| | | | | |
| **Cn biosynthesis** | **Phenotype** | **Expression** | **Gene** | **Inheritance** |
| First step | ASD susceptibility | ubiquitous | *TMLHE* | XL Xq28 |
| Last step | | Liver, kidney, brain | *BBOX1* | 11p14.2 |

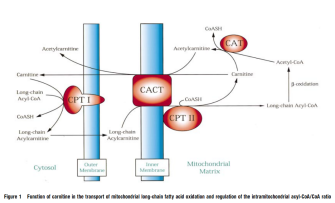



Figure 1 Function of carnitine in the transport of mitochondrial long-chain fatty acid oxidation and regulation of the intramitochondrial acyl-CoA/CoA ratio

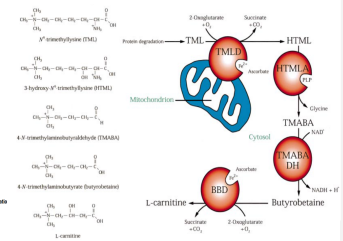
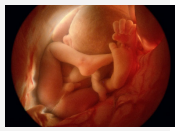


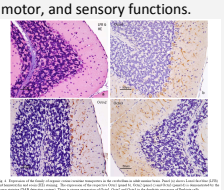

Figure 2 The carnitine biosynthesis pathway

Taken from Vaz FM and Wanders RJA; Biochem J 2002; 361:417-429

## CONCLUSIONS

Early identification of children with ASD and dysregulation of Cn homeostasis with implementation of L-Cn therapy should improve the clinical phenotype via the roles of Cn in (1) cerebral bioenergetics,
(2) cholinergic neurotransmission, (3) antioxidant role, (4) neuromodulation and (5) neuroprotection affecting early brain development.
mOctn1, -2, and -3 are expressed in many regions of the murine CNS with a pattern suggestive of roles in memory, limbic, olfactory, satiety, motor, and sensory functions.





Taken from Lamonwah AM et al.Brain & Dev 2008;30:31-42

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