MATERNAL THYROID DYSFUNCTION, LIKELY GENE DISRUPTING MUTATIONS AND THE IMPACT ON ASD SEVERITY

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AUTISM SPECTRUM DISORDER (ASD) IS A NEURODEVELOPMENTAL DISORDER CLASSIFIED BY DEFICITS IN SOCIAL COMMUNICATION AND RESTRICTED, REPETITIVE BEHAVIOR. SYMPTOMS MUST BE PRESENT IN EARLY DEVELOPMENT.[1]

BACKGROUND

- **Genetic contributions to ASD:** Structural and functional abnormalities to the genome contributing to ASD have been found.[2]
- **Likely Gene Disrupting Mutations (LGD):** LGD Mutations cause a single allele change that hinders function (figure 1).[3] Disruptions to these genes are key in early pathways in development.[3]

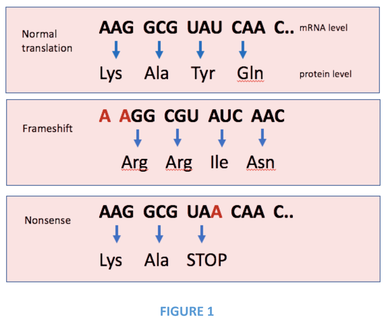


FIGURE 1

Most frequent LGD Mutations

	(n=100)
CHD8	16
DYRK1A	11
ADNP	9
SCN2A	8
GRIN2B	7
ARID1B	4
CHD2	4
FOXP1	4
DSCAM	3
CTNNB1	2
NRXN1	2
POGZ	2
PTEN	2
SETD2	2
TRIP12	2
WDFY3	2

Frequencies of LGD Mutations in our sample

- **Thyroid Dysfunction:** Thyroid hormones influence fetal brain development by stimulating neuronal synapses and impacting the formation of neurotransmitters.[4] Both hypothyroidism and hyperthyroidism have an impact on brain development and cognitive impairments.[5,6] Family history of autoimmune disease was associated with a greater risk for having a child with ASD, including associations in familial hypothyroidism.[7]
- **Gene by environment model:** Recent findings suggest a "two-hit model" where one variable elicits an initial risk for ASD, which is then compounded by a second variable, thus increasing severity symptoms.[8, 9]

HYPOTHESIS

>An interaction between the presence of an LGD Mutation and maternal thyroid dysfunction will indicate more severe behavioral phenotypes than either the presence of an LGD Mutation or maternal thyroid dysfunction alone.

METHODS

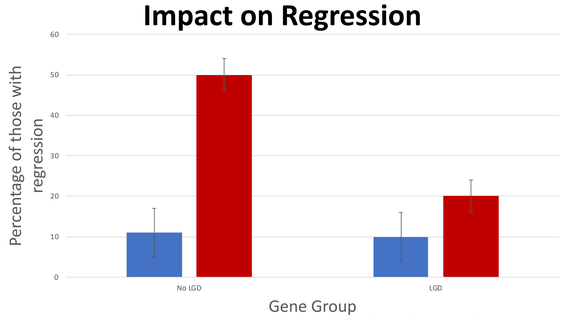
- 188 participants who have been clinically diagnosed with ASD between ages 3-24 (M: 11, SD: 4).
- We tested the presence of regression via the ADI-R, social impairments via the SRS-2, cognitive abilities/IQ via the DAS-II
- Whole exome sequencing or targeted sequencing was completed to identify any ASD-associated *de novo* disruptive LGD Mutations.
- Additionally, those with a presence of either maternal hyperthyroidism, hypothyroidism, or Hashimoto's thyroiditis were grouped together due to the influence of thyroid hormones on fetal brain development during pregnancy.
- 2x2 ANOVAs (LGD Mutation Status x Maternal Thyroid Dysfunction) were conducted in SPSS Version 19.

Summary of participant characteristics

Sex	
Male	138
Female	50
Mean (SD) age (months)	140.10 (49.19)
LGD Mutation	
Yes	100
No	88
Maternal Thyroid Dysfunction	
Hyperthyroidism	3
Hypothyroidism	17
Hashimoto's Thyroiditis	6
Mean Verbal IQ score (SD)	74.18 (34.290)
Mean Nonverbal IQ score (SD)	74.99 (32.730)

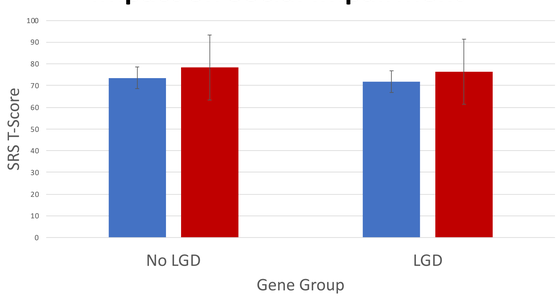
SYMPTOM SEVERITY RESULTS

Impact on Regression



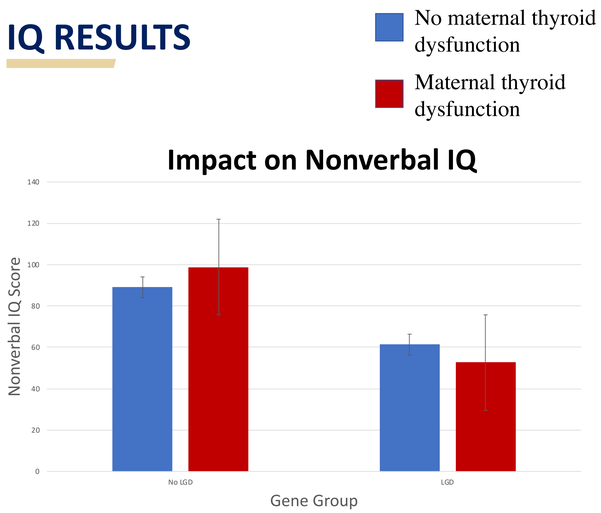
Maternal thyroid main effects: F(1, 180): <.0001, p=.983
LGD main effects: F(1, 180): .46, p=.831
Interaction effects: F(1, 180): .102, p=.750

Impact on Social Impairment



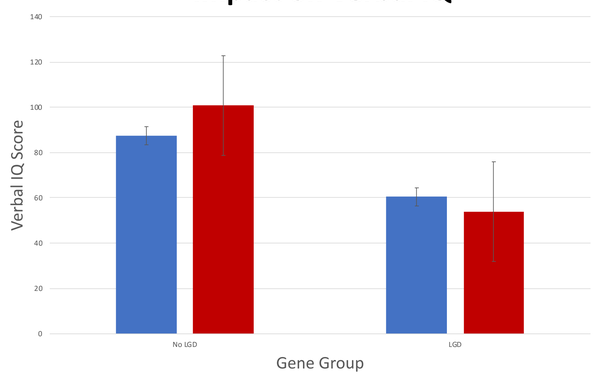
Maternal thyroid main effects: F(1, 184): 1.732, p=.190
LGD main effects: F(1, 184): .273, p=.602
Interaction effects: F(1, 184): <.0001, p=.986

IQ RESULTS



Maternal thyroid main effects: F(1, 172): .006, p=..941
LGD main effects: F(1, 172): .28.894, p= <.0001*
Interaction effects: F(1, 172): .1.814, p= .180

Impact on Verbal IQ



Maternal thyroid main effects: F(1, 170): .215, p=.643
LGD main effects: F(1, 170): 25.304, p= <.0001*
Interaction effects: F(1, 170): 1.823, p=.179

DISCUSSION

- Our results found a main effect with gene group and verbal and nonverbal IQ, but no interaction effects. This indicates that this specific gene by environment model was not able to pinpoint the varying phenotypes within ASD.
- **Strengths:** We included a large sample of participants with a known genetic event. This study is also the first to investigate the interaction between LGD Mutations and thyroid dysfunction.
- **Limitations:** Some of our measures relied on self report, and a portion of our participants were involved remotely, thus full data was not able to be completed. Additionally, when analyzing our data set, we grouped together all types of thyroid dysfunction, as well as grouped all types of gene events, rather then analyzing them individually. Our third limitation is our small sample size
- **Future implications:** This study allows us to get a closer step to exploring mechanisms of ASD. This warrants further investigation on gene events and different maternal immune activation on ASD severity.

CONCLUSION

- Those who carried an LGD Mutation in our sample had a significantly lower Verbal and Nonverbal IQ score compared to those without an LGD Mutation.
- We found no interaction between maternal thyroid dysfunction, LGD Mutations, and autism severity. This could be due to but not limited to differing biological interactions of the separate thyroid dysfunctions, sample size, or lack of awareness of the presence of a thyroid dysfunction.

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