Differences in Resting State Alpha Power between LGD Mutations, Idiopathic ASD, and Typically Developing Individuals

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BACKGROUND:

- Electroencephalography (EEG) alpha rhythms (~8-12 Hz) are associated with attention and sensation.[1, 2, 3]
- Alpha may be a possible biomarker for Autism Spectrum Disorder (ASD), as ASD is closely associated with atypical sensory processing.[4]
- Differences in alpha power occur during resting state between typically developing (TD) and ASD populations.[5] Yet, directionality of these differences in alpha varies drastically depending on brain region, sex[6], cognition, [7, 8] and age [9, 10, 11]
- An additional source of alpha variation may involve genetic etiology: Advances in genomic sequencing have warranted subgrouping the ASD population into those who also carry *de novo* likely gene disrupting (LGD) Mutation[12] that have known phenotypic heterogeneity between LGD Mutations [12, 13, 14, 15].

OBJECTIVE:

To characterize and compare resting-state alpha rhythms of children with different ASD genetic etiologies to typically developing controls.

METHODS:

- Data from 204 children **(Table 1)** were included in analyses in three different groups.
- LGD Mutation groups include verified pathogenic disruptions (N in parentheses): *CHD8* (8), *DYRK1A* (8), *SCN2A* (4), *ADNP* (4), *CHD2* (4), among other high-risk ASD genes.
- Resting state EEG paradigms: Screensaver-like videos of various shapes and colors were presented for two and a half minutes to participants as they were instructed to attend to the presentation monitor with their eyes open.
- Each child's peak alpha frequency within the 8-12 Hz range was extracted from 8 different bilateral regions **(Figure 1)** and included in linear mixed-effects analyses. A full factorial model included genetic group, region, and sex as predictors of alpha rhythm.
- Participant cognition was clinically assessed by the Mullen,[16] DAS,[17] or WASI-II.[18]

Table 1. Participant characterization.
Note: ASD Dx = Autism Spectrum Disorder diagnosis; ID Dx = Intellectual Disability diagnosis; NVIQ = nonverbal IQ

	LGD Mutation	ASD No Event	Typical development (TYP)
N	57	66	81
Male : Female	39 : 18	53 : 13	47 : 34
Age in Years (SD)	11.40 (5.15)	12.22 (2.57)	10.62 (4.15)
ASD Dx (%)	57 (100%)	66 (100%)	0 (0%)
ID Dx (%)	26 (45.6%)	13 (19.4%)	0 (0%)
NVIQ (SD)	66.68 (30.85)	93.23 (24.38)	115.93 (14.64)

RESULTS:

- **Medial Central (Figure 2):**
  - **Group**, F(2, 198) = 0.23, $p = 0.80$
    - LGDM participants have higher absolute alpha power than both ASD No Event ($p < 0.01$) and TYP ($p < 0.01$) groups in the medial central brain region.
  - **Group** by **Sex**, F(2, 198) = 1.69, p = 0.19
    - *Within females:* LGDM females have higher absolute alpha power than ASD No Event ($p < 0.01$) and TYP ($p < 0.01$) females in the medial central brain region.
    - LGDM females have higher absolute alpha power than ASD No Event males ($p < 0.01$) in the medial central brain region.
- **Posterior and Occipital (Figure 3)**:
  - No significant main effects of group for either region
  - **Sex**: male absolute alpha power is greater than female absolute alpha power in both posterior (F(1, 198) = 9.42, $p < 0.01$) and occipital F(1, 198) = 10.85, $p < 0.01$) brain regions
- **Medial Frontal and Prefrontal (Figure 3)**:
  - **Group** by **Sex**: While there was a significant interaction at both regions (MF, F(2, 198) = 3.7, p = 0.026; PF F(2, 198) = 5.17, p = 0.007), there were no significant group differences within females or within males.

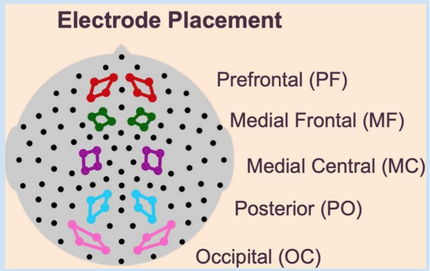

Figure 1. Bilateral location placement of EEG electrodes on EGI net used for data analysis

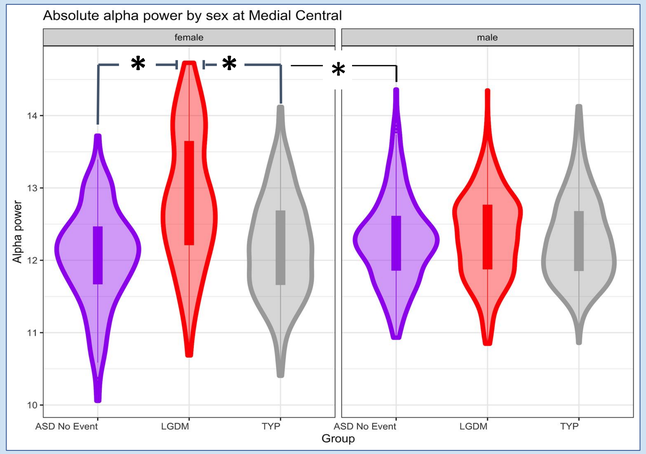

Figure 2. In females, the LGD Mutation (LGDM) group exhibited more absolute alpha power than the ASD No Event (ASD Dx, no LGD Mutation) group ($p < 0.01$) and the TYP group ($p < 0.01$). No differences in absolute alpha power were observed between ASD no event, LGD Mutation, or TYP groups for males in this sample. $*p < 0.01$

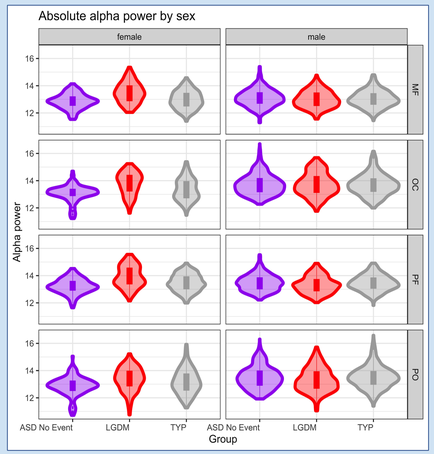

Figure 3. Violin plots show the frequency of absolute alpha power between ASD no event, LGDM, and TYP groups by sex in μV^2.

CONCLUSIONS:

Females who carry a likely gene disruptive mutation exhibit greater resting state alpha rhythm than their typically developing and idiopathic ASD peers across the medial central region.

Previous findings from research on LGD Mutation populations express heterogenous phenotypes, thus could give rise to our sex-specific findings within our sample. Werling & Geschwind[19] reported differing neural expressions between males and females with ASD; however, our results are contradictory as they do not indicate significant sex differences among ASD or TD groups.

Our current investigation seeks to add to a growing body of "genetics-first" work on EEG responses between genetic variations linked to ASD and idiopathic ASD [20, 21]. Our findings contribute to this subset of literature by introducing sex discrepancies in resting alpha power in de novo genetic mutations, thus emphasizing the need for more exploration in this population.

Future studies should aim to explore sex-differential genetic and neurophysiological factors among the LGD Mutation population, striving for a more balanced gender ratio, as current data over-represents males.

REFERENCES:

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