



A Natural History of NAA15-related Neurodevelopmental Disorder

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Introduction

- The NatA complex is composed of the catalytic sub-unit NAA10, and the auxiliary sub-units NAA15 and HYPK and has ubiquitous function in development
- Variants within *NAA15* lead to *NAA15*-related neurodevelopmental syndrome which is characterized by intellectual disability, atypical or delayed development, heart anomalies, and dysmorphic facies

Objective

To characterize the natural history of NAA15-related neurodevelopmental disorder

Methods

- Retrospective analysis of Vineland-3 data collected from probands with pathogenic NAA15 variants
- Further analysis compared Males (M) and Females (F) and loss of function (LOF) and missense (MIS) variants.
- Two-tailed equal variance t-tests and correlation coefficients were calculated
- p-value was set at .05
- NAA15-010 was excluded unless otherwise noted due to their age being 3 standard deviations greater than the mean and Vineland scores 2 standard deviations below
- All statistically significant results are **bolded**

Results

- 27 participants (9 F and 18 M and 17 LOF and 9 MIS) were administered the Vineland.
- Ages ranged from 1 - 24.5 years (mean = 9.0 years, standard deviation (SD) = 5.2).
- Mean cohort ABC standard score (SS) was 68.5 (SD = 22.1; global mean = 100; SD = 15)
- Mean ABC SS for M (mean = 65, SD = 20.0) and F (mean = 74.9, SD = 24.4, $p = 0.15$)
- Mean ABC SS for MIS (mean = 67.3, SD = 30.2) and LOF proband groups (mean = 69.1, SD = 17.3, $p = 0.81$)

Fig 1. Demographics
denotes a splice site variant

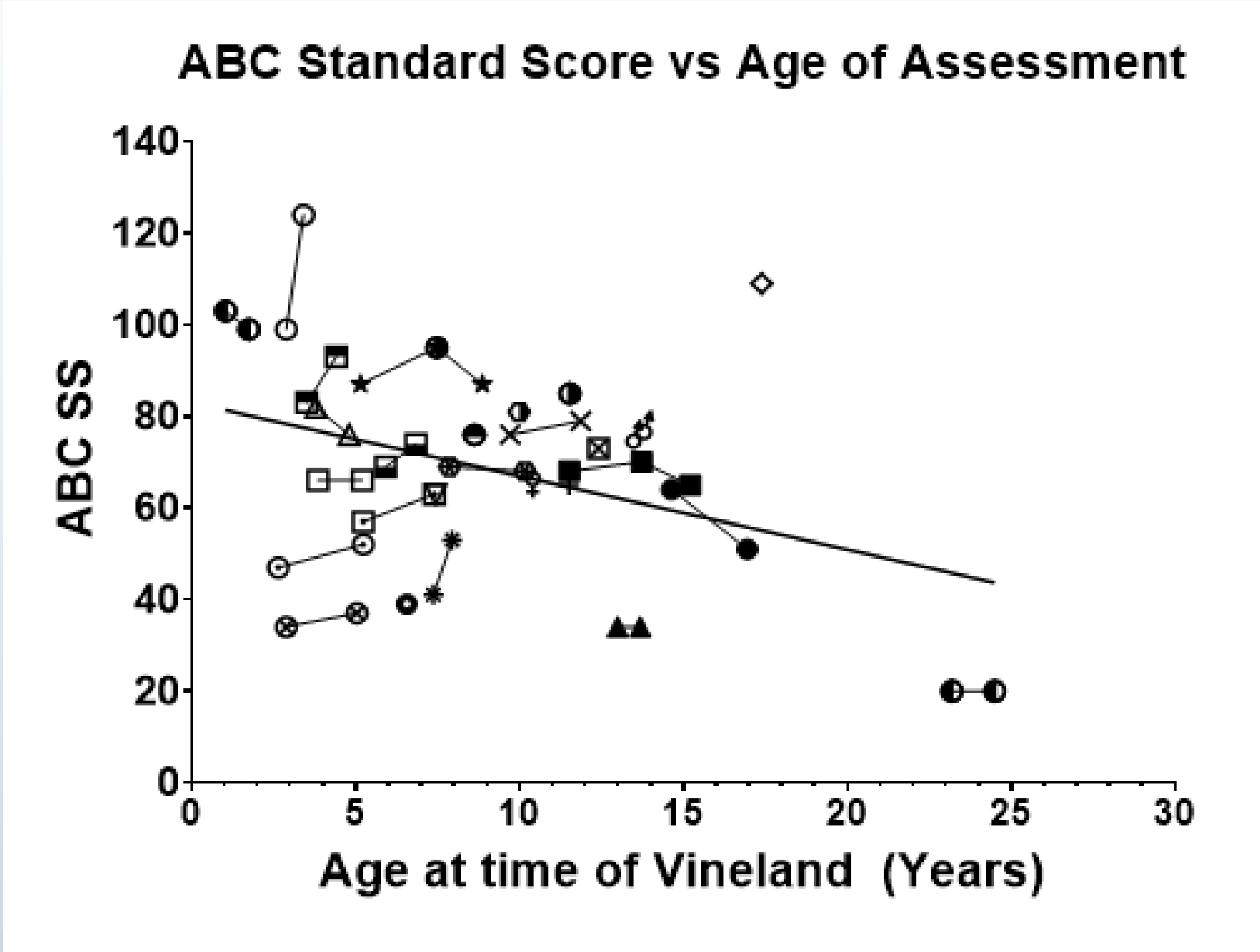


Figure 1. ABC Standard Score vs Age in Years at time of Vineland Administration. Each point on the graph represents a single participant’s ABC SS. Connected points show change in proband scores over time. There was a significant negative correlation between ABC SS and age ($r = -0.38$, $p = 0.01$).

NAA15 Variant	M	F
p.Arg27Gly	1	
p.His80Argfs*17	2	
p.Trp83*		1
p.Asn113Ser		1
p.Glu173*	1	
p.Glu173Asnfs*54	1	
p.Tyr333*	1	
p.Asp335Glu fs*7	1	
p.Asn362Metfs*36	1	
p.Cys484Arg	1	
p.Arg549*	1	
p.Ala585Thr	1	
p.Gln621*	1	
p.Asn623Ilefs*	1	
p.Lys628Glu	1	
p.Ala678Cysfs*3	1	
p.Tyr682*		1
p.Ala719Thr	1	
p.Arg782*		1
p.Asn864Ser		1
c.692-1G>T #	1	
c.139+2T>A #	1	
c.1087+2T>C #	1	
c.1753+1G>A #	1	
c.1947+2T>C #		1
c.2057-2A>G #		1
Total: 27	18	9

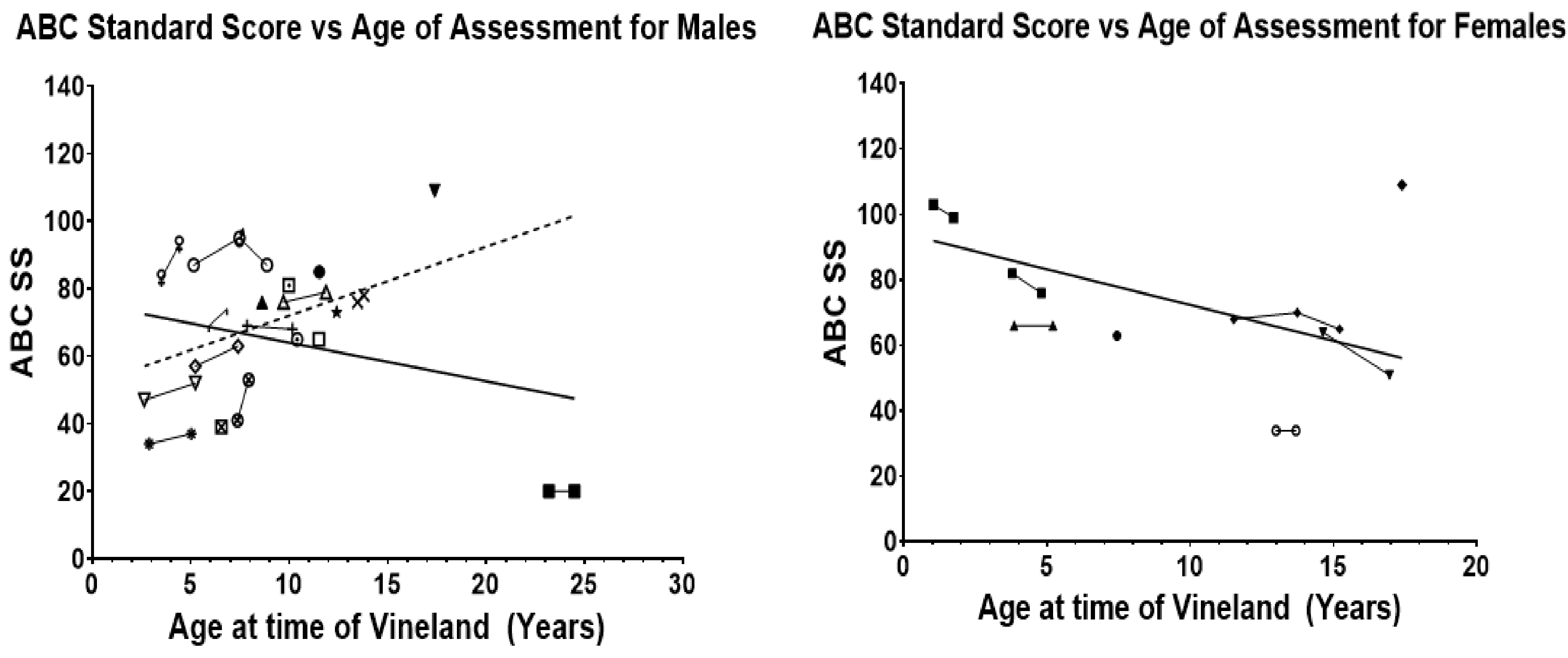


Figure 2. ABC Standard Score vs Age in Years at time of Vineland Administration by Sex. Each point on the graph represents a single participant’s ABC SS. Connected points show change in proband scores over time. The dashed line is a line of best fit generated without NAA15-010. There was a positive association between Males without NAA15-015 and their ABC over time ($r = 0.38$, $p = 0.04$). There were negative correlations between the Male group ($r = -0.28$, $p = 0.13$) and the Females ABC SS over time ($r = -0.51$, $p = 0.04$). (LEFT) Males (RIGHT) Females

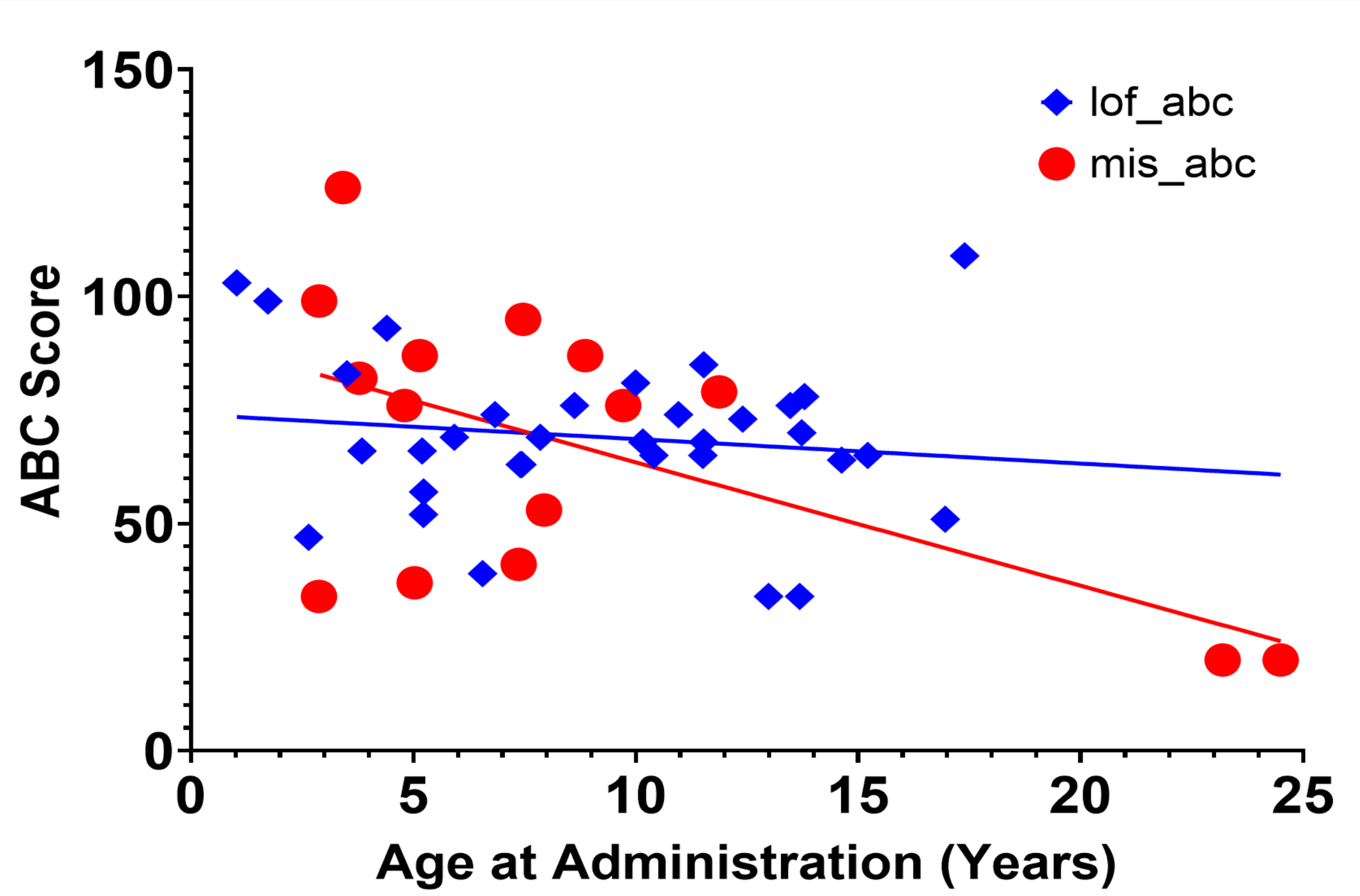
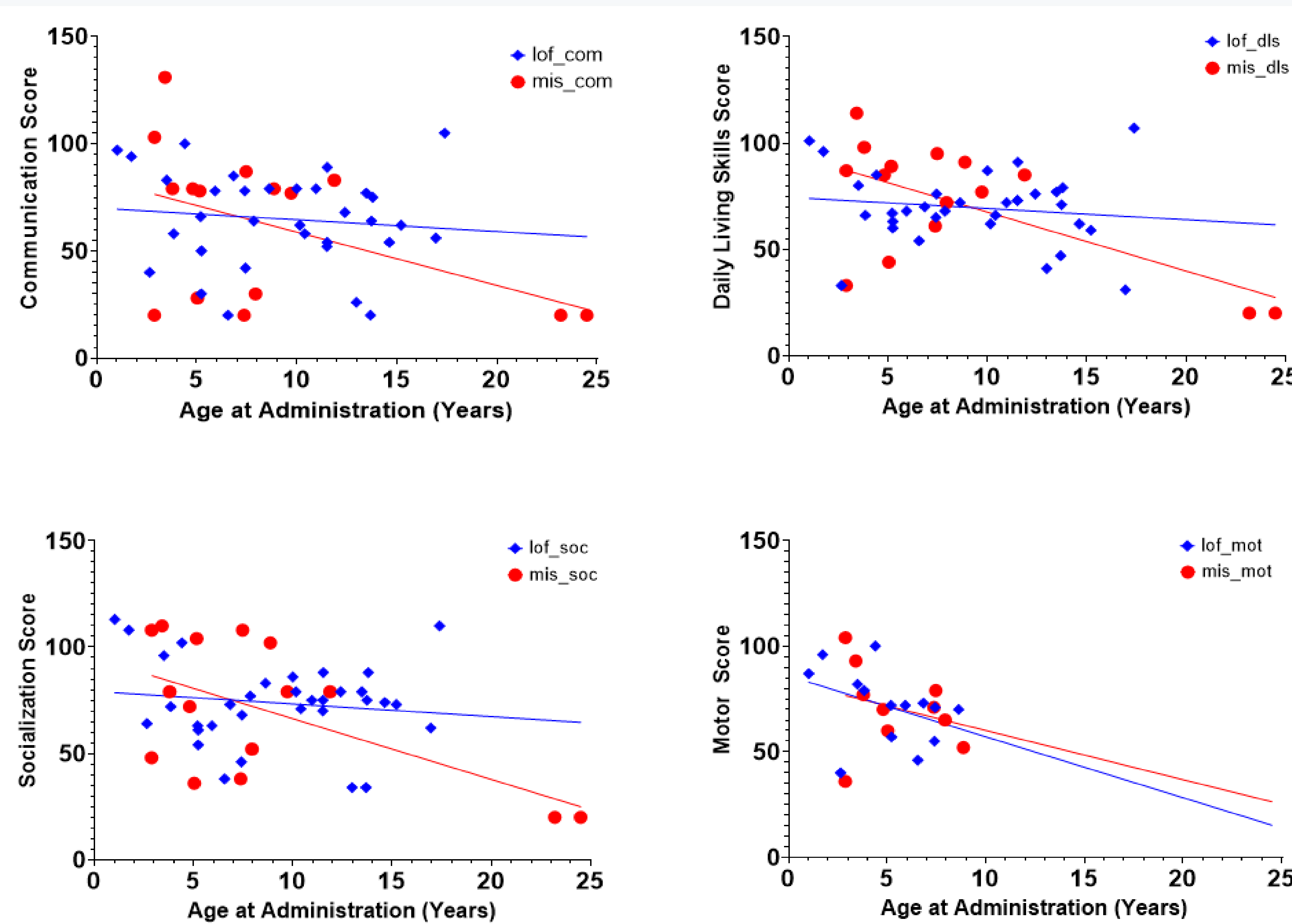


Figure 3. ABC Standard Score versus Age at Vineland Administration in Years by Variant Type. Each point on the graph represents a proband’s ABC score. Both the LOF ($r = -0.14$, $p = 0.44$) and MIS ($r = -0.59$, $p = 0.02$) groups had negative associations between ABC SS and age. Only the MIS association was statistically significant.



	Communication	Daily Living Skills	Social	Motor	ABC
LOF Correlation Coefficient (p-val)	-0.11 (0.54)	-0.14 (0.44)	-0.14 (0.45)	-0.38 (0.18)	-0.14 (0.44)
MIS Correlation Coefficient (p-val)	-0.47 (0.08)	-0.64 (0.01)	-0.59 (0.02)	-0.27 (0.45)	-0.59 (0.02)

Figure 4. Vineland Domain Standard Score versus Age at Vineland Administration in Years by Variant Type. Each point represents a proband’s domains standard score. Correlation coefficients for the MIS and LOF groups for each domain are present in tabular format above.

Conclusions

- Our cohort scored 2 standard deviations worse than the population Vineland-3 ABC SS mean
- In aggregate, females performed better on the Vineland than the males
- Conversely, males showed improvement with age whereas females appeared to do worse
- The MIS group showed statistically significant negative associations with age and greater magnitudes of these associations on performance than the LOF group
- Additional longitudinal data needs to be collected to determine the validity of the sex and variant differences that affect the adaptive behavioral outcomes in those with NAA15-neurodevelopmental disorder as they age