SUPPLEMENTAL TABLES

Table S1: Recurrence risk in multiplex AGRE families by sex and family type

A) All children born after 2nd affected. N=341 families, N=456 children, 36.0% affected

		N	Recur. rate	95% CI	Relative risk	P-value	Adj. P
All	**Males**	257	47.47%	41.45 – 53.57%	M/F		
	Females	199	21.11%	16.01 – 27.29%	2.25	3.11e-09	6.22e-08
All	**FC**	183	44.26%	37.26 – 51.50%	FC/MO		
	MO	273	30.40%	25.25 – 36.10%	1.46	1.78e-03	0.036
Males	**FC**	111	54.05%	44.80 – 63.03%	FC/MO		
	MO	146	42.47%	34.74 – 50.58%	1.27	0.043	0.86
FC	**Males**	111	54.05%	44.80 – 63.03%	M/F		
	Females	72	29.17%	19.94 – 40.51%	1.85	7.18e-04	0.014

B) First child born after 2nd affected. N=341 families, 38.4% affected

		N	Recur. rate	95% CI	Relative risk	P-value	Adj. P
All	**Males**	190	51.58%	44.51 – 58.58%	M/F		
	Females	151	21.85%	16.01 – 29.10%	2.36	1.21e-08	2.42e-07
All	**FC**	131	44.28%	36.05 – 52.82%	FC/MO		
	MO	210	34.76%	28.65 – 41.42%	1.27	0.051	1
Males	**FC**	76	56.58%	45.39 – 67.14%	FC/MO		
	MO	114	48.25%	39.28 – 57.32%	1.17	0.16	1
FC	**Males**	76	56.58%	45.39 – 67.14%	M/F		
	Females	55	27.27%	17.28 – 40.23%	2.07	7.19e-04	0.014

C) First child born after 2nd affected in families with exactly 3 children. N=198 families, 38.9% affected

		N	Recur. rate	95% CI	Relative risk	P-value	Adj. P
All	**Males**	111	52.25%	43.04 – 61.31%	M/F		
	Females	87	21.84%	14.45 – 31.61%	2.39	9.57e-06	1.91e-04
All	**FC**	72	48.61%	37.43 – 59.93%	FC/MO		
	MO	126	33.33%	25.70 – 41.95%	1.46	0.025	0.49
Males	**FC**	40	65.00%	49.51 – 77.87%	FC/MO		
	MO	71	45.07%	34.05 – 56.60%	1.44	0.034	0.68
FC	**Males**	40	65.00%	49.51 – 77.87%	M/F		
	Females	32	28.13%	15.56 – 45.37%	2.31	1.86e-03	0.037

D) First child born after 2nd affected is last child in family. N=258 families, 37.6% affected

		N	Recur. rate	95% CI	Relative risk	P-value	Adj. P
All	**Males**	144	50.69%	42.62 – 58.74%	M/F		
	Females	114	21.05%	14.58 – 29.42%	2.41	6.87e-07	1.37e-05
All	**FC**	90	46.67%	36.71 – 56.90%	FC/MO		
	MO	168	32.74%	26.10 – 40.15%	1.43	0.020	0.39
Males	**FC**	52	59.62%	46.07 – 71.84%	FC/MO		
	MO	92	45.65%	35.85 – 55.80%	1.31	0.075	1
FC	**Males**	52	59.62%	46.07 – 71.84%	M/F		
	Females	38	28.95%	17.00 – 44.76%	2.06	3.59e-03	0.072

E) Any 1 child selected after masking 2 affected children at random, 100 randomizations (Familial risk). N=556 families, 17.5% affected

		N	Recur. rate	95% CI	Relative risk	P-value	Adj. P
All	**Males**	270	25.56%	20.72 – 31.08%	M/F		
	Females	286	9.79%	6.86 – 13.79%	2.61	6.70e-07	1.34e-05
All	**FC**	208	22.60%	17.44 – 28.75%	FC/MO		
	MO	348	14.37%	11.07 – 18.44%	1.57	9.72e-03	0.19
Males	**FC**	99	31.31%	23.02 – 41.00%	FC/MO		
	MO	171	22.22%	16.64 – 29.03%	1.41	0.067	1
FC	**Males**	99	31.31%	23.02 – 41.00%	M/F		
	Females	109	14.68%	9.24 – 22.52%	2.13	3.38e-03	0.068

FC = female-containing family; MO = male-only family. Unadjusted P-values are from one-sided Fisher's exact tests for affection status by sex or by family type. Adjusted P-values have been corrected for 20 tests.

Table S2: Logistic regression for affection status by sex and family type

A) All children born after 2nd affected. N=341 families, N=456 children, 36.0% affected

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-0.662	0.109	37.16	1.09e-09
Sex [Male]	0.591	0.109	29.66	5.15e-08
Family type [FC]	0.299	0.109	7.61	5.80e-03
Sex[Male] by Family type [FC]	-0.066	0.109	0.37	0.54

B) First child born after 2nd affected. N=341 families, 38.4% affected

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-0.563	0.125	20.4	6.28e-06
Sex [Male]	0.660	0.125	28.06	1.18e-07
Family type [FC]	0.205	0.125	2.71	0.01
Sex[Male] by Family type [FC]	-0.038	0.125	0.09	0.76

C) First child born after 2nd affected in families with exactly 3 children. N=198 families, 38.9% affected

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-0.531	0.143	13.85	1.98e-04
Sex [Male]	0.720	0.143	25.44	4.56e-07
Family type [FC]	0.234	0.143	2.7	0.10
Sex[Male] by Family type [FC]	0.025	0.143	0.03	0.86

D) First child born after 2nd affected is last child in family. N=258 families, 37.6% affected

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-0.565	0.147	14.84	1.17e-04
Sex [Male]	0.673	0.147	21.03	4.52e-06
Family type [FC]	0.311	0.147	4.49	0.034
Sex[Male] by Family type [FC]	-0.029	0.147	0.04	0.84

E) Any 1 child selected after masking 2 affecteds at random, 100 randomizations (Familial risk). N=554 families, 17.5% affected

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-1.605	0.123	169.27	1.07e-38
Sex [Male]	0.586	0.123	22.55	2.05e-06
Family type [FC]	0.332	0.123	7.25	7.09e-03
Sex[Male] by Family type [FC]	-0.098	0.123	0.64	0.42

FC = female-containing family; MO = male-only family. Chi-squared statistics and unadjusted P-values are from the logistic regression for affection status by sex, family type, and the interaction between sex and family type.

Table S3: Logistic regression for affection status by inter-birth interval

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	2.891	1.193	5.88	0.015
ln(IBI)	-0.657	0.278	5.6	0.018
Sex [Male]	0.699	0.131	28.56	9.08e-08
ln(IBI) by sex [Male]	-0.410	0.270	2.3	0.13
Family type [FC]	0.194	0.126	2.35	0.13
Maternal age	-0.029	0.036	0.68	0.41
Paternal age	-0.010	0.029	0.12	0.73

IBI = interbirth interval (months). FC = female-containing family, which is contrasted with families classified as male-only (MO). Estimates, chi-squared statistics, and P-values (Prob>ChiSq) are from a logistic regression model of affection status in the child born after the second affected child from each family (N=341) by the natural log of IBI in months, sex of the child, family type (FC or MO), maternal age, and paternal age at the time of the child's birth.

Table S4: Concordance rates in monozygotic and dizygotic twin pairs

A) Monozygotic twin pairs, N=112, 93.8% concordant

	N	Concordance	95% CI	Relative risk	P-value
Female-Female	20	85.00%	63.96 – 94.76%	F-F/M-M	
Male-Male	92	95.65%	89.35 – 98.30%	0.89	0.11

B) Dizygotic twin pairs, N=193 pairs, 43.0% concordant.

		N	Recur. rate	95% CI	Relative risk	P-value	Adj P
All	**Male co-twin**	109	61.47%	52.09 – 70.07%	M/F co-twin		
	Female co-twin	84	19.05%	12.08 – 28.72%	3.23	1.92e-09	7.66e-09
All	**Co-twin of female proband**	36	50.00%	34.47 – 65.53%	F/M proband		
	Co-twin of male proband	157	41.40%	33.99 – 49.22%	1.21	0.23	0.90
Male co-twin	**Female proband**	21	71.43%	50.04 – 86.19%	F/M proband		
	Male proband	88	59.09%	48.65 – 68.77%	1.21	0.22	0.86
Female proband	**Male co-twin**	21	71.43%	50.04 – 86.19%	M/F co-twin		
	Female co-twin	15	20.00%	7.05 – 45.19%	3.57	2.97e-03	0.012

C) Logistic regression for co-twin affection status by co-twin sex and proband sex in dizygotic twin pairs.

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-0.391	0.222	3.08	0.079
Co-twin sex [Male]	1.033	0.222	21.55	3.45e-06
Proband sex [Female]	0.156	0.222	0.49	0.48
Proband sex [Female] by co-twin sex [Male]	0.119	0.222	0.28	0.60

Unadjusted P-values in A) and B) are from one-sided Fisher's exact tests for co-twin affection status by co-twin sex or by proband twin sex. Adjusted P-values in B) have been corrected for 4 tests. In C), chi-squared statistics and P-values (Prob>Chisq) are from logistic regression for co-twin affection status by co-twin sex, proband twin sex, and the interaction between co-twin and proband sex.

Table S5: Adaptive behavior, intellectual ability, and ASD symptoms by sex and family type

A) Males vs. females, 1 randomly selected proband per family

	Males			Females			Males vs. females				
	N	Mean	SD	N	Mean	SD	Diff.	SE	t	P	Adj. P
VABS	587	60.91	18.62	177	64.34	20.92	-3.43	1.75	-1.96	0.051	0.82
PPVT	505	85.34	26.68	153	85.73	25.23	-0.39	2.36	-0.17	0.868	1
Raven's NVIQ	464	104.27	23.04	145	101.09	22.20	3.18	2.13	1.49	0.138	1
SRS	373	103.85	33.34	120	101.53	37.33	2.32	3.82	0.61	0.544	1

B) FC vs. MO, 1 randomly selected proband per family

	FC			MO			FC vs. MO				
	N	Mean	SD	N	Mean	SD	Diff	SE	t	P	Adj. P
VABS	293	64.47	20.40	471	59.99	18.25	4.42	1.46	3.02	2.60e-03	0.042
PPVT	255	87.24	24.72	403	84.29	27.27	3.13	2.06	1.52	0.130	1
Raven's NVIQ	245	103.03	21.20	364	103.83	23.94	-0.63	3.00	-0.34	0.733	1
SRS	193	99.53	36.13	300	105.70	32.95	-6.16	3.22	-1.91	0.057	0.91

C) FC vs. MO, 1 randomly selected male proband per family

	FC			MO			FC vs. MO				
	N	Mean	SD	N	Mean	SD	Diff	SE	t	P	Adj. P
VABS	255	62.79	18.79	472	59.86	18.16	2.85	1.45	1.97	0.049	0.79
PPVT	213	88.18	25.92	404	84.48	27.16	3.90	2.23	1.75	0.081	1
Raven's NVIQ	200	105.37	21.23	366	104.13	23.89	1.44	1.95	0.74	0.461	1
SRS	158	105.66	32.85	301	106.19	32.99	-0.53	3.23	-0.16	0.870	1

D) Males vs. females within FC families, 1 randomly selected affected brother & sister, paired test

	Males			Females			Males vs. females				
	N	Mean	SD	N	Mean	SD	Diff	SE	t	P	Adj. P
VABS	251	62.77	18.86	251	65.62	20.27	-2.85	1.34	-2.12	0.035	0.56
PPVT	171	89.91	25.04	171	89.89	24.49	0.02	2.28	0.01	0.992	1
Raven's NVIQ	163	107.20	20.99	163	103.53	23.39	3.67	2.22	1.65	0.100	1
SRS	142	107.27	33.01	142	104.93	35.33	2.34	3.82	0.61	0.542	1

FC, female-containing family; MO, male-only family; VABS, Vineland Adaptive Behavior Scales composite standard score; PPVT, Peabody Picture Vocabulary Test standard score; Raven NVIQ, Raven's Progressive Matrices estimated non-verbal intelligence quotient; SRS, Social Responsiveness Scale raw total score. T statistics and unadjusted P-values are from two-sided t-tests allowing for unequal variances for affection status by sex or by family type. For D), a paired t-test was used to compare affected males and females from the same families. Adjusted P-values have been corrected for 16 tests.

Table S6: Adaptive behavior, intellectual ability, and ASD symptoms by family stoppage status

A) Families who stopped vs. continued having children, 1 randomly selected proband per family

	Stop			Continue			Stop vs. continue				
	N	Mean	SD	N	Mean	SD	Diff.	SE	t	P	Adj. P
VABS	533	60.9	19.0	231	63.6	19.6	-2.71	1.53	-1.77	0.077	0.82
PPVT	461	84.4	26.9	197	87.9	24.9	-3.56	2.17	-1.64	0.102	1
Raven NVIQ	421	103.2	23.6	188	104.1	21.1	-0.86	1.92	-0.45	0.653	1
SRS	353	101.5	33.6	140	107.9	35.8	-6.45	3.51	-1.83	0.068	1

B) Families with ≥3 full sibling children who stopped vs. continued having children, 1 randomly selected proband per family

	Stop			Continue			Stop vs. continue				
	N	Mean	SD	N	Mean	SD	Diff.	SE	t	P-value	Adj. P
VABS	138	57.8	20.2	231	63.6	19.6	-5.75	2.15	-2.68	7.90e-03	0.13
PPVT	114	82.4	30.3	197	87.9	24.9	-5.55	3.35	-1.66	0.099	1
Raven NVIQ	112	101.5	27.2	188	104.1	21.1	-2.63	2.99	-0.88	0.380	1
SRS	92	103.7	34.7	140	107.9	35.8	-4.23	4.72	-0.90	0.371	1

C) FC Families with ≥3 full sibling children who stopped vs. continued having children, 1 randomly selected proband per family

	Stop			Continue			Stop vs. continue				
	N	Mean	SD	N	Mean	SD	Diff.	SE	t	P	Adj. P
VABS	43	56.2	22.8	99	67.0	20.2	-10.73	4.03	-2.66	9.60e-03	0.15
PPVT	35	86.1	28.1	87	89.8	23.8	-4.03	5.40	-0.75	0.459	1
Raven NVIQ	38	101.3	23.9	84	103.9	21.7	-2.88	4.55	-0.63	0.529	1
SRS	32	109.2	29.7	51	101.3	38.3	7.85	7.51	1.05	0.299	1

D) MO Families with ≥3 full sibling children who stopped vs. continued having children, 1 randomly selected proband per family

	Stop			Continue			Stop vs. continue				
	N	Mean	SD	N	Mean	SD	Diff.	SE	t	P	Adj. P
VABS	95	58.6	19.0	132	61.0	18.7	-2.54	2.54	-1.00	0.318	1
PPVT	79	80.7	31.2	110	86.5	25.8	-5.50	4.28	-1.28	0.201	1
Raven NVIQ	74	101.6	28.9	104	104.3	20.7	-2.49	3.92	-0.64	0.527	1
SRS	60	100.7	37.0	89	111.7	33.9	-10.93	5.98	-1.83	0.070	1

VABS = Vineland Adaptive Behavior Scales composite standard score; PPVT = Peabody Picture Vocabulary Test standard score; Raven NVIQ = Raven's Progressive Matrices estimated non-verbal intelligence quotient; SRS = Social Responsiveness Scale raw total score. T statistics and unadjusted P-values are from two-sided t-tests allowing for unequal variances for family's stoppage status. Adjusted P-values are corrected for 16 tests.