Absence of AGG interruptions is a risk factor for a full mutation expansion among ethnically diversed FMR1 premutation carriers

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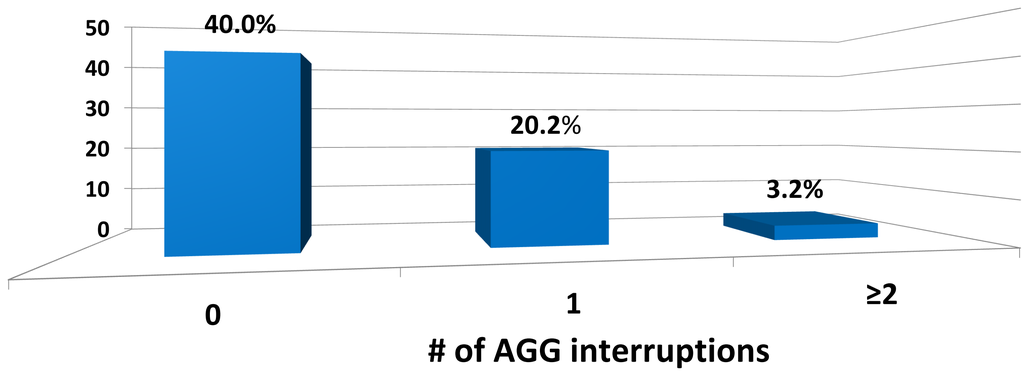
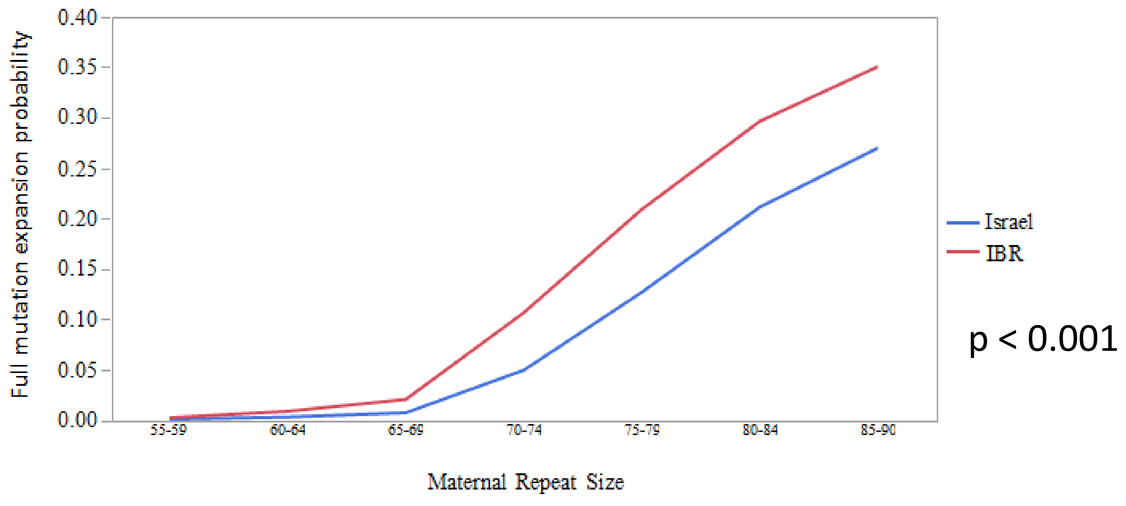
- Genetic counseling given to FMR1 premutation carriers is currently based solely upon the number of CGG repeats. However, recent studies revealed that AGG interruptions may decrease the risk of intergenerational expansion.
- All FMR1 premutation carriers who underwent chorionic villus sampling (CVS) or amniocentesis (AC) at Sheba Medical Center and the New York State Institute for Basic Research in Developmental Disabilities (IBR) during the period of 2011-2017 were included in this study. FMR1 PCR and Asuragen Kit were used to determine the # of CGG repeats and AGG interruptions in all women and fetuses.
- A combined data of 1471 transmissions of maternal premutation alleles:
  25.1% (369) stable; 74.9% (1,102) unstable;
  20.6% (303) Full mutation expansions
  <u>Unstable transmissions</u>:
  97.4% (388/397) of alleles with no AGGs;
  79.6% (513/644) of alleles with 1 AGG;
  46.7% (201/430) of alleles ≥ 2 AGGs.
- **<u>Full mutation expansions</u>:**
  40% (159/397) of alleles with **<u>no AGGs</u>**;
  20.2% (130/644) of alleles with **<u>1 AGG</u>**;
  3.2% (14/430) in alleles **<u>≥ 2 AGGs</u>**
- We recommend that the risk estimates for a full mutation expansion for FMR1 premutation carriers will include both CGG repeats and AGG interruptions .

Unstable transmissions and full mutation expansions sorted by repeat size and number of AGGs based on the combined Israeli and international data.

Maternal CGG repeat size	No. AGG	Total transmissions	unstable transmissions	%	Full mutations	%
55 to 59	0	52	49	94.2	1	1.9
	1	171	91	53.2	0	0
	2	145	21	14.5	0	0
	3	16	0	0	0	0
	4	3	0	0	0	0
	5	1	0	0	0	0
60 to 64	0	74	73	98.6	4	5.4
	1	121	90	74.4	0	0
	2	96	42	43.8	0	0
	3	7	3	42.9	0	0
	4	2	1	50	0	0
65 to 69	0	70	66	94.3	7	10
	1	77	63	81.8	0	0
	2	50	34	68	0	0
	3	3	1	33.3	0	0
70 to 74	0	54	53	98.1	28	51.9
	1	79	77	97.5	6	7.6
	2	33	27	81.8	0	0
75 to 79	0	60	60	100	43	71.7
	1	65	62	95.4	26	40
	2	28	28	100	3	10.7
80 to 84	0	51	51	100	45	88.2
	1	66	65	98.5	43	65.2
	2	29	29	100	6	20.7
85 to 90	0	36	35	97.2	31	86.1
	1	65	65	100	55	84.6
	2	17	16	94.1	5	29.4
Total		1471	1102	74.9	303	20.6

Risk for a FM Expansion according to # of AGG's





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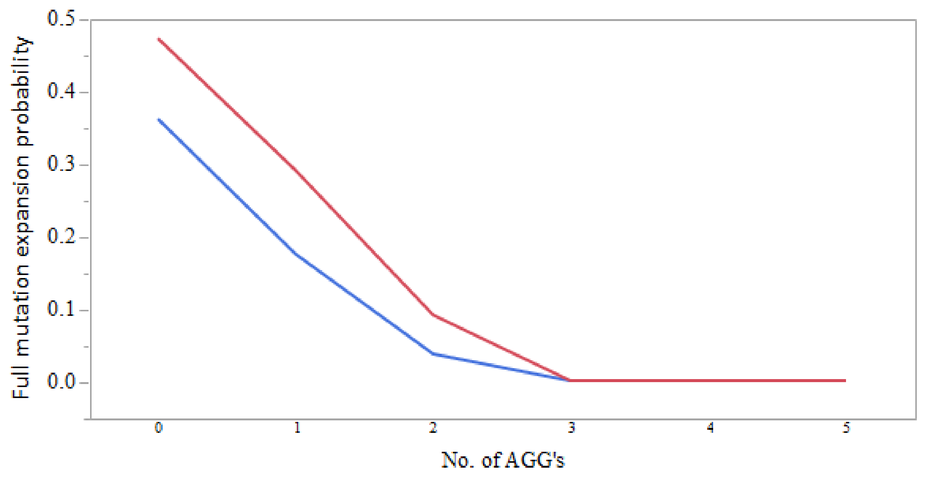

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