Supplementary Table S1. Additional details of CGG repeat testing in probands and information used to apply pathogenicity criteria for variants in Table 1.

Ref.	Location			# affected with variant, sex	CGG repeats	Other variants in proband	Inheritance/originating allele	Segregation	*FMR1* expression in patient	Ascertainment	ACMG criteria	Conclusion
	Proximal	Distal	Type									
[1]	>140198205 (DXS1232-DXS105), <7 Mb upstream	<148215436 (between 141R-DXS533), 264 kb downstream	Del	1M	Absent		Maternal (unaffected), origin de novo in mother (both grandparents lack deletion with normal CGG repeat counts)			ID, obesity	CNV 2A 5G_0.1	PATH (1.1)
[2]	>140784366 (CDR1-sWXD2905), <7 Mb upstream	<148203554 (DXS7847); >DXS8318, <252 kb downstream	Del	1M + mother	Absent		Maternal (mildly affected)			DD, clinical suspicion	CNV 2A 5G_0.1	PATH (1.1)
[3] #3	142254456, 5.7 Mb upstream	148191426, 240 kb downstream	Del het	1F	?		De novo			Epilepsy research database	CNV 2A 5A_0.15	PATH (1.15)
[4]	147158490, 753 kb upstream	148171882, 221 kb downstream	Mosaic del (90%)	1M	23 (weak signal)		Occurred on 23-repeat allele (mother has 23, 30-repeat alleles); breakpoints are LINE1 elements			ID	CNV 2A 5A_0.15	PATH (1.15)
[5]	147630212-147721930 (DXS532-DXS548), 200-300 kb upstream	Intragenic, ~30kb downstream of HTF island	Del	1M	no fragile site		De novo			ID, facies, testicle size	SVI PVS1_Strong PS2 PM2	PATH
[6]	147653688, 260 kb upstream	147955394, 4 kb downstream	Del	1M			Mosaic in mother (3/400 lymphocytes) & same deletion in subsequent pregnancy			Clinical FXS	CNV 2A 5G_0.1	PATH (1.1)
[7]	>147722126 (DXS548); >DXS477, <cosmid 494; <190 kb upstream	147932685-147932763, exon 9	Del	1M	Absent		? (mother "borderline intelligence")			ID	SVI PVS1_Strong PM2	LPATH
[8] #2	>147722126 (DXS548); >G9L, <FRAXAC1; <190 kb upstream	147936614-147937465, intron 10	Del	1M	no fragile site		De novo on 19-repeat allele (mother 19, 51 repeats)		mRNA absent (lymphoblastoid cell line RT-PCR)	ID, clinical FXS	SVI PVS1_Strong PS2 PS3 PM2	PATH

[9]	<147722126 (includes DXS548), not mapped further; >190 kb upstream	?, includes *FMR1*	Del	1M + infant brother	Absent	Mat germline mosaicism (2 brothers, absent in mother) (mother has congenital digit amputations)			DD	CNV 2A 5G_0.1	PATH (1.1)
[10] #18072	147787231, 125 kb upstream	148041310, 90 kb downstream	Del	2M		Maternal (unaffected het)	Present in both affected brothers in this family		Autism cohort	CNV 2A 5G_0.1	PATH (1.1)
[11] #3	147838064, 74 kb upstream	148103912, 400 kb downstream	Del	1M	no PCR product	De novo			Clinical lab sample	CNV 2A 5A_0.15	PATH (1.15)
[12]	15-80 kb upstream (G9L YAC)	147930245-147932424, intron 7	Del	1M	Absent	De novo (both maternal alleles normal repeat length)		FMRP absent (lymphoblastoid cell line)	DD	SVI PVS1_Strong PS2 PS3 PM2	PATH
[13], [14]	4.4 kb upstream	194 kb downstream	Del	1M	Absent	Maternal (unaffected mosaic); breakpoints are within L1MC2 and MIR3 elements			Preschool cohort with ID and >=1 FXS feature	CNV 2A 5G_0.1	PATH (1.1)
[15] #24	147910365, 1.5 kb upstream	147912050 (within CGG repeat, no AGG interspersions in remaining sequence)	Del	4M, 2F	~45	Maternal (unaffected)	Males: 4 affected/4 hemizygotes (#14, 15, 23, 24) and 0 affected/4 noncarriers (#5, 13, 18, 19); Females: 2 affected/7 het and 0 affected/3 noncarriers		Speech delay, hyperactivity	CNV 2C2_0.3 5D_0.3	VUS (0.6)
[8] #1	147911457, 462 bp upstream of transcription start	147912135, c.-45 (including entire CGG repeat)	Mosaic del (40%)	1M	no fragile site	De novo			Epilepsy, other clinical	CNV 2C2_0.3 5A_0.15	VUS (0.45)

[16]	~147911751 (~300 bp upstream of CGG)	? (~400 bp size deletion)	Del	1M	Absent	13p+ polymorphism (karyotype), father "mentally slow"	De novo (mother is FXS full mutation 700-900 repeat het, unaffected with 95% skewed XCI toward nl allele)		ID, aggressive behavior	CNV 2C2_05A_0.15	VUS (0.15)
[17]	147911831, 88 bp upstream of transcription start	147912185, c.6	Del	1M				FMRP absent (lymphoblastoid cell line)	ID male with >=2 FXS features	SVI PVS1_Moderate PS3 PM2	LPATH
[18]	147911966, c.-214	Within CGG repeats, 19 remaining (no AGGs)	Del	N/A (M)			Maternal (unaffected mosaic, het for 430-530 CGG full mutation); del on full mutation allele by haplotype		Unaffected, prenatal testing	CNV 2C2_05A_0	VUS (0)
[19]	147911981, c.-199	147912050 (within CGG repeats, 9 remaining)	Del het	N/A			Transmitted from unaffected female proband to male fetus		Unaffected individual, population screening study	CNV 2C2_05F_0	VUS (0)
[20]	147911984, c.-196	147912140, c.-40 (distal to CGG repeat)	Del het	N/A (F)	Absent	Large deletion involving FMR1 *in trans* (46,X,del[X][q24])	De novo, from maternal full mutation allele	FMRP present (lymphoblastoid)	Asymptomatic; due to brother with FXS	CNV 2C2_05A_-0.3	VUS (-0.3) with additional benign evidence
[21]	147912024, c.-156	147912111, c.-69 (1 bp distal to CGG repeat)	Del	N/A (M)			De novo, from maternal full mutation allele	mRNA level normal (whole blood qRT-PCR)	Asymptomatic; due to maternal full mutation	CNV 2C2_05A_-0.3 (unaffected)	VUS (-0.3) with additional benign evidence

[22] APN26, [23] #1	<147948682 (Deletion of exon 17)	>147964837 (Deletion of exon 17)	Del	3M		Maternal (unaffected)	Present in 3 affected brothers	Normal mRNA quantity but retained intron 16 sequence (1 brother) and 44 aa truncation of FMRP with 50% reduced level (2 brothers) (blood, lymphoblastoid cell line)	ID sequencing cohort	SVI PVS1_Moderate PS3_Moderate PM2 PP1	LPATH
[19]	Undetermined 5′ UTR	Loss of exon 1	Del	1 male fetus		Mother is full mutation (280 repeat) het			Population screening study	SVI PVS1_Strong PS3	PATH
[24] #3660	Intragenic (~197 bp flanking CGG repeat in exon 1)	Intragenic	Del	1M			?, FHx mild ID mother, psychiatric problems mother, 2 mat uncles with ID (no genotypes)		ID cohort	CNV 2C2(0) 5G_0.1	VUS (0.1)
Potentially including *AFF2* (additional reports of confirmed *FMR1-AFF2* deletions not shown)											
[11] #4	142773651, 5.1 Mb upstream	148673162, 722 kb downstream	Del het	1F		De novo			Clinical lab sample	CNV 2A 5A_0.15	PATH (1.15)
[3] #2	143096757, 4.8 Mb upstream	149186971, 1.2 Mb downstream	Del het	1F	?	De novo			Epilepsy research database	CNV 2A 5A_0.15	PATH (1.15)
Duplications											
[11] #1	147707513 (204 kb upstream)	148070742 (120 kb downstream)	Dup het	1		De novo			clinical testing (lab)	CNV 2H_0	VUS (0.6)

											4C_0.15x3 5A_0.15	
[11]	147709189 (203 kb upstream)	147976294 (25 kb downstream)	Dup	1						clinical testing for seizures (lab)	CNV 2H_0 4C_0.15x3 5A_0.15	VUS (0.6)
[11] #2	147796927 (115 kb upstream)	148144967 (194 kb downstream)	Dup het	1			De novo			clinical testing (lab)	CNV 2H_0 4C_0.15x3 5A_0.15	VUS (0.6)
[25]	147894723 (17 kb upstream)	147979356 (28 kb downstream)	Dup	1	29	hg18: 1q44[245,377,586-245,556,179]x3 (from unaffected father), 4p15.31[22,897,572-23,066,434]x1	De novo		Normal mRNA level (leukocyte qRT-PCR)	Myoclonic seizures	CNV 2H_0 4C_0.15x3 5A_0.15	VUS (0.6)
[26]	147912003 (c.-177)	147912051 (c.-129)	Dup	N/A (0.2-0.3% X chromosomes in study)				Present in multiple unaffected males		Finnish population samples	CNV 2I_0 4O_-1	BEN (-1)

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