Supplementary Table S1 Sample information NGS data statistics

Sample information			NGS data statistics	
Family ID	Sample ID	Proband gender	Average sequencing depth on target	Fraction of target covered with at least 20x
WS1	WS1-P	Male	125.55	0.983
WS1	WS1-F		124.84	0.978
WS1	WS1-M		174.45	0.989
WS2	WS2-P	Male	162.68	0.984
WS2	WS2-F		149.26	0.981
WS2	WS2-M		158.73	0.986
WS3	WS3-P	Male	157.49	0.984
WS3	WS3-F		124.63	0.976
WS3	WS3-M		124.21	0.977
WS4	WS4-P	Male	138.35	0.985
WS4	WS4-F		139.14	0.982
WS4	WS4-M		142.74	0.985
WS5	WS5-P	Male	160.11	0.991
WS5	WS5-F		148.37	0.985
WS5	WS5-M		143.94	0.981
WS6	WS6-P	Male	161.96	0.987
WS6	WS6-F		161.03	0.986
WS6	WS6-M		164.52	0.985
WS7	WS7-P	Male	153.05	0.989
WS7	WS7-F		135.77	0.981
WS7	WS7-M		123.62	0.976
WS8	WS8-P	Female	157.02	0.988
WS8	WS8-F		173.93	0.988
WS8	WS8-M		176.61	0.984
WS9	WS9-P	Male	160.05	0.993
WS9	WS9-F		166.48	0.987
WS9	WS9-M		137.19	0.979
WS10	WS10-P	Female	155.77	0.985
WS10	WS10-F		164.07	0.986

WS10	WS10-M		159.8	0.984
WS11	WS11-P	Male	164.86	0.992
WS11	WS11-F		147.95	0.984
WS11	WS11-M		161.81	0.985
WS12	WS12-P	Male	132.81	0.986
WS12	WS12-F		149.09	0.981
WS12	WS12-M		139.88	0.983
WS13	WS13-P	Male	165.14	0.985
WS13	WS13-F		132.46	0.974
WS13	WS13-M		130.61	0.969
WS14	WS14-P	Male	132.49	0.984
WS14	WS14-F		151.68	0.981
WS14	WS14-M		168.36	0.988
WS15	WS15-P	Male	156.18	0.99
WS15	WS15-F		161.3	0.986
WS15	WS15-M		151.99	0.984
WS16	WS16-P	Male	172.68	0.987
WS16	WS16-F		154.36	0.981
WS16	WS16-M		143.18	0.973
WS17	WS17-P	Male	134.73	0.985
WS17	WS17-F		141.47	0.985
WS17	WS17-M		171.75	0.988
WS18	WS18-P	Female	176.45	0.985
WS18	WS18-F		155.33	0.985
WS18	WS18-M		156.11	0.985
WS19	WS19-P	Female	182.15	0.988
WS19	WS19-F		138.59	0.981
WS19	WS19-M		149.98	0.981
WS20	WS20-P	Female	168.77	0.986
WS20	WS20-F		153.92	0.985
WS20	WS20-M		146.39	0.985
WS21	WS21-P	Female	169.75	0.984
WS21	WS21-F		131.81	0.979

WS21	WS21-M		144.42	0.982
WS22	WS22-P	Male	140.36	0.988
WS22	WS22-F		150.5	0.984
WS22	WS22-M		152.17	0.982
WS23	WS23-P	Male	179.96	0.986
WS23	WS23-F		162.38	0.986
WS23	WS23-M		159.48	0.986
WS24	WS24-P	Male	156.94	0.984
WS24	WS24-F		127.83	0.98
WS24	WS24-M		140.27	0.982
WS25	WS25-P	Male	155.4	0.981
WS25	WS25-F		143.07	0.981
WS25	WS25-M		160.65	0.983
WS26	WS26-P	Female	177.11	0.98
WS26	WS26-F		132.97	0.979
WS26	WS26-M		169.72	0.986
WS27	WS27-P	Male	188.66	0.987
WS27	WS27-F		163.03	0.986
WS27	WS27-M		160.95	0.986
WS28	WS28-P	Male	154.69	0.987
WS28	WS28-F		130.14	0.981
WS28	WS28-M		162.05	0.983
WS29	WS29-P	Male	173.77	0.986
WS29	WS29-F		144.56	0.982
WS29	WS29-M		139.19	0.983
WS30	WS30-P	Male	157.87	0.987
WS30	WS30-F		153.9	0.981
WS30	WS30-M		187.49	0.986
WS31	WS31-P	Male	150.54	0.99
WS31	WS31-F		148.25	0.983
WS31	WS31-M		130.31	0.98
WS32	WS32-P	Male	166.72	0.984
WS32	WS32-F		151.11	0.983

WS32	WS32-M		170.54	0.987
WS33	WS33-P	Male	138.28	0.986
WS33	WS33-F		159.84	0.986
WS33	WS33-M		159.39	0.984
WS34	WS34-P	Female	133.09	0.984
WS34	WS34-F		153.32	0.984
WS34	WS34-M		142.42	0.981
WS35	WS35-P	Male	164.82	0.983
WS35	WS35-F		168.35	0.984
WS35	WS35-M		158.76	0.986
WS36	WS36-P	Male	162.22	0.987
WS36	WS36-F		156.53	0.984
WS36	WS36-M		158.5	0.985
WS37	WS37-P	Female	152.29	0.982
WS37	WS37-F		132.29	0.981
WS37	WS37-M		141.11	0.982
WS38	WS38-P	Female	184.05	0.987
WS38	WS38-F		150.19	0.985
WS38	WS38-M		141.6	0.981
WS39	WS39-P	Male	155.85	0.99
WS39	WS39-F		165.15	0.986
WS39	WS39-M		184.45	0.993
WS40	WS40-P	Male	162.07	0.982
WS40	WS40-F		164.71	0.987
WS40	WS40-M		147.78	0.979
WS41	WS41-P	Female	155.29	0.981
WS41	WS41-F		140.16	0.983
WS41	WS41-M		133.02	0.981
WS42	WS42-P	Female	117.81	0.982
WS42	WS42-F		125.94	0.979
WS42	WS42-M		168.46	0.986
WS43	WS43-P	Female	161.04	0.985
WS43	WS43-F		127.65	0.976

WS43	WS43-M		135.73	0.984
WS44	WS44-P	Female	167.76	0.983
WS44	WS44-F		130.18	0.977
WS44	WS44-M		136.64	0.979
WS45	WS45-P	Male	154.86	0.987
WS45	WS45-F		156.64	0.985
WS45	WS45-M		127.39	0.98
WS46	WS46-P	Male	156.83	0.983
WS46	WS46-F		140.31	0.975
WS46	WS46-M		178.56	0.981
WS47	WS47-P	Male	147.28	0.988
WS47	WS47-F		142.94	0.992
WS47	WS47-M		158.77	0.99
WS48	WS48-P	Male	155.76	0.989
WS48	WS48-F		152.19	0.984
WS48	WS48-M		122.1	0.979
WS49	WS49-P	Male	160.61	0.982
WS49	WS49-F		163.63	0.984
WS49	WS49-M		138.12	0.981
WS50	WS50-P	Female	170.35	0.983
WS50	WS50-F		171.27	0.985
WS50	WS50-M		170.66	0.984
WS51	WS51-P	Male	130.53	0.984
WS51	WS51-F		180.78	0.988
WS51	WS51-M		175.82	0.985
WS52	WS52-P	Female	153.46	0.982
WS52	WS52-F		157.49	0.981
WS52	WS52-M		135.14	0.981
WS53	WS53-P	Male	116.79	0.977
WS53	WS53-F		157.49	0.987
WS53	WS53-M		172.37	0.988
WS54	WS54-P	Female	127.37	0.98
WS54	WS54-F		142.33	0.983

WS54	WS54-M		219.59	0.99
WS55	WS55-P	Male	144.06	0.988
WS55	WS55-F		132.62	0.983
WS55	WS55-M		139.22	0.983
WS56	WS56-P	Female	144.45	0.985
WS56	WS56-F		126.68	0.982
WS56	WS56-M		162.91	0.991

Supplementary Table S2 Sample age and gender used in mRNA express analysis

Age (year)	Number of male samples	Number of female samples	Total
-0.421917808	16		350
-0.402739726	15	16	31
-0.364383562	0	11	11
-0.326027397	0	14	14
-0.306849315	39	0	39
-0.249315068	28	16	44
-0.230136986	0	46	46
-0.17260274	14	0	14
-0.153424658	16	0	16
0.3	15	0	15
0.333333333	32	0	32
0.5	0	16	16
0.671232877	0	13	13
0.833333333	11	0	11
1	0	16	16
2	0	16	16
Total	186	164	350

Supplementary Table S3 mRNA expression data of candidate genes in different region of brain in 350 normal fetus and <3 years old children

Gene	Gender	A1C	AMY	CBC	DFC	HIP	IPC	ITC	M1C	MD	MFC	OFC	S1C	STC	STR	V1C	VFC
ABCA7	F	1.623333333	1.772727273	10.69714286	1.666923077	1.978333333	2.074545455	1.684545455	2.2375	5.508888889	1.946153846	1.767272727	1.961111111	1.77	2.193333333	2.832727273	1.896666667
C9orf163	F	0.245555556	0.25	0.432857143	0.203076923	0.233333333	0.241818182	0.221818182	0.16875	0.123333333	0.219230769	0.160909091	0.163333333	0.214545455	0.217777778	0.214545455	0.151666667
CASD1	F	11.87888889	13.23181818	15.33428571	15.82846154	14.45583333	12.37636364	12.71909091	14.66125	15.82222222	15.76769231	16.77909091	15.21111111	11.56909091	14.49444444	11.65545455	14.23583333
CES4A	F	4.981111111	3.880909091	7.73	3.606153846	3.908333333	5.232727273	5.267272727	4.43875	1.927777778	5.302307692	4.02	4.446666667	6.04	3.887777778	7.562727273	5.8625
COL9A2	F	11.32111111	15.47272727	12.75714286	7.803846154	16.445	9.64	11.53090909	11.80125	9.313333333	10.18153846	14.04272727	7.384444444	12.67636364	17.07777778	14.70090909	7.459166667
CYFIP2	F	88.72111111	81.57909091	90.99857143	86.09076923	78.05166667	102.4345455	88.58454545	96.54625	125.7677778	81.82153846	80.98090909	99.43222222	90.90727273	72.02111111	95.64181818	95.90583333
DOCK2	F	0.611111111	0.641818182	0.818571429	0.589230769	0.72	0.502727273	0.54	0.575	0.95	0.52	0.62	0.505555556	0.592727273	0.665555556	0.545454545	0.644166667
FAT3	F	13.31666667	9.12	4.485714286	12.51692308	5.209166667	17.22363636	10.05636364	19.025	12.19555556	10.11076923	9.130909091	17.18111111	11.86727273	23.69222222	17.43363636	12.05083333
GNB1	F	454.5077778	415.3990909	414.6714286	448.0561538	366.5758333	477.8863636	443.5654545	471.6675	388.71	393.9030769	395.88	476.5011111	436.5172727	435.2288889	444.8163636	484.6491667
KMT2D	F	10.56555556	11.15636364	13.85285714	9.552307692	8.885	11.66181818	9.991818182	11.80375	6.807777778	9.193076923	8.802727273	9.787777778	10.37090909	11.09444444	12.58818182	11.415
MAP3K12	F	16.59888889	14.07363636	41.04142857	14.97923077	13.72166667	18.31	15.68181818	16.3325	13.06	16.05307692	13.84727273	17.45333333	16.42909091	13.81777778	18.40727273	17.86
MYCBP2	F	32.21	33.44636364	31.80571429	30.99692308	26.96	37.24636364	35.74727273	39.23375	28.37222222	27.88769231	24.21909091	36.93222222	34.22090909	35.01666667	36.76636364	37.775
MYO1H	F	0.1	0.160909091	0.064285714	0.098461538	0.169166667	0.152727273	0.085454545	0.05375	0.078888889	0.157692308	0.037272727	0.05	0.133636364	0.054444444	0.213636364	0.070833333
NPC1L1	F	0.004444444	0.003636364	0.04	0.009230769	0.011666667	0.011818182	0.01	0.0025	0.006666667	0.022307692	0.015454545	0.008888889	0.018181818	0.006666667	0.015454545	0.020833333
PNMA1	F	121.7944444	111.3345455	116.4542857	124.9161538	117.5383333	135.9981818	127.75	128.1325	118.5866667	122.9892308	115.5181818	128.8966667	124.08	125.1966667	129.1290909	128.9375

POFUT2	F	4.412222222	6.041818182	9.795714286	4.803076923	6.569166667	4.410909091	4.675454545	4.38875	5.616666667	5.65	5.43	4.248888889	4.930909091	5.325555556	4.982727273	5.200833333
RYR1	F	2.477777778	2.908181818	4.138571429	1.324615385	3.474166667	2.069090909	1.63	3.16875	2.756666667	2.154615385	2.413636364	1.658888889	2.11	2.291111111	1.478181818	2.451666667
RYR3	F	2.565555556	2.117272727	4.151428571	1.502307692	2.1475	2.722727273	2.677272727	2.8	1.614444444	1.911538462	1.568181818	2.166666667	2.782727273	3.202222222	2.720909091	2.319166667
VWA3A	F	0.276666667	0.597272727	0.404285714	0.113076923	0.571666667	0.205454545	0.293636364	0.3075	0.676666667	0.207692308	0.248181818	0.168888889	0.225454545	0.395555556	0.168181818	0.130833333
ACE2	M	0.018	0.045	0.075555556	0.024545455	0.067272727	0.022727273	0.056666667	0.02	0.058181818	0.02	0.066	0.026666667	0.013333333	0.050909091	0.031	0.032727273
ADGRG4	M	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
ALG3	M	6.673	6.887	8.923333333	7.032727273	7.064545455	5.988181818	6.54	7.206666667	7.256363636	6.88	6.428	6.477777778	6.415555556	7.756363636	7.735	6.883636364
ARHGAP17	M	8.483	10.974	12.70555556	8.909090909	10.59818182	7.833636364	5.846666667	7.697777778	8.319090909	8.657272727	9.315	7.861111111	7.964444444	9.440909091	8.365	9.429090909
ARSF	M	0.816	1.048	0.314444444	0.898181818	2.340909091	0.77	1.005555556	0.698888889	0.852727273	0.77	0.87	0.657777778	0.907777778	1.03	0.904	0.78
ATP2A2	M	70.154	56.507	68.69222222	64.99	61.02363636	65.31909091	61.42444444	70.54888889	78.48545455	58.15090909	65.736	69.17222222	67.68333333	62.72363636	70.773	68.20909091
AWAT1	M	0.008	0	0.077777778	0.02	0	0.011818182	0	0.011111111	0.005454545	0.006363636	0	0	0	0	0.003	0.002727273
CAT	M	12.531	19.656	17.50555556	13.95818182	20.56090909	14.27090909	12.27333333	12.66111111	11.89363636	12.95454545	13.735	14.29888889	12.41333333	13.67090909	15.305	12.45090909
CCDC120	M	6.322	5.443	7	6.871818182	4.840909091	5.228181818	4.498888889	5.655555556	5.242727273	5.211818182	5.186	5.65	7.188888889	5.004545455	6.696	5.981818182
CCDC14	M	12.424	16.006	10.59777778	13.38181818	13.29727273	11.27363636	10.20111111	11.69222222	6.275454545	11.92181818	12.201	11.59777778	11.37333333	12.81545455	14.822	13.91363636
CCPG1	M	12.388	8.442	12.66666667	9.953636364	9.903636364	13.15727273	10.21777778	9.537777778	9.406363636	9.518181818	9.353	11.03333333	10.57222222	8.322727273	11.12	10.15818182
CD99L2	M	34.177	32.432	35.42777778	35.23	31.00090909	32.45545455	34.15333333	33.70444444	44.52909091	32.60818182	35.005	35.32888889	35.44777778	34.09090909	34.876	35.38272727
CDK16	M	84.724	78.896	106.1922222	93.35909091	78.17272727	72.59545455	87.28666667	81.83666667	88.22272727	77.67	84.906	80.76888889	104.6477778	81.08363636	85.29	91.55909091

CENPE	M	0.274	1.553	0.927777778	0.411818182	1.224545455	0.297272727	0.195555556	0.525555556	0.634545455	0.414545455	0.499	0.181111111	0.346666667	1.045454545	0.59	0.355454545
CFAP69	M	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A	#N/A
CLCN6	M	11.551	9.791	10.36222222	11.23909091	9.242727273	9.599090909	9.203333333	10.75555556	11.73181818	10.62909091	10.915	9.928888889	11.09333333	7.767272727	10.349	11.39363636
COL4A5	M	1.254	3.857	2.375555556	1.678181818	7.353636364	1.352727273	1.245555556	2.047777778	1.504545455	2.579090909	2.302	2.015555556	1.454444444	1.904545455	2.317	1.776363636
CXorf36	M	1.594	2.359	2.371111111	2.637272727	2.462727273	2.061818182	2.39	3.14	2.492727273	2.797272727	2.677	2.657777778	1.536666667	2.942727273	1.654	2.384545455
CYFIP1	M	17.891	23.321	20.99444444	17.72181818	19.95454545	16.43363636	16.97222222	13.68444444	13.43363636	14.94454545	15.244	17.86555556	18.47222222	12.96454545	18.301	17.87
DZANK1	M	2.956	2.78	2.691111111	3.222727273	3.199090909	2.409090909	3.177777778	2.39	3.319090909	3.008181818	2.762	3.031111111	3.026666667	3.132727273	2.802	3.158181818
EGR3	M	9.052	6.314	0.221111111	7.52	3.199090909	7.860909091	9.242222222	8.951111111	1.403636364	4.740909091	7.079	9.136666667	10.26888889	9.056363636	7.018	6.49
FBXO39	M	0.011	0.075	0.086666667	0.014545455	0.098181818	0.015454545	0.037777778	0.015555556	0.058181818	0.03	0.066	0.018888889	0.016666667	0.059090909	0.021	0.025454545
FRMPD3	M	1.267	1.687	4.278888889	1.985454545	1.754545455	1.3	1.133333333	2.043333333	0.738181818	1.714545455	1.707	1.857777778	1.437777778	0.919090909	1.832	1.745454545
GNL3L	M	2.247	2.326	2.688888889	2.165454545	2.472727273	1.954545455	1.557777778	1.794444444	2.322727273	2.209090909	2.022	2.082222222	2.577777778	2.112727273	2.709	2.207272727
GOLGA5	M	11.69	9.084	10.27555556	10.19363636	9.271818182	10.67454545	8.972222222	11.43333333	8.821818182	9.929090909	10.885	10.44	9.522222222	8.18	10.724	9.908181818
GPR119	M	0	0	0.02	0	0	0	0	0.016666667	0.002727273	0	0.015	0	0	0	0	0
GPRASP1	M	11.051	10.38	17.13111111	9.891818182	10.01090909	9.504545455	9.741111111	8.447777778	15.71454545	10.81545455	9.903	9.045555556	11.48777778	12.94545455	10.009	10.72181818
GPT2	M	15.237	25.922	16.71555556	16.26181818	24.45090909	14.21	15.81333333	13.92333333	15.83545455	15.71181818	14.758	12.68666667	17.86666667	18.89090909	14.71	16.47
HMCN1	M	0.416	0.347	1.253333333	0.829090909	2.121818182	0.251818182	0.347777778	0.833333333	0.993636364	0.550909091	0.746	0.472222222	0.426666667	0.604545455	0.517	0.477272727
HUWE1	M	32.61	30.199	35.42666667	32.58545455	28.87909091	27.59090909	27.65777778	31.72555556	25.52	31.99454545	30.508	30.47111111	34.08555556	26.53545455	37.302	31.97454545

ITM2A	M	47.782	85.339	69.94888889	77.14090909	79.95909091	73.5	78.01111111	86.91777778	84.62090909	86.73636364	89.729	96.19111111	54.28	99.22909091	53.532	81.84636364
LHFPL1	M	0.098	0.257	0.166666667	0.093636364	0.162727273	0.164545455	0.12	0.145555556	0.545454545	0.154545455	0.169	0.085555556	0.148888889	0.302727273	0.101	0.071818182
MACF1	M	61.037	57.27	66.62666667	71.15090909	51.48181818	56.60636364	47.30888889	58.74444444	54.44727273	68.69909091	67.756	59.00666667	62.26444444	54.39454545	62.171	70.49545455
MAOB	M	3.645	7.732	3.006666667	3.93	9.019090909	3.51	4.207777778	4.135555556	9.377272727	5.774545455	4.599	4.01	4.173333333	7.416363636	2.872	4.401818182
MAP3K15	M	0.315	0.278	0.431111111	0.275454545	0.309090909	0.290909091	0.241111111	0.203333333	0.2	0.391818182	0.376	0.237777778	0.327777778	0.322727273	0.274	0.31
MAP7D3	M	0.316	1.086	1.702222222	0.374545455	1.321818182	0.29	0.404444444	0.461111111	1.058181818	0.408181818	0.379	0.298888889	0.387777778	1.884545455	0.522	0.337272727
ME3	M	16.434	11.397	15.20777778	20.55	13.76545455	14.89272727	15.18222222	15.39555556	22.18090909	18.45545455	17.856	15.34666667	18.80777778	19.14454545	14.51	21.24909091
MRPL17	M	13.339	18.547	18.75555556	13.47545455	19.65090909	12.92272727	14.96777778	12.01666667	17.40818182	13.59818182	13.796	13.16555556	16.42777778	18.50818182	15.801	14.38181818
MSL3	M	18.226	13.181	14.59666667	17.27545455	14.69090909	17.72363636	13.42555556	13.39	17.06363636	16.55272727	16.366	15.48111111	15.53666667	15.79909091	14.668	17.23727273
MYO18A	M	29.192	23.2	23.47555556	30.46818182	22.24818182	25.64090909	26.51777778	26.32222222	28.73818182	25.99090909	26.634	28.92	33.94888889	22.94909091	29.445	27.76
NOS3	M	2.095	2.597	2.303333333	3.229090909	2.861818182	3.731818182	3.421111111	4.678888889	3.419090909	3.437272727	3.171	4.746666667	2.193333333	2.962727273	1.973	3.227272727
OR8D2	M	0	0	0	0	0	0	0	0.004444444	0	0	0	0	0	0	0	0
ORC3	M	11.587	11.441	14.63222222	8.513636364	12.52545455	10.41909091	10.92333333	7.875555556	11.62	9.221818182	9.549	8.745555556	9.792222222	10.83545455	9.578	9.264545455
PARS2	M	1.312	1.794	2.027777778	1.406363636	1.665454545	1.243636364	1.392222222	1.221111111	1.357272727	1.605454545	1.376	1.287777778	1.334444444	1.773636364	1.472	1.38
PFKFB4	M	5.997	5.002	6.097777778	6.410909091	5.534545455	6.247272727	5.336666667	5.702222222	6.39	6.097272727	5.8	6.01	6.327777778	4.869090909	6.478	6.645454545
PHKA1	M	0.674	1.441	0.84	0.734545455	1.267272727	0.621818182	0.732222222	0.733333333	1.367272727	0.749090909	0.704	0.732222222	0.716666667	1.41	0.795	0.693636364
PLEKHG2	M	15.299	16.543	11.72	18.23	14.44454	12.55	13.05	12.92444	8.947272	14.36909	16.406	14.00555	17.13	15.56090	19.246	15.07545

						545			444	727	091		556		909		455
PNMA3	M	7.045	5.547	6.123333333	7.101818182	5.552727273	5.637272727	6.621111111	5.34	6.178181818	6.126363636	6.165	6.234444444	8.068888889	5.85	6.53	6.593636364
PNPLA4	M	5.967	5.598	7.482222222	6.085454545	8.687272727	6.263636364	6.505555556	5.31	7.809090909	5.758181818	6.016	5.274444444	6.116666667	7.637272727	6.633	5.738181818
PRICKLE3	M	0.289	0.397	0.708888889	0.336363636	0.420909091	0.351818182	0.368888889	0.471111111	0.361818182	0.347272727	0.383	0.528888889	0.28	0.458181818	0.348	0.434545455
REPS2	M	4.317	4.581	4.368888889	3.967272727	2.914545455	3.537272727	3.905555556	3.953333333	3.200909091	3.63	3.664	4.353333333	4.58	3.131818182	3.945	4.11
RPGR	M	1.407	1.962	2.102222222	1.394545455	4.015454545	1.221818182	1.056666667	0.98	3.384545455	1.436363636	1.174	1.416666667	1.203333333	2.024545455	1.688	1.087272727
RYR2	M	11.042	5.446	7.957777778	5.151818182	4.030909091	6.669090909	7.778888889	5.105555556	1.728181818	4.774545455	6.402	7.48	10.61222222	8.235454545	10.566	5.868181818
SH3KBP1	M	16.608	12.007	11.29777778	14.85272727	18.90545455	15.60727273	13.88888889	11.95444444	22.16818182	14.70363636	14.015	14.17444444	20.34111111	17.38545455	16.307	14.06636364
SHROOM2	M	7.418	8.82	9.892222222	7.047272727	4.395454545	5.334545455	6.764444444	6.131111111	13.32545455	5.224545455	6.862	5.934444444	6.642222222	8.559090909	4.243	8.13
SIPA1L3	M	7.13	5.992	11.06777778	6.340909091	6.609090909	5.497272727	4.853333333	6.985555556	5.384545455	5.099090909	6	5.461111111	7	5.766363636	7.305	5.824545455
SLC37A1	M	8.521	7.072	9.792222222	10.85090909	6.817272727	7.61	7.475555556	8.436666667	14.91454545	11.59181818	9.916	8.233333333	9.356666667	9.804545455	6.817	10.66272727
TAF1	M	5.558	6.117	7.385555556	6.201818182	5.558181818	5.332727273	5.447777778	5.518888889	4.293636364	5.813636364	6.526	5.733333333	6.676666667	4.811818182	7.616	6.26
TAF7L	M	0.145	0.182	0.085555556	0.203636364	0.205454545	0.18	0.201111111	0.144444444	0.068181818	0.14	0.153	0.157777778	0.205555556	0.097272727	0.082	0.212727273
TDRD6	M	0.243	0.251	0.784444444	0.238181818	0.359090909	0.165454545	0.275555556	0.213333333	0.26	0.327272727	0.201	0.246666667	0.233333333	0.215454545	0.204	0.363636364
TECTA	M	0.871	0.676	0.674444444	1.065454545	0.667272727	0.792727273	0.588888889	1.198888889	0.508181818	1.015454545	0.957	1.066666667	0.825555556	0.79	1.163	1.005454545
TGM3	M	0.062	0.22	0.207777778	0.047272727	0.250909091	0.026363636	0.051111111	0.033333333	0.169090909	0.06	0.026	0.023333333	0.036666667	0.139090909	0.047	0.036363636
TPCN1	M	3.674	4.6	12.35333333	4.162727273	4.754545455	3.819090909	4.19	4.076666667	4.9	3.521818182	3.891	4.546666667	4.184444444	4.368181818	3.954	3.96

UBA1	M	121.901	119.033	128.1433333	130.42	114.45	110.4854545	108.1211111	114.6211111	126.6790909	123.0554545	118.956	113.7944444	129.3288889	111.7972727	123.006	130.0136364
ULK4	M	0.917	0.855	1.187777778	1.145454545	1.725454545	1.143636364	0.748888889	1.098888889	1.12	1.537272727	1.555	1.298888889	0.912222222	1.24	1.095	1.294545455
USP51	M	1.339	1.047	1.141111111	1.131818182	1.28	1.293636364	1.237777778	1.004444444	1.117272727	1.039090909	1.094	1.023333333	1.27	1.059090909	1.098	1.077272727
UTP6	M	21.329	20.39	27.30111111	21.54545455	20.85727273	20.83090909	20.46222222	15.36666667	17.54545455	21.47272727	22.377	20.31333333	20.56444444	18.08272727	24.304	22.82454545
WDFY4	M	0.48	0.364	0.834444444	0.52	0.663636364	0.287272727	0.368888889	0.377777778	0.469090909	0.361818182	0.534	0.391111111	0.43	0.428181818	0.655	0.345454545
ZCCHC16	M	0.023	0.011	0.041111111	0.032727273	0.039090909	0.046363636	0.011111111	0.038888889	0.022727273	0.031818182	0.019	0.042222222	0.023333333	0.036363636	0.003	0.035454545
ZRSR2	M	6.534	6.882	8.182222222	6.935454545	6.225454545	6.245454545	6.354444444	4.403333333	6.138181818	6.19	6.539	5.066666667	6.871111111	7.341818182	6.981	6.268181818

Supplementary Table S4 Comprehensive list of candidate variants

Gene	Family ID	Inheritance pattern	Inherited from	Variant type	Cytoband	POS	REF	ALT	Variants description	Frequency in gnomAD East Asian	CADD	RVIS	Epression in brain	Co-expression with EIEE genes	Physical interactions with EIEE protein	Additional command
ABCA7	WS8	AR	F	missense SNV	19p13.3	1052006	G	A	ABCA7:NM_019112:exon22:c.G3028A:p.V1010M	0		3.5151 (99.4037%)	+	+	-	
ABCA7	WS8	AR	M	missense SNV	19p13.3	1043371	C	T	ABCA7:NM_019112:exon9:c.C829T:p.H277Y	NA	15.96		+	+	-	
ACE2	WS27	XL	M	missense SNV	Xp22.2	15588434	G	A	ACE2:NM_021804:exon15:c.C1880T:p.A627V	0.000155678	19.94	0.1121 (57.6803%)	-	-	-	
ADGRG4	WS51	XL	M	nonsense	Xq26.3	135443672	G	A	ADGRG4:NM_153834:exon12:c.G7203A:p.(Trp2401*)	NA	50	2.6901 (98.9028%)	-	-	-	
ALG3	WS53	AD	de novo	missense SNV	3q27.1	183960694	C	T	ALG3:NM_001006941:exon8:c.G917A:p.R306H,ALG3:NM_005787:exon8:c.G1061A:p.R354H	0	28.7	-0.2495 (37.9472%)	+	-	-	
ARHGAP17	WS3	AD	de novo	missense SNV	16p12.1	24975556	C	T	ARHGAP17:NM_001006634:exon7:c.G535A:p.E179K,ARHGAP17:NM_018054:exon7:c.G535A:p.E179K	NA	34	-0.5951 (24.1935%)	+	-	+	
ARSF	WS39	XL	M	missense SNV	Xp22.33	3007644	A	T	ARSF:NM_001201538:exon7:c.A938T:p.D313V,ARSF:NM_001	0.000388651	12.13	1.3132 (92.7900%)	+	-	-	

									201539:exon7:c.A938T:p.D313V,ARSF:NM_004042:exon7:c.A938T:p.D313V							
ATP2A2	WS16	AD	de novo	missense SNV	12q24.11	110782747	G	A	ATP2A2:NM_001681:exon17:c.G2578A:p.G860S,ATP2A2:NM_170665:exon17:c.G2578A:p.G860S	NA	22.4	-1.9026 (3.4897%)	+	-	-	Calcium signaling pathway, FMRP
AWAT1	WS51	XL	M	missense SNV	Xq13.1	69459740	G	T	AWAT1:NM_001013579:exon6:c.G788T:p.G263V	NA		-0.3850 (28.5266%)	-	-	-	
C9orf163	WS37	AR	F&M	missense SNV	9q34.3	139378926	C	A	C9orf163:NM_152571:exon1:c.C26A:p.P9H	0.000616523		NA (NA)	-	-	-	
CASD1	WS10	AD	de novo	missense SNV	7q21.3	94163011	T	G	CASD1:NM_022900:exon7:c.T525G:p.N175K	NA	16.08	-0.2126 (39.5699%)	+	-	-	
CAT	WS32	AR	F	frameshift deletion	11p13	34470807	GC	G	CAT:NM_001752:exon2:c.139del:p.Arg47Valfs*88	0.000057977		-0.2426 (38.2209%)	+	-	-	
CAT	WS32	AR	M	splicing	11p13	34473759	G	A	NM_001752:exon4:c.480+5G>A	0.000231911	14.89		+	-	-	
CCDC120	WS36	XL	M	missense SNV	Xp11.23	48919807	G	C	CCDC120:NM_001163321:exon3:c.G105C:p.K35N	NA	16.45	0.6576 (81.8182%)	+	+	-	
CCDC14	WS14	AD	de novo	missense SNV	3q21.1	123665689	A	G	CCDC14:NM_001308317:exon7:c.T706C:p.Y236H,CCDC14:NM_022757:exon7:c.T1183C:p.Y395H	NA	21.7	0.1377 (56.1877%)	+	-	-	
CCPG1	WS17	AD	de novo	missense SNV	15q21.3	55652698	C	G	CCPG1:NM_001204450:exon8:c.G1273C:	NA		-0.3939 (31.7595%	+	-	-	

									p.A425P,CCPG1:NM_004748:exon8:c.G1273C:p.A425P,CCPG1:NM_020739:exon8:c.G1273C:p.A425P			)				
CD99L2	WS25	XL	M	inframe deletion	Xq28	149937525	GGGC	G	CD99L2:NM_001184808:exon8:c.549_551del:p.(Pro184del),CD99L2:NM_134445:exon8:c.552_554del:p.(Pro185del),CD99L2:NM_134446:exon9:c.621_623del:p.(Pro208del),CD99L2:NM_031462:exon11:c.768_770del:p.(Pro257del),CD99L2:NM_001242614:exon12:c.798_800del:p.(Pro267del)	0.000959693	7.491	0.8208 (85.4232%)	+	-	+	Recurrent variant
CD99L2	WS2	XL	M	inframe deletion	Xq28	149937525	GGGC	G	CD99L2:NM_001184808:exon8:c.549_551del:p.(Pro184del),CD99L2:NM_134445:exon8:c.552_554del:p.(Pro185del),CD99L2:NM_134446:exon9:c.621_623del:p.(Pro208del),CD99L2:NM_031462:exon11:c.768_770del:p.(Pro257del),CD99L2:NM_001242614:exon12:c.798_800del:p.(Pro267del)	0.000959693	7.491		+	-	+	Recurrent variant

CDK16	WS48	XL	M	missense SNV	Xp11.23	47082993	A	G	CDK16:NM_001170460:exon2:c.A259G:p.M87V,CDK16:NM_006201:exon2:c.A37G:p.M13V,CDK16:NM_033018:exon2:c.A55G:p.M19V	0	12.82	-0.4803 (24.7649%)	+	+	-	FMRP
CENPE	WS16	AR	M	missense SNV	4q24	104098199	T	C	CENPE:NM_001286734:exon14:c.A1247G:p.K416R,CENPE:NM_001813:exon14:c.A1247G:p.K416R	NA	16.93	-0.2468 (38.0352%)	-	-	+	
CENPE	WS16	AR	F	missense SNV	4q24	104032106	C	T	CENPE:NM_001286734:exon45:c.G7240A:p.G2414S,CENPE:NM_001813:exon47:c.G7603A:p.G2535S	0	18.45		-	-	+	
CES4A	WS10	AD	de novo	missense SNV	16q22.1	67029560	G	A	CES4A:NM_173815:exon2:c.G88A:p.V30I	0		0.2551 (61.4858%)	+	+	-	
CFAP69	WS14	AR	M	missense SNV	7q21.13	89909205	A	C	CFAP69:NM_001039706:exon12:c.A1370C:p.E457A,CFAP69:NM_001160138:exon12:c.A1316C:p.E439A	6.23752E-05	18.08	0.3879 (67.1848%)	-	-	-	
CFAP69	WS14	AR	F	missense SNV	7q21.13	89917639	T	C	CFAP69:NM_001039706:exon15:c.T1748C:p.L583P,CFAP69:NM_001160138:exon15:c.T1694C:p.L565P	0.000115982	15.5		-	-	-	
CLCN6	WS22	AD	de novo	missense	1p36.22	11884561	A	C	CLCN6:NM_001256	NA	17.32	-1.5930	+	-	-	Chloride channel

				SNV					959:exon7:c.A533C:p.E178A,CLCN6:NM_001286:exon8:c.A599C:p.E200A			(5.3763%)				
COL4A5	WS11	XL	M	missense SNV	Xq22.3	107869488	A	C	COL4A5:NM_000495:exon36:c.A3155C:p.Q1052P	7.78756E-05		0.5065 (76.0188%)	+	-	-	
COL9A2	WS42	AR	F	missense SNV	1p34.2	40775944	C	T	COL9A2:NM_001852:exon14:c.G730A:p.G244R	NA	16.26	1.2519 (90.7429%)	+	-	-	
COL9A2	WS42	AR	M	missense SNV	1p34.2	40781333	C	T	COL9A2:NM_001852:exon2:c.G79A:p.G27S	0	24.1		+	-	-	
CXorf36	WS22	XL	M	missense SNV	Xp11.3	45013424	C	A	CXorf36:NM_176819:exon4:c.G692T:p.G231V	0.00016446	19.38	0.8483 (86.2069%)	+	-	-	
CYFIP1	WS46	AD	de novo	inframe deletion	15q11.2	22939182	AGGT	A	CYFIP1:NM_014608:exon10:c.909_911del:p.303_304del,CYFIP1:NM_001287810:exon11:c.909_911del:p.303_304del	NA		-1.8425 (3.7830%)	+	-	+	FMRP
CYFIP2	WS1	AD	de novo	missense SNV	5q33.3	156721843	C	T	CYFIP2:NM_001037333:exon4:c.C259T:p.R87C,CYFIP2:NM_001291722:exon4:c.C259T:p.R87C,CYFIP2:NM_014376:exon4:c.C259T:p.R87C	NA	23.6	-1.5154 (5.9238%)	+	-	+	FMRP
DOCK2	WS21	AD	de novo	missense SNV	5q35.1	169108785	G	A	DOCK2:NM_004946:exon7:c.G508A:p.G170R	NA	27.7	-0.9425 (14.4868%)	-	-	-	
DZANK1	WS19	AD	de novo	missense	20p11.23	18424022	C	T	DZANK1:NM_00109	NA	23.7	0.8412	+	-	-	FMRP

				SNV					9407:exon8:c.G716A:p.G239D			(82.7370%)				
EGR3	WS15	AD	de novo	missense SNV	8p21.3	22548111	C	T	EGR3:NM_001199880:exon2:c.G925A:p.E309K,EGR3:NM_001199881:exon2:c.G877A:p.E293K,EGR3:NM_004430:exon2:c.G1039A:p.E347K	NA	26.7	-0.6773 (21.6422%)	+	-	-	
FAT3	WS1	AR	F	missense SNV	11q14.3	92532823	G	T	FAT3:NM_001008781:exon9:c.G6644T:p.G2215V	NA	18.58	NA (NA)	+	-	-	FMRP
FAT3	WS1	AR	M	missense SNV	11q14.3	92533768	A	C	FAT3:NM_001008781:exon9:c.A7589C:p.Q2530P	NA	14.54		+	-	-	FMRP
FBXO39	WS32	AD	de novo	missense SNV	17p13.1	6683407	G	A	FBXO39:NM_153230:exon2:c.G220A:p.E74K	NA	15.05	0.6868 (78.2796%)	-	-	-	
FRMPD3	WS51	XL	M	missense SNV	Xq22.3	106845170	T	C	FRMPD3:NM_032428:exon16:c.T4000C:p.C1334R	NA	15.61	-0.5750 (20.5329%)	+	+	-	
GNB1	WS43	AD	de novo	missense SNV	1p36.33	1720572	G	A	GNB1:NM_001282538:exon8:c.C536T:p.S179F,GNB1:NM_001282539:exon9:c.C836T:p.S279F,GNB1:NM_002074:exon10:c.C836T:p.S279F	NA	34	-0.4777 (28.3969%)	+	-	+	Mental retardation gene, FMRP
GNL3L	WS9	XL	M	missense SNV	Xp11.22	54565513	G	T	GNL3L:NM_001184819:exon3:c.G60T:p.K20N,GNL3L:NM_019067:exon3:c.G60T:p.K20N	NA	10.18	-0.2386 (37.1473%)	+	-	+	

GOLGA5	WS24	AD	de novo	nonsense	14q32.12	93299599	C	T	GOLGA5:NM_005113:exon10:c.C1852T:p.(Gln618*)	0	40	-0.0064 (49.1496%)	+	-	-	
GPR119	WS11	XL	M	missense SNV	Xq26.1	129519399	C	T	GPR119:NM_178471:exon1:c.G23A:p.G8E	0.000155473	17.37	-0.3671 (29.4671%)	-	-	-	
GPRASP1	WS46	XL	M	missense SNV	Xq22.1	101909904	T	A	GPRASP1:NM_001099411:exon3:c.T1063A:p.S355T,GPRASP1:NM_001099410:exon4:c.T1063A:p.S355T,GPRASP1:NM_014710:exon5:c.T1063A:p.S355T,GPRASP1:NM_001184727:exon6:c.T1063A:p.S355T	NA		0.2715 (66.7712%)	+	+	-	
GPT2	WS31	AD	de novo	frameshift deletion	16q11.2	46950598	GCT	G	GPT2:NM_001142466:exon7:c.582_583del:p.(Phe195Serfs*4), GPT2:NM_133443:exon7:c.882_883del:p.(Phe295Serfs*4)	NA		-0.1023 (44.6041%)	+	-	-	Mental retardation gene
HMCN1	WS48	AR	M	missense SNV	1q31.1	185947038	A	G	HMCN1:NM_031935:exon16:c.A2491G:p.N831D	NA	15.03	-1.0936 (11.3099%)	+	-	-	
HMCN1	WS48	AR	F	missense SNV	1q31.1	186136027	G	T	HMCN1:NM_031935:exon100:c.G15527T:p.R5176L	0	12.08		+	-	-	
HUWE1	WS40	XL	de novo	missense SNV	Xp11.22	53561638	C	A	HUWE1:NM_031407:exon82:c.G12670T:p.A4224S	0.000155848	12.68	-7.0236 (0.1567%)	+	+	+	Mental retardation gene, FMRP
ITM2A	WS51	XL	M	missense	Xq21.1	78619020	C	T	ITM2A:NM_004867:	NA		0.0872	+	-	-	

				SNV					exon2:c.G143A:p.G48D			(56.2696%)				
KMT2D	WS1	AD	de novo	missense SNV	12q13.12	49427485	G	A	KMT2D:NM_003482:exon39:c.C11003T:p.P3668L	0	10.77	-6.4882 (0.0880%)	+	+	-	Mental retardation gene, FMRP, recurrent in Epi4K study
LHFPL1	WS24	XL	M	missense SNV	Xq23	111914456	G	A	LHFPL1:NM_178175:exon2:c.C163T:p.R55W	NA	17.15	0.5292 (76.9592%)	-	-	-	
MACF1	WS36	AR	M	missense SNV	1p34.3	39926397	C	T	MACF1:NM_012090:exon87:c.C15277T:p.R5093W	0	21.4	-3.7057 (0.5474%)	+	-	+	FMRP
MACF1	WS36	AR	F	missense SNV	1p34.3	39816481	C	T	MACF1:NM_012090:exon37:c.C4804T:p.R1602C	0	24.6		+	-	+	FMRP
MAOB	WS47	XL	M	missense SNV	Xp11.3	43661501	C	T	MAOB:NM_000898:exon5:c.G394A:p.D132N	NA	19.48	-0.6599 (17.5549%)	+	-	-	
MAP3K12	WS21	AD	de novo	missense SNV	12q13.13	53879954	C	T	MAP3K12:NM_001193511:exon4:c.G707A:p.R236Q,MAP3K12:NM_006301:exon5:c.G608A:p.R203Q	NA	23.2	-0.9126 (15.3079%)	+	+	-	FMRP
MAP3K15	WS47	XL	M	frameshift deletion	Xp22.12	19478123	GGAGT	G	MAP3K15:NM_001001671:exon5:c.864_867del:p.(Leu288Phefs*14)	NA		2.1341 (97.3354%)	-	-	-	
MAP7D3	WS32	XL	M	missense SNV	Xq26.3	135313816	G	C	MAP7D3:NM_001173517:exon7:c.C1195G:p.P399A,MAP7D3:NM_001173516:exon8:c.C1246G:p.P416A,MAP7D3:NM_024	0	12.08	0.6871 (82.9154%)	-	-	-	

									597:exon8:c.C1300G:p.P434A							
ME3	WS27	AD	de novo	splicing	11q14.2	86382803	C	T	NM_001014811:exon2:c.183+1G>A;NM_001161586:exon3:c.183+1G>A;NM_006680:exon3:c.183+1G>A	0	18.46	-0.9008 (15.6305%)	+	-	-	
MRPL17	WS36	AD	de novo	startloss	11p15.4	6704527	T	G	MRPL17:NM_022061:exon1:c.A1C:p.M1L	0	18.74	-0.5005 (27.5367%)	+	-	+	
MSL3	WS53	XL	M	missense SNV	Xp22.2	11780303	A	G	MSL3:NM_001282174:exon5:c.A73G:p.I25V,MSL3:NM_006800:exon5:c.A22G:p.I8V,MSL3:NM_001193270:exon6:c.A484G:p.I162V,MSL3:NM_078628:exon6:c.A520G:p.I174V,MSL3:NM_078629:exon6:c.A520G:p.I174V	0	16.69	-0.2932 (34.0125%)	+	-	-	
MYCBP2	WS38	AD	F	missense SNV	13q22.3	77672537	C	T	MYCBP2:NM_015057:exon56:c.G8752A:p.A2918T	NA	16.95	NA (NA)	+	-	-	FMRP
MYCBP2	WS38	AD	de novo	missense SNV	13q22.3	77752076	T	C	MYCBP2:NM_015057:exon35:c.A5147G:p.N1716S	NA	15.22		+	-	-	FMRP
MYO18A	WS5	AR	M	missense SNV	17q11.2	27493915	C	T	MYO18A:NM_078471:exon2:c.G44A:p.R15Q,MYO18A:NM_203318:exon2:c.G44A:p.R15Q	0.000194818	21.8	-0.5903 (24.3597%)	+	+	+	FMRP

MYO18A	WS5	AR	F	missense SNV	17q11.2	27437031	C	T	MYO18A:NM_078471:exon19:c.G3176A:p.R1059H,MYO18A:NM_203318:exon19:c.G3176A:p.R1059H	0	19.11		+	+	+	FMRP
MYO1H	WS42	AD	de novo	splicing	12q24.11	109849791	G	A	NM_001101421:exon13:c.1454+1G>A	NA	19.66	0.5454 (73.3920%)	-	-	-	
NOS3	WS13	AD	de novo	missense SNV	7q36.1	150696101	C	T	NOS3:NM_001160109:exon7:c.C884T:p.A295V,NOS3:NM_001160110:exon7:c.C884T:p.A295V,NOS3:NM_001160111:exon7:c.C884T:p.A295V,NOS3:NM_000603:exon8:c.C884T:p.A295V	NA	17.61	0.1800 (58.1623%)	+	-	+	Calcium signaling pathway, Mouse model presented seizures
NPC1L1	WS34	AR	M	missense SNV	7p13	44574110	A	G	NPC1L1:NM_001101648:exon6:c.T2102C:p.V701A,NPC1L1:NM_001300967:exon6:c.T2102C:p.V701A,NPC1L1:NM_013389:exon6:c.T2102C:p.V701A	NA	21.3	0.6433 (76.8719%)	-	-	-	
NPC1L1	WS34	AR	F	missense SNV	7p13	44561319	G	A	NPC1L1:NM_001101648:exon12:c.C2945T:p.S982L,NPC1L1:NM_013389:exon12:c.C2945T:p.S982L	0	17.64		-	-	-	
OR8D2	WS34	AD	de novo	missense SNV	11q24.2	124189498	A	C	OR8D2:NM_001002918:exon1:c.T596G:p.L199R	NA	18.54	NA (NA)	-	-	-	

ORC3	WS46	AD	de novo	missense SNV	6q15	88374486	G	C	ORC3:NM_001197259:exon17:c.G1430C:p.G477A,ORC3:NM_012381:exon18:c.G1859C:p.G620A,ORC3:NM_181837:exon18:c.G1862C:p.G621A	0	17.58	0.4438 (69.5210%)	+	-	-	
PARS2	WS19	AR	F	nonsense	1p32.3	55224777	G	A	PARS2:NM_152268:exon2:c.C58T:p.(Gln20*)	NA	10.15	-0.2137 (39.5308%)	+	-	-	
PARS2	WS19	AR	M	missense SNV	1p32.3	55224299	A	G	PARS2:NM_152268:exon2:c.T536C:p.F179S	NA	14.5		+	-	-	
PFKFB4	WS11	AD	de novo	missense SNV	3p21.31	48573003	G	A	PFKFB4:NM_001317135:exon9:c.C929T:p.T310M,PFKFB4:NM_001317136:exon9:c.C896T:p.T299M,PFKFB4:NM_001317137:exon9:c.C929T:p.T310M,PFKFB4:NM_004567:exon9:c.C929T:p.T310M,PFKFB4:NM_001317134:exon10:c.C1016T:p.T339M,PFKFB4:NM_001317138:exon10:c.C356T:p.T119M	NA	22.5	-1.0328 (12.5318%)	+	+	-	
PHKA1	WS33	XL	M	missense SNV	Xq13.2	71855062	G	A	PHKA1:NM_001122670:exon16:c.C1657T:p.R553C,PHKA1:NM_001172436:exon16:c.C1657T:p.R553C,	0		-2.1944 (1.8809%)	-	-	-	Calcium signaling pathway

									PHKA1:NM_002637:exon16:c.C1657T:p.R553C						
PLEKHG2	WS30	AD	de novo	missense SNV	19q13.2	39915314	C	T	PLEKHG2:NM_022835:exon19:c.C3541T:p.L1181F	NA	15.16	1.5287 (93.9492%)	+	-	-
PNMA1	WS1	AD	de novo	missense SNV	14q24.3	74179463	C	A	PNMA1:NM_006029:exon1:c.G880T:p.V294F	NA	22.8	-0.3016 (35.6696%)	+	-	+
PNMA3	WS30	XL	M	missense SNV	Xq28	152225734	C	T	PNMA3:NM_001282535:exon2:c.C322T:p.R108C,PNMA3:NM_013364:exon2:c.C322T:p.R108C	0.000155448		-0.3484 (31.0345%)	+	-	-
PNPLA4	WS13	XL	M	missense SNV	Xp22.31	7889777	A	G	PNPLA4:NM_001172672:exon3:c.T127C:p.S43P,PNPLA4:NM_001142389:exon4:c.T388C:p.S130P,PNPLA4:NM_004650:exon4:c.T388C:p.S130P	NA		0.4179 (73.3542%)	+	-	-
POFUT2	WS42	AD	de novo	missense SNV	21q22.3	46705701	A	T	POFUT2:NM_015227:exon2:c.T274A:p.W92R,POFUT2:NM_133635:exon2:c.T274A:p.W92R	NA	24.3	-0.0472 (47.1848%)	+	+	-
PRICKLE3	WS16	XL	M	missense SNV	Xp11.23	49032467	C	T	PRICKLE3:NM_001307979:exon9:c.G1199A:p.R400H,PRICKLE3:NM_006150:exon9:c.G1403A:p.R468H	0	17.07	1.0143 (89.1850%)	-	-	-
REPS2	WS4	XL	M	missense	Xp22.2	17080566	C	T	REPS2:NM_0010809	NA	11.44	-0.5155	+	-	-

				SNV					75:exon9:c.C1117T:p.P373S,REPS2:NM_004726:exon9:c.C1120T:p.P374S			(23.0408%)				
RPGR	WS29	XL	M	missense SNV	Xp11.4	38180324	A	G	RPGR:NM_000328:exon4:c.T266C:p.V89A,RPGR:NM_001034853:exon4:c.T266C:p.V89A	NA	18.04	2.2110 (97.8056%)	+	-	-	
RYR1	WS21	AR	F	missense SNV	19q13.2	38946118	A	G	RYR1:NM_000540:exon15:c.A1604G:p.N535S,RYR1:NM_001042723:exon15:c.A1604G:p.N535S	0.000173933	15.5	-5.4856 (0.1271%)	+	+	-	Calcium signaling pathway
RYR1	WS21	AR	M	missense SNV	19q13.2	38935236	G	A	RYR1:NM_000540:exon7:c.G550A:p.A184T,RYR1:NM_001042723:exon7:c.G550A:p.A184T	0.000406457	12.97		+	+	-	Calcium signaling pathway
RYR2	WS29	AR	M	missense SNV	1q43	237729900	A	G	RYR2:NM_001035:exon28:c.A3248G:p.E1083G	0.000106078	17.67	-6.5324 (0.0782%)	+	+	-	Calcium signaling pathway, Mouse model presented seizures, FMRP, recurrent in Epi4K study
RYR2	WS29	AR	F	missense SNV	1q43	237798279	C	T	RYR2:NM_001035:exon44:c.C6779T:p.P2260L	0.000616523	22.6		+	+	-	Calcium signaling pathway, Mouse model presented seizures, FMRP, recurrent in Epi4K study

RYR3	WS56	AR	F	missense SNV	15q14	33936671	A	G	RYR3:NM_001036:exon28:c.A3716G:p.K1239R,RYR3:NM_001243996:exon28:c.A3716G:p.K1239R	0.0001161	24	-4.2466 (0.3421%)	+	-	-	Calcium signaling pathway
RYR3	WS56	AR	M	missense SNV	15q14	33941340	C	T	RYR3:NM_001036:exon31:c.C4046T:p.T1349I,RYR3:NM_001243996:exon31:c.C4046T:p.T1349I	0.000116	27.7		+	-	-	Calcium signaling pathway
SH3KBP1	WS32	XL	M	missense SNV	Xp22.12	19606776	G	A	SH3KBP1:NM_001184960:exon7:c.C569T:p.P190L,SH3KBP1:NM_001024666:exon11:c.C1172T:p.P391L,SH3KBP1:NM_031892:exon12:c.C1283T:p.P428L	0	20.6	-0.5977 (19.2790%)	+	-	+	
SHROOM2	WS4	XL	M	missense SNV	Xp22.2	9863900	C	A	SHROOM2:NM_001649:exon4:c.C1952A:p.T651N	NA		4.8639 (99.8433%)	+	-	-	
SIPA1L3	WS13	AR	F	missense SNV	19q13.13	38673323	G	C	SIPA1L3:NM_015073:exon16:c.G4373C:p.G1458A	0.000212044	16.89	1.3384 (91.9550%)	+	+	-	FMRP
SIPA1L3	WS13	AR	M	missense SNV	19q13.13	38684393	G	A	SIPA1L3:NM_015073:exon18:c.G4813A:p.A1605T	0.000616523			+	+	-	FMRP
SLC37A1	WS12	AD	de novo	missense SNV	21q22.3	43994967	C	A	SLC37A1:NM_018964:exon19:c.C1463A:p.P488Q	NA	17.17	0.3415 (65.2395%)	+	+	-	
TAF1	WS51	XL	M	missense SNV	Xq13.1	70587404	C	A	TAF1:NM_001286074:exon2:c.C236A:p.(Thr79Asn),TAF1:NM	NA	18.13	-2.7937 (0.9404%)	+	+	-	Mental retardation gene, recurrent in this

									_004606:exon2:c.C236A:p.(Thr79Asn),TAF1:NM_138923:exon2:c.C236A:p.(Thr79Asn)							and Epi4K study
TAF1	WS15	XL	M	missense SNV	Xq13.1	70644046	G	A	TAF1:NM_001286074:exon32:c.G4771A:p.(Asp1591Asn),TAF1:NM_004606:exon32:c.G4771A:p.(Asp1591Asn),TAF1:NM_138923:exon32:c.G4708A:p.(Asp1570Asn)	0	12.31		+	+	-	Mental retardation gene, recurrent in this and Epi4K study
TAF7L	WS45	XL	M	missense SNV	Xq22.1	100531008	C	T	TAF7L:NM_001168474:exon11:c.G1006A:p.V336M,TAF7L:NM_024885:exon11:c.G1264A:p.V422M	NA	18.7	0.1024 (57.0533%)	-	-	-	
TDRD6	WS19	AR	F	inframe insertion	6p12.3	46656920	A	AGTT	TDRD6:NM_001010870:exon1:c.1055_1056insGTT:p.E352delinsEL,TDRD6:NM_001168359:exon1:c.1055_1056insGTT:p.E352delinsEL	0.000883046		1.4798 (93.5093%)	-	-	-	
TDRD6	WS19	AR	M	missense SNV	6p12.3	46656046	G	T	TDRD6:NM_001010870:exon1:c.G181T:p.A61S,TDRD6:NM_001168359:exon1:c.G181T:p.A61S	NA	10.12		-	-	-	
TECTA	WS28	AR	M	missense SNV	11q23.3	121039502	G	A	TECTA:NM_005422:exon19:c.G5867A:p.R1956Q	0.000106	36	-1.0022 (13.1672%)	-	-	-	Mouse model presented seizures

TECTA	WS28	AR	F	missense SNV	11q23.3	120996138	A	G	TECTA:NM_005422:exon7:c.A1331G:p.Y444C	5.79845E-05	19.55		-	-	-	Mouse model presented seizures
TGM3	WS16	AD	de novo	missense SNV	20p13	2306536	A	G	TGM3:NM_003245:exon8:c.A1025G:p.D342G	NA	17.33	1.1626 (89.3157%)	-	-	+	
TPCN1	WS36	AD	de novo	missense SNV	12q24.13	113731111	C	T	TPCN1:NM_001301214:exon26:c.C2087T:p.T696I,TPCN1:NM_017901:exon27:c.C2291T:p.T764I,TPCN1:NM_001143819:exon28:c.C2507T:p.T836I	0	25.1	-1.4431 (6.5200%)	+	+	-	
UBA1	WS45	XL	M	missense SNV	Xp11.23	47071859	C	T	UBA1:NM_003334:exon21:c.C2501T:p.P834L,UBA1:NM_153280:exon21:c.C2501T:p.P834L	NA	14.42	-1.3428 (6.7398%)	+	+	+	FMRP
ULK4	WS49	AR	M	missense SNV	3p22.1	41756745	C	A	ULK4:NM_017886:exon25:c.G2618T:p.S873I	0	14.03	1.0038 (86.4516%)	-	-	-	
ULK4	WS49	AR	F	missense SNV	3p22.1	41759338	G	C	ULK4:NM_017886:exon23:c.C2337G:p.I779M	0.000106033	15.59		-	-	-	
USP51	WS29	XL	M	missense SNV	Xp11.21	55513883	G	A	USP51:NM_201286:exon2:c.C1490T:p.T497I	NA	15.78	-0.7490 (15.9875%)	-	-	-	
UTP6	WS31	AR	F	missense SNV	17q11.2	30205767	A	G	UTP6:NM_018428:exon12:c.T1001C:p.L334S	NA	13.78	0.1365 (56.1290%)	+	+	-	
UTP6	WS31	AR	M	missense SNV	17q11.2	30221704	C	A	UTP6:NM_018428:exon4:c.G272T:p.R91	0	32		+	+	-	

									L						
VWA3A	WS20	AR	F	splicing	16p12.2	22142603	A	G	NM_173615:exon18:c.1727+3A>G	0	13.49	1.8918 (96.3441%)	-	-	-
VWA3A	WS20	AR	M	missense SNV	16p12.2	22162070	C	T	VWA3A:NM_173615:exon30:c.C3184T:p.P1062S	0.000292432	18.23		-	-	-
WDFY4	WS13	AR	M	missense SNV	10q11.23	50109854	C	G	WDFY4:NM_020945:exon47:c.C7532G:p.S2511C	NA	13.09	NA (NA)	-	-	-
WDFY4	WS13	AR	F	missense SNV	10q11.23	50167799	G	A	WDFY4:NM_020945:exon53:c.G8164A:p.V2722M	0.000195351	21.9		-	-	-
ZCCHC16	WS16	XL	M	missense SNV	Xq23	111698773	C	T	ZCCHC16:NM_001004308:exon3:c.C817T:p.R273C	0	10.93	0.7419 (84.4828%)	-	-	-
ZRSR2	WS14	XL	M	missense SNV	Xp22.2	15808631	G	A	ZRSR2:NM_005089:exon1:c.G13A:p.E5K	NA	14.81	0.3806 (71.9436%)	+	+	-

Inherited from: F-father, M-mother, de novo-neither from father or mother; Frequency in gnomAD East Asian:0- not recorded but different varaint recorded at the same loci, NA-none variant recoeded in this loci

Supplementary Table S5 Comparison of mental retardation gene variants carriers phenotypes in our study and literature

Clinical features		*GPT2*		*HUWE1*		*GNB1*		*KMT2D*		*TAF1*		
		Previous reports	WS31-P	Previous reports	WS40-P	Previous reports	WS43-P	Previous reports	WS1-P	Previous reports	WS51-P	WS15-P
GSex		Male,female	Male	Male	Male	Male, female	Male	Male, female	Female	Male	Male	Male
Age (years)		4–22.4	6.5 (died)	10–56	6.5	1–20	4	0.25–22	3	1–22	5.3	6.8
Perinatal period		Normal	Normal	Normal	Normal	Feeding difficulty, sucking problem	Normal	Feeding difficulty	Normal	Feeding difficulty, seizure, icterus neonatorum	Normal	Normal
Growth	Intrauterine growth restriction	N/A	-	+	-	N/A	-	+/-	-	+	-	-
	Postnatal retardation	+	-	+	-	+	-	+	Underweight, moderate malnutrition	+	-	-
Psychomotor development	General retardation (+–+++)	+++	+++	+–+++	+++	+++	++–+++	++–++	+++	+–++	-	+++
	Motor delay	+	+	+	+	+	+	+	+	+	+	+
	Language retardation	+(Dysarthria)	+	+	+	+	+	+	+	+	-	+
	Cognitive impairment	+	+	+	+	+	+	+	+	N/A	-	+
	Dependence	+	+	+	+	+	+	+	+	N/A	-	+
Facial feature		Low-set ears, high palatal arch, upper teeth projecting	Supplementary Figure 2	Long face, high palatal arch, micrognathia, bulbous nose	Supplementary Figure 2	Fissura palatina, high palatal arch, short philtrum, protruding incisors	Supplementary Figure 2	Lower palpebral eversion, short nasal septum, arched eyebrows, prominent ear	Supplementary Figure 2	Aural abnormality (low-set ear/protruding ear), high palatal arch, nasal abnormality (wide upturned nose, bulbous nose), long face	Supplementary Figure 2	Supplementary Figure 2

Nervous system	Physical examination	Microencephalopathy, spastic paralysis, hyperreflexia	Limbs hypotonia	Microencephalopathy	Slightly hypertonia	Muscle tension change (hypotonia or hypertonia)	-	Microencephalopathy, hypotonia	Hypertonia	Dystonia, encephalopathy, spastic paralysis	-	Flaccid paralysis
	Epilepsy	+	WS	+/−	WS	+	WS	+	WS	+	WS	WS
	Radiology	Callosal agenesis, cerebellar atrophy	3 days after birth subarachnoid hemorrhage	Holoprosencephaly, ventriculomegaly	Bilateral frontal and parietal lobes atrophy: cerebral hypoplasia	Ventriculomegaly, cerebellar atrophy	-	Polymicrogyria, hydrocephalus, subarachnoid edema	Mild ventriculomegaly, widened cerebral sulci, cerebral fissures and cerebral cisterns	Corpus callosum dysplasia, ventriculomegaly, cerebellar atrophy	Left temporal site arachnoid cyst	-
Other systems	Eyes	N/A	-	Strabismus	-	Nystagmus,strabismus	-	Ptosis, strabismus	-	Nystagmus, strabismus	Normal	Normal
	Cardiovascular system	Mitralvalve murmur	-	Aortic valve murmur	-	-	-	Aorta coarctation, atrial septal defect, ventricular septal defect, trilogy of Fallot	-	Atrial septal defect, aorta coarctation	Atrial septal defect, ventricular septal defect	Normal
	Skeletal system	Scoliosis, adduction of thumb	-	Short fifth fingers and toes, thorax abnormal	-	Limited motion of joints, Joint hypermotility, pectus excavatum	-	Short and incurved fifth fingers, mainly from brachymesophalangy V, deformed vertebrae and/or rib anomalies and dislocation of the hip joints	-	Joint hypermotility, gluteal crease with sacral caudal remnant, sacral dimple, prominent protruding coccyx	N/A	N/A
	Urogenital system	Normal	-	Phimosis, cryptorchidism	-	Hydronephrosis	-	Hydronephrosis, cryptorchidism, micropenis	-	Cryptorchidism,hydronephrosis, vesicoureteric reflux	-	-
	Others	Hypotonia, oromotor dysfunction, drooling	-	Eczema, constipation	-	Cleft palate, hypotonia	-	Aspiration pneumonia, cafe au	Congenital laryngeal	Hypotonia	-	-

lait spots, hirsutism	cartilage dysplasia

Supplementary Table S6 *TTN* variants

Gene	Family ID	Inheritance pattern	Inherited from	Variant type	Cytoband	POS	REF	ALT	Variants description	Frequency in gnomAD East Asian
TTN	WS38	AR	F	missense SNV	2q31.2	179426023	T	A	TTN:NM_003319:exon151:c.A41417T:p.H13806L,TTN:NM_133432:exon152:c.A41792T:p.H13931L,TTN:NM_133437:exon152:c.A41993T:p.H13998L,TTN:NM_133378:exon272:c.A60908T:p.H20303L,TTN:NM_001256850:exon273:c.A63689T:p.H21230L,TTN:NM_001267550:exon323:c.A68612T:p.H22871L	NA
TTN	WS38	AR	M	missense SNV	2q31.2	179435385	T	G	TTN:NM_003319:exon154:c.A48279C:p.L16093F,TTN:NM_133432:exon155:c.A48654C:p.L16218F,TTN:NM_133437:exon155:c.A48855C:p.L16285F,TTN:NM_133378:exon275:c.A67770C:p.L22590F,TTN:NM_001256850:exon276:c.A70551C:p.L23517F,TTN:NM_001267550:exon326:c.A75474C:p.L25158F	0
TTN	WS38	AR	M	missense SNV	2q31.2	179435385	C	G	TTN:NM_003319:exon104:c.G25713C:p.E8571D,TTN:NM_133432:exon105:c.G26088C:p.E8696D,TTN:NM_133437:exon105:c.G26289C:p.E8763D,TTN:NM_133378:exon225:c.G45204C:p.E15068D,TTN:NM_001256850:exon226:c.G47985C:p.E15995D,TTN:NM_001267550:exon276:c.G52908C:p.E17636D	0.00118
TTN	WS1	AR	M	missense SNV	2q31.2	179446909	C	T	TTN:NM_003319:exon143:c.G38992A:p.V12998I,TTN:NM_133432:exon144:c.G39367A:p.V13123I,TTN:NM_133437:exon144:c.G39568A:p.V13190I,TTN:NM_133378:exon264:c.G58483A:p.V19495I,TTN:NM_001256850:exon265:c.G61264A:p.V20422I,TTN:NM_001267550:exon315:c.G66187A:p.V22063I	0
TTN	WS1	AR	M	missense SNV	2q31.2	179477562	T	G	TTN:NM_003319:exon93:c.A22691C:p.N7564T,TTN:NM_133432:exon94:c.A23066C:p.N7689T,TTN:NM_133437:exon94:c.A23267C:p.N7756T,TTN:NM_133378:exon214:c.A42182C:p.N14061T,TTN:NM_001256850:exon215:c.A44963C:p.N14988T,TTN:NM_001267550:exon265:c.A49886C:p.N16629T	0
TTN	WS1	AR	F	missense SNV	2q31.2	179427284	T	C	TTN:NM_003319:exon154:c.A56380G:p.K18794E,TTN:NM_133432:exon155:c.A56755G:p.K18919E,TTN:NM_133437:exon155:c.A56956G:p.K18986E,TTN:NM_133378:exon275:c.A75871G:p.K25291E,TTN:NM_	0.000935

									001256850:exon276:c.A78652G:p.K26218E,TTN:NM_001267550:exon326:c.A83575G:p.K27859E	
TTN	WS1	AR	F	missense SNV	2q31.2	179428309	G	A	TTN:NM_003319:exon154:c.C55355T:p.T18452I,TTN:NM_133432:exon155:c.C55730T:p.T18577I,TTN:NM_133437:exon155:c.C55931T:p.T18644I,TTN:NM_133378:exon275:c.C74846T:p.T24949I,TTN:NM_001256850:exon276:c.C77627T:p.T25876I,TTN:NM_001267550:exon326:c.C82550T:p.T27517I	NA
TTN	WS49	AR	F	missense SNV	2q31.2	179442541	T	A	TTN:NM_003319:exon151:c.A41417T:p.H13806L,TTN:NM_133432:exon152:c.A41792T:p.H13931L,TTN:NM_133437:exon152:c.A41993T:p.H13998L,TTN:NM_133378:exon272:c.A60908T:p.H20303L,TTN:NM_001256850:exon273:c.A63689T:p.H21230L,TTN:NM_001267550:exon323:c.A68612T:p.H22871L	0.000176
TTN	WS49	AR	M	missense SNV	2q31.2	179599581	C	T	TTN:NM_133378:exon48:c.G11338A:p.E3780K,TTN:NM_001256850:exon49:c.G14119A:p.E4707K,TTN:NM_001267550:exon51:c.G15070A:p.E5024K	0.000698
TTN	WS49	AR	M	missense SNV	2q31.2	179458585	C	T	TTN:NM_003319:exon126:c.G31247A:p.G10416E,TTN:NM_133432:exon127:c.G31622A:p.G10541E,TTN:NM_133437:exon127:c.G31823A:p.G10608E,TTN:NM_133378:exon247:c.G50738A:p.G16913E,TTN:NM_001256850:exon248:c.G53519A:p.G17840E,TTN:NM_001267550:exon298:c.G58442A:p.G19481E	NA
TTN	WS53	AR	F	missense SNV	2q31.2	179480143	C	G	TTN:NM_003319:exon87:c.G21334C:p.D7112H,TTN:NM_133432:exon88:c.G21709C:p.D7237H,TTN:NM_133437:exon88:c.G21910C:p.D7304H,TTN:NM_133378:exon208:c.G40825C:p.D13609H,TTN:NM_001256850:exon209:c.G43606C:p.D14536H,TTN:NM_001267550:exon259:c.G48529C:p.D16177H	0.0001163
TTN	WS53	AR	M	missense SNV	2q31.2	179550007	T	C	TTN:NM_133378:exon126:c.A28711G:p.K9571E,TTN:NM_001256850:exon127:c.A31492G:p.K10498E,TTN:NM_001267550:exon129:c.A32443G:p.K10815E	NA

Inherited from: F-father, M-mother, de novo-neither from father or mother; Frequency in gnomAD East Asian:0- not recorded but different varaint recorded at the same loci, NA-none variant recoeded in this loci

Supplementary Table S7 Treatment detail of patient with cadidate variants in calcium signaling pathway genes

Gene	*ATP2A2*	*NOS3*	*PHKA1*	*RYR1*	*RYR2*	*RYR3*
Patient ID	WS16-P	WS13-P	WS33-P	WS21-P	WS29-P	WS56-P
Gender	Male	Male	Male	Female	Male	Female
calcium channel blockers related drugs	VPA, TPM	TPM	LEV	LEV	LEV, VPA, TPM	VPA, TPM, LEV, LTG
Effective drugs in calcium channel blockers related drugs	VPA, TPM	NA	NA	NA	TPM	VPA, LTG
Other drugs	ACTH	prednisone，ACTH	ACTH, VGB	ACTH	PHB, ACTH, KD, VGB	NA
effective drugs in other drugs	NA	ACTH	ACTH	ACTH	VGB	NA
Outcome of seizure	controlled	relapse	relapse	controlled	controlled	controlled

VPA: Valproic acid sodium; TPM: topiramate; LEV: levetiracetam; LTG: lamotrigine; ACTH：Adrenocorticotropic Hormone；VGB: Vigabatrin; PHB: phenobarbital; KD: ketogenic diet.