Supplemental Material

Contents:

Supplemental Tables

Supplemental_Table_S1.pdf

Family	**Affected genes**	**Inheritance**	**ACMG Classification**	**Proband phenotype**	**Other family members**
Family 1	*ELOVL6, ENPEP, PITX2, FAM241A, AP1AR, TIFA, ALPK1, NEUROG2, ZGRF1, LARP7, hsa-miR-297,* ***ANK2***	Maternal	Class 3	ASD, seizures at age 1, congenital heart disease (VSD, pulmonary stenosis; PDA, muscle bundle heart); generalized joint laxity	One 1st cousin with ASD, two 1st cousins with language delay
Family 2	*ELOVL6, ENPEP, PITX2, FAM241A, AP1AR, TIFA, ALPK1, NEUROG2, ZGRF1, LARP7, hsa-miR-297,* ***ANK2***	Maternal	Class 3	ASD, long palpebral fissures, small feet	Mother: Stargardts disease Sister: Speech and language impairment
Family 3	***IL1RAPL1, DMD***	Maternal	Class 3	ASD, IQ 83 (Wechsler)	Brother: ASD, IQ 76 (Leiter)
Family 4	*RNASE13, SUPT16H,* ***CHD8***	Paternal	Class 3	ASD, IQ 122 (Wechsler) ADHD features +VE on SWAN	N/A
Family 5	*DNASE1, TRAP1,* ***CREBBP***	Paternal	Class 3	ASD, IQ 117 (Wechsler)	N/A

Supplemental Table S1. Clinical information about the proband and their families. Candidate ASD genes in each region are in bold. ACMG – American College of Medical Genetics.

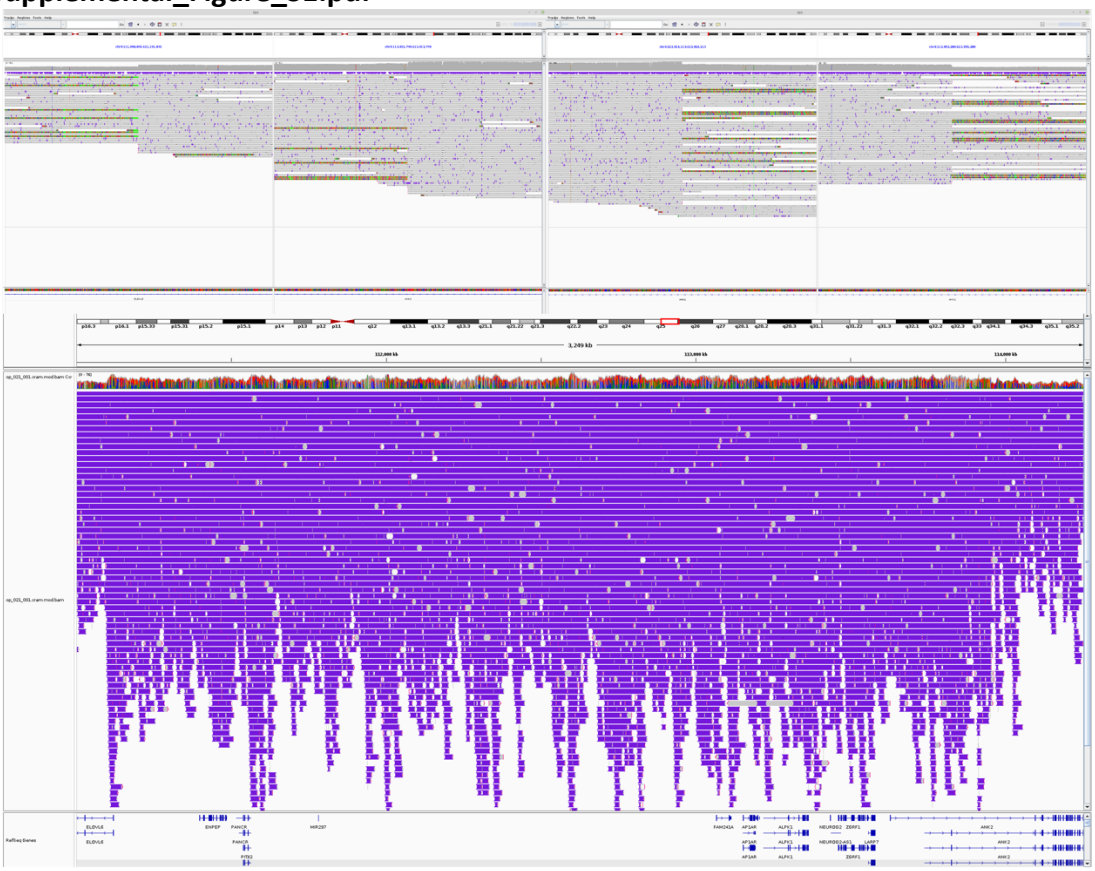
Supplemental_Table_S2.pdf

Family	Relation	Gender	Sequence Data File Name	SampleID (MSSNG ID)
Family 1	Mother	Female	op_021_001	3-0465-100
Family 1	Father	Male	op_021_006	3-0465-101
Family 1	Proband	Male	op_021_005	3-0465-000
Family 1_additional data	Proband	Male	op_035_001	3-0465-000
Family 2	Mother	Female	op_021_010	3-0772-100
Family 2	Father	Male	op_021_008	3-0772-101
Family 2	Proband	Female	op_021_009	3-0772-001
Family 3	Mother	Female	op_021_017	2-0264-001
Family 3	Father	Male	op_021_018	2-0264-002
Family 3	Proband	Male	op_021_019	2-0264-003
Family 3	Affected sibling	Male	op_021_011	2-0264-004
Family 3_additional data	Affected sibling	Male	op_035_002	2-0264-004
Family 3	Unaffected sibling	Female	op_021_012	2-0264-008
Family 3	Unaffected sibling	Female	op_021_020	2-0264-007
Family 3	Unaffected sibling	Female	op_021_021	2-0264-006
Family 4	Mother	Female	op_021_016	2-1375-001
Family 4	Father	Male	op_021_015	2-1375-002
Family 4	Proband	Male	op_021_014	2-1375-003
Family 4	Unaffected sibling	Male	op_021_007	2-1375-004
Family 5	Mother	Female	op_021_003	5-0138-001
Family 5	Father	Male	op_021_002	5-0138-002
Family 5	Proband	Male	op_021_004	5-0138-003

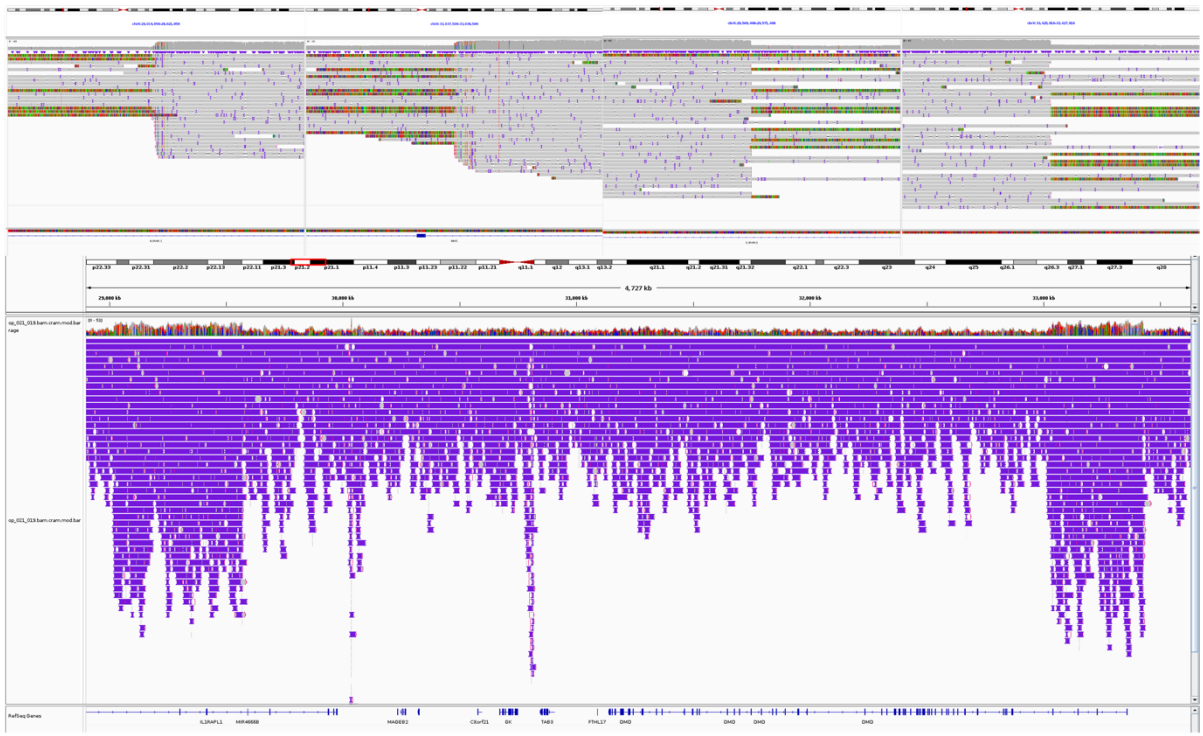
Supplemental Table S2. Table linking each sample to a unique sample ID and to the source datafile submitted to EGA.

Supplemental Figures

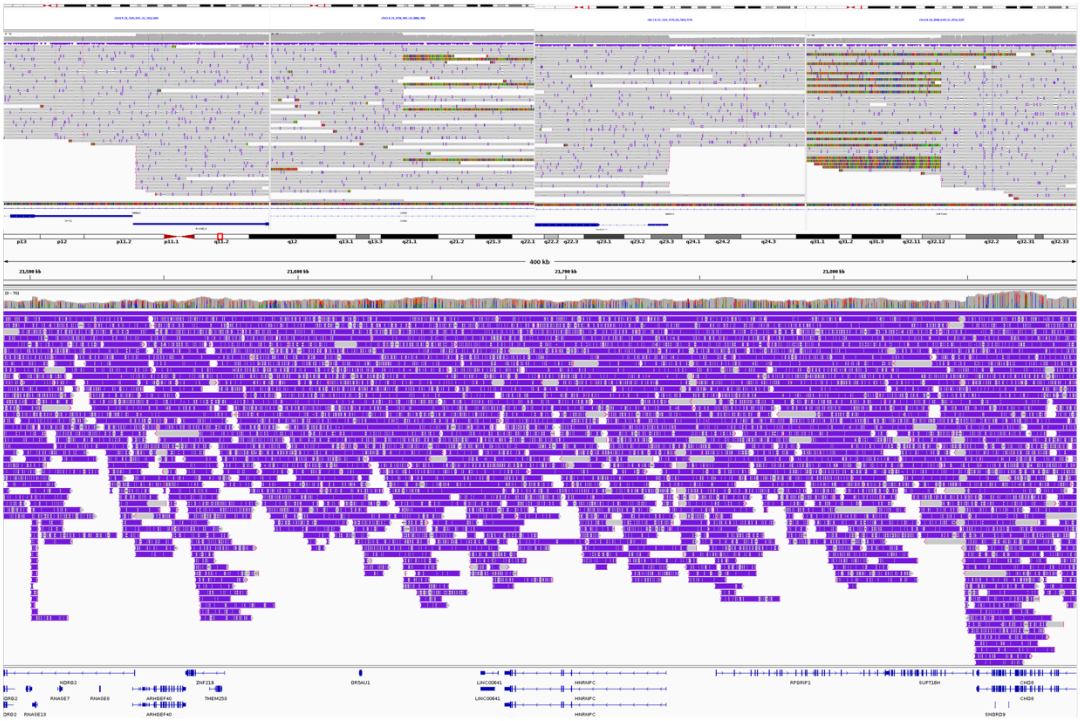
Supplemental_Figure_S1.pdf



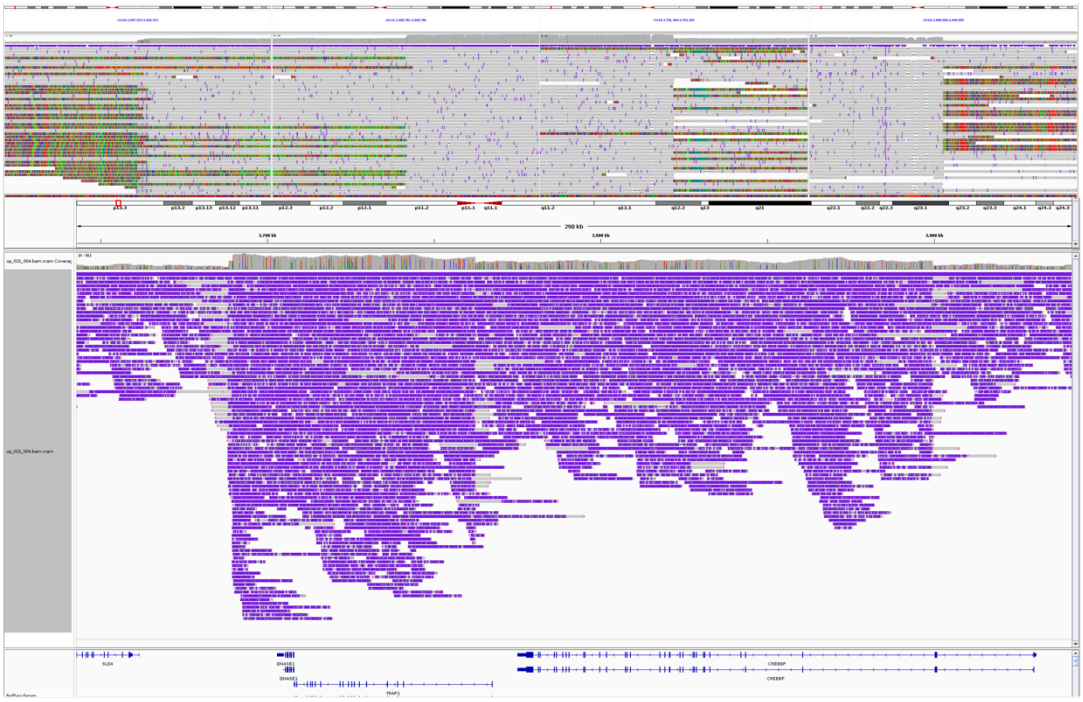
A. *ANK2* rearrangement. Family 1 and 2



B. *DMD* rearrangement. Family 3



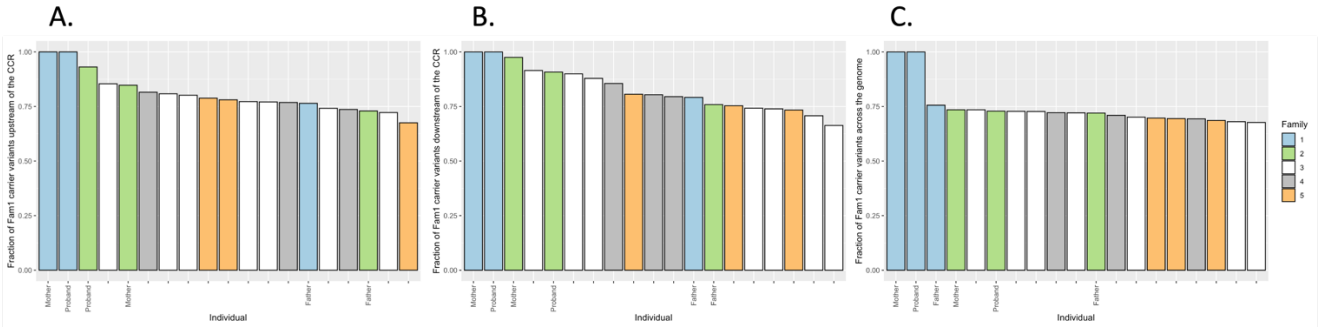
C. *CHD8* rearrangement. Family 4



D. *CREBBP* rearrangement. Family 5

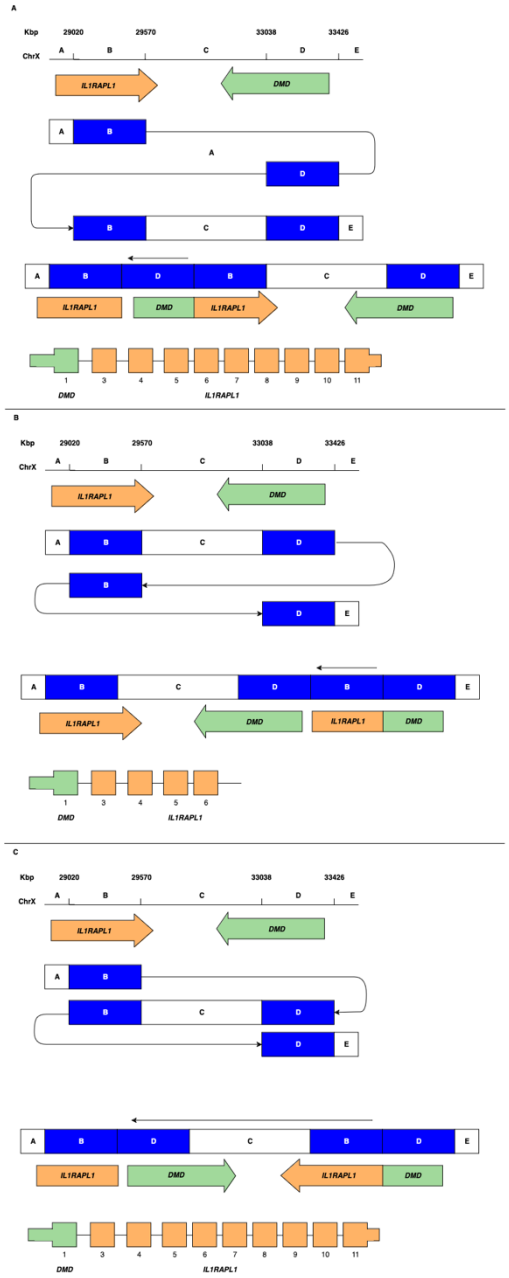
Supplemental Figure S1. IGV display of each CGR, showing breakpoint reads and coverage plots for each region. **A.** *ANK2*-region in family 1 and 2, **B.** *DMD*-region in family 3, **C.** *CHD8*-region in family 4 and **D.** *CREBBP*-region in family 5.

Supplemental_Figure_S2.pdf



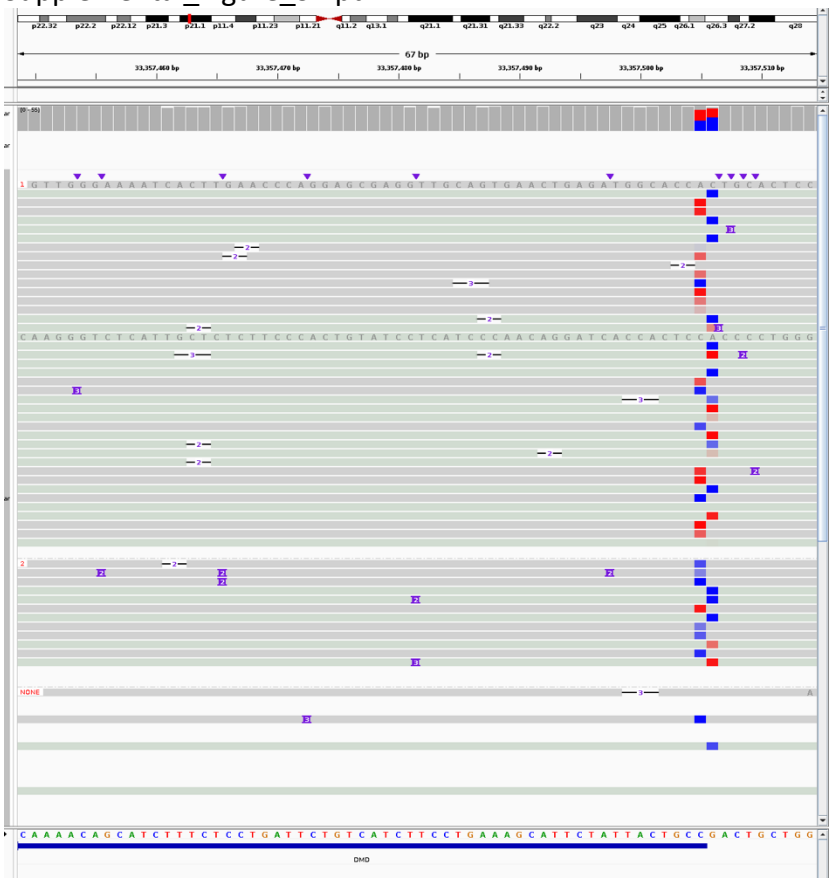
Supplemental Figure S2. Sharing of alleles present in both proband and mother of family 1 across the upstream (A), downstream (B) and whole genome (C) for individuals from all families. Results indicate a tendency towards allele sharing between family 1 and 2 outside the duplicated segment (main figure 2), but it is not significant compared to the other families, and there is no increased variant sharing across the whole genome.

Supplemental_Figure_S3.pdf



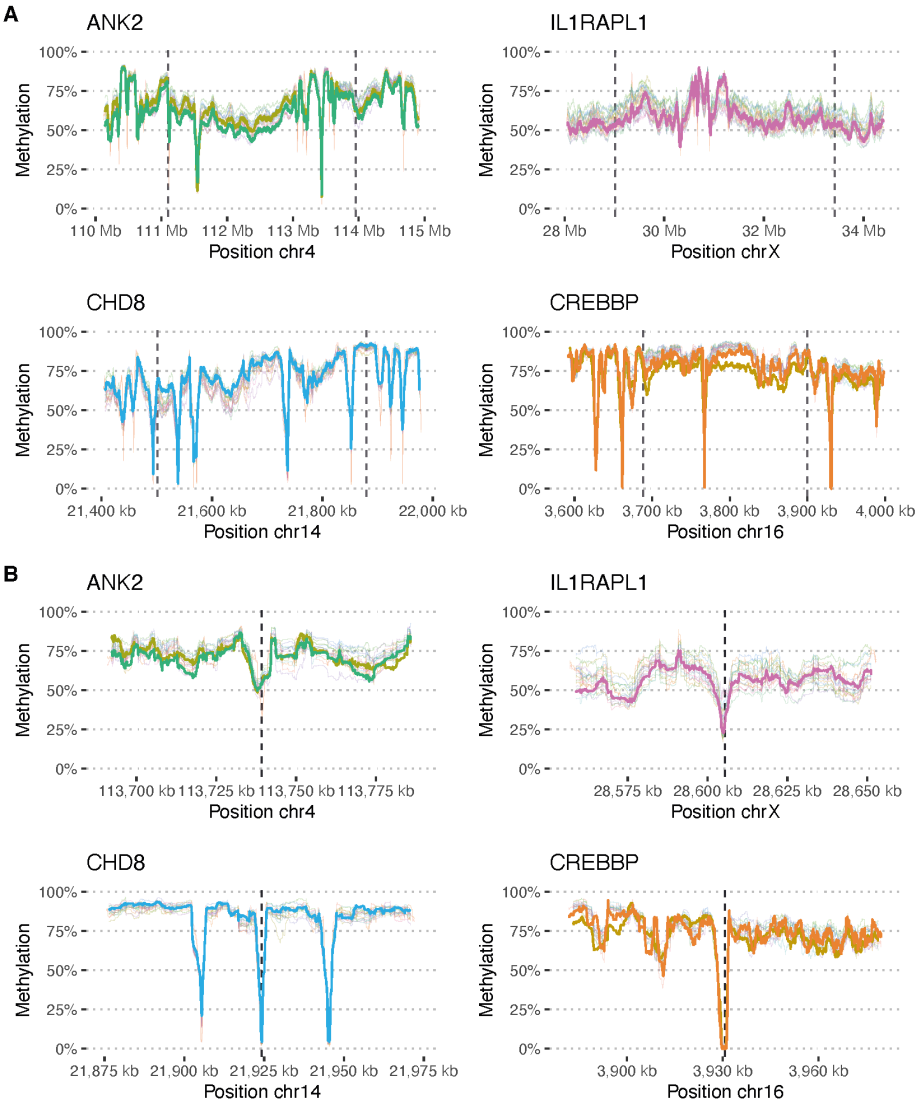
Supplemental Figure S3. The rearrangement across *IL1RAPL1* and *DMD* has three theoretical solutions based on the breakpoint and coverage information from the lrGS data. The architecture shown in A and C would both give rise to an in-frame *DMD-IL1RAPL1* fusion transcript. The architecture shown in (B) would also merge *DMD* and *IL1RAPL1*, but would not contain a complete 3'-end of either transcript.

Supplemental_Figure_S4.pdf



Supplemental Figure S4. Methylation site in the DMD promoter in an unaffected carrier female, with methylation status indicated in the maternal and paternal haplotypes, respectively.

Supplemental Figure S5.pdf



Supplemental Figure S5. Methylation calls for CpGs across all sequenced samples. Proband in each family highlighted by thicker lines, and the father is also highlighted in *CREBBP* to match main Figure 5. Shown in (A) is methylation across all CGR regions (A) with the boundaries of the CGR are indicated by dashed lines. In (B), the methylation is shown across the promoter region of each of the candidate ASD genes, with the transcription start site indicated by a dashed line +/- 50kb. Methylation signal in (A) is shown as mean number of methylated calls in rolling windows of 500 CpG sites for *ANK2* and *Il1RAPL1*, and for 50 CpG sites for *CHD8* and *CREBBP*. In (B) all methylation signals are shown in rolling windows of 50 CpG sites.