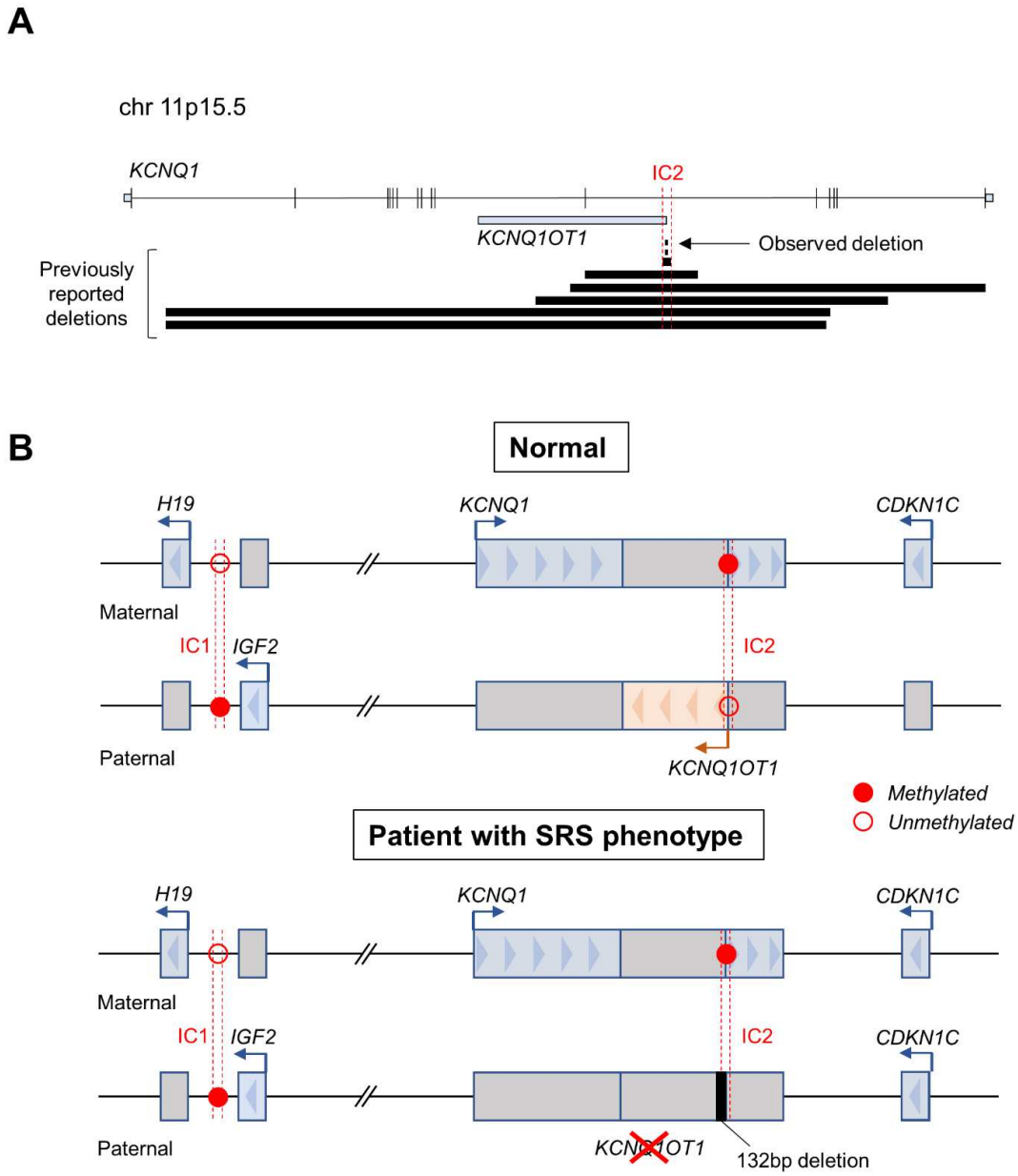

Figure S1: Selective methylation of maternally and paternally inherited copies of chromosome 11 at imprinting centers 1 and 2 (chr11p15.5). A) Previously reported deletions within the *KCNQ1* gene. B) Overview of the proposed model for gene expression and methylation events in the observed patient with SRS phenotype.

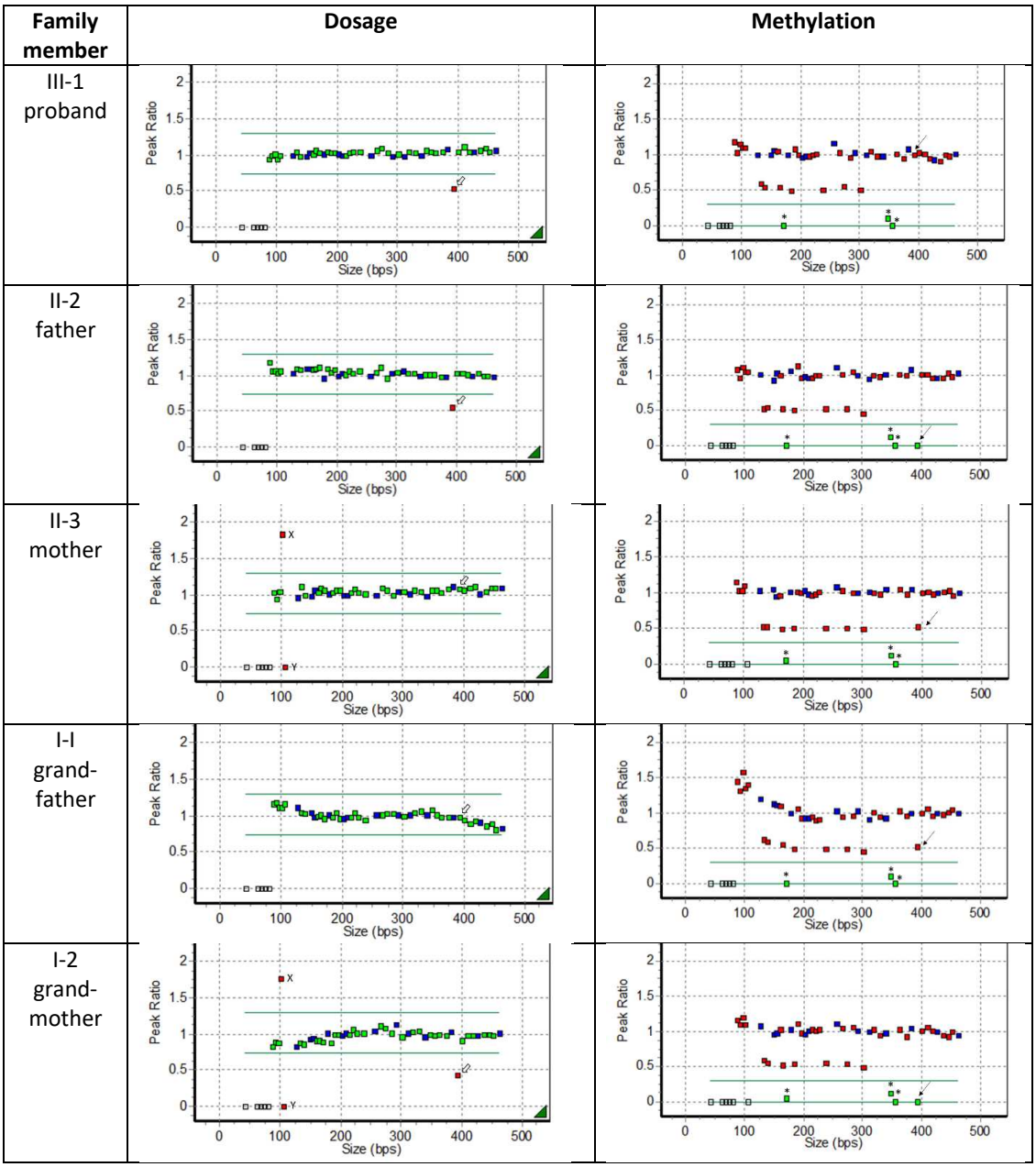

Figure S2. MS-MLPA data plots. The left and right panels show dosage and methylation data, respectively. Left: MS-MLPA probe 07172-L06781 (open arrow) shows the presence of a heterozygous loss in the proband (III-1), father (II-2) and grandmother (I-2). Right: In total eight methylation sensitive probes are assessed in this assay. Normally, the methylation sensitive regions are 50% methylated, which shows as a ratio of 0.5 in the plot. Four of the methylation-sensitive probes target KCNQ1OT1 in IC2, including MS-MLPA probe 07172-L06781. The latter probe (black arrow) has a hypermethylation signature in the proband (III-1) and hypomethylation in father (II-2) and grandmother (I-2), respectively. The asterisk shows control probes.

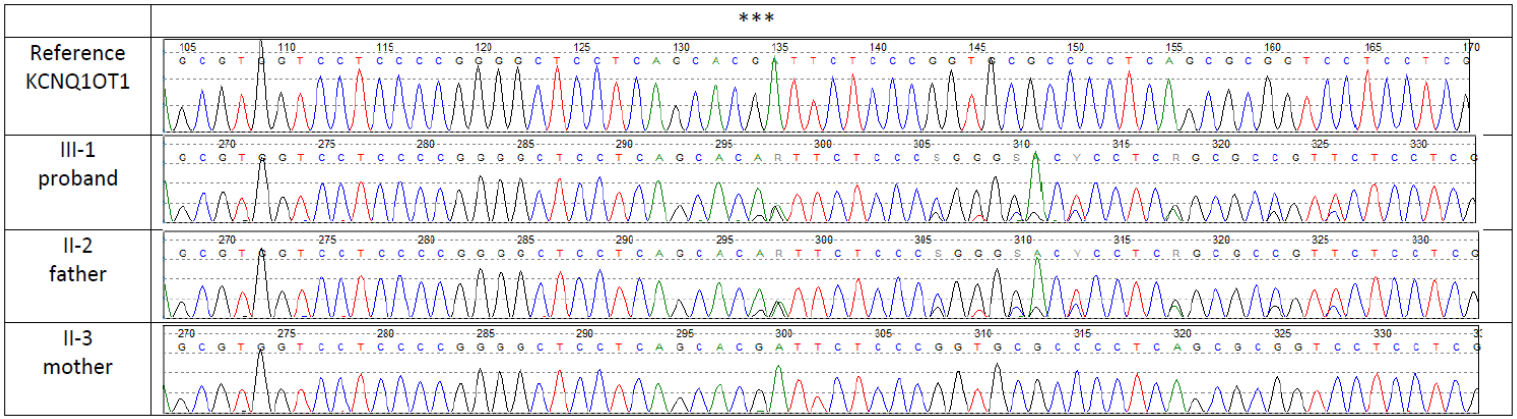

Figure S3. Sanger sequencing detects a 132-bp deletion in KCNQ1OT1. Sanger traces show a heterozygous 132-bp deletion in the KCNQ1OT1 gene (NR_002728.3) in the proband (III-1) and his unaffected father (II-2). The asterisks indicate the site of the deletion. The sequence from unaffected mother of the proband corresponds to the reference sequence.

Table S1: Overview of reported cases of deletions within imprinting centre 2 (IC2)

Deletion size	**Subjects & family members**	**Inheritance**	**Condition**	**Phenotype**	***KCNQ1OT1***	***KCNQ1***	**Genomic position (hg19)**	**Reference**
250 kb	Daughter (III-1)	Maternal	BWS	Prenatal overgrowth, ear creases and pits, undescended testes, macroglossia	Total gene	Exons 1b-14	-	Neimitz et al., 2004
	Son (III-2)	Maternal	BWS	Stillborn at 28 weeks, prenatal overgrowth and macroglossia				
	Son (III-4)	Maternal	BWS	Hemihypertrophy of right arm and leg, hypospadias, cleft palate, midline abdominal wall defect, ear pits and creases, undescended testes, macroglossia				
	Mother (II-2)	(Paternal)	Healthy	Normal				
330 kb	Daughter (III-1)	Maternal	BWS	Exomphalos, magroglossia, hypoglycemia, naevus flammeus, coarse facial appearance with upturned nose and right ear creases	Total gene	Introns 1-15	-	Algar et al., 2011
	Maternal Uncle (II-1)	Maternal	BWS	Macroglossia, naevus flammeus, hypoglycemia				
	Mother (II-2)	Maternal	BWS	Macroglossia, naevus flammeus, umbilical hernia				
	Maternal Grandmother (I-2)	Paternal	Healthy	Normal				
198 kb	Daughter	Maternal	BWS	Height disproportionately elevated, coarse facial appearance with proptosis, hypertelorism, upslanting palpebral fissures, M shaped upper lip, wide mandibule, prognathism, ear creases	Total gene	Exons 11-16	Chr11:2,671,855-2,870,191	Gurrieri et al., 2013
	Mother	(Paternal)	Healthy	Short stature				
60 kb	Fetus 1	Paternal	Severe IUGR	Fetal demise at 27 weeks, no malformations	Most 5' 40 kb	Exon 11	Chr11:2,679,858-2,739,436	De Crescenzo et al., 2013
	Fetus 2	Paternal	Severe IUGR	Fetal demise at 27 weeks, no malformations				

164 kb	Case 3	*De novo* paternal	SRS	IUGR, ventriculoseptal defect, post-natal growth failure, mild speech delay, triangular face with pointy chin, downturned mouth, fifth finger clinodactyly, hypoglycemia	Total gene	Exons 11-15	Chr11:2,656,421-2,820,617	Cytrynbaum et al., 2016
1.4 kb	Daughter	Paternal	Mild SRS	IUGR, low birth weight and lengh, growth failure, protruding forehead, apocrine sweating, clinodactyly, precocious puberty	5' end with promoter	Intron 11	Chr11:2,720,674-2,722,054	Mio et al., 2021
	Father	Maternal	Healthy	Normal				
	Paternal Grandmother	Paternal	Healthy	Short stature				
132 bp	Daughter	Paternal	SGA, Short stature	Growth delay, prominent forehead, low set prominent ears, downturned corners of mouth	132 bp in exon 1	Intron 11	Chr11:2,720,964-2,721,095	Eggermann et al., 2021
	Father	(Maternal)	Healthy	Normal				
132 bp	Son	Paternal	SRS phenotype	IUGR, feeding difficulties, head sparing failure to thrive, ADHD, motor and speech delay, learning difficulties, ODD, excessive sweating, variable appetite, triangular face, frontal bossing, high nasal bridge, long eye lashes, two urethras, micrognathia	132 bp in exon 1	Intron 11	Chr11:2,720,964-2,721,095	Present case

*Roman numerals refer to patient identification in the original publications
**Postulated inheritance without genetic testing in parenthesis