Maternal versus paternal inheritance of a 132 bp 11p15.5 microdeletion affecting KCNQ1OT1 and associated phenotypes

In this brief communication, we address the possible associations of a 132 bp deletion within the antisense gene KCNQ1OT1 on 11p15.5 to growth abnormalities. We question its recently suggested connection of paternal inheritance with Silver-Russell syndrome (SRS; OMIM #180860) and demonstrate maternal inheritance of the same variant in a 16-year-old girl with a tumour of the left leg. She also had mild isolated hemihypertrophy, suggesting a possible link to Beckwith-Wiedemann syndrome (BWS; OMIM #130650). Our findings underscore the complexity of 11p15.5 structural variations and the diffidence required when assessing their pathogenicity.

Genetic alterations of 11p15.5 imprinted gene clusters (regulated by imprinting centres H19/IGF2:IG-DMR (IC1) and KCNQ1OT1:TSS-DMR (IC2)) contribute to the phenotypically inverse growth disorders Beckwith-Wiedemann syndrome (BWS; OMIM #130650) and Silver-Russell syndrome (SRS; OMIM #180860).1–2

BWS shows locus heterogeneity within the 11p15.3 chromosomal region, where IC2 loss of methylation, IC1 gain of methylation, 11p15.5 UPD/CNV or CDKN1C pathogenic variants may lead to a wide spectrum of BWS features ranging from isolated cancer predisposition3 to severe dysmoria.2 The predominant cause of SRS is IC1 loss of methylation, with UPD7, 11p15.5 CNVs or CDKN1C variants constituting rarer causes.4 5

As recently summarised by Eggermann et al.,6 eight individuals with microdeletions in IC2 have been observed in five families. The deletions, all spanning 60 kb or more, affected the KCNQ1OT1 gene, the IC2, and part of the exonic sequence of KCNQ1. Paternal loss of KCNQ1OT1 should lead to expression of paternal CDKN1C, theoretically impeding growth. Among the eight individuals, five had paternally inherited deletions (three showing SRS phenotype and two asymptomatic) and three had maternally inherited deletions (all showing BWS phenotype).

In a sixth family, they presented a 132 bp deletion located in the non-coding gene KCNQ1OT1, which overlapped with intron 11 of KCNQ1 (KCNQ1OT1: NR_002728.3:n.134_265del; KCNQ1: LRG287t1:c.1514+37_654_1514+37 85del; Chr11(GRCh37):g.2,720,964–2721,095del). The proband, a 4-year-old girl, inherited this alteration paternally and scored 2 of 6 on the Netchine-Harbison scale (postnatal biometrics and prominent forehead). Thus, the affected girl did not meet the clinical criteria for the diagnosis of SRS. The authors postulate that her short stature is the result of paternal expression of CDKN1C. They also suggest that the father was unaffected as his deletion was inherited maternally and KCNQ1OT1 is therefore already silenced.

Figure 1  (A) Evidence of the 132 bp deletion in the proband (on the left) and her mother (on the right). In the proband, the deletion was evident in both germline and tumour whole genome sequencing (WGS) data, showing a distinct coverage drop and split reads. As expected, methylation-specific multiplex ligation-dependent probe amplification analysis confirmed the deletion with a single probe located in this genomic region (KCNQ1OT1-393bp, 07 172 06781). Heterozygous deletion of the same probe was identified in the mother. In the proband, the observed hypomethylation of the probe (highlighted by red rectangle) indicates a deletion on the maternal allele (confirmed); while, in the mother, hypermethylation (highlighted by red rectangle) of the probe indicates a deletion on the paternal allele (surmised). (B) Pedigree with the arrow indicating the proband. Carriers of the 132 bp deletion were either confirmed (+) or surmised (*). Proband’s father tested negative (−). Adult height with percentile and SD for the gender are presented below each subject.

We report a seventh family harbouring precisely the same 132 bp deletion described in the family presented by Eggermann et al. The proband was identified as part of the STAGING project (Sequencing Tumor And Germline DNA – Implications and National Guidelines), a national cohort of Danish paediatric cancer patients, offering extensive prospective sequencing of germline DNA. The first 198 patients have been published, including the sequencing and bioinformatics pipeline methods.

The 15 11/12 years old female proband was included in STAGING following a diagnosis of an unspecified tumour located in the right popliteal region. Whole genome sequencing (WGS) of a needle biopsy from the tumour revealed a somatic CTNNB1 (NM_001904.4: c.121A>G, p.(Thr41Ala)) gain-of-function variant strongly associated with desmoid fibromatosis tumours cooperated by histopathology. The fibromatosis mass was deemed unsuited for radical surgery due to involvement of the tibial nerve and major vessels. Clinical and radiological progression of the lesion during a wait-and-see approach prompted initiation of chemotherapy with methotrexate and vinblastine followed by tyrosine kinase inhibitors, which both proved largely ineffective (figure 1). Alternative limb-sparing surgical therapies are now being explored.

The proband had an uncomplicated birth at 37 weeks of gestation with a birth weight of 3200 g (−0.37 z). She never experienced feeding difficulties. She presented with right-sided toe walking at 15 months of age and was diagnosed with a likely causative congenital shortening of the right Achilles tendon, surgically corrected at age 4. She had menarche around age 10 years and stopped growing at age 13 9/12 years, with a final height of 164 cm (33.7 percentile, −0.4SD). She had both foot (left foot two European sizes smaller) and leg length (left leg 0.5 cm longer) discrepancy, although the latter falls within normal range. She presented no other features of BWS.

Methylation-specific multiplex ligation-dependent probe amplification analysis (MS-MLPA, ME030-C3, MRC Holland, Amsterdam, The Netherlands) was carried out to verify the 132 bp germline deletion, and a heterozygous deletion of a single probe located in the same region (KCNQ1OT1-393bp, 07172-L06781) was detected in the proband and her mother. MS-MLPA of the proband’s mother indicated paternal inheritance of the deletion (hypermethylation). The proband and her mother indicated paternal inheritance of the deletion (hypermethylation). The breakpoints of the 132 bp deletion were obtained from WGS of the germline and tumour DNA and were identical to the deletion of the previously family reported by Eggermann et al (figure 2).

According to the mechanism proposed by Eggermann et al, the mother of the proband of our study reports no significant health issues and she is of normal height (168 cm; 55.6 percentile, 0.1SD), fulfilling none of the Netchine-Harbison criteria. This suggests that the deletion presents with incomplete penetrance, is benign or mosaic.

The proband of our study displays a phenotype that overlaps somewhat with BWS; mild isolated hemihypertrophy and a shortened Achilles tendon (previously reported in BWS). Finally, CTNNB1 gain-of-function variants are known to drive a significant proportion of paediatric BWS cancers. Among 5213 childhood cancers reported in the St. Jude Cloud, 63 had somatic CTNNB1 variants; medulloblastoma (39/722), Wilms’ (10/252), adrenal cortical carcinoma (4/41), hepatoblastoma (3/16) and rhabdosarcoma (2/60). While medulloblastomas are not linked to BWS, the four other types constitute the hallmark cancers associated with the syndrome.

Importantly, a 117 bp deletion (chr 1 (GRCh37): g.2,720,978–2,721,095del) fully overlapping with the 132 bp deletion reported here and by Eggermann et al was detected in 6 out of 10 847 individuals in gnomAD, with 5 out of 3812 Europeans being carriers.

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We have elaborated on the phenotypes associated with a rare germline 132 bp deletion within KCNQ1OT1, suggesting a, perhaps incidental, link to tumour predisposition. Overall, our findings have
direct implications for the genetic counseling of families with this variant. Existing empirical evidence is inconsistent, and we consider the variant to be of unknown significance. Further investigations of small deletions within this region are required to clarify any link to BWS/SRS-related disorders.

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