Short Report

Beckwith–Wiedemann syndrome and long QT syndrome due to familial-balanced translocation t(11;17)(p15.5;q21.3) involving the \textit{KCNQ1} gene

Kaltenbach S, Capri Y, Rossignol S, Denjoy I, Soudée S, Aboura A, Baumann C, Verloes A. Beckwith–Wiedemann syndrome and long QT syndrome due to familial-balanced translocation t(11;17)(p15.5;q21.3) involving the \textit{KCNQ1} gene.

We report a child with Beckwith–Wiedemann syndrome (BWS) as the consequence of an apparently balanced, maternally inherited reciprocal translocation t(11;17)(p15.5;q21.3). His mother and aunt, who inherited the translocation from their father, did not have BWS. At birth, long QT syndrome (LQTS) was diagnosed in this child and, secondarily, among apparently healthy family members carrying the translocation. By FISH analysis, the breakpoint in 11p15.5 interrupts the \textit{KCNQ1} gene between exons 2 and 10 and causes a loss of methylation of the IC2 (and thus BWS) on the maternally inherited der(11) chromosome. To explain the presence of LQTS segregating with the t(11;17) translocation in this family, we hypothesize that the translocation that interrupts \textit{KCNQ1} allow translation of an abnormal short allele that interferes in a dominant negative way with the normal isoform 1 of \textit{KCNQ1} in the heart (where this allele is not subject to parental imprint). This appears to be the first report of BWS with congenital LQTS, which should be considered as a rare but serious complication to be searched systematically in patients with BWS due to 11p15 rearrangements.

Conflict of interest

The authors have no conflict of interest to declare.

Beckwith–Wiedemann syndrome (BWS; OMIM 130650) is a congenital overgrowth syndrome characterized by prenatal and postnatal overgrowth, macroglossia and anterior abdominal wall defects (1). Additional, variable features include organomegaly, neonatal hypoglycemia, hemihypertrophy, urogenital abnormalities, and in about 5% of children, embryonic tumors. The incidence is estimated to be 1 per 13,700 live births. BWS usually occurs sporadically (85%), but familial transmission occurs in 15% of cases (2, 3). BWS is caused by dysregulation of the expression of imprinted genes in the 11q15.5 region. The 11p15.5 region contains two clusters of imprinted genes. The most telomeric imprinted region (domain 1) includes insulin like growth factor 2 (\textit{IGF2}) and \textit{H19}. The imprinting center 1 (IC1) is a differentially methylated region (DMR) about 5 kb upstream of \textit{H19} allowing differential expression of \textit{IGF2} and \textit{H19}. The imprinted centromeric region contains \textit{CDKN1C}, \textit{KCNQ1} and \textit{KCNQ1OT1} (\textit{KCNQ1} overlapping transcript 1) which encodes an untranslated RNA inhibiting the transcription of \textit{CDKN1C} and \textit{KCNQ1}. The imprinting center 2 (IC2) is a DMR located in intron 10 of \textit{KCNQ1}, known as \textit{KvDMR1}. Maternal methylation...
at the KvDMR1 is thought to prevent transcription of the KCNQ1OT1 gene and enables the expression of CDKN1C and KCNQ1. The majority of BWS cases results from epimutations of the distal IC1 or proximal IC2 11p15.5 imprinting centers, either hypomethylation of KvDMR (50%) or hypermethylation of H19 (5%), 20% of cases are due to paternal uniparental disomy of chromosome 11 (UPD11) (4), CDKN1C mutations occur in 10% of cases. Chromosomal rearrangements, occurring in less than 2% of BWS cases, are in half cases balanced chromosomal translocations. Many balanced chromosomal translocation breakpoints fall in the KCNQ1 locus (4). Disruption of this locus on the maternally transmitted chromosome is responsible for the loss of methylation of IC2, leading to the loss of expression of CDKN1C and KCNQ1 (3, 5).

KCNQ1 is also involved in the congenital long QT syndrome (LQTS). LQT1, or Romano–Ward syndrome, is usually dominantly inherited (6, 7). A recessive form is associated with congenital deafness [Jervell and Lange–Nielsen syndrome (JLNS)] (8). LQTS manifests with episodes of syncope, and a high risk of potentially fatal ventricular arrhythmias especially in stressful situations. LQTS is characterized on surface ECG by prolongation of the QT interval (QTc $>440$ ms) and abnormal T wave. The prevalence is estimated at about 1/2500 births. In congenital LQTS, mutations have been reported in KCNQ1, KCNH2, KCNE1, KCNE2, SCN5A, and ANK2. In 30% of cases, no mutations are identified (9). These genes encode subunits of ion channels or proteins involved in modulating ionic currents. LQT1, representing 60% of all LQTS, is caused by mutations in the KCNQ1 (or KvLQT1) gene (7). KCNQ1 contains 19 exons and spans more than 400 kb on chromosome 11p15.5 (10). IC2 is located within intron 10. There are four isoforms of KCNQ1. Isoform 2 is more abundant in the heart and isoform 1 is expressed in many other tissues. KCNQ1 encodes a member of a class of potassium channel expressed predominantly in heart and epithelia: the $\alpha$ subunit of the Iks channel, a hetero-tetrameric key delayed rectifier potassium channel which has been shown in animal models to be crucial to control the duration of cardiac action potential (11). Several examples of digenism have been reported (12–14). There is no parent of origin effect in the transmission of LQTS (7). Examination of fetal hearts showed that isoform 2 is biallelically expressed, whereas isoform 1 is paternally imprinted: KCNQ1 appears not to be subject to parental imprinting in myocardial tissue (4, 15). In LQT1, most KCNQ1 mutations are missense or frameshift. These mutations not only abolish or reduce the protein activity but also have a dominant-negative effect on wild-type proteins (16, 17) secondary to a trafficking defect. Diminution in the repolarizing current results in prolongation of the cardiac action potential and predispose to cardiac arrhythmias.

Surprisingly, BWS has never been reported with LQTS. We describe here a familial balanced translocation t(11;17)(p15.5;q21.3) associated with both disorders.

**Case report**

Omphalocele was detected at the first trimester ultrasound scan (US) in a G1P1 20-year-old woman. Amniocentesis, at 20 weeks gestation revealed apparently balanced t(11p;17q), maternally inherited. US showed hydramnios, omphalocele, macrosomia, macroglossia and nephromegaly, suggesting BWS. The girl was born after 34 weeks of pregnancy. Her birth weight was 2710 gram (well above the 90th centile for the term), and head circumference was 33 cm (90th centile). Apgar score was 7/5. The baby showed typical BWS features (posterior pits of the ear lobes, naevus flammeus and macroglossia). Abdominal US confirmed nephromegaly. The omphalocele was surgically cured soon after birth and the child was monitored for hypoglycemia. LQTS was diagnosed at day 2 in the workup of an abnormal cardiac rhythm. Electrocardiogram (ECG) showed a prolonged corrected QT Interval (QTc) interval. At the age of 2, her psychomotor development was normal. She has remained asymptomatic, with a $\beta$-blocking treatment. QT interval remained significantly lengthened (550 ms).

**Familial investigations (Fig. 1)**

The mother of the proband, the maternal grandfather and the maternal aunt similarly had long QTc. None of them experienced syncope and none had BWS features. The aunt gave birth to two children in Romania, who both passed in the perinatal period. We have no reliable data on the first baby, but the second one, born at 30 weeks gestation, had BWS, based on the presence of macrosomia and omphalocele. Amniocentesis performed after prenatal detection of the abdominal anomaly showed the presence of the translocation. Formal methylation studies of the child were not carried out.

**Genetic investigations**

Fetal karyotype was performed on cultured amniocytes using G- and R-banding techniques. Chromosomal
studies on the parents, grandparents, and aunt and aunt’s second child were performed on cultured lymphocytes using G- and R-banding. Fluorescent in situ hybridization (FISH) studies of cultured amniocytes and lymphocytes were performed with chromosome 11 whole paint probe, chromosome 17 whole paint probe (Vysis, Des Plaines, IL), probes for the 11p, 11q, 17p and 17q telomeres (Total, Vysis), and specific bacterial artificial chromosomes (BACs) and plasmid artificial chromosomes (PACs) (RP11-889I17, RP4-608B4, RP11-116D18 and RP11-494F04 located on 11p15.5).

Single nucleotide polymorphism (SNP) array analysis was performed with the Illumina Human Cyto SNP-12 V2 array. Data analysis was performed with Illumina Genome studio v2009 software and CNV partition 2.4.4 human algorithm; Genomic annotations were based on NCBI human genome build 36, March 2006 (hg18) assembly.

Methylation status of IC1 and IC2 on 11p15.5 was analyzed by methyl-sensitive Southern blot on DNA from peripheral blood as previously described (18). Sequencing of exons and intron–exon junctions of KCNQ1 in the proband and her mother was performed after PCR amplification on ABI 3830 DNA sequencer (PE Applied Biosystems, Foster City, CA). The analysis of chromatograms was done with the software SeqScape (PE Applied Biosystems).

UPD11 was investigated by studying microsatellite polymorphisms by PCR and fragment analysis on sequence analyzer using samples of DNA of the proband and both parents. Four markers located on chromosome 11 were studied (D11S956, D11S1924, D11S1899, and D11S488).

Results

Fetal karyotype was defined as 46, XX, t(11;17)(p15.5;q21.3)mat using conventional karyotype, chromosome painting and targeted FISH. The translocation was found in the mother, the maternal grandfather, the maternal aunt and her second, healthy child. The RP11-889I17 probe covering IGF2 locus was localized on the derivative der(17), RP11-116D18 spanning CDKN1C locus, targeted the derivative der(11) and the PAC probe RP4-608B4 that maps between introns 2 and 10 of KCNQ1 gene cohybridized on der(11) and der(17), allowing to map the breakpoint between exons 2 and 10 of KCNQ1 (Fig. 2). SNP array did not detect loss of material at the breakpoints on chromosomes 11 and 17 at its level of resolution (30–40 kb). It revealed only copy number variations (CNVs) listed as polymorphism in the Database of Genomic Variants: (http://projects.tcag.ca/variation). No other pathogenic genomic rearrangement was identified. Proband’s DNA (III-1) showed a normal methylation pattern of IC1 (H19) and a loss of methylation of IC2 (KCNQ1OT1), confirming the diagnosis of BWS. Microsatellite markers and SNP pattern showed normal biparental contribution for the studied loci. No non-synonymous mutation or indels were found in KCNQ1 exons by direct sequencing. The breakpoint on chromosome 17q21.3 has not been further explored.

Discussion

Our results indicate that BWS in the index case is due to a translocation of maternal origin whose breakpoint is
The translocation was located by FISH between the section of genes in the region. The breakpoint of causing a loss of methylation of IC2 and deregulates Beckwith–Wiedemann syndrome chromosome rearrangements. Nat Genet 1997: 15: 181–185.


