

Supplementary Note.

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Note on accession numbers for *CDC45*

Human *CDC45* encodes a 20-exon gene that has been annotated as including three major spliceforms. As well as the full-length version which encodes a protein of 598 amino acids, alternative splicing to skip either exon 7 alone or both exons 4 and 7 leads to shorter isoforms with in-frame deletions of 32 and 78 amino acids, respectively. Whereas exon 4 shows high conservation in mammalian species both in sequence and occurrence of exon skipping, neither is the case for exon 7, so the physiological significance of the isoform including exon 7 is currently uncertain. Virtually all previous publications investigating the structure and function of *CDC45* employ the numbering of the middle-sized, 566 amino acid isoform, so for consistency with prior work all numbering used here refers to NM_003504.4.

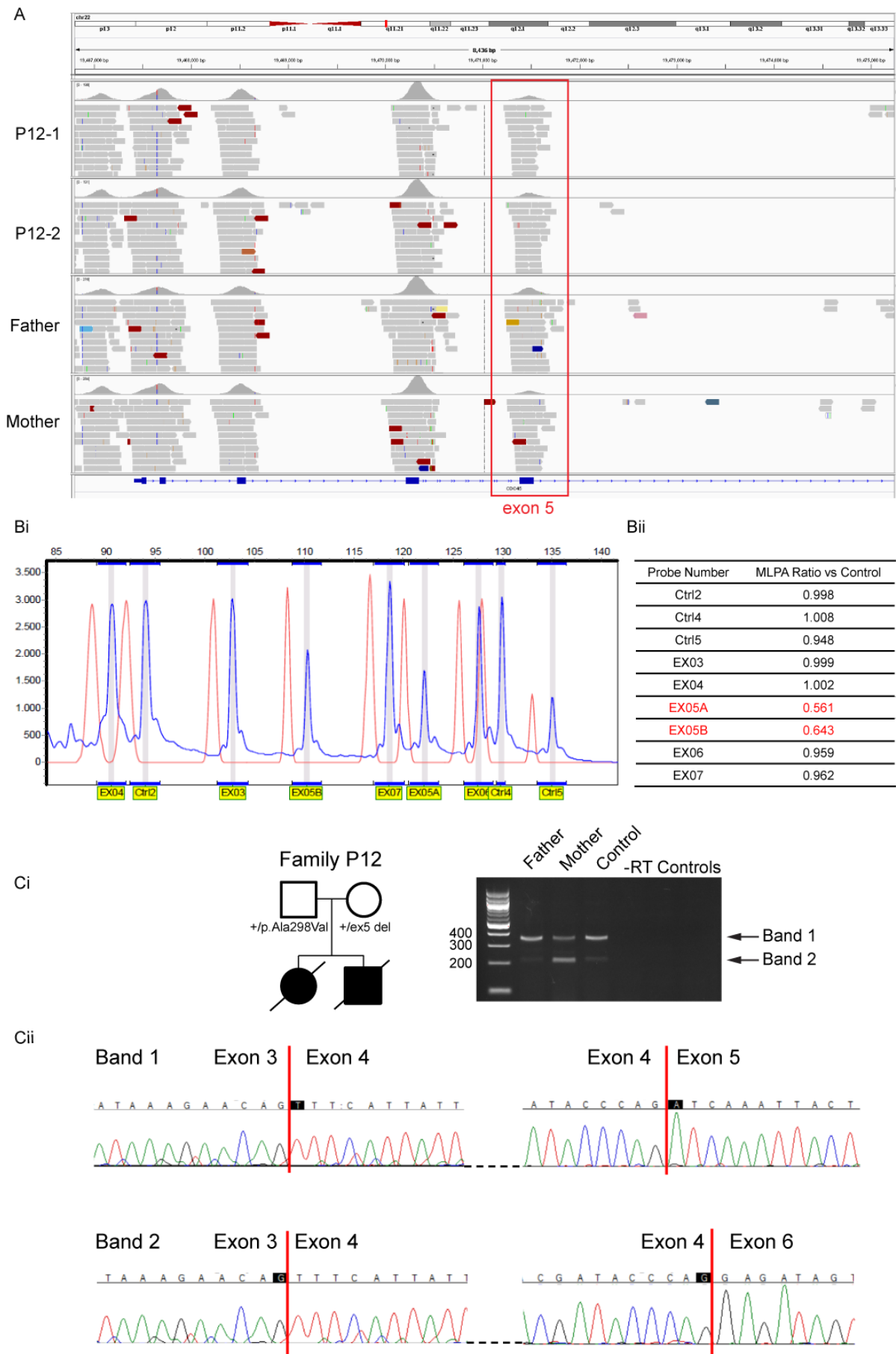


Figure S1. Family P12 segregates a genomic deletion encompassing exon 5 of *CDC45*.

(A) Manual interrogation of exome sequencing reads across the *CDC45* gene suggested a decrease in coverage across exon 5 in both affected samples and the carrier mother, compared to the father, who carries the c.893C>T, p.Ala298Val variant. While the reduction in coverage was not statistically significant, the presence of a rare variant on the *trans* allele in both affected samples prompted further investigation. BAM files visualized using IGV. (B) MLPA, comparing the quantity of DNA in a test sample vs a synthetic control with multiple probes across *CDC45*, was performed in both affected samples and the mother, and all samples showed a deletion of exon 5. (Bi) Peak traces of control (red) and affected (blue). (Bii) Calculated ratio of DNA. Both probes for exon 5 demonstrate an approximately 50% reduction, consistent with a heterozygous deletion of exon 5. Probes for exon 4 and exon 6 do not show a reduction, indicating the breakpoints for the deletion lie within intron 4 and intron 5, respectively. Reports generated using GeneMarker Software (SoftGenetics Inc.). (C) RT-PCR and sequencing of cDNA from carrier parents in family P12. (Ci) RT-PCR of exons 3-6 in *CDC45* from cDNA derived from parents in family P12. There is an increase in a lower migrating band in the mother, who carries the exon 5 deletion allele (a faint co-migrating lower band visible in all samples is caused by physiological skipping of exon 4, see figure 5). (Cii) Sequencing of each band from the maternal sample indicates the lower migrating band (labelled Band 2) comprises exons 3, 4 and 6, with complete skipping of exon 5, resulting in an in-frame transcript.

Table S1. Experimental details for next-generation sequencing undertaken in this study.

Family	Clinical Diagnosis/ Study Focus	Design	Library Kit	Platform	Analysis Software			Coverage	Filtering parameters	Control populations
					Mapping	Variant Calling	Annotation			
P1	Craniosynostosis (SC_2930), clinical genome sequencing	Genome	NEBNext DNA Sample Prep Master Mix Set 1 Kit	Illumina HiSeq2000	BWA ¹ , Stampy (v1.0.12-1.0.22) ²	Platypus (v.0.2.4) ³	ANNOVAR ⁴	28x	Minor allele absent	1000 Genomes, ESP
P2	Craniosynostosis	Exome	TruSeq V2	Illumina HiSeq2000	Novoalign (Novocraft Technologies)	SAMtools (v0.1.19)	ANNOVAR	55x	Minor allele absent	1000 Genomes, ESP
P4	Primordial dwarfism	Exome	SureSelect V4	Illumina HiSeq2500	BWA, Stampy	SAMtools, Dindel	Ensembl VEP	50x	MAF < 0.005, ≥ 1 deleterious consequence prediction	1000 Genomes, ESP
P12	Diagnostic	Exome	SureSelect ^{XT} V5	Illumina HiSeq2500	Custom in-house pipeline MAGPIE (based on BAM-MEM and GATK)			70x	SeattleSeq, LOVDplus	GoNL, 1000 Genomes

MAF, minor allele frequency; GoNL, genomes of The Netherlands.

Table S2. Primers and amplification conditions for resequencing.

Dideoxy-sequencing primers to confirm variants in the craniosynostosis cohort ^a				
Variant	Primers	Primer sequence 5'→3'		Product size (bp)
		Forward	Reverse	
c.226A>C	4F/4R	TAGTGATGAAGGAAAAGGGGCCTCCTCG	CTGTTCCCAGTCCCACAGGGTAGTCAG	314
c.318C>T				
c.469C>T	5F/5R	ACCACGTATGGTGTAACCTCTGGTGCCTCAC	CTTGGCCTGGCAGGCTTCAGGATGAC	436
c.653+5G>A	8F/8R	CATGAGCCTTAGACTTCTCTGCTTCCTTAC	ATCACACACATACCCAGAAAGGGGGCTGCA	240
c.677A>G	9F/9R	GAGAGAGGCCACCTGACTGAGGCAAG	CAGTCCTCACTTCTCAATAGGACCCTA	335
c.1487C>T	16F/16R	CATAGACAAAGAACCGGCGCTGCAAACTG	GACACTAGAGGCAAATACCACTCTACTCAG	223
Dideoxy-sequencing primers for <i>CDC45</i> in the MGS cohort ^b				
Exon(s)	Forward		Reverse	Product size (bp)
1-2	GATTTGGCGGGAGTCTTG		ACGCAGCACCCCTCACCTC	382
3	TCTTTTCAAGGTAAATTGCTAATGTC		TGGAAATAGAATGCTGTGTCAA	230
4	AGTGATGAAGGAAAAGGGGC		CCAAGAACACCAGGTGAGAC	274
5	TCAGCTTATTAGGAAATGATAAGATTC		CCACTGCCCTCAGTACACC	343
6	CTGGGCCTACTGACTTCTGC		TCACTTCAAGCTAGAATAACCTTTC	519
7	TTTTCCAAAATATTTGGCTTCC		AGGACACTGACCCCTGGAG	174
8	TCAAGTCCAGTCTGGCTGC		TTATGTGGCACTGACCAAGG	201
9	CCTCATTGAGCCCAGGTG		GTGGCTATGGTCAGGCTGTG	179
10	CTGCCTGGTAAGAGCTGGAG		ACCCACAGAGGGTGACAAAG	257
11-12	CCACCTGCTGGAGTTACGAG		CCCTTCACTTTAATGAACCTGG	610
13	GCAGTGAGAGCTTGCCAC		CCCGTAACTGACCTCCCTG	293
14-15	CAAGCAAATATTTGTGACTTTGG		GGAGCTCTCCAAGCACCTG	437
16-17	CTCTGAGTGTTGAGCTGGGG		AACTTGCTTGTTCCAGGG	506
18	TTCTGTGCCCTGTCTTGTG		AGCAGGGCATCAGGGTC	199

Primers for Fluidigm resequencing in the craniosynostosis cohort ^c			
ID	Forward	Reverse	Length (bp, excluding universal adaptors)
CDC45_1	ACACTGACGACATGGTTCTACAAGTCTTGACCGCCGCC	TACGGTAGCAGAGACTTGGTCTCCCCTCATCCCTTCCCCA	173
CDC45_2	ACACTGACGACATGGTTCTACACCTCGGACGTGGATGCT	TACGGTAGCAGAGACTTGGTCTCTCACTTGCTGTTACCTCCT	186
CDC45_3	ACACTGACGACATGGTTCTACAGTCCAGAGCCAGGTGACG	TACGGTAGCAGAGACTTGGTCTCTGAAGGATCTTGACGCAC	210
CDC45_4	ACACTGACGACATGGTTCTACAAGATAGGCTTTGAAAACACTCTCTCT	TACGGTAGCAGAGACTTGGTCTTGCTGTGTCAAGAAATTACAATTGAGTA	186
CDC45_5	ACACTGACGACATGGTTCTACAATGAAGACACTATATTCTTTGTGTGTGAC	TACGGTAGCAGAGACTTGGTCTTAGTCAGACACACACCTTACCAAG	167
CDC45_6	ACACTGACGACATGGTTCTACATCAGAGGCTTAGTGATGAAGGAAAA	TACGGTAGCAGAGACTTGGTCTATTGACGACATTGACTGGCCTAT	192
CDC45_7	ACACTGACGACATGGTTCTACACCGTAGAAAGAGGAGAGGCTTAATT	TACGGTAGCAGAGACTTGGTCTGATAGCTGTGAGAGACCCAACT	215
CDC45_8	ACACTGACGACATGGTTCTACAGGCCTACTGACTTCTGCCAAA	TACGGTAGCAGAGACTTGGTCTGGCTTCTGGTGCTGGGAG	193
CDC45_9	ACACTGACGACATGGTTCTACAGTGCCACCCATACCTCTGAC	TACGGTAGCAGAGACTTGGTCTCCATGGTCTCTAATGGATGGCA	188
CDC45_10	ACACTGACGACATGGTTCTACACTTCCTGTACTGCTACTTCCTGTT	TACGGTAGCAGAGACTTGGTCTACATTTGAGGACACTGACCCC	164
CDC45_11	ACACTGACGACATGGTTCTACAGCCTTAGACTTCTCTGCTTCCTT	TACGGTAGCAGAGACTTGGTCTGTGGCACTGACCAAGGCA	145
CDC45_12	ACACTGACGACATGGTTCTACACATCATCTCACTCCATCCCCC	TACGGTAGCAGAGACTTGGTCTGCTATGGTCAGGCTGTGCA	200
CDC45_13	ACACTGACGACATGGTTCTACATTCCCGCCACAACCACC	TACGGTAGCAGAGACTTGGTCTCACCTGCTTCCCTCCTGG	191
CDC45_14	ACACTGACGACATGGTTCTCACTGCCTGGTAAGAGCTGGAG	TACGGTAGCAGAGACTTGGTCTGAGTGTGTTCTCCTCATCCTCG	141
CDC45_15	ACACTGACGACATGGTTCTCAATTCAAGCTGTGGTCTGTGCA	TACGGTAGCAGAGACTTGGTCTTTCTGGGATCTAGGGCAAGGA	194
CDC45_16	ACACTGACGACATGGTTCTACAGCTTGCATGCTCCTTGACTG	TACGGTAGCAGAGACTTGGTCTCTCCTGGAGCCGCTTCTG	144
CDC45_17	ACACTGACGACATGGTTCTCAGTCGGTGTGTGGTGACCTC	TACGGTAGCAGAGACTTGGTCTCTTTAATGAACCTGGATGTAATGAAGATAAATC	200
CDC45_18	ACACTGACGACATGGTTCTCAGCTGTGTTTGCTCCCATGAC	TACGGTAGCAGAGACTTGGTCTCAAACCCACAGCCCTCCT	207
CDC45_19	ACACTGACGACATGGTTCTCAAACCTCGCCAAGAAGCAGCT	TACGGTAGCAGAGACTTGGTCTAGACGAAGCCACTGGTGC	161
CDC45_20	ACACTGACGACATGGTTCTCAATTACCAAGAGTTCCTGACAAGCA	TACGGTAGCAGAGACTTGGTCTAATGGTCTGCTGGGTGGC	127
CDC45_21	ACACTGACGACATGGTTCTCACAGTGGCTTCGTCTGACCAT	TACGGTAGCAGAGACTTGGTCTGGCCAGCATCTAACTCCCC	201
CDC45_22	ACACTGACGACATGGTTCTCACTCTGAGTGTTGAGCTGGGG	TACGGTAGCAGAGACTTGGTCTGGACGAGTGGAAGCTGCTC	200
CDC45_23	ACACTGACGACATGGTTCTCACATGTCTTGTGTGTACAGAGC	TACGGTAGCAGAGACTTGGTCTCCAGCCATGCCAACTTGC	187
CDC45_24	ACACTGACGACATGGTTCTCAGTGAGCAGCTTCCACTCGT	TACGGTAGCAGAGACTTGGTCTCTTCTCAAACGCCCTCCCAA	196
CDC45_25	ACACTGACGACATGGTTCTCATCCCTTCTCACGGCTGTTTTT	TACGGTAGCAGAGACTTGGTCTCCAAGTAGAAGCCTCCGTTGA	201

MLPA Primer Sequences ^d	
ID	Sequence
CDC45-EX4-5	GGGTTCCCTAAGGGTTGGAAGCCAGTCAATGTCGTCATGTATA
CDC45-EX4-3	CAACGATACCCAGGTACTTTTTGTGTCTAGATTGGATCTTGCTGGCAC
CDC45-EX3-5	GGGTTCCCTAAGGGTTGGAATAGGCTTTGAAAACACTCTCTCTCCAGGC
CDC45-EX3-3	CTTGTTCCAGTGTGACCACGTGCAATATACGTCTAGATTGGATCTTGCTGGCAC
CDC45-EX5B-5	GGGTTCCCTAAGGGTTGGAAGCGCACACGGTTAGAAGAGGTGAGTTGGGTCTCT
CDC45-EX5B-3	CACAGCTATCCCAGAGGAACCTTGCACTCCCAGAGGTCTAGATTGGATCTTGCTGGCAC
CDC45-EX7-5	GGGTTCCCTAAGGGTTGGAATACGAGCAGTATGAATATCATGGGACATCGGTAAGTAT
CDC45-EX7-3	GAATAGGTGGAACCTCACTATAAAGTTCTGACTCCAGGGGTCTAGATTGGATCTTGCTGGCAC
CDC45-EX5A-5	GGGTTCCCTAAGGGTTGGAATGATGACCTTGAAGTTCCCGCCTATGAAGACATCTTCAG
CDC45-EX5A-3	GGATGAAGAGGAGGATGAAGAGCATTACAGAAATGACAGTGTCTAGATTGGATCTTGCTGGCAC
CDC45-EX6-5	GGGTTCCCTAAGGGTTGGAAGCTGTGGGGATAAATTCCTGGTGCATTTGCTCCACCTTTTGT
CDC45-EX6-3	CTCTTTGTCCCTGTATCAGGAGATAGTGGAGCAAACCATGCGGTCTAGATTGGATCTTGCTGGCAC

^aDNA was extracted from either venous blood collected into EDTA, lymphoblastoid cell lines or cultured fibroblasts established from skin biopsies obtained from the scalp incision at the time of surgical intervention. All DNA was extracted using the Nucleon Blood and Cell Culture (BACC) DNA extraction kit (Gen-Probe Inc.) according to the manufacturer's instructions. PCR amplification of DNA was performed in a volume of 20 µl, containing 15 mM TrisHCl (pH 8.0), 50 mM KCl, 2.5 mM MgCl₂, 100 µM each dNTP, 0.4 µM primers, and 0.75 units of FastStart Taq DNA Polymerase (Roche). Cycling conditions comprised a 5 min initial denaturation step at 94°C, followed by 35 cycles of 94°C for 30 s, annealing at 63°C for 30 s and extension at 72°C for 30 s, with a final extension at 72°C for 7 min. For dideoxy-sequencing, amplified PCR products were treated with *ExoI* (NEB) and shrimp alkaline phosphatase (FastAP; Thermo Scientific) to remove PCR primers and dNTPs respectively, by incubating at 37°C for 30 min, followed by 85°C for 15 mins to denature the enzymes. Sequencing was then carried out using the BigDye Terminator v3.1 cycle sequencer system (Applied Biosystems).

^bPCR amplification of DNA was performed in a volume of 10 µl, using ReddyMix PCR master mix with 1.5 mM MgCl₂ (Thermo Scientific), 0.5 µM primers and 10 ng DNA. Cycling conditions employed a touchdown approach and were as follows: 5 min initial denaturation step at 95°C, then 3 cycles of 94°C for 30 s, 65°C for 30 s, 72°C for 45 s, then 3 cycles of 94°C for 30 s, 62°C for 30 s, 72°C for 45 s, then 3 cycles of 94°C for 30 s, 59°C for 30 s, 72°C for 45 s with a final 35 cycles of 94°C for 30 s, 56°C for 30 s, 72°C for 45 s, then a final extension of 72°C for 10 min. Dideoxy-sequencing was performed as in ^a.

^cPrimer pairs were designed to amplify 25 target regions of approximately 200 bp, covering all 19 exons and intron/exon boundaries for use with the Access Array™ IFC system (Fluidigm). Universal CS1 and CS2 adaptor sequences were included on the 5' ends of all target-specific forward and reverse primers, respectively. Primers were multiplexed into pools of 4-5 optimised pairs, with a final concentration of 1 µM per primer. Amplicon tagging, thermal cycling using the Biomark HD™ system (Fluidigm) and product harvesting were performed following the manufacturer's instructions. Ion PGM™ sequence-specific adaptors and sample indexes were attached to each amplicon pool for DNA extracted from 48 individual craniosynostosis patients using a DNA Engine Dyad® Peltier thermal cycler (Bio-Rad). Indexed PCR products were pooled, purified with AMPure XP beads (Beckman Coulter Ltd.) and quantified using an Agilent High Sensitivity DNA Kit with the 2100 Bioanalyzer (Agilent Technologies, Inc) or

the 2200 TapeStation (Agilent Technologies) with a High Sensitivity D1000 ScreenTape. In total, 467 patient samples were processed for downstream sequencing applications. Pooled and indexed PCR products were sequenced using the Ion PGM™ System (Life Technologies Ltd.). Pooled libraries were diluted to a final concentration of 10 pM and emulsion PCR and enrichment were performed with the Ion PGM™ Template OT2 200 Kit (Life Technologies Ltd.) according to the manufacturer's instructions. Enriched target regions were sequenced with the Ion PGM™ Sequencing 200 Kit v2 for 125 cycles, using an Ion 318 chip.

Underperforming amplicons (CDC45_2, CDC45_3 and CDC45_24) were re-sequenced independently. PCR products were amplified from 40 ng DNA with Q5® Hot Start High Fidelity polymerase (NEB) in the recommended standard reaction mixture, with the inclusion of Q5 High GC Enhancer. Cycling conditions were denaturation at 98°C for 30 s, followed by 35 cycles of 98°C for 10 s, 60°C for 30 s and 72°C for 30 s, followed by a final extension at 72°C for 2 min. Amplification products were diluted 100-fold and used in a second PCR reaction to incorporate Ion PGM™ sequence-specific adaptors and sample indexes as above, for 9 cycles. Pooled samples were purified and sequenced for 100 cycles as described above, using an Ion 314 chip. Sequence read alignment and variant analysis were performed using the Ion Torrent platform-specific software v4.2.1. In total 361 samples fulfilled minimum coverage parameters (x10 reads) for all amplicons.

^dThe MLPA reactions were performed according to a protocol based on the methods described previously.^{5,6} Products were separated by capillary electrophoresis on the ABI 3130 (Applied Biosystems) and data analyzed using GeneMarker (SoftGenetics Inc). Threshold ratios for deletion and duplication were set at <0.75 and >1.3, respectively. The colored primer sequences are universal for the MLPA procedure.

Table S3. Primer sequences used for cDNA analysis of *CDC45*.

Target Primers	Primer sequence 5'→3'		Product size (bp)
	Forward	Reverse	
Exon 1-3	TCCGATTTCCGCAAAGAGTTCTACG	CAGCGTATATTGCACGTGGTCACA	138
Exon 3-4	GGTGGCAAGAAGCTTGAAACTG	ACATTGACGACATTGACTGGCCTAT	166
Exon 3-5	GGTGGCAAGAAGCTTGAAACTG	ATGTCTTCATAGGCGGGAAC	238/100 if exon 4 skipped
Exon 5-6	GTTCCCGCCTATGAAGACAT	CTCCTCCGCATGGTTTGCTC	137
Exon 2F-5R	GACGTGGATGCTCTGTGTGC	GCTTCTCAGAAGGCTCTGACC	394/301 if exon 3 skipped /256 if exon 4 skipped
Exon 2_3F-5_4R	AGATCCTTCAGGCCTTGTTC	TAATTTGATCTGGGTATCGTTGTATAC	251
Exon 2_3F-5_3R	AGATCCTTCAGGCCTTGTTC	TAATTTGATCTGTTCTTTATGCTCAAG	113
<i>GAPDH</i>	GGACTCCACGACGTACTCAGCGCCAGC	GTGGATATTGTTGCCATCAATGACC	213

Table S4. *In silico* prediction of mutation effects on canonical splice sites.

Patient	Mutation	Allele	Sequence	MAXENT Score	Sum Difference	Sum Variation	Significance Threshold	Significant ^a
P3	c.653+5G>A	G (WT)	tcagtaagg	8.61	5.95	-69%	-30%	Yes – 5' donor site lost
		A (MUT)	tcagtaaag	2.66				
P9-1 & P9-2	c.203A>G, p.Gln68Arg	A (WT)	caggtattg	8.35	3.48	-42%	-30%	Yes – 5' donor site lost
		G (MUT)	cgggtattg	4.87				
P10	c.1440+14C>T	C (WT)	caggcgggt	0.81	-7.75	+1157%	+30%	Yes – cryptic 5' donor site created
		T (MUT)	cagg ^t gggt	8.56				

^aSignificance based on thresholds applied by prediction software, Alamut Batch (Interactive Biosciences Inc) and Human Splicing Finder.⁷

Table S5. *In silico* splicing predictions for synonymous mutations in *CDC45*.

Patient	Mutation	Motif affected	Predicted Consequence
P1	c.318C>T, p. V106V	Multiple potential silencing motifs created	Skipping of exon 4
P9-1 & P9-2	c.333C>T, p.N111N	SRp40 exonic splice enhancer motif lost	Skipping of exon 4

Predictions calculated using Human Splicing Finder.⁷

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