Mutations in *CENPE* define a novel kinetochore-centromeric mechanism for Microcephalic Primordial Dwarfism in humans.

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Online Resource Tables.

Sample Designation	Phenotype	Workup
MPD-001	MPD IUGR MSG	*PCNT* sequencing
MPD-002	MPD IUGR MSG	*PCNT* sequencing
MPD-003	MPD IUGR MIC PMG	*PCNT* sequencing. ATR-dependent G2-M checkpoint normal
MPD-004	MPD IUGR MSG	WES – known MPD genes negative.
MPD-005	MPD IUGR MSG Seckel-like	ATR-dependent G2-M checkpoint normal
MPD-006	MPD IUGR MSG	*PCNT, ASPM, CENPJ*
MPD-007	MPD IUGR MSG	WES – known MPD genes negative
MPD-008	MPD IUGR MSG ISS	–
MPD-009	MPD IUGR MSG	Targeted sequencing for all MIC and MPD genes
MPD-010	MIC MPD-like	*CENPJ, MCPH1, ASPM, PCNT, STIL*

Supplementary Table 1. MIC MPD cohort screened (negative) for *CENPE* mutations (n=10).

All 49 coding *CENPE* exons were sequenced. ISS, infantile spasms; MIC, microcephaly; MPD, microcephalic-osteodysplastic primordial dwarfism; MSG, microcephaly with simplified gyri; WES, whole exome sequencing.

Algorithim	Mutation	Score	Interpretation
PolyPhen-2	p.D933N P.K1355E	0.055 0.956	*Benign* **Possibly damaging**
SIFT	p.D933N P.K1355E	0.49 0.04	*Tolerated* **Damaging**
ALIGN-GVGD	p.D933N P.K1355E	C15 C55	*Unlikely to impact.* **Very likely to impact.**
Mutation Taster	p.D933N P.K1355E	23 56	**Protein features *might be* affected (both variants)**

Supplementary Table 2. Bioinformatic analysis of *CENPE* variants.

PolyPhen: http://genetics.bwh.harvard.edu/pph2/index.shtml

SIFT: http://sift.jcvi.org/

ALIGN-GVGD pathogenicity prediction: http://agvgd.iarc.fr/

Class C0 (no impact) to Class C65 (most likely to impact).

Mutation Taster: http://www.mutationtaster.org/

Grantham matrix 0-215.

	PCNT	***CENPE***
Primary phenotype	MPD (MOPD type II*)	MPD
Common phenotypic features	Severe intra-uterine and postnatal growth restriction, MIC, ID, typical facies (prominent nose micrognathia), delayed ossification, abnormal teeth	
Distinct phenotypic features	Skeletal anomalies* High juvenile mortality due to cerebral vessel insults, cardiomyopathy, early onset type 2 diabetes, dislipidemia.	Severe MIC with simplified gyri (OFC -5 to -9 SD) Congenital restrictive cardiomyopathy *(1 sibling)*
Function	Centrosome-structural role?	Kinetochore-associated; spindle microtubule capture and attachment
Mutations	Recessive (Nonsense, splice site, frameshift, missense)	Recessive (Missense)
Patient LCL Characteristics	***PCNT***	***CENPE***
Mitotic spindles	Disorganized, multipolar spindles	Disorganized, monopolar and multipolar spindles
Mitotic segregation	Impaired; elevated levels of bi-nucleated cells (with nuclei of equal size)	Impaired, elevated levels of bi-nucleated cells (with 50% nuclei unequal in size)
Mitotic progression	Delayed	Delayed
ATR-dependent DDR	Defective	Functional
Centromeric accumulation of CENP-E in mitotic cells	Reduced	Reduced
CENPE-dependent BubR1-autophos	Impaired following colcemid treatment	Impaired following colcemid treatment

Supplementary Table 3. Comparison between the clinical and biochemical characteristics of *CENPE*-related MPD and *PCNT*-related MOPD type II patients.

*Skeletal anomalies in MOPD type II include: (small iliac wings, coxa vara, V-shaped distal femoral metaphyses, triangular distal femoral epipyses, pseudoepiphyses, brachymesophalangy V, metaphyseal flaring of the radius and ulna, relatively short arms). These features often develop in an age-dependent manner. BubR1; kinetochore associated kinase; DDR; DNA damage response.

ABCC9	*ACTC*	*ACTC1*	*ACTN2*	*ANKRD1*	*BAG3*
BRAF	*CAV3*	*CRYAB*	*CSRP3*	*DES*	*DMD*
DSC2	*DSG2*	*DSP*	*DTNA*	*EMD*	*FKTN*
GATAD1	*GLA*	*HRAS*	*ILK*	*JPH2*	*JUP*
KRAS	*LAMA4*	*LAMP2*	*LDB3*	*ZASP*	*LMNA*
MAP2K1	*MAP2K2*	*MTND1*	*MTND5*	*MTND6*	*MTTD*
MTTG	*MTTH*	*MTTI*	*MTTK*	*MTTL1*	*MTTL2*
MTTM	*MTTQ*	*MTTS1*	*MTTS2*	*MYBPC3*	*MYH7*
MYL2	*MYL3*	*MYLK2*	*MYOZ2*	*MYPN*	*NEBL*
NEXN	*NRAS*	*PDLIM3*	*PKP2*	*PLN*	*PRKAG2*
PTPN11	*RAF1*	*RBM20*	*RYR2*	*SCN5A*	*SGCD*
SOS1	*TAZ*	*TCAP*	*TMEM43*	*TMPO*	*TNNC1*
TNNI3	*TNNT2*	*TPM1*	*TTN*	*TTR*	*VCL*

Supplementary Table 4. Cardiomyopathy-associated genes. A list of the known cardiomyopathy-related genes that were interrogated for variants in the exome sequence of LR05-054a1.

Supplementary Table 5. A list of the variants identified in the cardiomyopathy-related genes from the exome sequence of LR05-054a1.

Of the 218 variants identified, all but one are commonly represented in dbSNP. The one exception is the intronic variant chr2:g.179549378G>C in the gene *TTN*, that is most likely not pathogenic.

Gene	Chr	Coordinate	rsID	Ref	Subject
ABCC9	12	21958399	rs829060	G	C
ABCC9	12	21970019	rs2638441	C	T
ABCC9	12	22005003	rs2307024	T	G
ABCC9	12	22017422	rs697250	A	G
ABCC9	12	22017486	rs697251	C	G
ABCC9	12	22047151	rs704216	G	T
ABCC9	12	22047174	rs704217	C	T
ABCC9	12	22063115	rs10770865	A	G
ABCC9	12	22063337	rs4148656	A	G
ABCC9	12	22063737	rs4762719	G	T
ABCC9	12	22063749	rs4762720	T	C
ABCC9	12	22063971	rs4148654	A	G
ABCC9	12	22068849	rs3759236	G	T
ABCC9	12	22078838	rs2277405	T	G
ACTN2	1	236849952	rs138279482	C	T
ACTN2	1	236882303	rs1341864	T	C
ACTN2	1	236883421	rs1341863	C	T
ACTN2	1	236899042	rs2288600	G	A
ACTN2	1	236902594	rs2288601	C	G
ACTN2	1	236924506	rs2282366	A	G
BAG3	10	121435955	rs196294	A	C
BAG3	10	121436362	rs196295	A	G
BRAF	7	140449071	rs3789806	C	G
BRAF	7	140449150	rs9648696	T	C
BRAF	7	140487202	rs1267632	C	T
DES	2	220285309	rs1058261	C	T
DES	2	220286142	rs1058284	G	A
DSG2	18	29104714	rs2230234	A	G
FKTN	9	108366734	rs34787999	G	A
FKTN	9	108380355	rs17309806	C	A
HRAS	11	534242	rs12628	A	G
ILK	11	6629665	rs1043388	C	T
ILK	11	6630833	rs1043390	G	A
JPH2	20	42747247	rs3810510	C	T
JPH2	20	42814931	rs6031442	T	C
JPH2	20	42815190	rs1883790	G	A
JUP	17	39912145	rs1126821	T	A
JUP	17	39912581	rs9890858	A	G

Gene	Chr	Coordinate	rsID	Ref	Subject
JUP	17	39913645	rs7216034	T	C
JUP	17	39914070	rs8067890	G	T
JUP	17	39923614	rs12942034	A	G
JUP	17	39925713	rs41283425	C	T
KRAS	12	25362777	rs1137282	A	G
KRAS	12	25368462	rs4362222	C	T
KRAS	12	25378456	rs76433096	T	C
LAMA4	6	112451367	rs34752945	G	T
LAMA4	6	112454185	rs764587	A	G
LAMA4	6	112457390	rs2032567	C	T
LAMA4	6	112457471	rs2032568	G	A
LAMA4	6	112493872	rs1050348	A	G
LAMA4	6	112506375	rs9374309	G	A
LAMA4	6	112506583	rs6908219	G	T
LAMA4	6	112508769	rs9387061	T	G
LAMA4	6	112508770	rs9400522	G	T
LAMA4	6	112522852	rs11757455	G	A
LAMA4	6	112537682	rs78871662	A	G
LMNA	1	156104292	rs12117552	G	A
MYH7	14	23888617	rs200234670	G	T
MYH7	14	23894565	rs139882431	G	A
MYH7	14	23902753	rs2069540	G	A
NEBL	10	21074724	rs2296614	T	C
NEBL	10	21104694	rs4748727	A	T
NEBL	10	21108247	rs1006362	C	T
NEBL	10	21115332	rs1409348	T	C
NEBL	10	21120116	rs10491056	A	G
NEBL	10	21129588	rs41277368	T	C
NEBL	10	21134282	rs41277370	C	G
NEBL	10	21139389	rs4025981	T	C
NEBL	10	21141469	rs703089	T	C
NEBL	10	21148584	rs4748729	C	A
NEBL	10	21157492	rs2296609	T	C
NEBL	10	21176945	rs703100	G	A
NEBL	10	21185821	rs788971	A	C
NEBL	10	21399813	rs3864841	C	G
NEBL	10	21401765	rs4748749	T	C
NEBL	10	21414892	rs625223	C	G
NEBL	10	21415006	rs11591355	T	C
NEBL	10	21461232	rs35856892	G	A
PDLIM3	4	186423637	rs4635850	G	A
PDLIM3	4	186423655	rs12644280	G	A
PDLIM3	4	186423677	rs10866276	G	A
PDLIM3	4	186427841	rs2306705	T	C
RYR2	1	237617757	rs3765097	C	T
RYR2	1	237620049	rs2045955	T	C
RYR2	1	237711797	rs2253273	A	G
RYR2	1	237730124	rs2805390	A	G

Gene	Chr	Coordinate	rsID	Ref	Subject
RYR2	1	237730169	rs2779401	C	T
RYR2	1	237753364	rs2805409	A	C
RYR2	1	237753390	rs2805410	A	G
RYR2	1	237796837	rs10802626	G	A
RYR2	1	237797082	rs1967579	T	G
RYR2	1	237801770	rs707189	T	C
RYR2	1	237813126	rs625006	A	G
RYR2	1	237814783	rs684923	C	T
RYR2	1	237881770	rs2797441	C	T
RYR2	1	237890437	rs2685301	C	T
RYR2	1	237923053	rs2253831	C	T
RYR2	1	237946964	rs790889	T	C
RYR2	1	237951451	rs2256242	A	G
RYR2	1	237955680	rs146659498	T	C
RYR2	1	237955684	rs78394746	T	C
RYR2	1	237957146	rs790902	G	A
RYR2	1	237957161	rs790901	A	G
RYR2	1	237957309	rs790900	A	C
RYR2	1	237965043	rs2790347	A	G
RYR2	1	237965094	rs2794820	G	T
RYR2	1	237965131	rs9428384	G	A
RYR2	1	237969638	rs790879	A	G
SCN5A	3	38592406	rs1805126	A	G
SCN5A	3	38598669	rs41312393	A	G
SCN5A	3	38622467	rs7430407	T	C
SCN5A	3	38645420	rs1805124	T	C
SCN5A	3	38646423	rs7428779	C	T
SCN5A	3	38674712	rs6599230	T	C
SGCD	5	155756414	rs11740347	G	A
SGCD	5	155771579	rs1801193	T	C
SGCD	5	155771773	rs4434364	A	G
SGCD	5	155885469	rs11954391	T	C
TCAP	17	37822311	rs1053651	A	C
TNNT2	1	201331554	rs1104859	T	G
TNNT2	1	201331664	rs2365652	C	A
TNNT2	1	201334382	rs3729547	G	A
TNNT2	1	201335899	rs1573230	C	T
TNNT2	1	201337170	rs3729842	A	G
TNNT2	1	201338896	rs10920184	T	C
TNNT2	1	201339043	rs12049476	C	T
TNNT2	1	201341341	rs868407	C	T
TPM1	15	63349096	rs4775613	G	A
TPM1	15	63351687	rs4775614	A	G
TPM1	15	63351840	rs1071646	C	A
TTN	2	179392080	rs16866373	A	T
TTN	2	179395958	rs3813250	T	C
TTN	2	179396354	rs3829748	G	A
TTN	2	179397561	rs3829747	C	T

Gene	Chr	Coordinate	rsID	Ref	Subject
TTN	2	179398823	rs2857265	G	A
TTN	2	179403593	rs2303539	G	A
TTN	2	179404786	rs2288325	A	T
TTN	2	179406191	rs3731749	C	T
TTN	2	179411665	rs2288327	A	G
TTN	2	179412966	rs35445420	G	A
TTN	2	179413110	rs3731748	G	A
TTN	2	179414633	rs890578	C	A
TTN	2	179421694	rs9808377	A	G
TTN	2	179427186	rs2366751	A	G
TTN	2	179427536	rs3829746	T	C
TTN	2	179430997	rs3731746	G	A
TTN	2	179436020	rs744426	G	A
TTN	2	179444137	rs2288571	A	G
TTN	2	179444768	rs4145333	C	G
TTN	2	179444939	rs2303838	C	T
TTN	2	179447848	rs4894029	T	C
TTN	2	179448911	rs16866400	G	A
TTN	2	179451420	rs2042996	G	A
TTN	2	179454394	rs1560221	A	G
TTN	2	179455207	rs2163009	T	C
TTN	2	179457147	rs16866406	G	A
TTN	2	179458591	rs2288569	C	T
TTN	2	179464527	rs1001238	T	C
TTN	2	179514433	rs2562845	T	C
TTN	2	179523590	rs146110527	C	A
TTN	2	179539903	rs2472751	C	A
TTN	2	179542674	rs72650048	C	T
TTN	2	179543217	rs35112591	C	T
TTN	2	179549378	.	G	C
TTN	2	179558366	rs2042995	T	C
TTN	2	179576596	rs2742331	A	T
TTN	2	179578730	rs2562839	G	A
TTN	2	179579093	rs12693164	T	C
TTN	2	179579212	rs2562838	T	C
TTN	2	179579822	rs2562836	T	A
TTN	2	179580093	rs12622914	A	C
TTN	2	179582162	rs62178977	C	T
TTN	2	179582327	rs13390491	C	T
TTN	2	179582537	rs2627043	G	T
TTN	2	179582605	rs6750145	A	G
TTN	2	179582853	rs72648982	T	C
TTN	2	179583398	rs62178978	T	C
TTN	2	179583496	rs16866465	T	G
TTN	2	179585266	rs2562831	C	T
TTN	2	179585393	rs2562830	A	G
TTN	2	179587130	rs12693166	C	G
TTN	2	179587687	rs2742327	T	C

Gene	Chr	Coordinate	rsID	Ref	Subject
TTN	2	179591708	rs114742263	C	T
TTN	2	179595117	rs17076	C	G
TTN	2	179598228	rs12993099	A	G
TTN	2	179600563	rs2742348	G	A
TTN	2	179605180	rs746578	C	T
TTN	2	179614952	rs10803917	A	G
TTN	2	179615887	rs922984	T	C
TTN	2	179615931	rs922985	C	G
TTN	2	179615994	rs922986	T	C
TTN	2	179620951	rs7585334	C	T
TTN	2	179621477	rs6433728	C	T
TTN	2	179623758	rs2291310	C	T
TTN	2	179623939	rs6705594	T	C
TTN	2	179629363	rs4894043	T	C
TTN	2	179629461	rs2291311	C	T
TTN	2	179632710	rs2291313	T	C
TTN	2	179633298	rs4471922	G	T
TTN	2	179634392	rs13388274	A	T
TTN	2	179634421	rs200875815	T	G
TTN	2	179634961	rs33917087	C	A
TTN	2	179635919	rs13011633	C	T
TTN	2	179642425	rs719201	G	A
TTN	2	179643886	rs2291302	A	G
TTN	2	179643934	rs2291301	A	G
TTN	2	179644035	rs1552280	G	A
TTN	2	179644855	rs10497520	T	C
TTN	2	179650408	rs35813871	G	A
TTN	2	179650701	rs6715406	C	T
TTN	2	179667090	rs3816849	C	T
TTR	18	29175210	rs121918074	C	A
VCL	10	75865065	rs767809	G	A
VCL	10	75866929	rs2131957	C	A
VCL	10	75871735	rs2131956	C	G
VCL	10	75873892	rs10824072	C	T
VCL	10	75874192	rs28639484	T	C