Supplementary material:

Mutation of *HERC2* causes developmental delay with Angelman-like features

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Supplementary Figures

Individual

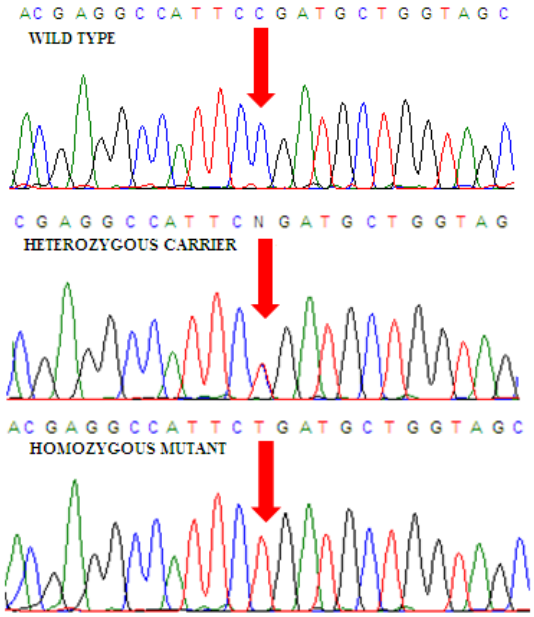
Marker	Position (Mb)	VII:15		VII:16		VIII:3		VIII:4		VIII:10		IX:2	
19xGT	24.53	3	3	1	5	5	3	6	3	1	3	1	3
18xCA	24.73	3	3	2	5	5	3	5	3	2	3	1	3
25 CT	25	2	2	2	2	2	2	2	2	1	2	1	2
20xTG	25.05	1	1	1	1	2	1	1	1	1	1	1	1
25xAC	25.07	2	2	2	2	2	2	1	2	3	2	3	2
24xGT	25.11	1	1	3	1	3	1	3	1	2	1	2	1
D15S1002	25.52	4	4	1	4	4	4	3	4	2	4	5	4
D15S156	25.58	2	2	1	2	2	2	1	2	1	2	1	2
21xGT	25.84	1	2	3	2	1	2	3	2	4	2	3	2
22xCA	25.92	1	2	3	2	1	2	3	2	3	2	1	2
NM_004667.4:c.1781C>T	26.18	C	T	C	T	C	T	C	T	C	T	C	T
29xGT	27.11	-	-	-	-	4	1	7	1	8	1	4	3

Marker	Position (Mb)	VIII:7		VIII:8		IX:1		IX:6		IX:7		IX:8		IX:9		X:1		X:2	
19xGT	24.53	3	5	3	5	3	3	3	3	3	3	6	3	6	1	3	3	3	3
18xCA	24.73	3	5	3	5	3	3	3	3	3	3	5	3	5	2	3	3	3	3
25 CT	25	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2
20xTG	25.05	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
25xAC	25.07	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2
24xGT	25.11	1	1	1	1	1	1	1	1	1	1	4	1	4	2	1	1	1	1
D15S1002	25.52	4	4	4	4	4	4	4	4	4	4	2	4	2	2	4	4	4	4
D15S156	25.58	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2
21xGT	25.84	2	2	2	2	2	2	2	2	2	2	1	2	1	4	2	2	2	2
22xCA	25.92	2	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2	2	2
NM_004667.4:c.1781C>T	26.18	T	T	T	T	T	T	T	T	T	T	C	T	C	T	T	T	T	T
29xGT	27.11	1	1	1	1	1	1	1	1	1	1	1	1	8	1	1	3	1	3

Marker	Position (Mb)	IX:10		IX:11		IX:12		IX:13		X:3	
19xGT	24.53	8	3	4	3	8	6	5	3	5	3
18xCA	24.73	4	3	3	3	4	5	5	3	6	3
25 CT	25	1	2	2	2	1	2	2	2	2	2
20xTG	25.05	1	1	1	1	1	1	2	1	2	1
25xAC	25.07	4	2	3	2	4	2	2	2	2	2
24xGT	25.11	2	1	5	1	2	1	3	1	3	1
D15S1002	25.52	4	4	4	4	4	4	1	4	6	4
D15S156	25.58	2	2	1	2	2	2	2	2	1	2
21xGT	25.84	3	2	1	2	3	2	3	2	5	2
22xCA	25.92	7	2	2	2	7	2	8	2	5	2
NM_004667.4:c.1781C>T	26.18	C	T	C	T	C	T	C	T	C	T
29xGT	27.11	2	1	1	3	1	2	6	3	5	1

Marker	Position (Mb)	X:5		X:6		XI:1		XI:2		XI:3		XI:4	
19xGT	24.53	3	3	3	6	5	6	3	6	3	6	7	3
18xCA	24.73	3	3	3	5	6	4	3	4	3	4	2	3
25 CT	25	2	2	2	2	2	2	2	2	2	2	2	2
20xTG	25.05	1	1	1	1	2	1	1	1	1	1	1	1
25xAC	25.07	2	2	2	2	2	2	2	2	2	2	5	2
24xGT	25.11	1	1	1	1	3	1	1	1	1	1	4	1
D15S1002	25.52	4	4	4	4	6	4	4	4	4	4	4	4
D15S156	25.58	2	2	2	2	1	2	2	2	2	2	2	2
21xGT	25.84	2	2	2	2	5	2	2	2	2	2	3	2
22xCA	25.92	2	2	2	2	5	2	2	2	2	2	6	2
NM_004667.4:c.1781C>T	26.18	T	T	T	T	C	T	T	T	T	T	C	T
29xGT	27.11	1	3	1	3	5	1	1	1	-	-	4	1

Supplementary Figure 1. Microsatellite marker genotypings in the Amish family 1A across the Chr:15q13.1-q13.3 region as well as the c.1781C>T variant.



Supplementary Figure 2. Electropherograms showing the DNA sequence at the position of the *HERC2* (c.1781C>T) variant in a wild-type control, heterozygous carrier parent and homozygous affected individual.

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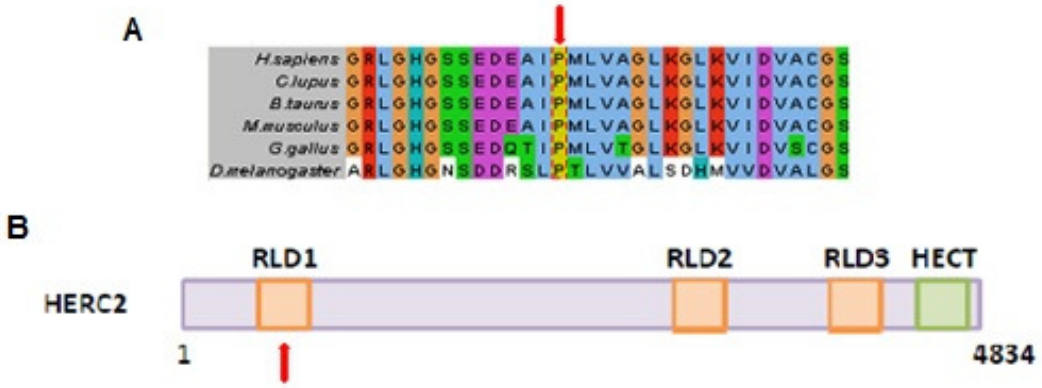

Supplementary Figure 3A) ClustalW2 alignment of amino acid sequences of the *HERC2* gene in Homo sapiens and 5 other species illustrating that the proline residue altered by the c.1781C>T substitution (indicated with the red arrow) is highly conserved, reformatted using online Jalview software. **B)** Secondary structure of human HERC2 illustrating the positions of the RCC1-like domains (RLD), HECT2 domain and Pro594Leu substitution (indicated with the red arrow)