

Additional files

Additional table 1. Primer sequences used for genetic diagnosis and for vector construction in EMSAs.

Additional figure 1. (A, B) Structure of the IRE motif of the wild type (panel A) or Badalona +36C>U mutation (panel B). (C, D) RNAfold Web Server folding predictions of the FTL IRE wild type (panel C) or the Badalona +36C>U change (panel D). Colored scale indicates the probability of base pairing from 0 (low, blue) to 1 (high, red).

Additional table 2. Table summarizing all HHCS mutations described up to now in the literature. The table shows for each mutation, the conventional nomenclature according to HGVS (corresponding to [NCBI:NM_000146.3] reference sequence), the traditional nomenclature, the position in the IRE structure, the number of families and patients described, the patients' ancestry and the corresponding published report. In bold is indicated the first time a mutation was described; § indicates *de novo* mutations; NA (not available).

Additional table 1

Primers used for PCR and plasmids construction

Name	Sequence 5' -> 3'	Purpose
hs_FTL_2F	GGGCTGAGACTCCTATGTGC	PCR and sequencing (pedigree 1)
hs_FTL_2R	GCAGCTGGAGGAAATTAGGG	PCR and sequencing (pedigree 1)
hs_FTL_for	GGGCTGAGACTCCTATGTGC	PCR and sequencing (pedigree 2)
hs_FTL_rev	GA CTCCGCCCTCTGTTACC	PCR and sequencing (pedigree 2)
hsFTL-IRE-WT-forward	CGGTCCC GCGGGTCTGTCTCTTGCTTCAACAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-WT-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTGTTGAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation
hsFTL-IRE-39ΔC-forward	CGGTCCC GCGGGTCTGTCTCTTGCTTCAAAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-39ΔC-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTTTGAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation
hsFTL-IRE-36C>U-Badalon-a-forward	CGGTCCC GCGGGTCTGTCTCTTGCTTTAACAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-36C>U-Badalon-a-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTGTTAAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation
hsFTL-IRE-36C>G-Milano-forward	CGGTCCC GCGGGTCTGTCTCTTGCTTGAACAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-36C>G-Milano-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTGTTCAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation
hsFTL-IRE-52G>C-Heidelberg-forward	CGGTCCC GCGGGTCTGTCTCTTGCTTCAACAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-52G>C-Heidelberg-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTGTTGAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation
hsFTL-IRE-29C>G-Torino-forward	CGGTCCC GCGGGTCTGTCTGTTGCTTCAACAGTGTGGACGGAACAGATCCGGGGACTT	EMSA probe generation
hsFTL-IRE-29C>G-Torino-reverse	CTAGAAGTCCC CGGATCTGTTCCGTCCAAACACTGTTGAAGCAAGAGACAGACCCGCGGGACCGGTAC	EMSA probe generation

Additional table 2

Summary of HHCS identified mutations (September 2012)

HGVS nomenclature [NCBI:NM_000146.3]	Traditional nomenclature	Mutation position	N°families / patients	Country origin of patients	Reference publication
c.-193C>G + c.-160A>G	+7C>G & +40A>G	lower stem + hexanucleotide loop	1/1	Italy	[1]
c.-186C>G	+14C>G	lower stem	1/1	Italy	[2]
c.-182c>T + c.-178T>G	Pavia-2 +18C>U & +22U>G	lower stem	1/3	Italy	[3]
c.-182c>T + c.-178T>G	Pavia-2 +18C>U & +22U>G	lower stem	NA	NA	[4]
c.-176T>C	+ 24U>C	lower stem	1/3	Switzerland	[5]
c.-171C>G	Torino +29C>G	lower stem	1/2	Italy	[6]
c.-171C>G	Torino +29C>G	lower stem	1/4	Spain	[7]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/8	Italy	[3]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/4	Italy	[8]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/5	Italy	[9]
c.-168G>A	Pavia-1 +32G>A	lower stem	NA	NA	[4]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/7	Netherlands	[10]
c.-168G>A	Pavia-1 +32G>A	lower stem	2/5	France	[11]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/2	Netherlands	[12]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/1	Italy	[13]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/15	India	[14]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/12	Spain	[15]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/17	Germany	[16]
c.-168G>A	Pavia-1 +32G>A	lower stem	1/13	USA (German ancestry)	[17]
c.-168G>C	Baltimore-1 +32G>C	lower stem	NA	Italy	[18]
c.-168G>C	Baltimore-1 +32G>C	lower stem	NA	NA	[4]

c.-168G>C	Baltimore-1 +32G>C	lower stem	1/7	Italy	[19]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/4	Australia (English ancestry)	[20]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/10	Netherlands	[10]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/2	France	[11] §
c.-168G>C	Baltimore-1 +32G>C	lower stem	2/7	UK (1 patient of Thai ancestry)	[21]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/NA	UK	[22]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/1	Switzerland	[23]
c.-168G>C	Baltimore-1 +32G>C	lower stem	1/4	Israel (Rumanian ancestry)	[24]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	2/8	France / Italy	[25]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/1	Australia	[20] [26] §
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	NA	NA	[4]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	5/>6	France	[11]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/2	UK	[27]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/1	Italy	[13]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/5	UK	[21]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/8	Canada	[28]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/3	Israel	[29]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/4	Germany	[30]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/9	USA (British/German ancestry)	[17]
c.-168G>T	Paris-2 or Milano-1 +32G>U	lower stem	1/1	Spain	[7] §
c.-167C>A	Paris +33C>A	C bulge	1/1	France	[31]
c.-167C>A	Paris +33C>A	C bulge	NA	NA	[4]
c.-167C>A	Paris +33C>A	C bulge	1/1	France	[11]
c.-167C>A	Paris +33C>A	C bulge	1/4	Switzerland	[23]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/6	Spain	[32]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	NA	NA	[4]

c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/5	USA	[33]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	3/>4	France	[11]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/1	Italy	[13]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/6	Spain	[34]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/4	UK	[21]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/3	Spain	[35]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/1	Ireland	[36] §
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/4	Spain	[37]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/4	Spain	[38]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/2	Germany	[39]
c.-167C>T	Madrid or Philadelphia +33C>U	C bulge	1/3	Spain	[7]
c.-166T>C	Paris +34U>C	upper stem	1/3	France	[11]
c.-164C>A	London-2 +36C>A	upper stem	1/9	UK	[40]
c.-164C>A	London-2 +36C>A	upper stem	NA	NA	[4]
c.-164C>A	London-2 +36C>A	upper stem	1/1	France	[11]
c.-164C>A	London-2 +36C>A	upper stem	1/17	UK	[21]
c.-164C>G	Milano +36C>G	upper stem	1/1	Italy	[13]
c.-164C>G	Milano +36C>G	upper stem	1/2	Italy	[41]
c.-164C>T	Badalona +36C>U	upper stem	1/7	Spain	this study
c.-163A>T	Zaragoza +37A>U	upper stem	1/7	Spain	[35]
c.-163A>C	Pavia +37A>C	upper stem	1/1	Italy	[42]
c.-163A>C	Pavia +37A>C	upper stem	1/6	Italy	[43]
c.-163A>G	Milano +37A>G	upper stem	1/1	Italy	[13]
c.-161C>A	Geelong +39C>A	hexanucleotide loop	1/2	Australia (Italian ancestry)	[20] [26]
c.-161C>G	Paris +39C>G	hexanucleotide loop	1/3	France	[44]
c.-161C>G	Paris +39C>G	hexanucleotide loop	3/19	Greece	[45]

c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/2	UK	[40]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/1	Italy	[46] §
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/8	Italy	[8]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	NA	NA	[4]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	3/5	France	[11]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/1	Italy	[13]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/4	UK	[21]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/11	Austria	[47]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/2	Belgium	[48]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/1	Spain	[49] §
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/NA	Italy	[50]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/11	Germany	[39]
c.-161C>T	London-1 +39C>U	hexanucleotide loop	1/3	Spain	[51]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/5	France	[52]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/3	France	[53]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/6	UK	[54]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/2	UK (French/German ancestry)	[55]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/8	Italy	[8]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/6	UK	[56]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/NA	Spain	[57]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	NA	NA	[4]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/18	Australia (Irish ancestry)	[20] [26]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	4/>7	France	[11]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/1	Italy	[13]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/6	UK	[21]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	2/7	Belgium (1 family of Turkish ancestry)	[48]

c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/1	Italy	[58]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/3	Spain	[59]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/3	UK	[60]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/NA	Italy	[50]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/3	Germany	[61]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/2	UK	[62]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	2/9	Germany	[39]
c.-160A>G	Paris-1 or Montpellier-1 +40A>G	hexanucleotide loop	1/3	Belgium	[63]
c.-160A>G + c.-159G>C	Paris-1 or Montpellier-1 +40A>G & Verona-1 +41G>C	hexanucleotide loop	1/3	Italy	[2, 64]
c.-159G>C	Verona-1 +41G>C	hexanucleotide loop	1/9	Brazil (Spanish ancestry)	[65]
c-157G>A	Salt Lake City +43G>A	hexanucleotide loop	1/14	USA (German ancestry)	[66]
c.-154T>G	+46U>G	upper stem	1/4	Italy	[50]
c.-153G>A	Paris +47G>A	upper stem	1/3	France	[11]
c.-151A>C	+49A>C	upper stem	1/1	Italy	[1]
c.-150C>A	+50C>A	lower stem	1/11	Mexico	[67]
c.-149G>C	Torino +51G>C	lower stem	1/2	Canada	[68]
c.-149G>C	Torino +51G>C	lower stem	1/2	USA	[69]
c.-148G>C	Heidelberg +52G>C	lower stem	1/4	Germany	this study
c.-144A>T	Paris +56A>U	lower stem	1/1	France	[42]
NG_008152.1; g.4980_5004del25		New transcription starting site (resulting IRE lacks nt 1-24)	1/12	Australia	[70]
c.-190-162del29	Verona-2 +10_38del29	eliminating IRE	1/6	Italy	[71]
c.-178-173del6	+22_27del6	eliminating part of lower stem	1/2	Italy	[72]
c.-178-173del6	+22_27del6	eliminating part of lower stem	1/1	Italy	[13]
c.-162-161delAC	+38_39del AC	eliminating part hexanucleotide loop	NA	NA	[4]
c.-162-161delAC	+38_39del AC	eliminating part hexanucleotide loop	1/1	Canada	[11]

c.-161delC	+39delC	eliminating part hexanucleotide loop	1/2	Spain	[7]
c.-158-143del16	+42_57del16	eliminating IRE	1/3	France	[11] [73]
c.-158-143del16	+42_57del16	eliminating IRE	NA	NA	[4]

Supplementary references

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