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Gene Section
Review

RMRP (RNA component of mitochondrial RNA processing endoribonuclease)

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Identity

Hugo: RMRP
Other names: CHH; RMRPR
Location: 9p21-p12

DNA/RNA

Note: RMRP is the RNA component of the RNase MRP protein complex. It functions as a RNA and is not translated into a protein.

Transcription

The RMRP gene is transcribed by the DNA dependent RNA polymerase III. The gene contains typical sequence elements of a RNA Pol III type 3 promoter. The core sequence elements such as the PSE element and a TATA box can be found upstream of the transcription initiation site of the RMRP gene. In addition, transcription factor binding sites like a SP1 binding element and an octamer (recruits the transcription factor Oct-1) sequence could serve as distal sequence elements (DSE) to enhance the transcription of RMRP similar to the DSE element of the human U6 snRNA gene.

Expression: RMRP is strongly and ubiquitously expressed in mouse embryos (as an example an E15.5 mouse embryo is shown). In bone Rmrp is more strongly expressed in hypertrophic chondrocytes and pericondrium than in the zone of proliferating chondrocytes. There is also very strong expression in the epiphysis. In humans RMRP shows also a very strong expression in adult tissues. A little weaker expression is observed in skeletal muscle when compared to the GAPDH hybridization control. In Xenopus laevis oocytes RMRP is stronger expressed in developmental stages with a higher content of mitochondria.

Function: RMRP has been mostly studied in yeast and multiple functions have been attributed to this ribonucleoprotein complex, called RNase MRP. The yeast orthologues gene is called nme1. Firstly, it plays a role in mitochondrial DNA replication. It cleaves the RNA primer of RNA/DNA hybrid. This hybrid formation initiates the mitochondrial DNA replication.

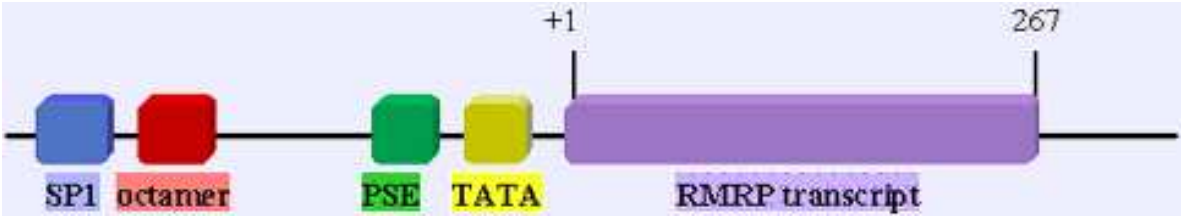

Figure 1: Cartoon of the RMRP genomic gene structure. The RMRP gene is an intronless gene that is 267 bp long (violet). The promoter region contains a SP1 binding site (blue), an octamer (red), a proximal sequence element (PSE) (green) and a TATA box (yellow).

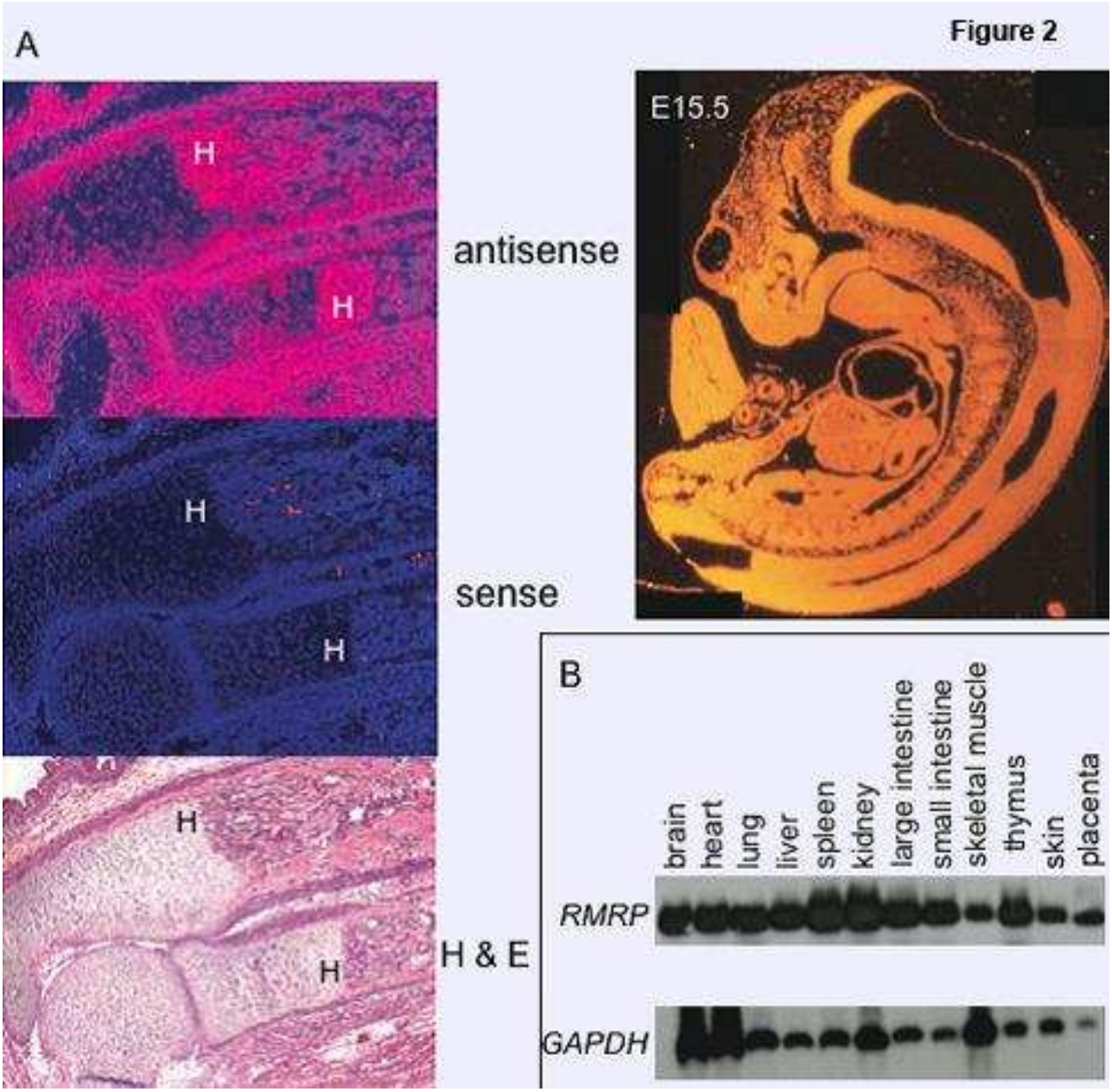

Figure 2: Expression pattern of the Rmrp gene. A: in situ hybridization of an E15.5 mouse embryo. B: adult human Multiple tissue Northern Blot. Rmrp is ubiquitously expressed in human and mouse. H: hypertrophic chondrocytes.

It is also involved in the RNA primer formation. Secondly, RMRP is involved in the progression of the cell cycle at the end of mitosis. Some nme1 mutants arrest in the late cycle of mitosis. These mutants present morphologically as large budded cells with dumbbell-shaped nuclei, and also exhibit extended spindles. This cell cycle arrest might be due to an increased level of CLB2. In wild type yeast strains the 5'UTR of CLB2 is cleaved by the RNase MRP complex. This causes a rapid degradation of the CLB2 mRNA, which leads to a cell cycle progression.
Thirdly, RMRP also plays a role in the ribosomal RNA processing. In yeast, it cleaves pre-ribosomal RNA at the A3 site thus helps the maturation of the short and active form of the 5.8S rRNA.

Homology: RNase P is also a ribonucleoprotein endoribonuclease that is mainly involved in tRNA precursor maturation. RNase P and RNase MRP have eight proteins in common. The protein RPR2p is unique to the RNase P complex. In yeast two RNase MRP specific proteins have been identified; snm1 and rmp1. The loss of function of snm1 leads to a defect in the chromosome segregation during mitosis. But the exact mechanism is not understood yet.

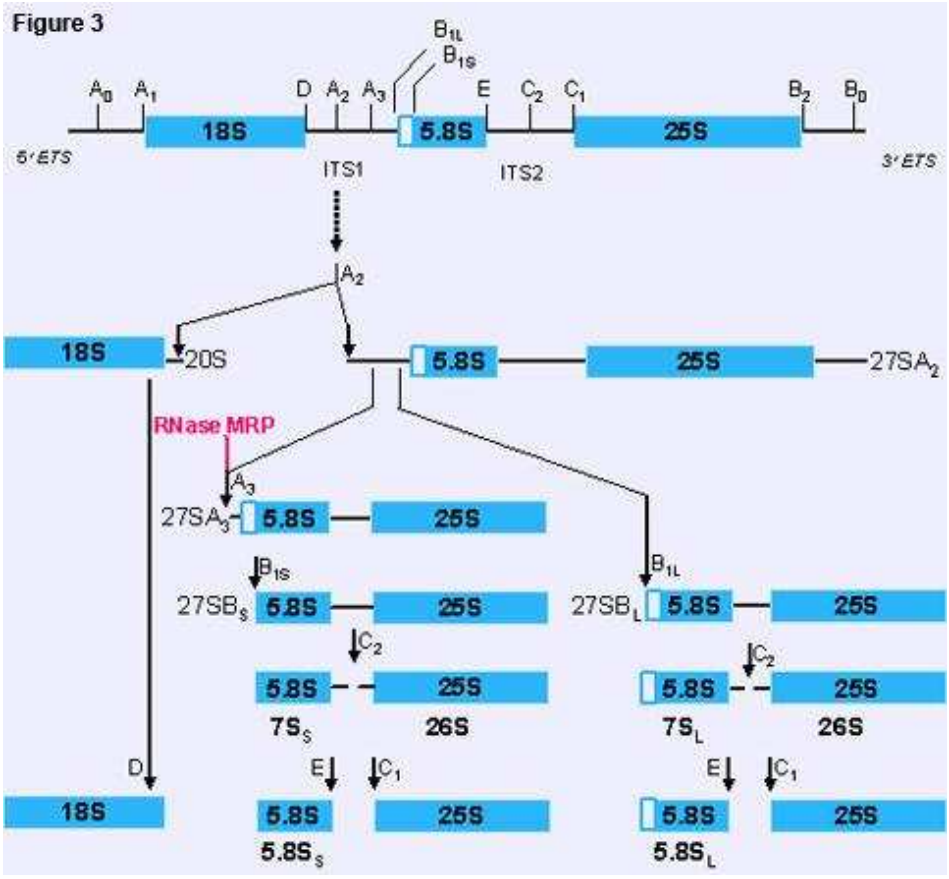

Figure 3: Cartoon of the ribosomal RNA processing. If Rnase MRP cleaves the 27SA2 rRNA at the A3 site, this leads to the formation of the short form of the 5.8S rRNA (5.8SS). In a second, less effective alternative pathway, the 27SA2 rRNA is directly cleaved at the B1L site that leads at the end to the formation of the long form of the 5.8S rRNA (5.8SL).

Mutations

Note: So far 93 different mutations have been identified in CHH patients. These include 24 promoter mutations that are either duplications, triplications or insertions that occur exclusively between the TATA box and the transcription start site. The size of the promoter mutations varies between 6 and 24 bp. In vitro studies have shown that these promoter mutations decrease the level of the RMRP transcript but do not abolish the RNA transcription completely. 69 different mutations in the 267 bp long transcript have been found up to now. 57 of these are single base pair substitutions spread out over the entire transcript. Also 11 small insertions, duplications and deletions have been found. The largest deletion identified so far involves the last 10 bp of the RMRP transcript.

The mutations lead to a significant decrease of the RMRP RNA level in CHH, despite the nature of the mutation. These mutations might influence the secondary structure of the RNA, the binding of the proteins to the RNA or the RNA stability itself.

The most frequently found mutation among CHH patients is a 70 A>G transition mutation with an ancient founder origin established in Finland and is the only mutation found in Amish CHH patients. Patients either carry two mutations in the RMRP transcript or are compound heterozygous for a promoter mutation and a transcript mutation. Interestingly, none of the patients exhibit two promoter mutations.

In addition 11 polymorphisms and 17 rare sequence variants have been observed. This is very remarkable considering the small size of the RMRP gene.

So far no complete deletion of the entire RMRP gene has been observed. This suggests that complete loss of RMRP function might be incompatible with life. This is also supported by the fact that the knock out of the yeast NME1 gene is lethal.

Implicated in

Cartilage Hair Hypoplasia (CHH)

Prognosis

The adult height ranges between 111 and 151 cm in males and between 104 and 137 cm in females. Around 20% of Cartilage Hair Hypoplasia patients exhibit recurrent to severe infections. These patients show evidence of immune deficiency in vivo and in vitro.

Oncogenesis

A predisposition to certain cancers primarily lymphomas has been reported.

Table 1: Mutations in the *RMRP* transcript identified in CHH patients

mutation	first described by (Reference)
4C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
5G>A	Loeys et al., 2003 clinical genetics meeting poster
9T>C	Hermanns et al., 2006, *Am J Med Genet* 40:2121-30
14G>A	Thiel et al., 2005, *Am J Hum Genet* 77:795-806
14G>T	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
35C>T	Bonafé et al., 2005, *PLoS Genet* 1:e47
40G>A	Bonafé et al., 2005, *PLoS Genet* 1:e47
45_53dupTGTTCCTCC	Bonafé et al., 2005, *PLoS Genet* 1:e47
56_64insTTCCGCCT	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
63C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
64T>C	Bonafé et al., 2005, *PLoS Genet* 1:e47
64T>A	Lam et al., 2006, *Prenat Diagn* 26:1018-1020
65delA	Casas et al., clinical genetics meeting posters 2003
70A>G	Ridanpää et al., 2001, *Cell* 104;195-203
76C>T	Hermanns et al., unpublished
79G>A	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
79G>T	Lam et al., 2006, *Prenat Diagn* 26:1018-1020
80A>G	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
89C>G	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
90-91AG>GC	Thiel et al., 2005, *Am J Hum Genet* 77:795-806
91G>A, 101C>T	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
94_95delAG	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
97G>A	Bonafé et al., 2005, *PLoS Genet* 1:e47
96_97dupTG	Ridanpää et al., 2001, *Cell* 104:195-203
99C>T	Ridanpää et al., unpublished
111_112insACGTAGACATTCCT	Thiel et al., 2005, *Am J Hum Genet* 77:795-806
116A>G	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
118A>G	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
124C>T	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
126C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
127G>A	Bonafé et al., 2005, *PLoS Genet* 1:e47
127G>C	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
146G>A	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
146G>C	Bonafé et al., 2005, *PLoS Genet* 1:e47
152A>G	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
154G>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
168G>A	Nakashima et al., 2007, Am J Med Genet in press
179_180insC	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
180G>A	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
182G>A	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
182G>C	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
182G>T	Bonafé et al., 2005, *PLoS Genet* 1:e47
193G>A	Ridanpää et al., 2001, *Cell* 104:195-203
195C>T	Bonafé et al., 2002, *Clin Genet* 61:146-151; Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
194_195insT	Kuijppers et al., 2003, *J Med Genet* 40:761-766
195C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
211C>G	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
213C>G	Bonafé et al., 2005, *PLoS Genet* 1:e47
214A>G	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
214A>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
218A>G	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
220T>C	Bonafé et al., 2005, *PLoS Genet* 1:e47
230C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
236A>G	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
238C>T	Bonafé et al., 2002, *Clin Genet* 61:146-151; Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
240A>C	Guggenheim et al., 2006, *Bone Marrow Transplantation* 38:751-756
242A>G	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
243C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
244G>A	Bonafé et al., 2005, *PLoS Genet* 1:e47
248C>T	Bonafé et al., 2005, *PLoS Genet* 1:e47
252T>G	Ridanpää et al., unpublished
254_263delCTCAGCGCGG	Thiel et al., 2007, *Am J Hum Genet* 81:519-529
256-265delCAGCGCGGCT	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
260C>G	Bonafé et al., 2005, *PLoS Genet* 1:e47
261C>T	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
262G>C	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
262G>T	Ridanpää et al., 2001, *Cell* 104;195-203
264C>A	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
indel	Loeys et al., 2003 clinical genetics meeting poster

Table 2: *RMRP* promoter mutations identified in CHH patients	
promoter duplications	**first described by (Reference)**
7_3dupGGACGTGGTT	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
15_3dupGAAGCTGAGGAC GTGGT	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
8_-1dupAGGACGTG	Bonafé et al., 2005, *PLoS Genet* 1:e47
14_-1dupAAGCTGAGGACGTG	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
21_-1dupCTCTGTGAAGCTG AGGACGTG	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
14_-3dupAAGCTGAGGACG	Bonafé et al., 2002, *Clin Genet* 61:146-151
20_-4dupTCTGTGAAGCTGAG GAC	Ridanpää et al., 2001, *Cell* 104:195-203
20_-4dupTCTGTGAAGCTGGG GAC	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
23_-4dupTACTCTGTGAAGCTG AGGAC	Harada et al., 2005, *Bone* 36:317-322
25_-5dupACTACTCTGTGAAGC TGAGGA	Bonafé et al., 2005, *PLoS Genet* 1:e47
26_-5dupTACTACTCTGTGAAG CTGAGAA	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
7_-6insCCTGAG	Ridanpää et al., 2001, *Cell* 104;195-203
7_-6insAACGAAGCTGAG	Ridanpää et al., unpublished
25_-6dupACTACTCTGTGAAGC TGAGA	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
14_-7dupAAGCTGAG	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
16_-7dupTGAAGCTGAG	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
15_-8dupGAAGCTGA	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
22_-10dupACTCTGTGAAGCT	Bonafé et al., 2005, *PLoS Genet* 1:e47
25_-10tripACTACTCTGTGAAG CT	Bonafé et al., 2005, *PLoS Genet* 1:e47
25_-11tripACTACTCTGTGAAGC	Ridanpää et al., 2001, *Cell* 104:195-203
20_-14dupTCTGTGA	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
23_-14dupTACTCTGTGA	Ridanpää et al., 2001, *Cell* 104:195-203
23_-15dupTACTCTGTG	Bonafé et al., 2005, *PLoS Genet* 1:e47
24_-15dupCTACTCTGTG	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130

Table 3: *RMRP* Polymorphisms	
polymorphisms	**first described by (Reference)**
282A>G	Hermanns et al., 2006, *Am J Med Genet* 40:2121-2130
149T>A	Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
58T>C	Bonafé et al., 2002, *Clin Genet* 61:146-151, Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
56A>G	Bonafé et al., 2002, *Clin Genet* 61:146-151, Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
48C>A	Bonafé et al., 2002, *Clin Genet* 61:146-151, Ridanpää et al., 2002, *Eur J Hum Genet* 10:439-447
21C>G	Graf et al., 2007,*Clin Genet* 71:468-470
6G>A	Bonafé et al., 2002, *Clin Genet* 61:146-151
156G>C	Bonafé et al., 2002, *Clin Genet* 61:146-151
177C>T	Bonafé et al., 2002, *Clin Genet* 61:146-151
272T>C (+5T>C)	Bonafé et al., 2002, *Clin Genet* 61:146-151
274T>C (+7T>C)	Bonafé et al., 2002, *Clin Genet* 61:146-151

Table 4: Rare variants of *RMRP*	
rare variants	**first described by (Reference)**
55T>C	Graf et al., 2007,*Clin Genet* 71:468-470
25 A>G	Graf et al., 2007,*Clin Genet* 71:468-470
24C>G	Bonafé et al., 2002, *Clin Genet.* 61:146-151
22 A>C	Graf et al., 2007,*Clin Genet* 71:468-470
21 C>G	Graf et al., 2007,*Clin Genet* 71:468-470
13 A>C	Graf et al., 2007,*Clin Genet* 71:468-470
11 C>T	Graf et al., 2007,*Clin Genet* 71:468-470
4 C>T	Graf et al., 2007,*Clin Genet* 71:468-470
36T>G	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
55_56insC	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
57_58insA	Bonafé et al., 2002, *Clin Genet* 61:146-151
119C>T	Graf et al., 2007,*Clin Genet* 71:468-470
162C>T	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
172C>T	Nakashima et al., 2003, *Am J Med Genet* 123A:253-256
G>A	Graf et al., 2007,*Clin Genet* 71:468-470
227C>T	Graf et al., 2007,*Clin Genet* 71:468-470
250C>T	Bonafé et al., 2002, *Clin Genet* 61:146-151

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