Compound RYR1 heterozygosity with MH-susceptibility, central cores and multiminicore disease in one family.

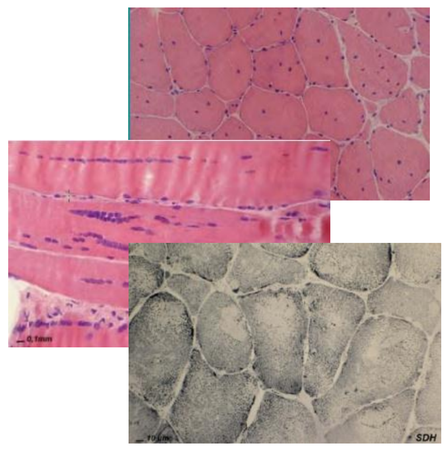
L Heytens, J Baets, JJ Martin. Onderzoeksgroep MH, University of Antwerp , Belgium
luc.heytens@uantwerpen.be

❖**Proband** : female, born 1977

First investigations at age 3 because of delayed motor milestones : 'myopathy with cores'

2004 Pt contacts centre for NMD,University of Antwerp because of child wish : new investigations

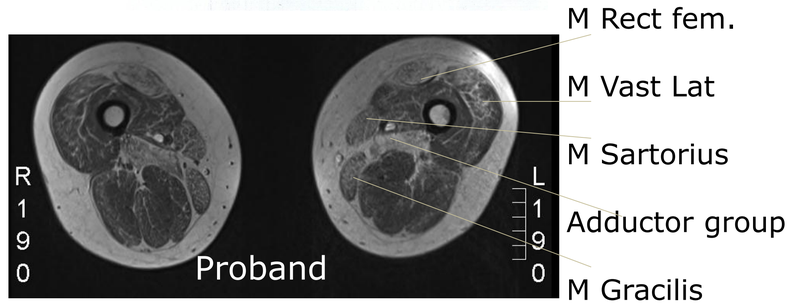
▪ **Clinical findings : +/-** invalidating weakness shoulder/hip girdles



- **Muscle biopsy 2004**
- Fatty infiltration, fibrosis, necrotic fibres,centralization of several nuclei in numerous fibres
- Almost type 1 fibre 'uniformity'
- EM : multiple core-like myofibrillar alterations corresponding to 'multi-minicore type lesions, focal
- loss of striations, rods in atrophic fibres
- Conclusion : **"Multi-minicore disease + rods"**

fragment	AA	Variant +/-	Polymorphismes +/-
01	1-138	-	Leu198Leu
02	123-338	-	-
03	315-500	-	Ala359ala
04	470-709	-	Ser556ser
05	662-844	-	Pro762pro
06	824-1049	-	His973His, Thr981Thr
07	992-1220	-	Ile1152Ile
08	1154-1347	-	-
09	1333-1532	-	-
10	1517-1713	Ile1571Val	-
11	1690-1918	-	-
12	1872-2071	-	Gly2060Cys , Lys2013Lys
13	2054-2536	-	Gly2060Cys
14	2213-2467	-	-
15	2415-2562	-	Arg2624Arg
16	2561-2767	-	Thr2659Thr, Ile2706Ile, Asp2730Asp
17	2720-2912	-	Asp2730Asp, Glu2779Glu, Ser2863Ser
18	2899-3101	-	Pro3062Pro
19	3062-3569	-	Leu3230Leu
20	3240-3442	Arg3366His	-
21	3422-3608		Glu3583Gln
22	3593-3784	-	-
23	3768-3948	Tyr3933Cys	-
24	3938-4154	-	-
25	4112-4234	-	-
26	4224-4361	-	-
27	4342-4474	-	-
28	4463-4631	-	-
29	4629-4808	-	-
30	4803-4973	Val4849Ile	-
31	4932-stop	-	-

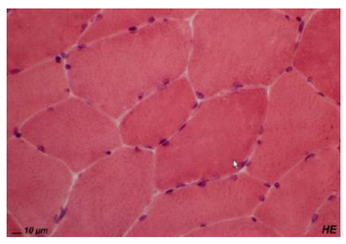
- **IVCT 2004**: 16 mN at 2 mM caff, 35 mN at 2% Hal, 20 mN at 75 microM 4CmC : **MHS**
- **106 exon RYR1 sequencing 2005** CHU Grenoble **proband** : 20 polymorphisms, 4 'variants of unknown signficance including p.Val4849Ile , no 'causative mutations'.
- **Western blot analysis Basel 2013** : **50% less RYR1 protein** compared to control
- **Muscle MRI 2013 :** symm T1-weighted signal abnormalities in select muscle



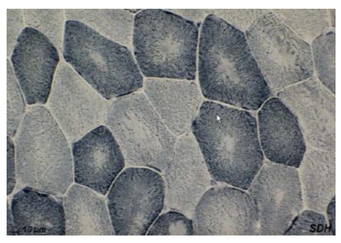
❖Father of proband

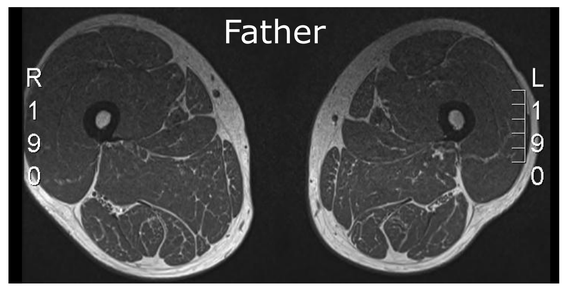
- **No** clinical symptoms/complaints
- Histology : Normal fibre type distribution (1 & 2)

  No centralization of nuclei. **Central cores** on histology



- IVCT : 16 mN at 2 mM caff, 35 mN at 2% Hal, 20 mN at 75 microM 4CmC : **MHS**
- MRI : normal
- **Western blot analysis** : RYR1 **equal** to control
- **106 exon RYR1 sequencing**
  - variant p.Val4849Ile , polymorphism p.Glu3583Gln.



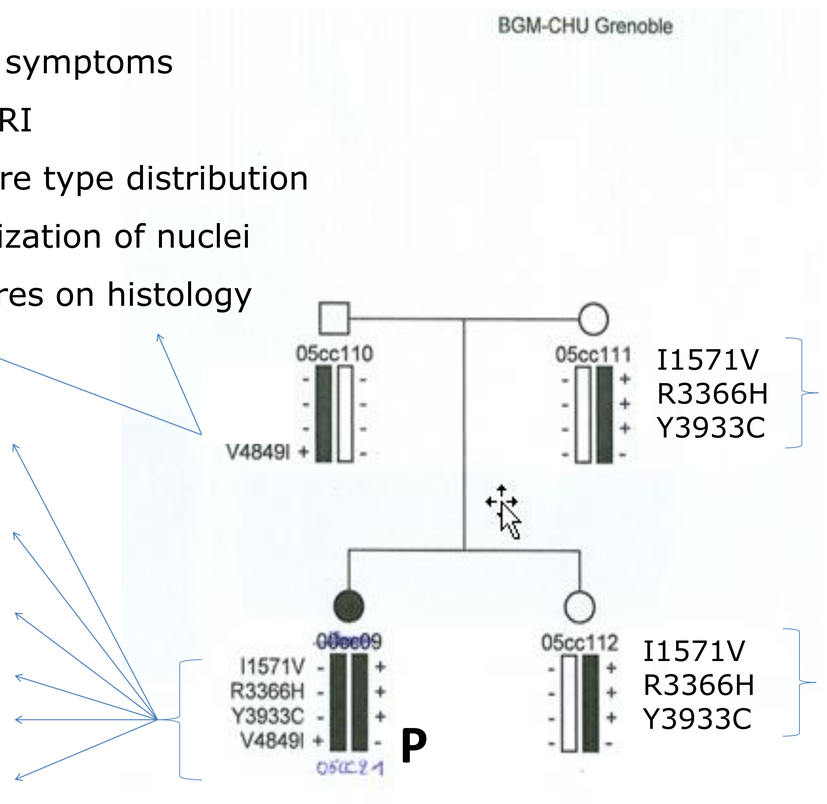


❖**Mother and sister of proband :** no consent for investigations except DNA testing

- variants p.Ile1571Val, p.Arg3366His, p.Tyr3933Cys polymorphism p.Gly2060Cys.

Present assessment

- ➢ No clinical symptoms
- ➢ Normal MRI
- ➢ Normal fibre type distribution
- ➢ No centralization of nuclei
- ➢ Central cores on histology
- ➢ MHS



- ➢ Invalidating girdle weakness
- ➢ Selective muscle involvement on MRI
- ➢ Histological findings of myopathy
- ➢ Multi-minicore disease + rods
- ➢ 50% less RYR1 expression
- ➢ MHS

- ➢ No symptoms
- ➢ (No histology)
- ➢ (No IVCT)

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