Exome Sequencing in young patients with acute-onset cardiomyopathy requiring mechanical support and/or heart transplantation

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Purpose

The aim of the project was to identify genetic basis of acute onset cardiomyopathy requiring mechanical support and/or heart transplantation using whole exome sequencing in young adults.

Patients

- ten young (23.4±3.8 y, 9 male) patients with acute onset cardiomyopathy (3 with diagnosis of myocarditis - 2 on MRI and 1 biopsy-proven myocarditis)
- all male patient underwent HTX (in 7 preceded by VAD) and female was treated with LVAD to recovery

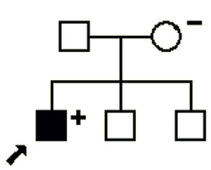
Methods

- next generation whole exome sequencing (WES) on Illumina HiSeq 1500 platform
- Sanger sequencing of selected variants in probands and in available relatives

Results I

Variants found in six patients

1) *DMD* NM_004006.2:c.1280T>C:(p.Leu427Pro) - likely pathogenic



- Variant affecting N-terminal region of dystrophin decribed in 2 brothers (age 8 and 10) with mild Becker muscular dystrophy without heart involvement [Acsadi G et al. 2012]

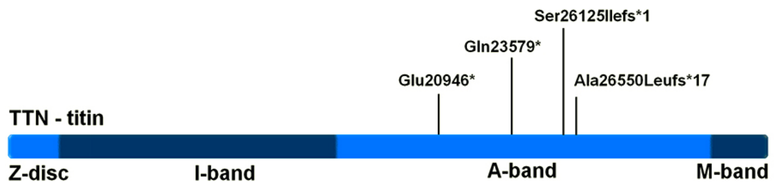
- whole exome sequencing confirmed molecular diagnosis of Becker muscular dystrophy (*DMD* MLPA tests performed earlier were negative)

Pedigrees : An arrowhead denotes the proband. A diagonal line marks deceased individuals. Solid black symbols denote DCM and grey shading treated for heart failure. The presence or absence of a mutation is indicated by a +/− symbol.

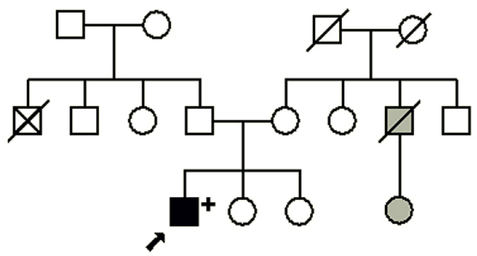
Results II

Titin (*TTN*) truncating variants - likely pathogenic

- all variants located in A-band
- 3 novel, one previously described

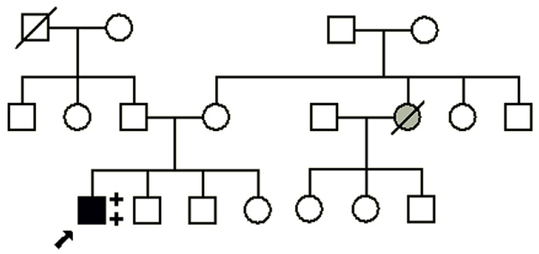


2) *TTN* NM_133378.4: c.62836G>T:(p.Glu20946*)



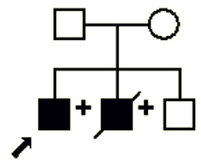
3) *TTN* NM_133378.4: c.70735C>T:(p.Gln23579*)
***MYH7* NM_000257.3:c.709C>T:(p.Arg237Trp)**

- variant in MYH7 described in patient with DCM and second *LDB3* p.Ala698Thr variant [Hershberger RE et al. 2008]



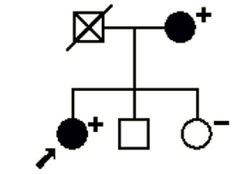
Results III

4) *TTN* NM_133378.4: c.78372_78373insA:(p.Ser26125Ilefs*1)



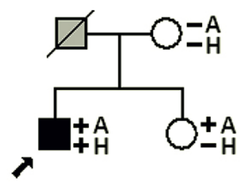
- variant described in the literature in 3 generation family with DCM [Yoskovitz G et al. 2012]
- variant found in our patient and his deceased brother (at age 23) both after HTX at age 23 and 19

5) *TTN* NM_133378.4: c.7951_79652delG: (p.Ala26550Leufs*17)



- variant in 30-years old female patient treated with VAD and her mother with left ventricular dysfunction (LVEF 30%) without left ventricle dilatation.

6) *ACTA1* NM_001100.3:c.472G>A:(p.Gly158Ser) - variant of unknown significance (VUS)
***HSPB6* (Hsp20) NM_144617.2:c.59C>T:(p.Pro20Leu) - VUS**



- DCM is rarely found in patients with *ACTA1* myopathy. *HSPB6* p.Pro20Leu variant was reported to cause loss of cardioprotective effect of Hsp20 however is found in DCM patients and controls [Nicolaou P et al. 2008]

Conclusions

Titin truncating mutations are frequently found in acute onset heart failure patients similar to other DCM patients. Accurate interpretation of next generation sequencing data remains a challenge.

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