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 [Acasdi G et al. 2012]
   - whole exome sequencing confirmed molecular diagnosis of Becker muscular dystrophy (DMD MLPA tests performed earlier were negative)

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.Arg237Thr)
   - variant in MYH7 described in patient with DCM and second LDB3 p.Ala698Thr variant [Hershberger RE et al. 2008]

Results II
Titin (TTN) truncating variants - likely pathogenic
- all variants located in A-band
- 3 novel, one previously described

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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