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VIII Congresso Novas Fronteiras em Cardiologia

Titin-truncating variants affect heart function in disease cohorts and the general population

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Disclosures

- No conflicts of interest

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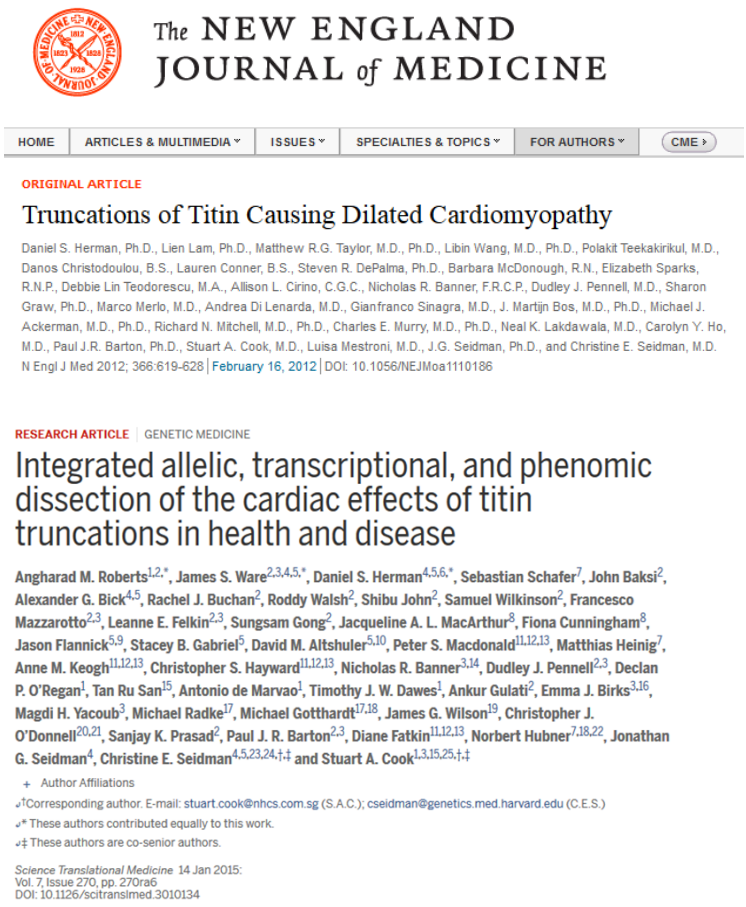
Role of TTNtv in Dilated Cardiomyopathy (DCM)

- Prevalence of DCM ~1:250
- Results in progressive cardiac failure, arrhythmia and sudden death. Most frequent indication for cardiac transplantation
- Titin-truncating variants (TTNtv) account for about 25% of cases of end-stage dilated cardiomyopathy
- TTNtv occur in ~15% of ambulant DCM but also in ~2% of the population
  ?effects position dependent



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ORIGINAL ARTICLE

Truncations of Titin Causing Dilated Cardiomyopathy

Daniel S. Herman, Ph.D., Lien Lam, Ph.D., Matthew R.G. Taylor, M.D., Ph.D., Libin Wang, M.D., Ph.D., Polakit Teekakirikul, M.D., Danos Christodoulou, B.S., Lauren Conner, B.S., Steven R. DePalma, Ph.D., Barbara McDonough, R.N., Elizabeth Sparks, R.N.P., Debbie Lin Teodorescu, M.A., Allison L. Cirino, C.G.C., Nicholas R. Banner, F.R.C.P., Dudley J. Pennell, M.D., Sharon Graw, Ph.D., Marco Merlo, M.D., Andrea Di Lenarda, M.D., Gianfranco Sinagra, M.D., J. Martijn Bos, M.D., Ph.D., Michael J. Ackerman, M.D., Ph.D., Richard N. Mitchell, M.D., Ph.D., Charles E. Murry, M.D., Ph.D., Neal K. Lakdawala, M.D., Carolyn Y. Ho, M.D., Paul J.R. Barton, Ph.D., Stuart A. Cook, M.D., Luisa Mestroni, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

N Engl J Med 2012; 366:619-628 | February 16, 2012 | DOI: 10.1056/NEJMoa1110186

RESEARCH ARTICLE | GENETIC MEDICINE

Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease

Angharad M. Roberts[1,2,*], James S. Ware[2,3,4,5,*], Daniel S. Herman[4,5,6,*], Sebastian Schafer[7], John Baksi[2], Alexander G. Bick[4,5], Rachel J. Buchan[2], Roddy Walsh[2], Shibu John[2], Samuel Wilkinson[2], Francesco Mazzarotto[2,3], Leanne E. Felkin[2,3], Sungsam Gong[2], Jacqueline A. L. MacArthur[8], Fiona Cunningham[8], Jason Flannick[5,9], Stacey B. Gabriel[5], David M. Altshuler[5,10], Peter S. Macdonald[11,12,13], Matthias Heinig[7], Anne M. Keogh[11,12,13], Christopher S. Hayward[11,12,13], Nicholas R. Banner[3,14], Dudley J. Pennell[2,3], Declan P. O'Regan[1], Tan Ru San[15], Antonio de Marvao[1], Timothy J. W. Dawes[1], Ankur Gulati[2], Emma J. Birks[3,16], Magdi H. Yacoub[3], Michael Radke[17], Michael Gotthardt[17,18], James G. Wilson[19], Christopher J. O'Donnell[20,21], Sanjay K. Prasad[2], Paul J. R. Barton[2,3], Diane Fatkin[11,12,13], Norbert Hubner[7,18,22], Jonathan G. Seidman[4], Christine E. Seidman[4,5,23,24,†,‡] and Stuart A. Cook[1,3,15,25,†,‡]

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* These authors contributed equally to this work.

‡ These authors are co-senior authors.

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Remaining questions:

- Do proximal and distal truncations affect TTN RNA and protein in a similar or dissimilar way?
- What are the molecular mechanisms underlying the cardiomyopathy?
- Do all TTNtv have an effect on the heart that can be revealed using advanced imaging?

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TTNtv in health and disease: study design

1. meta-analysis of TTNtv in DCM patients (n = 2,495) and controls (n = 61,834)

2. RNA-sequencing (RNA-seq) and ribosome profiling (Ribo-seq) + metabolic and signalling studies to outline potential disease mechanisms

3. deep phenotyping of rats with TTNtv at opposite ends of the Ttn molecule

4. deep phenotyping and genetic sequencing of healthy volunteers (n = 1,409)

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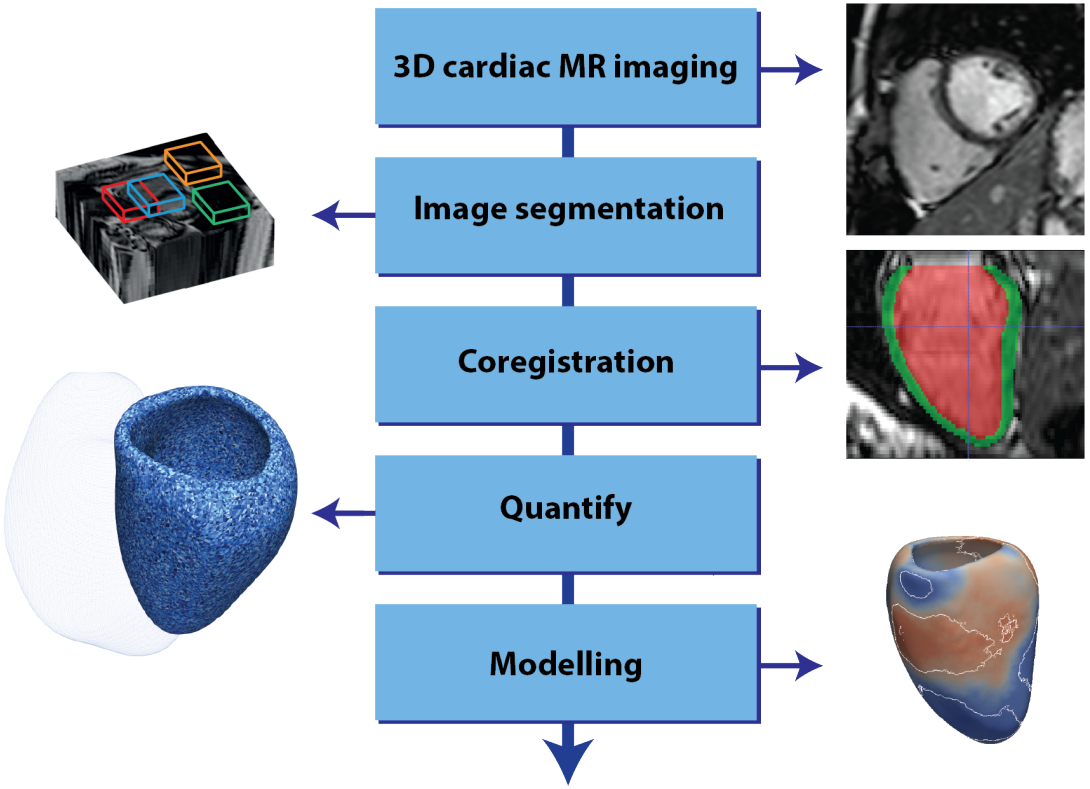
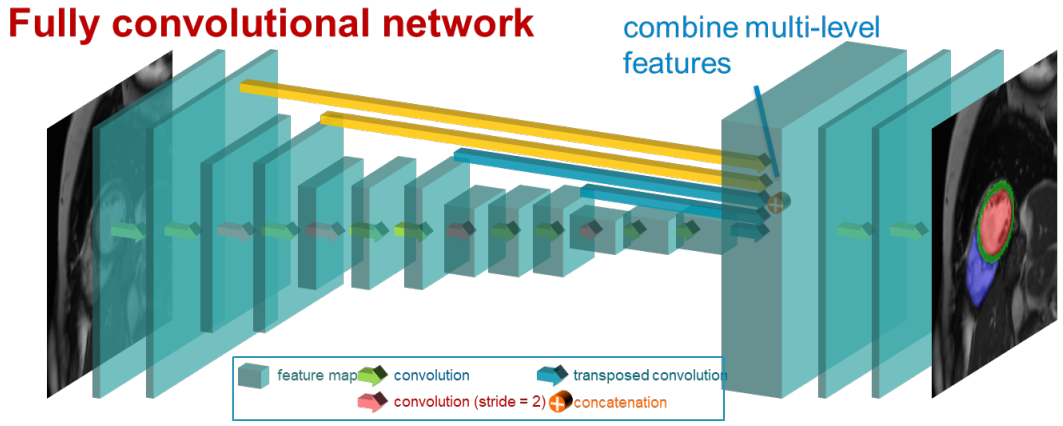
CMR machine learning analysis





Unpublished work with Jinming Duan and Wenjia Bai

- **de Marvao A, et al**. Population-based studies of myocardial hypertrophy: high resolution cardiovascular magnetic resonance atlases improve statistical power. *J Cardiovasc Magn Reson*. 2014.
- **de Marvao A, et al**. Precursors of Hypertensive Heart Phenotype Develop in Healthy Adults: A High-Resolution 3D MRI Study. *JACC Cardiovasc Imaging*. 2015.
- **Corden B*, de Marvao A*, et al**. Relationship between body composition and left ventricular geometry using three *dimensional cardiovascular magnetic resonance. J Cardiovasc Magn Reson.* 2016.

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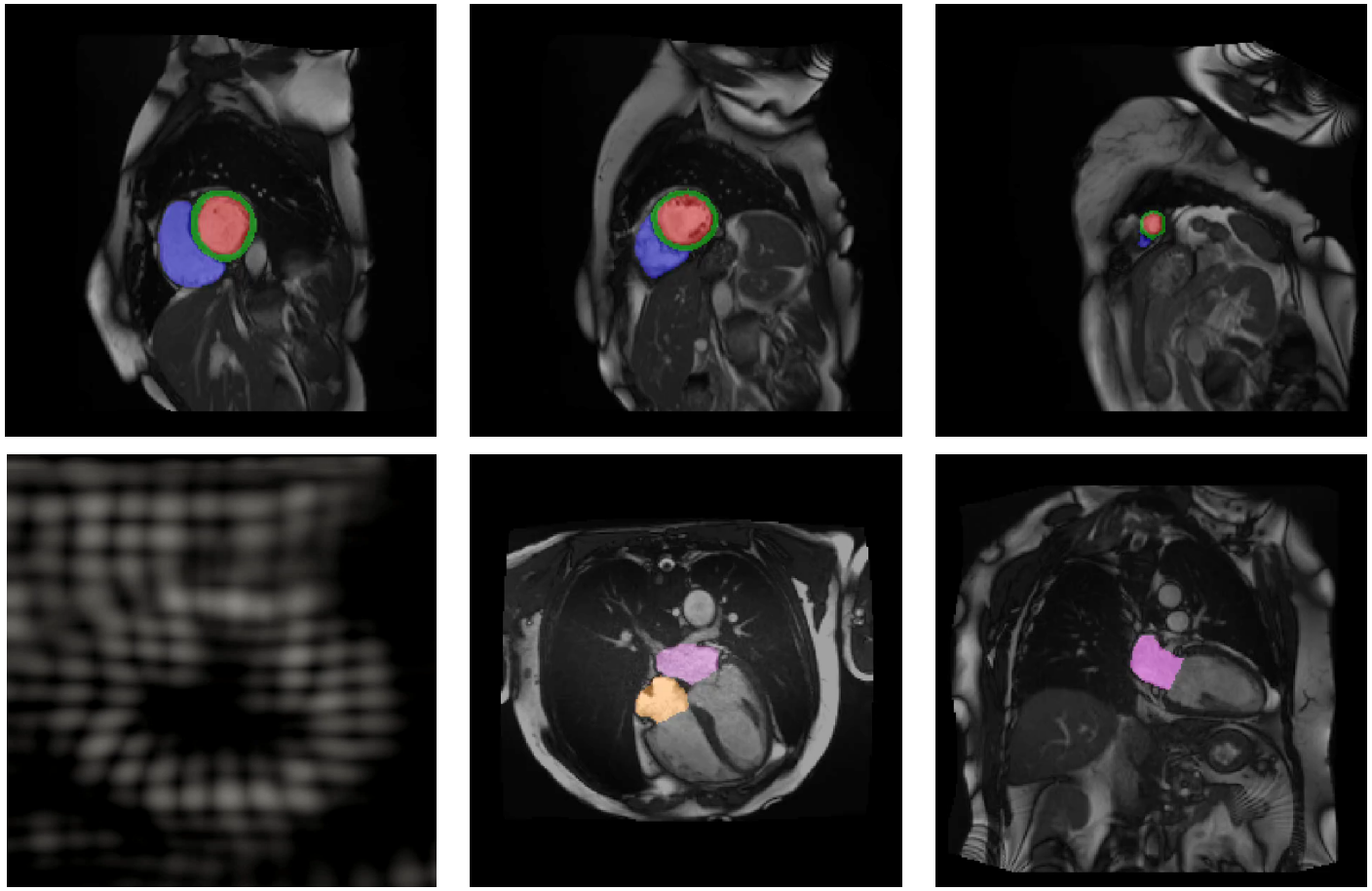
Deep learning analysis methods



Bai W, et al. A bi-ventricular cardiac atlas built from 1000+ high resolution MR images of healthy subjects and an analysis of shape and motion. *Med Image Anal*. 2015;26:133-45.

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TTNtv in constitutive exons throughout TTN are associated with DCM

TTN sarcomere domain affected by variant	DCM (n=2,495)	Controls (n=61,834)	DCM prevalence (%)	Control prevalence (%)	Odds ratio	*P* value
A-band (constitutive)	268	149	10.74	0.24	49.8	2.4×10^{-260}
I-band (distal, constitutive, post-Cronos)	9	7	0.36	0.01	32	2.5×10^{-9}
I-band (distal, constitutive, pre-Cronos)	18	23	0.72	0.04	19.5	6.6×10^{-15}
I-band (non-constitutive)	6	102	0.24	0.17	1.5	0.46
I-band (proximal, constitutive)	22	29	0.88	0.05	19	1.1×10^{-17}
M-band (constitutive)	6	40	0.24	0.07	3.7	0.01
Z-disc (constitutive)	7	33	0.28	0.05	5.3	0.001
Z-disc (non-constitutive)	0	11	0	0.02	NA	NA

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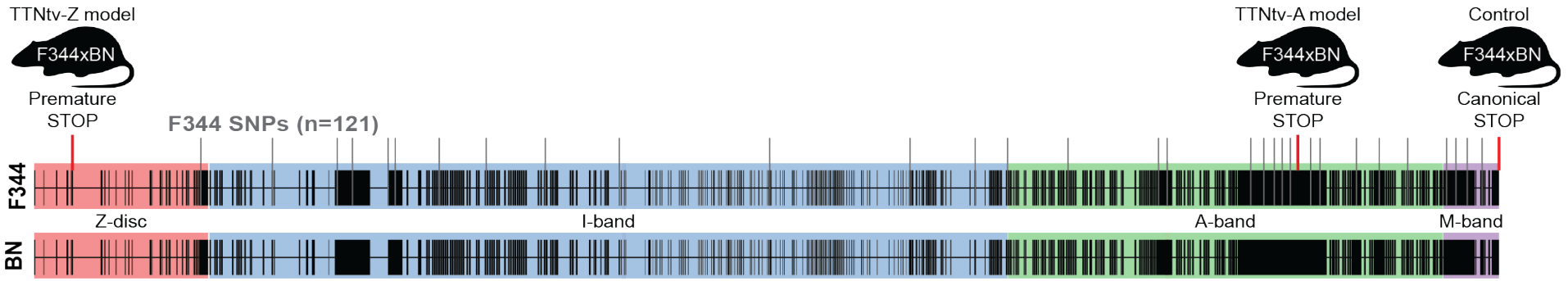
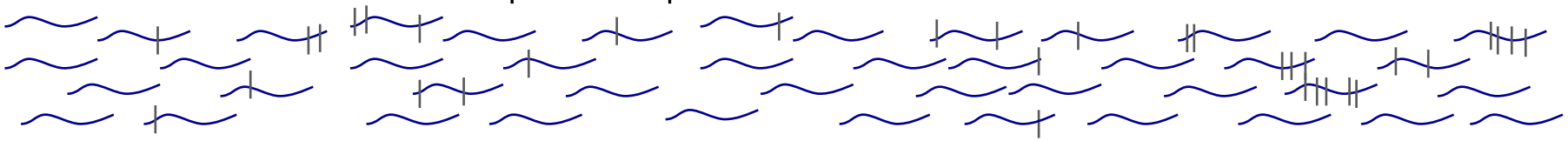
Transcriptional and translational profiles of TTNtv



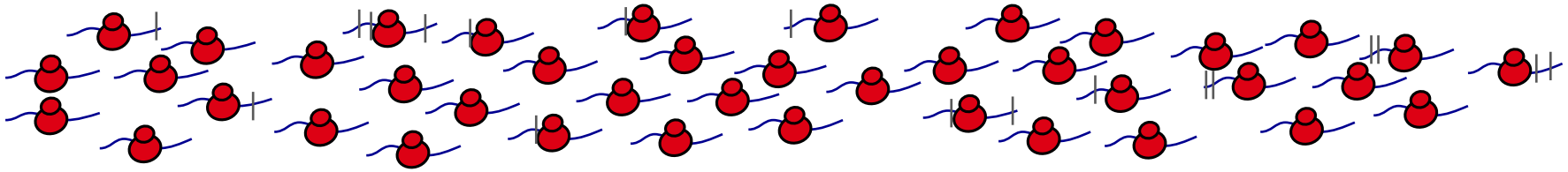
Transcriptional profile of TTNtvA & TTNtvZ

RNA-seq



Translational profile of TTNtvA & TTNtvZ

Ribo-seq



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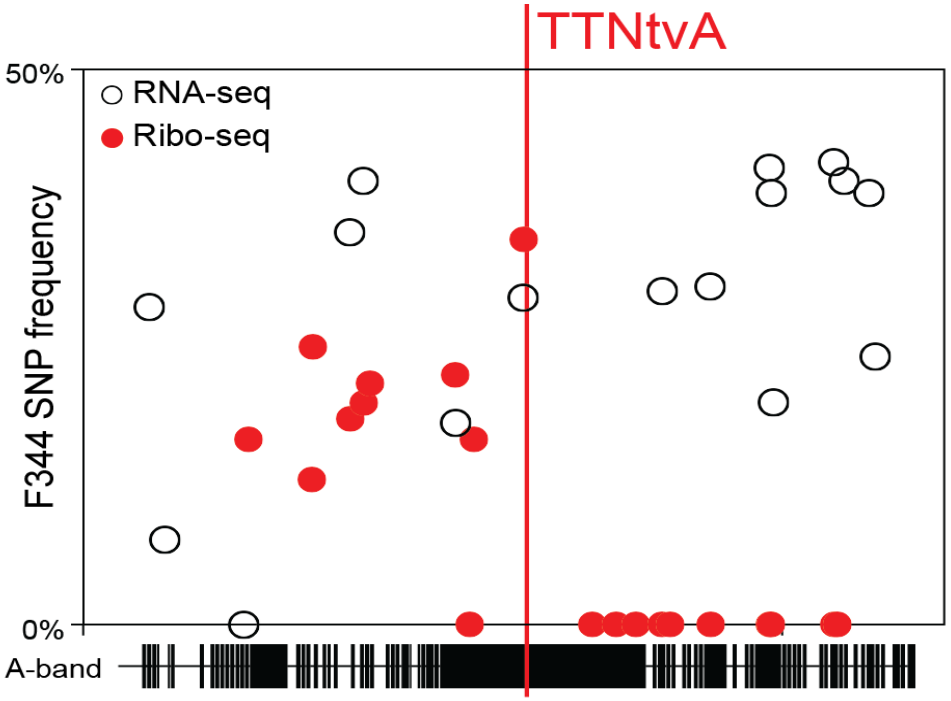
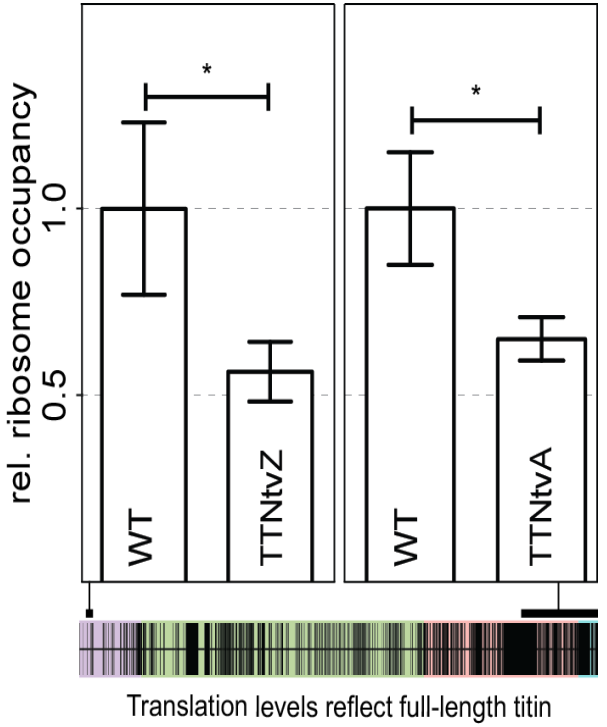
TTNtv efficiently stop translation

First time we saw translation / synthesis of a short mutant TTN and demonstrate nonsense mediated decay



Disease mechanism is haploinsufficiency



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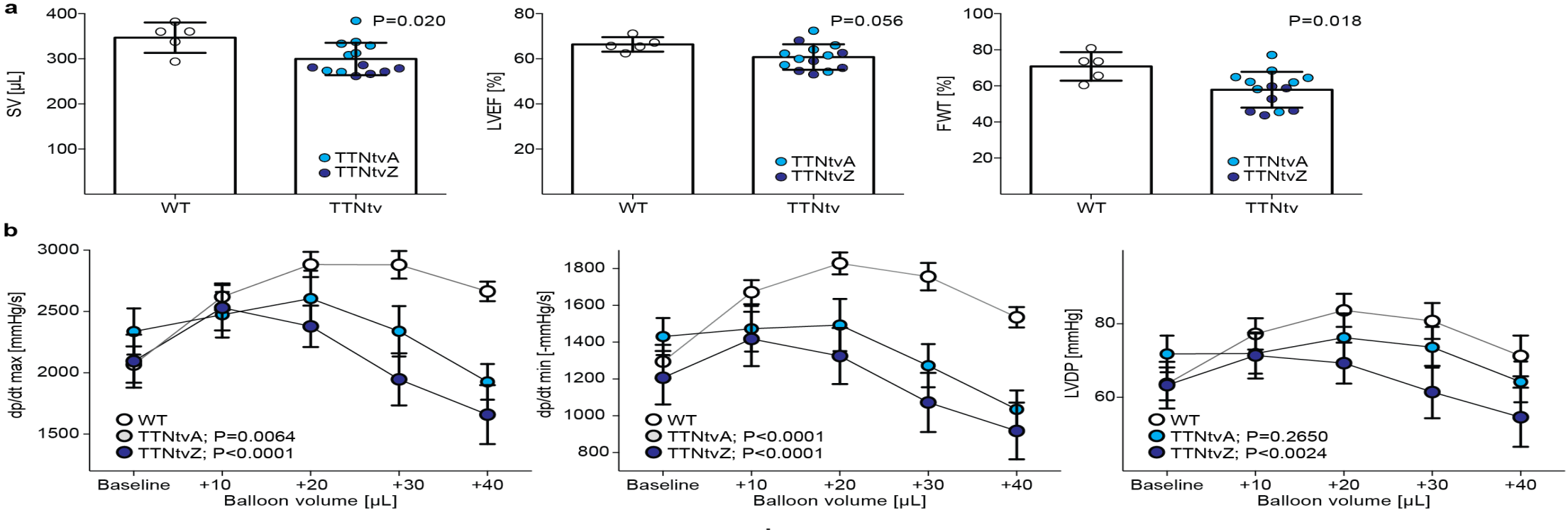
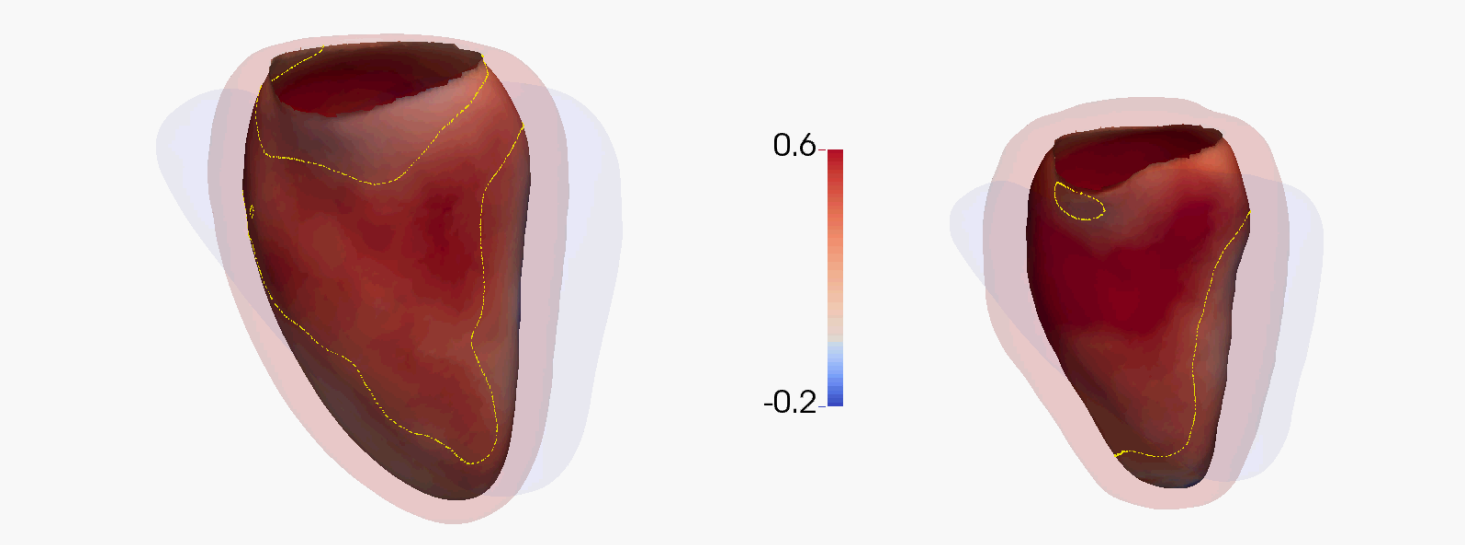
TTNtv in rats adversely affect cardiac function



a CMR derived SV (Stroke Volume), LVEF (Left Ventricular Ejection Fraction) and FWT (Fractional Wall Thickening) in 13-16 month old male WT and TTNtv rats

b Measurements of *ex vivo* myocardial function during volume overload stress in 4 month old WT and TTNtv rats

Application of Machine learning:
The effects of titin-truncating variants in health and in DCM



TTNtv are present in ~1% of the population and are penetrant: Positive standardised beta coefficients (red) indicate where TTNtv genotype is associated with enlargement of the LV cavity

Biffi C, de Marvao A, et al. Three-dimensional cardiovascular imaging-genetics: a mass univariate framework. *Bioinformatics*. 2018;34(1):97-103.

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Conclusions

- TTNtv are present in about 1% of the population and are penetrant.
- In TTNtv disease mechanism is haploinsufficiency.
- Computational modelling enables a deeper understanding of genotype-phenotype associations.
- The heart is maintained in a compensated state and therefore inflexible to additional stress.

Schafer S*, de Marvao A*, et al. Titin-truncating variants affect heart function in disease cohorts and the general population. Nature Genetics. 2017;49, 46-53.

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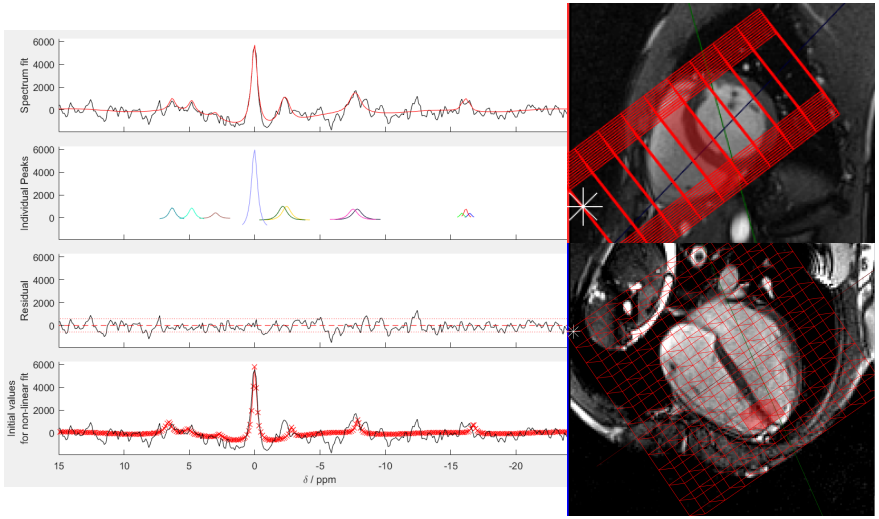
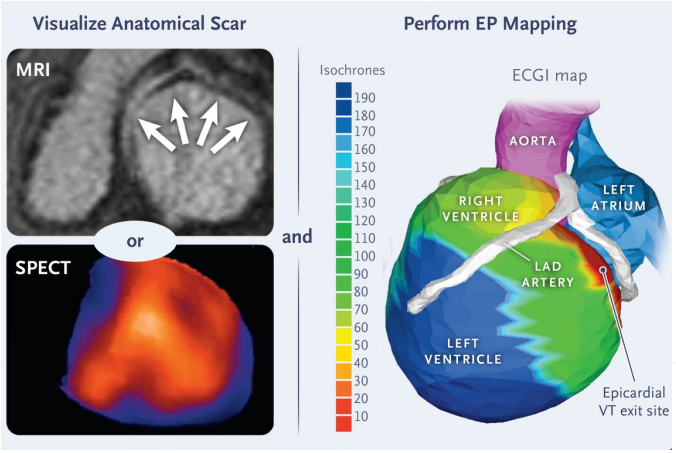
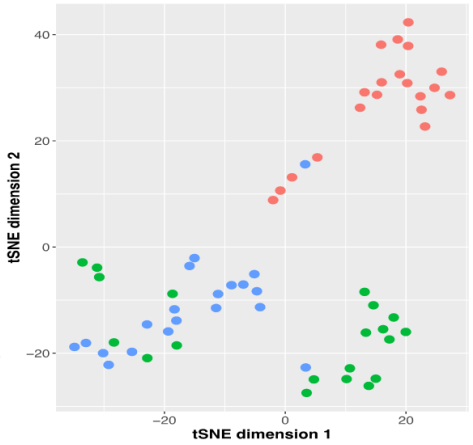
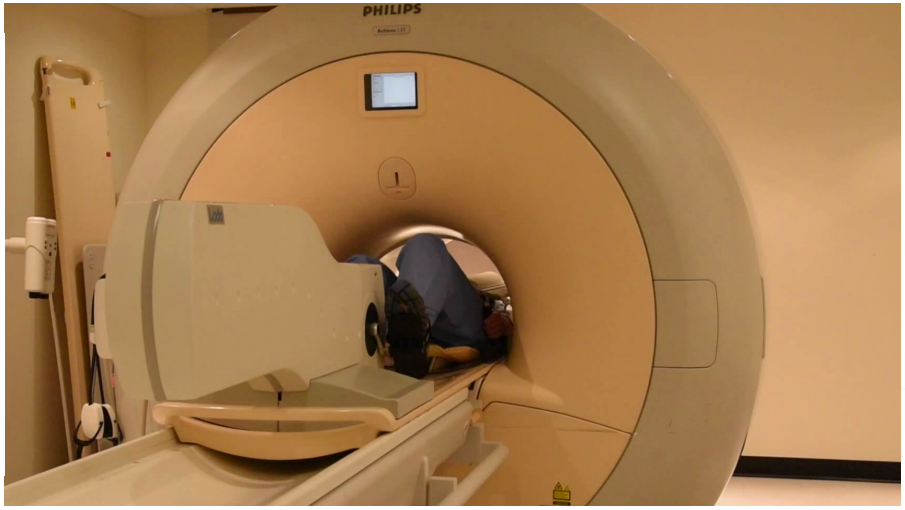
The next frontier: ECGI, MRS, exercise CMR, AI…









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Sebastian Schafer, Carlo Biffi, Roddy Walsh, Georgia Doumou, Timothy Dawes, Wenzhe Shi, Wenjia Bai, Alaine Berry, Rachel Buchan, Iain Pierce, Pawel Tokarczuk, Ben Statton, Ghalib Bello, Catherine Francis, Jinming Duan, Marina Quinlan, Leanne Felkin, Thu-Thao Le, Anish Bhuva, Hak Chiaw Tang, Paul Barton, Calvin Woon-Loong Chin, Sanjay Prasad, Daniel Rueckert, Jonathan G Seidman, Christine E Seidman, James Ware, Declan P O'Regan, Norbert Hubner, Stuart Cook

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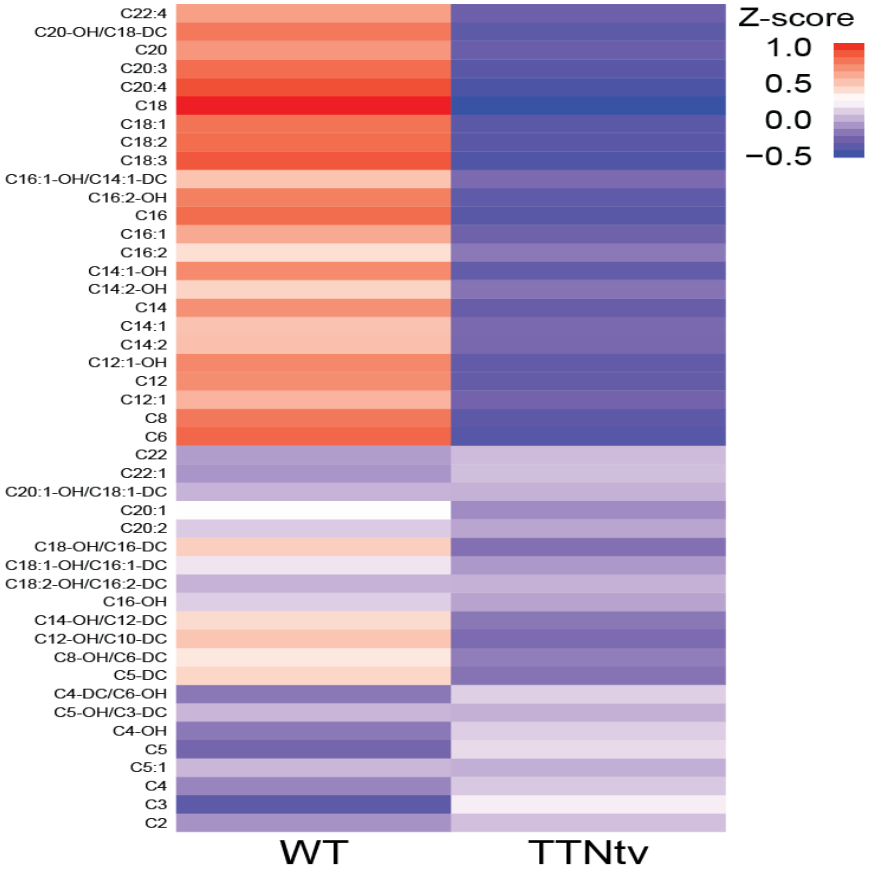
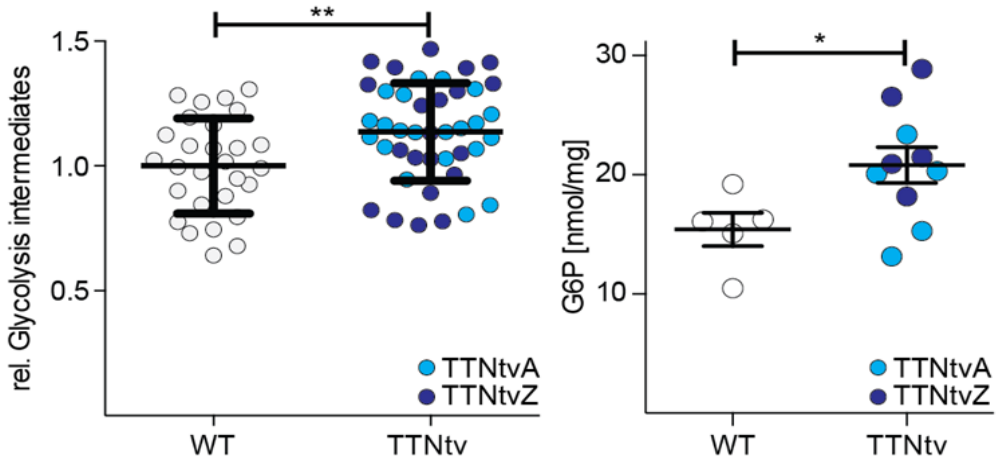
TTNtv shift heart metabolism from lipids to sugars





Work by Sebastian Schafer

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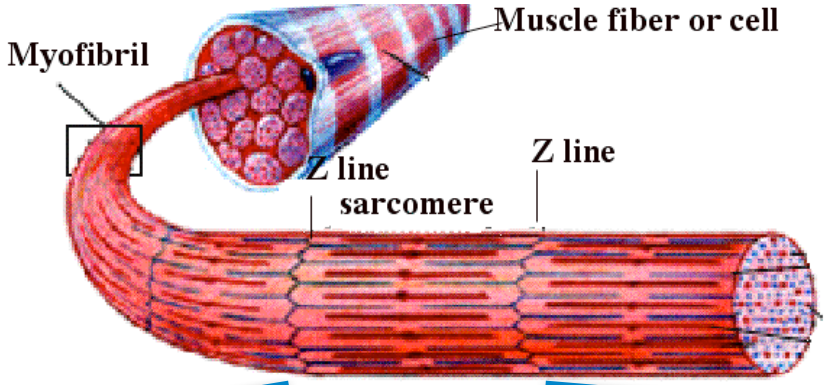
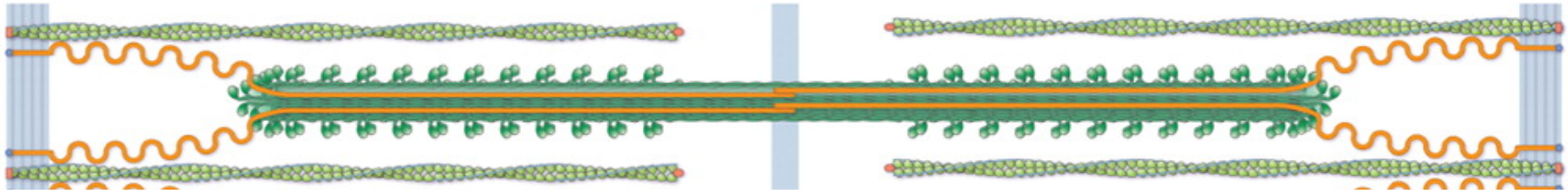
Titin (TTN) in the sarcomere



~3μm



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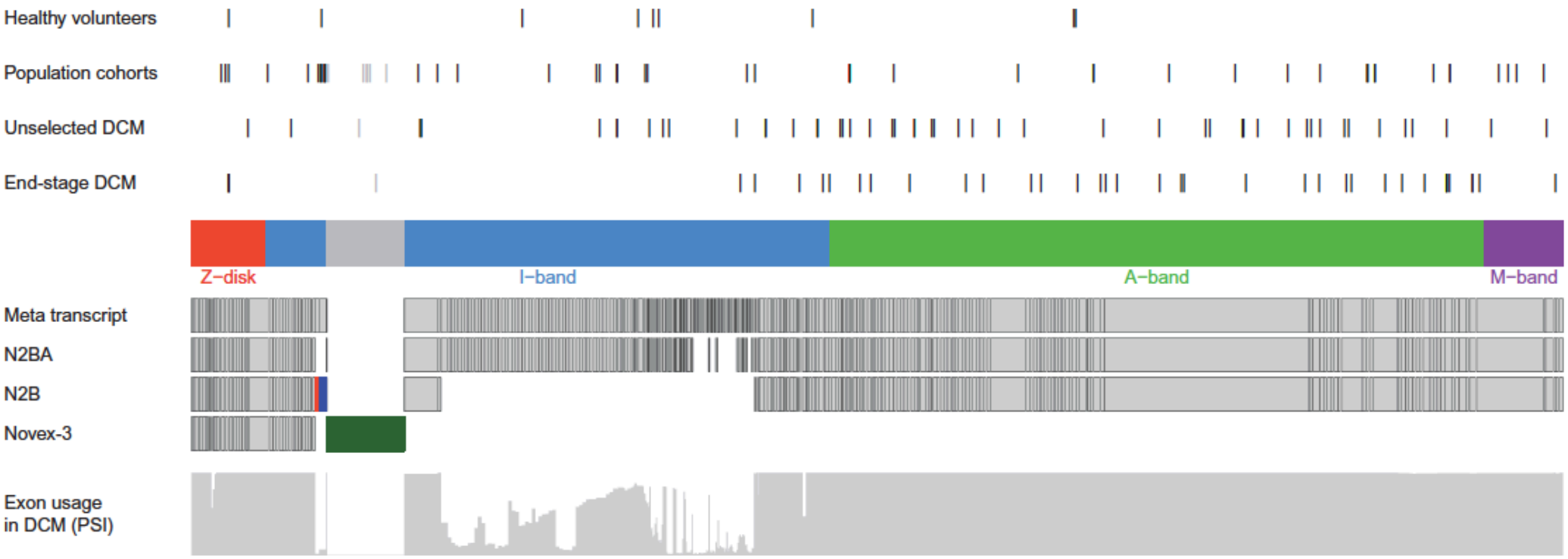
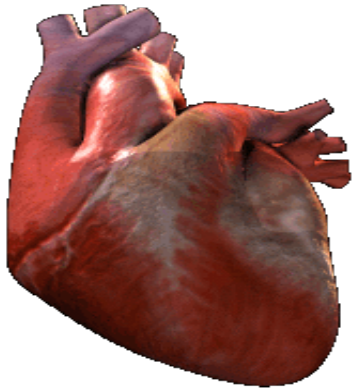
Is the effect of TTNtv position dependent?



Roberts AM, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Sci Transl Med. 2015;7:270ra6.

Information

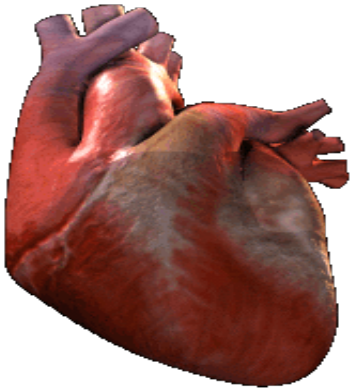


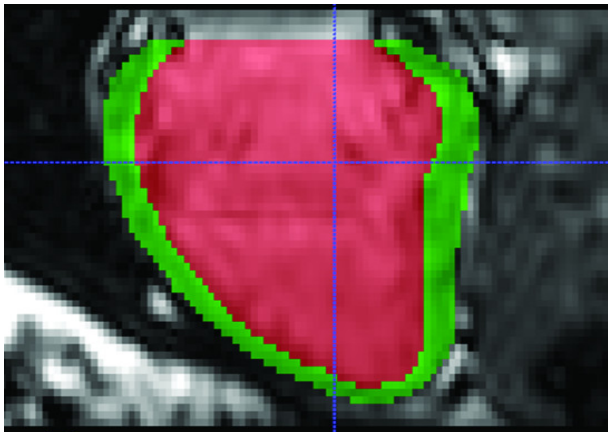
SAX3D Stack LV Function	
EDV:	119 ml
ESV:	42 ml
SV:	78 ml
EF:	65 %
CO:	4805 ml/min
CI:	2 l/min/m²
HR:	62.0/min
Myo Mass (Diast):	96 g
Phase Diastole:	1
Phase Systole:	12
EDV/H:	64 ml/m
EDV/BSA:	59 ml/m²
ESV/H:	22 ml/m
ESV/BSA:	21 ml/m²
SV/H:	42 ml/m
SV/BSA:	38 ml/m²
Myo Mass/H (Diast):	52 g/m
Myo Mass/BSA (Diast):	48 g/m²

Biological ground truth

1D volumes/mass

Information





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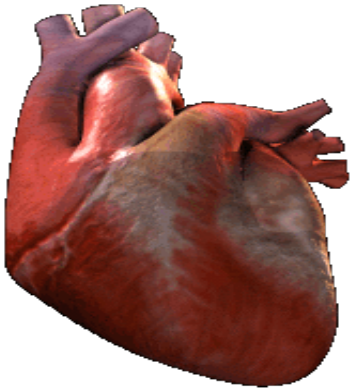
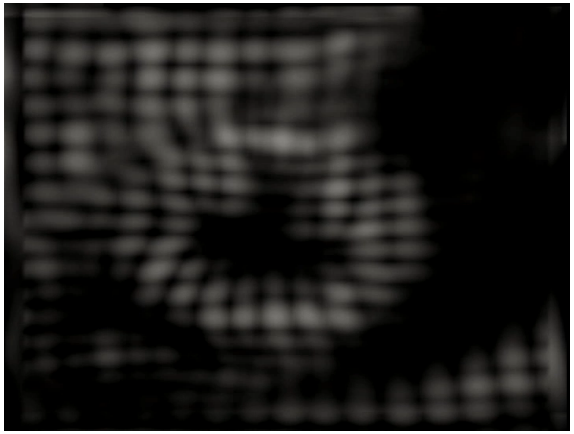
Biological ground truth

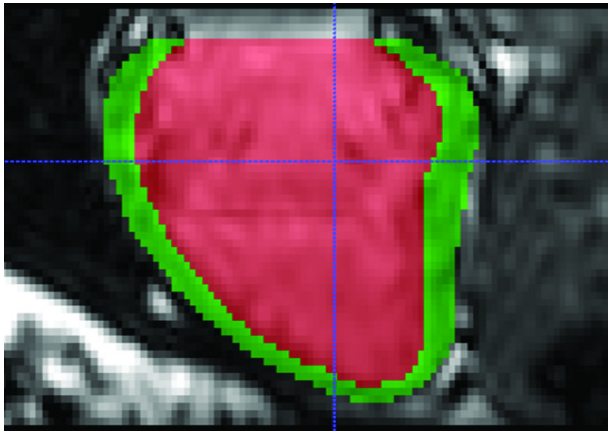
3D approximation

1D volumes/mass

Information







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Biological ground truth

Complete 3D model

3D approximation

1D volumes/mass