A Titin Truncation Variant Co-segregating with Dilated Cardiomyopathy in a Large Maori Kindred

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What is Titin?

- Large gene with most # transcripts
- Sarcomeric protein, spring and mechanosensory function
- Titin truncations (TTNtv) associated with:
  - Familial DCM 20-40%
  - Idiopathic DCM 10-15%
  - PPCM 15%
  - Cardiac Tx ~40%
  - Normal population 0.5 - 1%
# TTNtv burden across all regions

<table>
<thead>
<tr>
<th>Sarcomere domain affected by variant</th>
<th>DCM Positive (n=2,695)</th>
<th>Control Positive (n=61,834)</th>
<th>DCM Prevalence (%)</th>
<th>Control Prevalence (%)</th>
<th>OR</th>
<th>OR (hi)</th>
<th>OR (lo)</th>
<th>EF</th>
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<tbody>
<tr>
<td>A-band (constitutive)</td>
<td>288</td>
<td>149</td>
<td>10.74</td>
<td>0.24</td>
<td>49.8</td>
<td>61.1</td>
<td>40.6</td>
<td>0.98</td>
<td>2.4x10⁻⁷⁰⁰</td>
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<tr>
<td>I-band (Distal constitutive Post-Cronos)</td>
<td>9</td>
<td>7</td>
<td>0.36</td>
<td>0.01</td>
<td>32.0</td>
<td>85.9</td>
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<td>18</td>
<td>23</td>
<td>0.72</td>
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<td>I-band (Non-constitutive)</td>
<td>6</td>
<td>102</td>
<td>0.24</td>
<td>0.17</td>
<td>1.5</td>
<td>3.3</td>
<td>0.6</td>
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<td>8.6</td>
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Tayal et al. J Am Coll Cardiol 2017;70:2264–74

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**Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias**

Job A. J. Verdonschot¹,², Mark R. Hazebroek¹, Kasper W. J. Derks¹,³, Arantxa Barandiarán Aizpurua¹, Jort J. Merken¹, Ping Wang⁴, Jörgen Bierau⁵, Arthur van den Wijngaard⁶, Simon M. Schalla¹,³, Myurgia A. Abdul Hamid⁷, Marc van Bilzen⁸, Vanessa P. M. van Empel⁹, Christian Knackstedt¹⁰, Hans-Peter Brunner-La Rocca¹¹, Han G. Brunner¹², Ingrid P. C. Krepels¹³, and Stephanie R. B. Heymans¹⁴,¹⁵,¹⁶

European Heart Journal (2018) 39, 1–10

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**Clinical Research**

Heart failure cardiomyopathy

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Proband

- 41-year old Maori male rapid atrial fibrillation (AF) and a dilated LV (LVEDD 69mm, LVEF 50%)
- DDx marathon runner an athlete’s heart with a rate-related cardiomyopathy
- LVEF later ↓to 30% and a FHx DCM apparent
- DCCV with ↑LVEF with SR, Bb and ACEi
- cMRI showed NICM (LVEDVi 164mls, LVEF 46%, LV mass 152g with no LGE).

Proband

- At 45 years, AF so DCCV and amiodarone
- Despite medical advice ran a marathon age 50 years in 4:15 hrs (best previous time 3:50 hrs). DCCV at 52 years for AF failed
- Subsequent deterioration in LV dimensions and systolic function (LVEDD 71mm, LVEF <20%), though 10mins Bruce protocol ETT whilst in AF.
- At 54 yrs underwent thoracoscopic PVI, however had a VT arrest
- In 2017 worsening heart failure and severe functional MR on Echo, listed for cardiac Tx
Proband’s progress

- Timepoints 2, 3 — AF, demonstrating worsened LVEDV/BSA and LVEF in association with rate-related cardiomyopathy, and subsequent improvement.
- Timepoints 1, 4, 5, 6, 7 - Sinus rhythm, but showing progressive DCM.
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**Case Study**

- **Proband**
  - 48 yrs old
  - Transplant W/L

- **41 yrs old**
  - Cardiac transplant GLH
  - 40 yrs old

- **53 yrs old**
  - LVEF 25-30% SR
  - NICM on MRI
  - VE’s 28%, Primary ICD

- **Cardiac transplant**
  - St. Vincents, Aus
  - 52 yrs old

- **41 yrs old**
  - AF RRCM EF 30%
  - Recovered EF 50-55%
Summary

- Large Maori kindred, demonstrating highly penetrant TTNtv co-segregating with progressive DCM
  - 2 with cardiac Tx, 1 on W/L
  - Presentations with AF and RRCM
  - VT common feature for 2
  - Issues surrounding cascade screening and gene positive, phenotype negative family members

- Cont’d
The first titin (c.59926 + 1G > A) founder mutation associated with dilated cardiomyopathy

- TTNtv importance in Maori (x8 risk of HF, x8 mortality) – no data
- Founder effect in Maori – need population sequence data

![Map of the Netherlands showing the distribution of carriers and grandparents.](image)

**Figure 1** Geographic map of the Netherlands showing the distribution of 30 carriers and 36 grandparents. (A) Carriers' places of residence. (B) Birthplaces of the grandparents of carriers of the oldest generations from the different families. The six common ancestors linking seven of the 10 families all originated from a small area in the southern part of the province of Overijssel, indicated by the red circle (10 km radius).


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**Repatriating ICC genomics**

- $600 in NZ
- Overseas $2-3,000
Future of TTNtv Management?

- Prevention for gene +ve family members
- ICD thresholds?
- Spermidine alters TTN phosphorylation
  - Soy
- Metabolic modulation
- SGLT2 alter N2B/N2BA
- Antisense, CRISPR-Cas9, RBM20 splicing

TTNtv:
European population [EUR]: 0.27%,
African population [AFR]: 0.46%,
Asian population [AS]: 0.53%; P = 2.7 × 10⁻⁵

Maori, Pacific People?
Role of titin in cardiomyopathy: from DNA variants to patient stratification

James S. Woolf and Stuart A. Cook

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Take home figure: Truncating TTN mutations and Dilated Cardiomyopathy. Truncating mutations in the TTN gene can lead to DCM associated with ventricular arrhythmias, increased interstitial fibrosis, lower ventricular mass and alterations of the mitochondrial energy pathways.