**Supplementary information**

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This study aimed to reveal mechanisms underlying atrial fibrillation due to the p.Met207Val PITX2c mutation using the modified Courtemanche-Ramirez-Nattel (CRN) model. The original CRN model1 was modified to reflect the observed kinetic properties of the *INaL*current that was based on the work of Grandi et al.2, who developed it using experimental data from human atrial myocardium.3 All the equations, parameter values and initial conditions necessary to carry out the single cell simulations in this study were provided here.

**Membrane voltage:**

|  |
| --- |
|  |

**Equilibrium potentials:,,**

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| --- |
|  |

**Na+ current: and**

|  |
| --- |
| = |

**Inward rectifier K+ current:**

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| --- |
|  |

**Transient outward K+ current:**

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| --- |
|  |

**Ultrarapid delayed rectifier K+ current:**

|  |
| --- |
|  |

**Rapid delayed outward rectifier K+ current:**

|  |
| --- |
|  |

**Slow delayed outward rectifier K+ current:**

|  |
| --- |
| /2 |

**L-type Ca2+ current:**

|  |
| --- |
|  |

**Na+-K+ pump current:**

|  |
| --- |
|  |

**Na+/Ca2+ exchanger current:**

|  |
| --- |
|  |

**Background currents:and**

|  |
| --- |
|  |

**Ca2+ pump current:**

|  |
| --- |
|  |

**Ca2+ release current from JSR:**

|  |
| --- |
|  |

**Transfer current from NSR to JSR:**

|  |
| --- |
|  |

**Ca2+ uptake current by the NSR:**

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| --- |
|  |

**Ca2+ leak current by the NSR:**

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| --- |
|  |

**Ca2+ buffers**

|  |
| --- |
|  |

**Intracellular ion concentrations:,,，，**

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| --- |
|  |

**Parameter values**

|  |  |
| --- | --- |
| =8.3143 | =310 |
| =96.4867 | =100 |
| =20100 | =13668 |
| =1109.52 | =96.48 |
| =5.4 | =140 |
| =1.8 | =7.8 |
| =0.0025 | =0.09 |
| =0.1652 | =0.0294 |
| =0.129 | =0.1238 |
| =0.00113 | =0.000674 |
| 0.6 | 1600 |
| 0.275 | 0.005 |
| 3 | 0.35 |
| 10 | 1.5 |
| =87.5 | =1.38 |
| 0.1 | 30 |
| 0.00092 | 15 |
| 0.05 | 0.07 |
| 10 | 0.00238 |
| 0.0005 | 0.8 |

**Initial conditions**

|  |  |
| --- | --- |
| =-81.2 mV | =0.00291 |
| =0.965 | =0.978 |
| =0.043738860135 | =0.000137 |
| =0.999837 | =0.775 |
| =0.0304 | =0.999 |
| =0.00496 | =0.999 |
| =0.0000329 | =0.01869 |
| =0.00 | =1.00 |
| =0.9992 | =0.0001013 mM/L |
| =11.2 mM/L | =139 mM/L |
| 1.49 mM/L | 1.49 mM/L |

**Properties of action potentials, and in the Original CRN and the Modified CRN models driven at 1Hz from their steady states.**

|  |  |  |
| --- | --- | --- |
|  | Original CRN | Modified CRN |
| RMP (mV) | -81.50 | -81.49 |
| APA (mV) | 104.30 | 104.23 |
| dV/dtmax (mV/ms) | 200.22 | 199.92 |
| APD50 (ms) | 117.42 | 123.36 |
| APD90 (ms) | 256.40 | 260.62 |
|  | 13.30 | 13.35 |
|  | 0.000114 | 0.000115 |

**The initial values of state variables in the tissue models were set to be the values at the steady state (700 s at 1 Hz stimulation) in single cells under WT, MT/WT and MT conditions.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | WT | MT/WT | MT |
|  | -81.491781 | -81.839533 | -81.977914 |
|  | 13.353808 | 13.676521 | 13.795061 |
|  | 134.672116 | 134.387074 | 134.28451 |
|  | 0.000115 | 0.000108 | 0.000106 |
|  | 0.002763 | 0.002609 | 0.002551 |
|  | 0.967204 | 0.969614 | 0.970524 |
|  | 0.979027 | 0.980698 | 0.981320 |
|  | 0.000131 | 0.000126 | 0.000124 |
|  | 0.950379 | 0.967668 | 0.973744 |
|  | 0.018888 | 0.018470 | 0.018321 |
|  | 0.000735 | 0.000437 | 0.000355 |
|  | 0.029917 | 0.029347 | 0.029123 |
|  | 0.999285 | 0.999330 | 0.999348 |
|  | 0.004809 | 0.004639 | 0.004573 |
|  | 0.991409 | 0.991948 | 0.992165 |
|  | 0.751808 | 0.763288 | 0.768245 |
|  | 0.137465 | 0.15093 | 0.156622 |
|  | 1.105541 | 0.965978 | 0.908732 |
|  | 1.518534 | 1.379184 | 1.320642 |
|  | 0.00000 | 0.00000 | 0.00000 |
|  | 1.000000 | 1.000000 | 1.000000 |
|  | 0.999213 | 0.999229 | 0.999235 |

1 Courtemanche, M., Ramirez, R. J. & Nattel, S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *American Journal of Physiology-Heart and Circulatory Physiology* **275**, H301-H321 (1998).

2 Grandi, E. *et al.* Human atrial action potential and Ca2+ model: sinus rhythm and chronic atrial fibrillation. *Circulation research* **109**, 1055-1066 (2011).

3 Sossalla, S. *et al.* Altered Na+ currents in atrial fibrillation: effects of ranolazine on arrhythmias and contractility in human atrial myocardium. *Journal of the American College of Cardiology* **55**, 2330-2342 (2010).