A  
NPY secretion:  
*Cis-QTL by sib-pair linkage*  
Trait: Plasma NPY concentration (pM)  
Peak LOD = 4.27 at 34 cM on chromosome 7p15  
SOLAR multipoint linkage

B  
Human *NPY*: Systematic polymorphism determination by re-sequencing

C  
Genetic variation in the proximal human *NPY* promoter:  
Impact on domains and motifs
A  Association of NPY haplotype ΔTGTGC with plasma NPY and delta DBP in cold stress test

GEE:
NPY: $\chi^2 = 6.71$, $p = 0.01$
Delta DBP: $\chi^2 = 5.85$, $p = 0.016$
Covariates: Age, sex

ΔTGTGC
2 copies, $n = 29$

ΔTGTGC
0 or 1 copy, $n = 371$

B  Association of NPY promoter polymorphism \(\nabla-880\Delta\) with plasma NPY and ΔDBP in cold stress test

GEE:
NPY: $\chi^2 = 12.26$, $p = 0.00046$
Delta DBP: $\chi^2 = 7.22$, $p = 0.0072$
Covariates: Age, sex

Δ/Δ
$n = 38$

Δ/Δ
$n = 361$

C  NPY promoter variant \(\nabla-880\Delta\) in twin and sibling pairs:
Deletion variant predicts higher SVRI with lower CI

GEE:
CI: $\chi^2 = 11.04$, $p = 0.004$
SVRI: $\chi^2 = 6.47$, $p = 0.039$
Covariates: Age, sex

\(\nabla/\nabla\)
$n = 172$

\(\nabla/\Delta\)
$n = 143$

\(\Delta/\Delta\)
$n = 36$

Cardiac index (CI), L/min/m²

SVRI (SVR/BSA), dynes/s/cm²/m²
NPY promoter common variant \( \nabla -880\Delta \) (Ins/Del, TG/--): Disruption of a glucocorticoid response element (GRE) motif

**GRE and \( \nabla -880\Delta \) across species**

<table>
<thead>
<tr>
<th>Species</th>
<th>GRE motif</th>
<th>Direct</th>
<th>Spacer</th>
<th>Inverted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human TG</td>
<td>GACAGAAGCTGTTGTTT</td>
<td>8/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>GACAGAATCTGTTGTTT</td>
<td>6/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chimp</td>
<td>GACAGAAACTGTTGTTT</td>
<td>7/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orangutan</td>
<td>GACAGAAACTGTTGTTT</td>
<td>5/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marmoset</td>
<td>GACAGAAATCTGTTGTTT</td>
<td>9/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horse</td>
<td>GACAGAAATCTGTTGTTT</td>
<td>6/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>GACAGAAATCTCCCGT</td>
<td>4/12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**\( \nabla -880\Delta \) (rs3037354)**

| Bold: Sequence identity with GRE motif. GRE: Glucocorticoid Response Element.

**Glucocorticoid effect on NPY promoter \( \nabla -880\Delta/C-399T \) haplotype expression in chromaffin cells**

Two way ANOVA:
- Overall: F=3.217, p=0.009
- Dex: F=11.211, p=0.002

-880 -399

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Vehicle</th>
<th>Dex 1 ( \mu )M</th>
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-880 -399

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</tbody>
</table>

**Glucocorticoid receptor interaction with NPY promoter Ins/Del variant \( \nabla -880\Delta \) (TG/--): EMSA.**

<table>
<thead>
<tr>
<th>Specific shift</th>
<th>Free oligo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC12 NX</td>
</tr>
<tr>
<td></td>
<td>Labeled (*)</td>
</tr>
<tr>
<td></td>
<td>Unlabeled</td>
</tr>
<tr>
<td></td>
<td>Anti-GR</td>
</tr>
<tr>
<td></td>
<td>Ctl antibody</td>
</tr>
</tbody>
</table>

I: Insertion of TG (\( \nabla \))
D: Deletion of TG (\( \Delta \))
GR: Glucocorticoid Receptor
Ctl: Control
NX: Nuclear Extract
A  **NPY haplotype ΔTGTGC on BP in the population**

**NPY haplotype ΔTGTGC on blood pressure in the population**

ANOVA:
- SBP: $F=8.67$, $p=0.003$
- DBP: $F=5.77$, $p=0.016$

Covariates: Age, sex

$\Delta$TGTGC present: $n=475$

$\Delta$TGTGC absent: $n=646$

B  **NPY promoter variant $\Delta-880\Delta$ in the population:**

Deletion variant predicts higher SBP/DBP and hypertension

**NPY promoter polymorphism $\Delta-880\Delta$ (rs3037354) on blood pressure in BP extremes**

ANOVA:
- SBP: $F=8.54$, $p=0.004$
- DBP: $F=4.08$, $p=0.044$

$\Delta/\Delta$ or $\Delta/\Delta$: $n=496$

$\Delta/\Delta$: $n=622$

**NPY promoter polymorphism $\Delta-880\Delta$ (rs3037354) on BP status in the population**

Fisher's exact test: $p=0.029$

$\Delta/\Delta$: $n=320$

$\Delta/\Delta$ or $\Delta/\Delta$: $n=302$

$\Delta/\Delta$: $n=225$
Human NPY promoter genetic variant \(\nabla-880\Delta\): Schema for effects on autonomic and disease traits

**Event:**
- Gene variant
- Mechanism in cells
- Biochemical trait *in vivo*
- Physiological traits
- Disease trait

**Experimental setting:**
- Promoter sequencing
- Promoter/reporter transfection
- Twin plasma RIA
- Twin monitoring
- Population exam

**Application to NPY:**
- NPY promoter -880\(\Delta\)
  - Glucocorticoid response
  - \(\uparrow\) NPY transcription
  - \(\uparrow\) NPY secretion
  - \(\uparrow\) SVR, \(\uparrow\) Stress BP
  - \(\uparrow\) Hypertension
*NPY* promoter variation: 
*Coordinate directional functions in cella and in vivo* 

Plasma NPY: \( p = 0.007 \)  
Luciferase activity: \( p < 0.001 \) 

Supplementary Figure 6