Genetic Factors Influencing the Development of Peyronie’s Disease

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Disclosures

• I have no relevant financial relationships to disclose

• I will not discuss off-label management of clinical conditions
Peyronie’s Disease

Peyronie’s Disease (PD):
- Fibrosis of the penile tunica albuginea
- Affects 3-5% of men 40-70 years old

Pathogenesis:
- Trauma / Inflammation
- Profibrotic Factors (TGF-β, ROS)
- Myofibroblast / Osteoblast Differentiation
- Collagen Deposition / Calcification

- Autosomal dominant inheritance
- Dupuytren’s Disease associated with 20% of men with PD
- Current treatments incompletely effective
Negative Impact of PD on Sexual & Psychological Health

Sexual Health
• Penile curvature → limited ability to have sex
• Penile narrowing / shortening / pain
• Biplanar deformities

Psychological Health
• Social isolation
• Stigmatization
• "Emotional difficulties" → 81%
• Clinical depression → 48%
• Relationship problems → 54%

Dupuytren’s Disease – Another Fibrotic Diathesis

Dupuytren’s Disease (DD)
- Aberrant fibrosis of the palmar fascia → digital contractures
- Affects 4% of the U.S. population
  - 30% of Norwegian men >60 years old!
  - 5x more common in men!

Pathogenesis:

Trauma / Inflammation →
Profibrotic Factors (TGF-β, ROS) →
Myofibroblast / Osteoblast Differentiation →
Collagen Deposition / Calcification

Fibrotic Diatheses Have a Genetic Predisposition

Co-Prevalence
- 22% of men with PD also have DD
- 15% of men with DD have Ledderhose Disease (LD)

Inheritance / Genetic Factors:
- PD, DD and LD → male predominance
- Autosomal dominant inheritance
- Incomplete penetrance

Gene Expression → Overlap Between PD and DD:
- Genes differentially expressed in common between PD and DD:
  - MMP2/9
  - TMβ4/10
  - OSF1/2
  - ARHGDIA

Urology. 2004; 64:399
Chromosomal Abnormalities in Peyronie’s Disease

Structural / Numerical Chromosomal Abnormalities in PD

- 58% of patients have variable chromosomal abnormalities in *PD plaque cells* → ?genomic instability?

- Other somatic cells appear unaffected

<table>
<thead>
<tr>
<th>Structural Abnormalities</th>
<th>Numerical Abnormalities</th>
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<tbody>
<tr>
<td>46XY,t(11;12)(q11,p11)</td>
<td>Trisomy 7</td>
</tr>
<tr>
<td>46XY,t(1;5)(q25;q11)</td>
<td>Trisomy 8</td>
</tr>
<tr>
<td>46XY,inv(7)(p22q36)</td>
<td>45X, -Y</td>
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</table>

Numerical Chromosomal Abnormalities Occur in Both PD Plaque and Normal Tissue

- Compared Chr 7, 8, 17, 18, X, Y between PD plaque-derived and normal tunica albuginea cells

- Increase in numerical chromosomal abnormalities with cell passage in PD and unaffected TA fibroblasts

PD Fibroblasts

Non-Plaque TA Fibroblasts

TGFβ/Smad Pathway and Fibrosis

Osteoblast Differentiation

Collagen I / III Deposition

Calcification / Bone Formation

Fibrosis

Aims & Approaches

Aim:

To identify genes with variations in copy number in men with both PD and DD that may play a role in fibrotic diatheses.

Approach:

Identify copy number variations (CNVs) in men with PD/DD using array comparative genomic hybridization (aCGH).

Identify roles of these genes in fibrosis using cell-based assays and animal models.
Chromosome deletions NOT detected by Karyotype
Microdeletions in NELL1 & CTDSPL in Men with PD & DD

Patient Cohort:
- 19 Men with PD & DD
- 4 Control Males - no PD or DD, no FHx

11p15.1 → 16.0 kb  3p22.2 → 4.3 kb  11p15.1 → 23.2 kb
NELL1 – A Secreted Growth Factor Involved in Fibrosis & Inflammation

**NELL1**
- Neural epidermal growth factor-like 1
- Secreted growth factor

**NELL1, Fibrosis, and Inflammation**
- Osteoblast differentiation, terminal mineralization $\Rightarrow$ BMP and TGF-β pathways
- Associated with human Crohn’s, ankylosing spondylitis

**Mouse Phenotype:**
Ankylosing spondylitis

CTDSPL – A Phosphatase Effecting TGF-β Signaling

CTDSPL Background
• Carboxy-terminal domain small phosphatase-like
  • Upregulates TGF-β pathway signaling via interaction with Smad1 or Smad2/3 proteins
• Modulates the epithelial-mesenchymal transition
  • Effects myofibroblast differentiation and fibrosis
CTDSPL and NELL1 in Peyronie’s Disease
A Potentially Deleterious SNP in NELL1

NELL1 R82Q SNP
- Associated with human Crohn’s disease and ankylosing spondylitis

<table>
<thead>
<tr>
<th>SNP</th>
<th>Mutation Taster</th>
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<tr>
<td>Rs8176785 G→A (R82Q)</td>
<td>Damaging</td>
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<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>R82Q</th>
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<tr>
<td>PD</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>24</td>
</tr>
</tbody>
</table>

p=0.03
NELL1 Overexpression Downregulates Profibrotic and Upregulates Antifibrotic Genes in TA Fibroblasts

**Profibrotic**

-2.4 fold*

-4.2 fold*

-3.4 fold*

**Antifibrotic**

9.0 fold*

1.8 fold*

2.0 fold*

2.4 fold*

2.3 fold*

Expressed Gene mRNA ➔ Fibrosis Pathway ➔ TA Fibroblasts

**Knockdown**

Anti-NELL1 or CTDSPL RNAi

BMPR1B, GDNF, HGF, LIF, STAT1
CTDSPL Overexpression Downregulates Profibrotic Genes in TA Fibroblasts

* p<0.0001
CTDSPL Overexpression Differentially Affects Profibrotic Genes in Control and PD TA Fibroblasts

- **AGT**: -7.6 fold*  
- **COL3A1**: -13.0 fold*  
- **ITGB8**: -4.3 fold*  
- **PLAU**: -4.3 fold*  
- **TGFBR1**: -1.2 fold

* p<0.0001
Nell1 Deficient Mice Have Increased Penile Collagen Deposition

![Chart showing hydroxyproline levels in different genotypes]

- Wt: N=3
- Het: N=3, P=0.04
- Null: N=3, P=0.04

Hydroxyproline (μg/μl)

P=0.04
A Role for NELL1 & CTDSPL in Regulating Fibrosis in PD

- Fibroblast
- Myofibroblast
- TGF-β
- Fibrosis
- Collagen
  - Scar
  - Tissue Contraction

NELL1 / CTDSPL
Summary

- A genetic predisposition to fibrosis exists in some men with fibrotic diatheses.
- Microdeletions in NELL1 and CTDSPL occur more frequently in men with PD and DD than in controls or the general population.
- NELL1 and CTDSPL modulate fibrotic signaling pathways in TA fibroblasts.
- Do NELL1 and CTDSPL drive fibrosis, predisposing to PD / DD?
- Nell1-deficient mice manifest more significant penile collagen deposition than WT mice.

Data support a genetic predisposition to aberrant fibrosis as a result of gene dosage alterations in NELL1 and CTDSPL.
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