The Current State of SCLERODERMA RESEARCH

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GOALS OF RESEARCH

To answer these questions:
What causes scleroderma?
How can it be cured?
Telangiectasias in formerly called “CREST” syndrome
SEVERE HAND INVOLVEMENT
OVERVIEW of SSc Research

1. LABORATORY STUDIES

2. COHORT STUDIES

3. CLINICAL TRIALS
LABORATORY STUDIES - UTH

Genetic Studies
- **GWAS** - completed (Scleroderma Registry)
- **MHC** Region Genes in SSc & AS – completed
- **GRASP** (Genome Research in African-American Scleroderma Patients)– NIH/Hopkins multicenter study with exome sequencing (ongoing)

Epigenetic Studies
- Micro-RNAs that control gene activity

Biomarker Studies
- Gene expression in skin (skin biopsies) and blood
- Cytokine and Serum Analytes in SSc

Animal Models of SSc
WHAT CAUSES SCLERODERMA?

NATURE or NURTURE?
WHAT CAUSES SCLERODERMA?

NATURE or NURTURE?

YES
EVIDENCE for HERITABILITY:
Family Studies

**SLE**
Familial Recurrence Rate in 1st Degree Relatives: 
~ 5%

**SSc**
Familial Recurrence Rate in 1st Degree Relatives: 1.6%

(1st Degree Relatives have 98.4% chance of NOT developing SSc)
Family 001

101

201

SSc Limited
ANA 1:160 Speckled
Scl 70 -
Date Raynaud's: 1993
Date Dx: 1995
Age Dx: 22

202

102

SSc Limited
ANA 1:80 Speckled
Scl 70 -
Date Raynaud's: 1991
Date Dx: 1996
Age Dx: 16

204
**Family 002**

1. **101**
   - SSc Limited
   - ANA +
   
2. **102**
   - Date Dx: 1978
   - Age Dx: 59
   
3. **103**
   - SLE
   
4. **201**
   - SSc Limited
   - ANA 1:640
   - Centromere
   - Scl 70 -
   - Date Dx: 1988
   - Age Dx: 47

5. **202**

6. **203**

7. **204**
   - SLE

8. **205**
   - MS
SSc Genome Wide Association Study (GWAS)

Collaboration with 10 U.S. sites
Canadian Scleroderma Research Group
Multiple European Researchers
GENETICS 101

Refresher
46 Human Chromosomes: 44 somatic XY determine sex
Variations in Genome

Common Sequence

Variations

Polymorphism

Deletions

Insertions

Chromosome

Translocations
WHAT ARE THE GENE VARIANTS RESPONSIBLE FOR SSc HERITABILITY?
Genome Wide Association Study (GWAS)

SCLERODERMA REGISTRY
aka “THE REGISTRY”
AUTOIMMUNITY REGIONS FROM GENOME SCANS in 2001

Wandstrat and Wakeland: Nature Immunol, 2001. (without Chr 6)
SSc GWAS Results
GWAS of 2,296 SSc Patients and 5,171 Healthy Controls – Discovery Cohort

# Selected Genetic Associations and SSSc (2016)

**Non-MHC (MORE THAN 30)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
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<tr>
<td>CD247</td>
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<tr>
<td>TN1P1</td>
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</tr>
<tr>
<td>RHOB</td>
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</tr>
<tr>
<td>BANK1</td>
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<td>STAT4</td>
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<tr>
<td>BLK</td>
<td>X Chromosome</td>
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<tr>
<td>TNFSF4</td>
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<tr>
<td>ITGAM</td>
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<td>MIF</td>
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<tr>
<td>PTPN22</td>
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<td>GRB10</td>
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**MHC- HLA**

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<tbody>
<tr>
<td>HLA-DPB1</td>
<td>*1301</td>
<td>ATA+ (White)</td>
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<tr>
<td></td>
<td>*0901</td>
<td>ATA+ (Asian)</td>
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<tr>
<td></td>
<td>*0402</td>
<td>ACA+ (Asian)</td>
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<tr>
<td>HLA-DQA1</td>
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<tr>
<td>HLA-DQB1</td>
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<td></td>
</tr>
<tr>
<td>HLA-DRB1</td>
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</table>

**MHC- nonHLA**

<table>
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<th>Function</th>
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<tbody>
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<td>NOTCH4</td>
<td></td>
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<tr>
<td>PSORS1C1</td>
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INTERPRETATION of GENETIC STUDIES

• Most of the associated genes influence immune-related pathways rather than fibrosis or vascular pathways

• The precise role of the genetic variants has not yet been identified
LABORATORY STUDIES

• **Skin biopsies:**
  
• Development of “gene signatures”
  – what cells or genes are active in SSc skin?
  – how does this change over time or with treatment?
  – what pathways are over-expressed (or under-expressed) that could be targets for new therapies?
LABORATORY STUDIES

• BLOOD studies: are there blood analytes (cells or serum proteins) that can:
  – Predict SSc organ involvement?
  – Can identify “active” periods of the disease?
  – Can predict which patients are likely to respond to one form of therapy rather than another (personalized/precision medicine)?
CLINICAL TRIALS
TYPES of CLINICAL STUDIES

• **Observational** – to address the question of prediction of outcomes:
  – What features in early SSc will predict presence and severity of organ involvement?
  – Characterize less frequent SSc complications

• **Randomized Controlled Trials (RCTs)** – the “Gold Standard”
CLINICAL TREATMENT TRIALS 1
Stem-Cell Transplant

• High-dose Chemotherapy & Stem Cell Tx compared to standard treatment
  – **ASTIS (European)** - Autologous Stem Cell Treatment International Study compared to 12 IV monthly cyclophosphamide (CYC):
    • **Conclusion**: In early diffuse SSc, transplanted subjects had increased short-term mortality but improved long-term survival in Transplant arm vs CYC arm
  – **SCOT (U.S. NIH)** – Scleroderma Cyclophosphamide or Transplant – study is completed but analysis of results are pending (due this Fall, 2016)
SCLERODERMA LUNG STUDY II

aka SLS II
HRCT showing significant fibrosis
SLS II

Randomized, double-blind, parallel, controlled trial of:

1 year daily oral cyclophosphamide (Cytoxan)

versus

2 years of daily oral mycophenolate mofetil (MMF, Cellcept)

SLS II Conclusions

- **PRIMARY OUTCOME MEASURE:**
  Pulmonary function test - FVC% at 24 months.

- **RESULTS:**
  - Both treatment arms resulted in improvements in lung function, imaging (CAT scan), shortness of breath and skin scores.
  - Treatment with MMF was associated with fewer drug-related SAEs and fewer deaths compared with CYC.
SELECTED ONGOING RCTs

1. **Abatacept** (FDA approved for RA) in early SSc skin disease
2. **Riociguat** (FDA approved for PAH) in early SSc skin disease
3. **Tocilizumab** (FDA approved for RA) in early SSc skin disease
4. **Nintedanib** (FDA approved for idiopathic pulmonary fibrosis) in early SSc-ILD
5. **Rituximab** (FDA approved for RA) in recently diagnosed SSc-PAH
6. **Injection of adipose-derived progenitor** cells into SSc fingers to improve hand function.
7. **Ajulemic acid** (nonpsycho-active cannabinoid derivative) for SSc skin disease

(See ClinicalTrials.gov for details)
CURRENT STATE OF SSce RESEARCH

• Laboratory research is identifying SSce-specific pathways that will likely lead to new therapies.
• There are more clinical trials now in SSce than ever before.
• Many of these trials are multi-center and international.
• The future looks bright for SSce treatment!
THE END

C’est Fini