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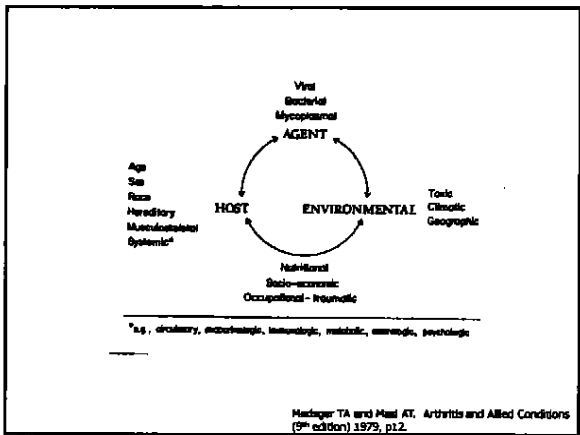


WHAT IS THE ROLE OF HEREDITY IN SCLERODERMA?

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DOES SYSTEMIC SCLEROSIS AGGREGATE IN FAMILIES?

Studies:

- risk of SSC in general population: 0.026%
- risk in siblings of SSC patients: 0.40%
- risk in first-degree relatives of SSC patients: 1.60% (3 studies; 11 fold increased risk)
- risk in identical twins: 5.0%

Conclusion: A positive family history of SSC increases the risk of a person's developing SSC.

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SELF-REPORT OF CONNECTIVE TISSUE DISEASES

Study:

- Women's Health Initiative study enrolled over 160,000 post-menopausal women age 50-79 from 40 US centers
- Authors used 2 centers and examined medical records of self-reported RA (286) and SLE (34)
- Medical records confirmed diagnosis in only 15% of RA patients and 12% of SLE patients
- Adding medication history improved these proportions to 55% for RA and 50% for SLE

Conclusion: Self-report of autoimmune diseases is often not confirmed.

Walter BT, et al. J Rheumatol 2008; 35(5):811-8.

INFLUENCES OF ETHNIC FACTORS ON OCCURRENCE OF SSC

- higher incidence in females vs. males (3:1) and African-Americans vs. Caucasians (4:3)
- younger age at onset in African-Americans
- more severe disease and worse survival in African-American women
- high incidence in Oklahoma Choctaw Indians

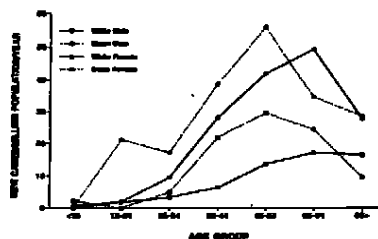


Figure 1. Age-specific incidence of systemic sclerosis in Pittsburgh and Allegheny County, PA, 1963-1982.

Steen VD et al. Arthritis Rheum 1997; 40:441-5.

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CONCORDANCE FOR DISEASE IN TWINS STUDIES

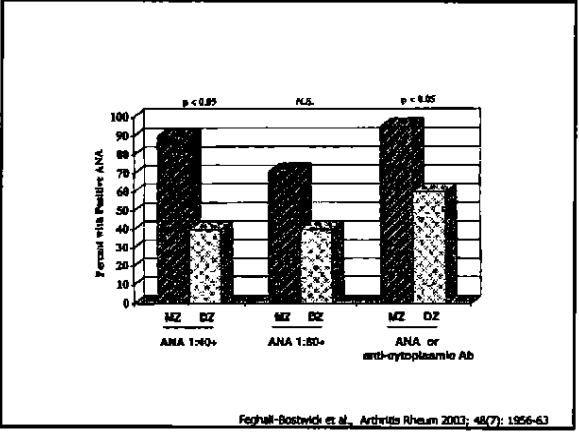
	<u>RA (4 reports)</u>	<u>SLE (4 reports)</u>
Identical Twins (MZ or monozygotic)	12-21%	10-69%
Fraternal Twins (DZ or dizygotic)	0.0-4%	0-2%

Conclusion: A genetic component plays an important role in the development of RA and SLE

UNIVERSITY OF PITTSBURGH SSc TWINS STUDY

- 42 sets of twins, at least one having SSc, recruited nationwide (24 MZ and 18 DZ)
- proportion with both twins having SSc (concordance) low at 4.7%
- concordance similar in MZ and DZ twins (suggests role for environment)
- occurrence of positive ANA significantly higher in unaffected MZ twins compared with unaffected DZ twins, 70% vs. 40% (suggests role for genetics)
- no unaffected twin had a SSc-associated blood antibody

Feghall-Bostwick C, et al. Arthritis Rheum 2003; 46(7):1956-63.



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SKIN FIBROBLAST GROWTH

Study:

- skin biopsies taken from 15 MZ and DZ discordant twin pairs and 5 normal persons
- fibroblasts grown in culture from biopsies
- gene expression profile of fibroblasts differed
 - affected and unaffected MZ similar
 - unaffected DZ and normals similar
 - if serum from affected or unaffected MZ added to normal fibroblast, a SSc profile could be produced

Conclusion: A point in favor of the role of heredity.

Zhou X et al., Arthritis Rheum 2005; 52(10):3305-14.

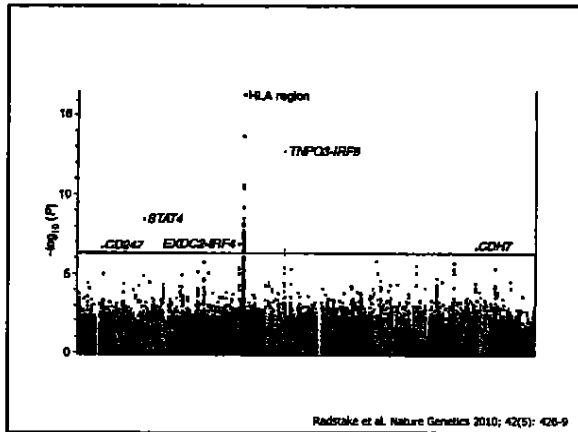
GENOME-WIDE ASSOCIATION STUDIES (GWAS)

- The entire human genome has now been characterized.
- Some genetic factors are associated with many connective tissue diseases.
 - HLA (human leukocyte antigen) region on chromosome 6 is most important.
 - Some SSc antibodies have HLA associations.
 - Only a few non-HLA region genes are implicated in small studies.

GWAS

- Radstake et al. examined over 270,000 of the over 3,000,000 genes for their association with SSc.
- They identified a gene (CD247) whose structure more frequently differs from normal in SSc patients of European ancestry than in normal subjects (>2200 SSc patients, >5100 normal subjects); results confirmed on >2700 SSc patients and >4500 normals.
- CD247 is responsible for determining the structure of 1 of a group of proteins (chain) on the surface of T-cells. The chain permits the cell to respond appropriately to certain external stimuli.
- This chain is altered in chronic autoimmune and inflammatory disorders.

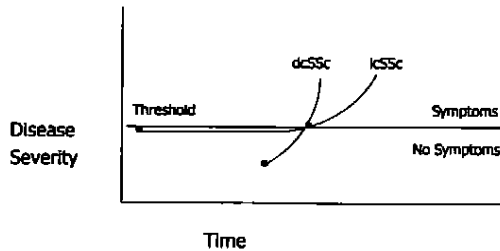
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ENVIRONMENTAL RISK FACTORS FOR SYSTEMIC SCLEROSIS

- (1) occupational associations:
 - silica dust exposure (underground mining, sandblasting)
 - solvents (trichloroethylene, benzene, trichloroethane, carbon tetrachloride, polyvinyl chloride)
- (2) medications:
 - chemotherapy drugs (bleomycin, taxanes)
 - estrogen replacement therapy
- (3) toxins:
 - adulterated L-tryptophan (toxic oil syndrome, eosinophilia-myalgia syndrome)
 - cocaine

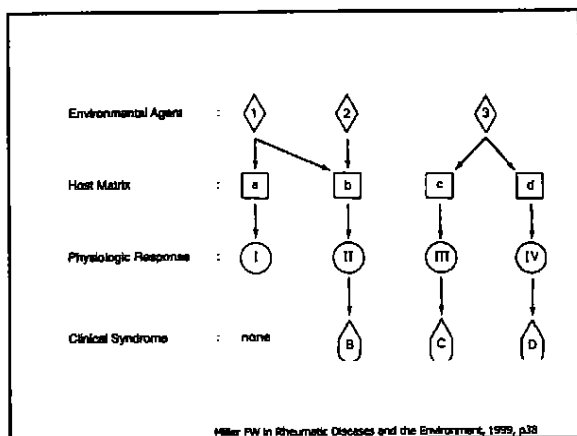
IDENTIFYING TIME OF DISEASE ONSET



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INTERACTION OF GENETICS AND ENVIRONMENT IN RA

- Past cigarette smoking is a strong predictor of RA with a positive anti-CCP antibody.
- HLA-DR4 and smoking are synergistic in increasing risk (more than additive).
- Disease severity may be greater when all of these factors are present.



SUMMARY

- Genetic factors contribute to the risk of developing SSc.
- HLA-related genes have a much stronger association with risk than non-HLA-related genes.
- Having multiple genes may be required to increase SSc susceptibility.
- Environmental factors contribute to SSc susceptibility.
- A complex interaction of genetics and environment are likely required for a person to develop SSc.
- For SSc and other related diseases, the concept of "personalized medicine" remains a distant hope.
