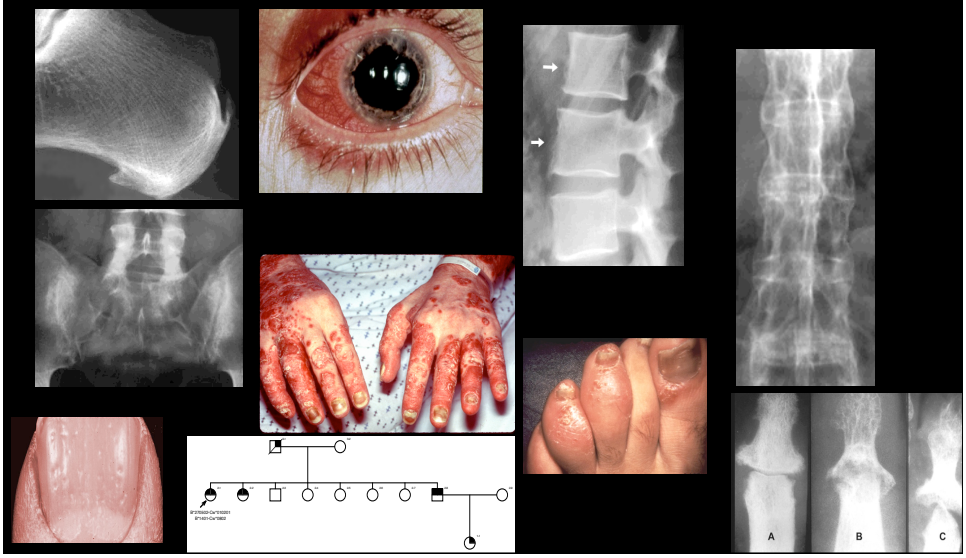
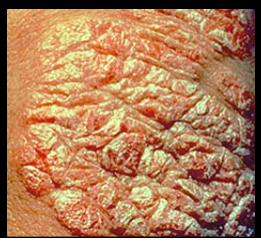
Spondyloarthritis Diseases

A group of individually distinctive diseases with common, unifying clinical, genetic and pathophysiological features



Spondyloarthritis Diseases

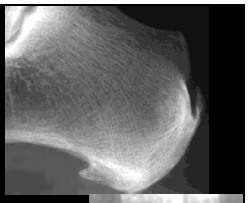
- ✔ Ankylosing spondylitis (ASp)
- ✔ Psoriatic arthritis (PsA)
- ✔ Reiter's syndrome (RS) / reactive arthritis (ReA)
- Undifferentiated spondyloarthritis (USpA)
- Enteropathic arthritis (ulcerative colitis, regional enteritis)



Psoriasis, a related condition

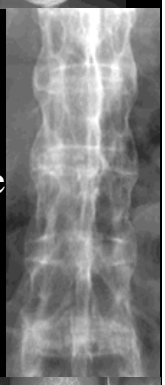
Spondyloarthritis Diseases

Unifying features



Clinical:

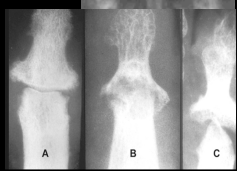
Each distinguished by three main target sites of inflammation



Enthesitis: fibrocartilage insertions of ligame tendons & fascia

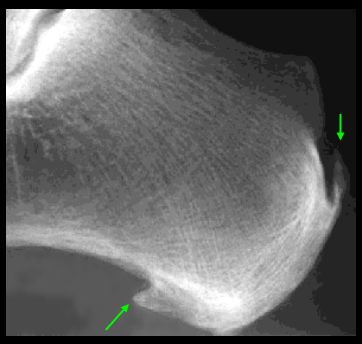
Spondyloarthritis: spine and sacroiliac joints

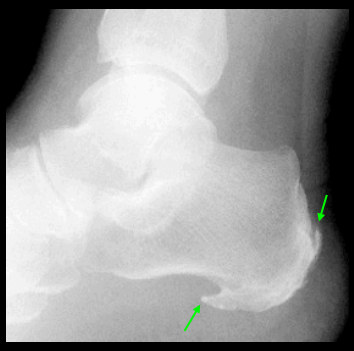
Synovitis: peripheral joints



Enthesitis (enthesopathy): the central inflammatory unit of spondyloarthritis

Classic example: Calcaneal spurs at plantar fascia and Achilles tendon (Lover's heel)

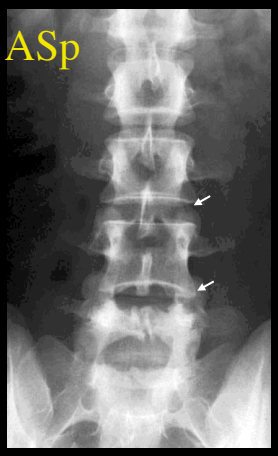




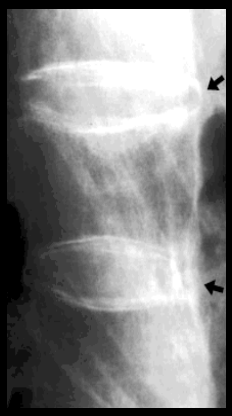
Features of inflammation:

- Infiltration of entheses by activated T cells
- Granulation tissue forms (activated macrophages and fibroblasts)
- Bone erosions and heterotopic **new bone formation**

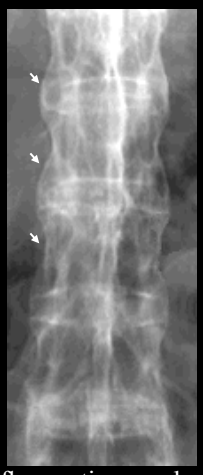
Spondylitis: syndesmophytes and ankylosis



Activated T cells invade the junction of annulus fibrosis and vertebral body, triggering granulation tissue response

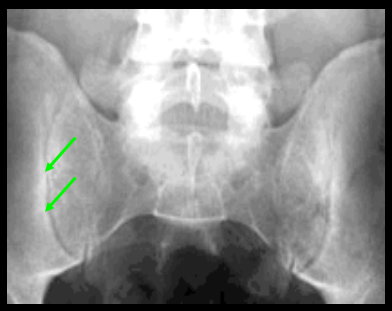


Annulus fibers eroded, then replaced by fibrocartilage:
- Subperiosteal new bone formation
- Fibrocartilage ossifies to form syndesmophytes

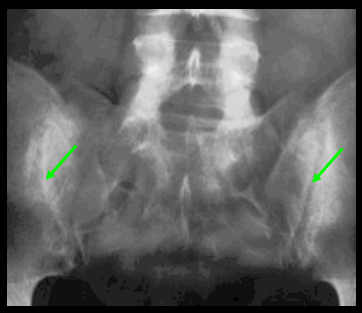


Inflammation resolves, but progressive cartilaginous and periosteal ossification forms a "bamboo spine"

Sacroiliitis



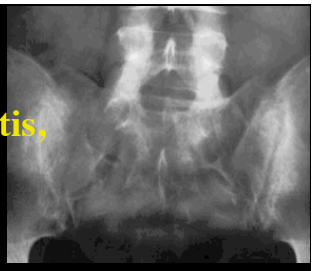
- Subchondral regions of synarthrotic SI joints invaded by Activated T cells and granulation tissue



- Erosion of cartilage on iliac side
- Bone plate blurring, joint space "widening" and reactive sclerosis
- Fibrous ankylosis replaced by bone obliterating SI joint

Resolution of inflammation by heterotopic bone formation

Inflammatory back pain



Due to the initial inflammation of **enthesitis, spondylitis** or **sacroiliitis**

- Onset before age 40
- Insidious persistent (> 3 mo) dull deep buttock or low back pain
- Poorly localized, does not follow nerve root
- Stiffness/pain upon arising in the morning, or awakens from sleep
- Improves with exercise

Spondyloarthritis Diseases

Unifying features

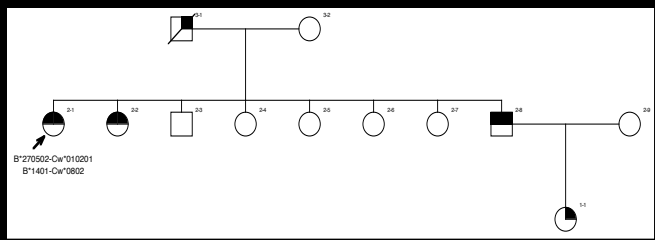
Genetics

Strong familial aggregation

50-70% FHx +

High identical twin concordance

Genetically complex pattern of inheritance

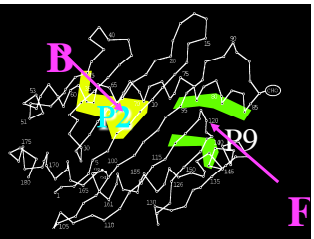


Spondyloarthritis Diseases

Unifying features

Genetics

Susceptibility associated with certain **Class I MHC alleles**



- *HLA-B27 !!*

	HLA-B27 frequency (%)
Ankylosing spondylitis	**95**
Reiter's syndrome (reactive arthritis)	60-70
Psoriatic arthritis	15-20
Ethnically matched controls	3-8

- Other class I alleles also involved

Spondyloarthritis Diseases

Unifying features

Pathophysiologic Mechanism

A clue from clinical medicine

Unlike other autoimmune diseases that regress during development of AIDS, most spondyloarthritis diseases worsen or develop *de novo* at this time

Implication:

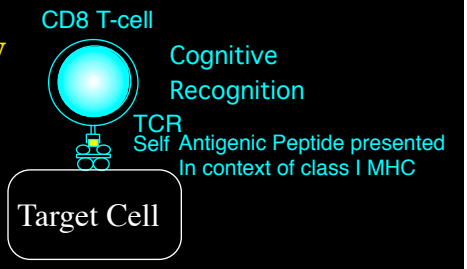
CD4 T cells not required for development of symptomatic disease

Spondyloarthritis Diseases

Unifying features

Pathophysiology

Activation of autoreactive CD8 T cells that recognize self-peptides in the context of class I MHC molecules



Autoantibodies such as ANA or RF are ***not*** present, hence they are sometimes called "seronegative arthritides"

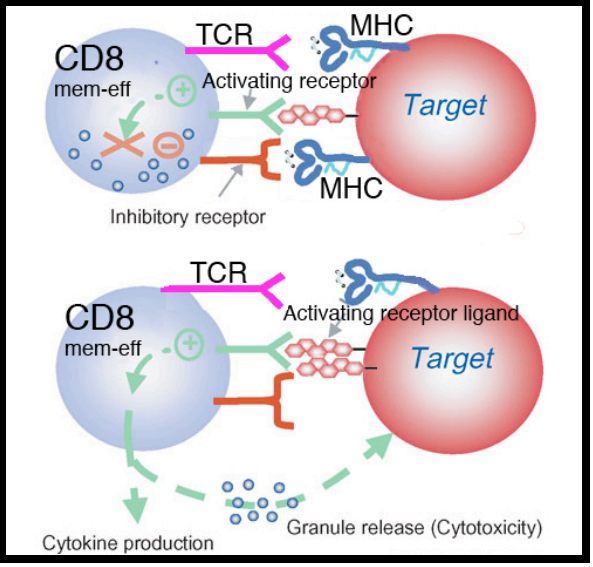
Pathogenesis incompletely understood but seems to be at the interface of triggering CD8 T cell clones of the adoptive immune system by receptors recognizing innate immune system ligands

Memory effector CD8 T cells loose CD28 and express natural killer receptors that bind Class I molecules and other ligands induced by stress and tissue injury

Triggers:

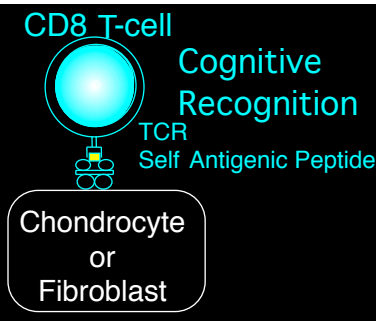
Loss of self-MHC (missing self) or increased expression of ligands reflecting tissue stress or danger

IL-15



Spondyloarthritis Disorders

CD8 T cell effector mechanisms of tissue injury



- Activated CD8 T cells injure target cell and release cytokines (γ-IFN), reprogramming gene expression of nearby cells
- CD8 T cells are CD28-negative, memory / effector cells that receive "signal 2" from NK receptor engagement by stress-induced ligands
- Macrophages activated by γ-IFN release cytokines (TNF-α)
- Fibroblasts usually have fibrogenic and osteoblastic program activated resulting in heterotopic bone formation

Spondyloarthritis Disorders

Therapy

T cell-directed

Biologics, e.g. anti CD28 (abatacept)

Calcineurin inhibitors

Cytokine inhibition

Methotrexate

TNF blockers

Anti inflammatory

NSAIDS

Physical medicine

Spondyloarthritis Diseases

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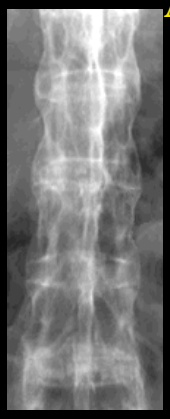
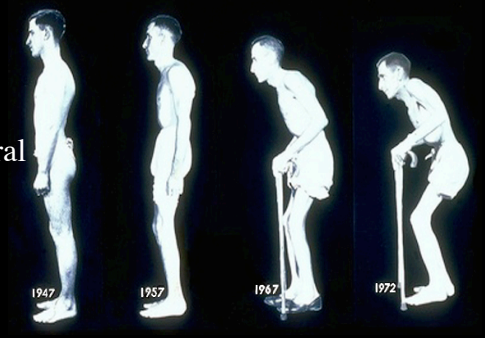


Ankylosing spondylitis

- Widespread spondylitis and sacroiliitis
- Male: female =3-10:1
- Culminates in boney ankylosis of spine
- Onset, age 10-25 with dull pain in lumbar or gluteal regions
- Hip, shoulder knee arthritis in ~30%

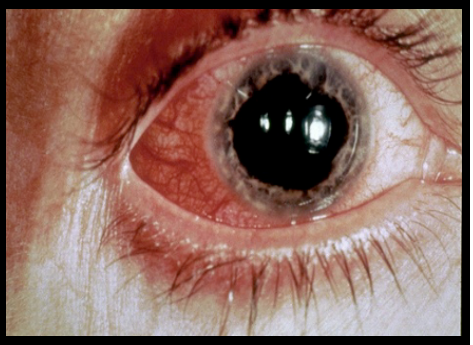
- Epidemiology: **>95% of those affected are HLA-B27**
- Disease prevalence follows circumpolar distribution of HLA-B27
- Affects 1-3% of HLA-B27 individuals,
- No evidence for triggering by microorganisms

Ankylosing spondylitis - Course



- Begins with sacroiliitis
- Inflammatory back pain and tenderness worsens and over several months to years ascends, with increasing stiffness and loss of mobility
- Postural changes: loss of lumbar lordosis, buttock atrophy and kyphosis; chest expansion compromised
- Peripheral joints, notably hips develop flexion contractures or ankylosis; compensatory knee flexion
- Peripheral arthritis (~30%) and peripheral enthesopathy (~30%) dominate the early phase of disease, then bony ankylosis predominates

Ankylosing spondylitis - systemic involvement



- Acute anterior uveitis (25%) may occur at any time; (syncheae and glaucoma)
- Apical pulmonary fibrosis, often with cavitation (<5%)
- Restrictive pulmonary disease due to costovertebral ankylosis (~ 10%)
- Granulomatous aortitis: complete heart block due to interventricular septum inflammation and /or aortic insufficiency (~5%)

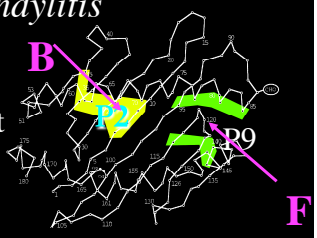
Ankylosing spondylitis- different types of *HLA-B27*

HLA-B27 alleles differ from one another in polymorphic amino acids, in ethnic distribution and, importantly, whether they determine disease susceptibility

Allele	Features	Ank.Spon
*B*2701*	Rare	Yes
*B*2702*	10% of AS in Europe and Middle East	Yes
*B*2703*	Rare West African allele	Yes
*B*2704*	Major HLA-B27 allele in China and India	Yes
→ *B*2705*	90% of AS, circumpolar Caucasians & Asians	Yes
*B*2706*	SE Asia	**No**
*B*2707*	Minor allele in SE Asia, China and India	Yes
*B*2708*	Rare, UK and Azores	Yes
*B*2709*	Sardinia	**No**

A self-peptide likely drives ankylosing spondylitis

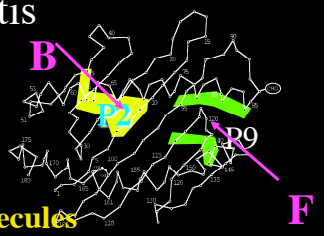
HLA-B27 alleles share the same P2 "B"pocket, but differ from one another in the "F" P9 pocket



		P9 Pocket				
Allele	59	77	80	116	114	Ank.Spon
*B*2701*	Tyr	Agn	Thr	Asp	His	Yes
*B*2702*	Tyr	Agn	Ile	Asp	His	Yes
*B*2703*	His	Asp	Thr	Asp	His	Yes
*B*2704*	Tyr	Ser	Thr	Asp	His	Yes
→ *B*2705*	Tyr	Asp	Thr	Asp	His	Yes
B*2706	Tyr	Ser	Thr	**Tyr**	**Asp**	No
*B*2707*	Tyr	Asp	Thr	Asp	His	Yes
*B*2708*	Tyr	Ser	Ile	Asp	His	Yes
B*2709	Tyr	Asp	Thr	**His**	His	No

Current theories of why HLA-B27 predisposes to Ankylosing Spondylitis

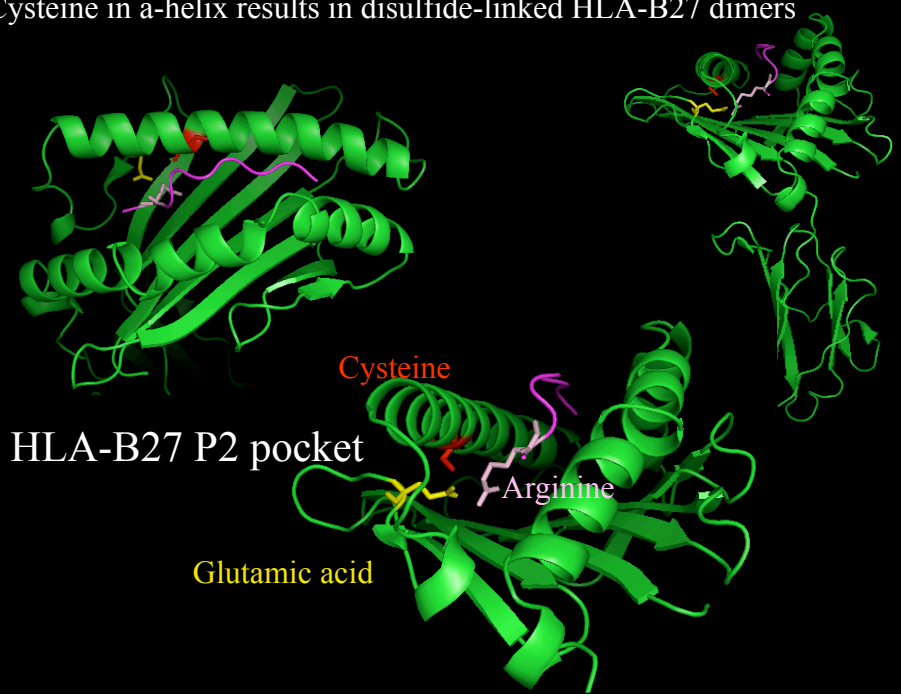
Peptide binding properties of HLA-B27



Distinctive chemical state of HLA-B27 molecules

- Transgenic rats expressing >100 copies of HLA-B27 develop a disease with some features of ankylosing spondylitis
- HLA-B27 misfolds and elicit an altered protein stress response in endoplasmic reticulum

Cysteine in a-helix results in disulfide-linked HLA-B27 dimers

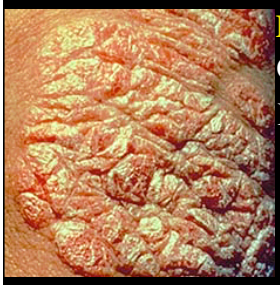


Psoriasis / Psoriatic Arthritis

Psoriasis: skin disease with retardation in kertinocyte differentiation induced by activated T cells

Perhaps keratinocyte peptides are presented by class I molecules?

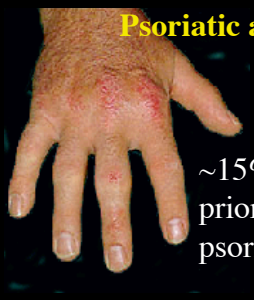
Psoriatic arthritis: spondloarthritis and psoriasis



Psoriasis
Onset age 15-30 yrs
Prevalence ~3%

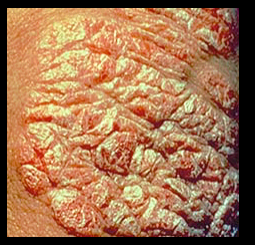
10-20%
0-20+ years between Ps & PsA

Psoriatic arthritis



~15% no prior psoriasis

Clinical Diagnostic Features of Psoriatic Arthritis



Characteristic features:

- Psoriasis present or documented
- Enthesitis
- Ankylosed joints, e.g. hallux rigidus
- Juxta-articular new bone formation
- Sacroiliitis and/or spondyloarthritis
- DIP joint arthritis
- Onychodystrophy
- Dactylitis

Exclusions:

- Fibromyalgia, RF positive rheumatoid arthritis
- Intercurrent arthritis, e.g. Lyme disease
- Repetitive motion-induced musculoskeletal syndromes

Psoriatic arthritis - features

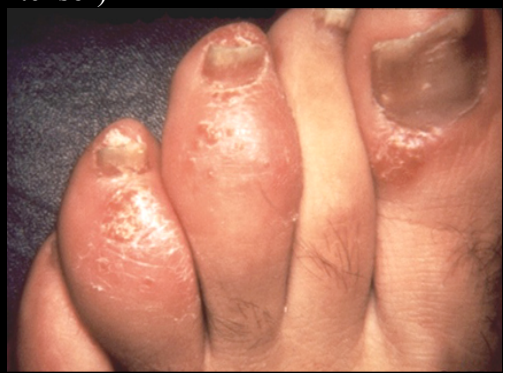
- Presentation: with obvious, subtle or no psoriasis, sometimes only isolated nail disease
- Onset typically insidious with stiffness; sometimes acute mimicking gout; can follow joint injury
- Sex: Male = female
- Early onset (<40 yrs) psoriatic arthritis has strong family history

Psoriatic arthritis

Dactylitis (Sausage digit) widespread inflammatory edema due to:

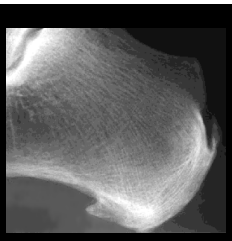
- DIP and PIP arthritis of same ray
- Enthesitis
- Tenosynovitis (flexor > extensor)
- Periostitis
- Onychodystrophy

Acral dystrophic state



Psoriatic arthritis

Enthesitis



- Sometimes subtle and easy to overlook
- Nonspecific foot pain, "tennis elbow" in the non dominant hand, or isolated posterior tibial tendinitis
- Widespread and symmetric, distribution differentiates from posttraumatic or occupational tendon injury
- Can be fulminant and combined with intense tenosynovitis

Psoriatic arthritis-peripheral joint patterns

- **Asymmetric oligoarthritis of small and medium-sized joints**

  Classic, with time more joints accumulate

- **DIP arthritis joints, also involves nails**

  Classic and unique to psoriatic arthritis, but only ~5-10%

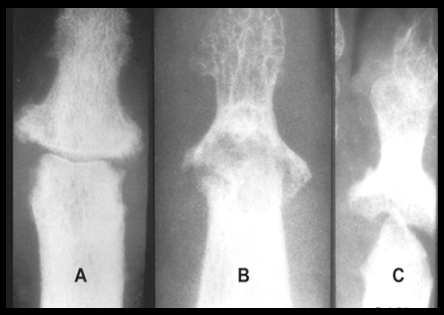
  Associated paronychia and swelling of the digital tuft may make appreciation of arthritis difficult; DDx Heberden's nodes

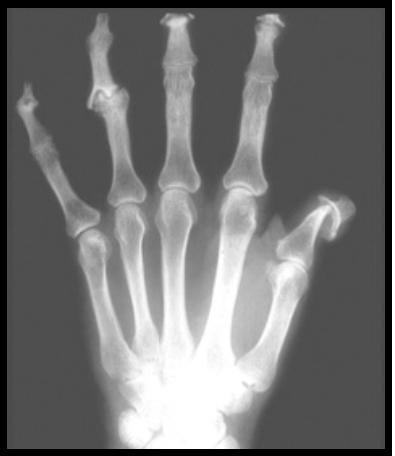
- **Arthritis mutilans**

  Osteolytic dissolution of joint with redundant overlying skin and telescoping digits (opera-glass hand)

  Typical but uncommon; males and early-onset disease

Progression of DIP arthritis





Narrowed joint space & condylar erosions

Reactive sub periosteal new bone

Pencil in cup appearance

Psoriatic arthritis-peripheral synovitis patterns

- Symmetric polyarthritis

  Most common pattern at onset, but is least specific for PsA

  Hands, wrists, ankles, and feet

  Differentiated from RA by enthesopathy and dactylitis, DIP joint involvement, relative asymmetry, new bone formation, pencil in cup deformity, absence of subcutaneous nodules, and negative RF

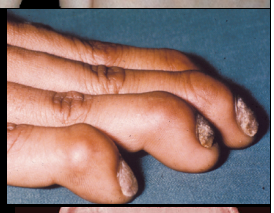
Important to distinguish RA from PsA because steroids contraindicated

Psoriatic Arthritis-Nail Involvement

~80-85% PsA, vs. 20-30% in Ps

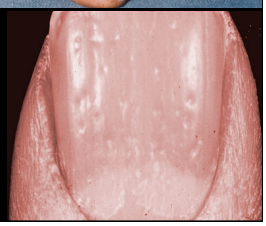
Nail matrix abnormalities

- Pitting
- Onychodystrophy, crumbling
- Transverse ridging (Beau's lines)
- Subungual hyperkeratosis
- Leukonychia
- Onycholysis
- Ectatic capillaries

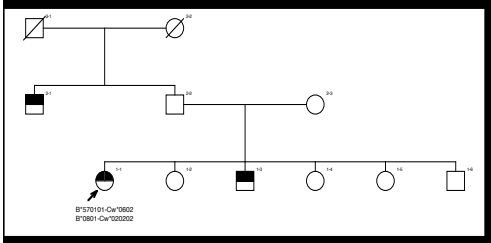


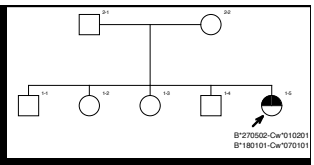
Acral dystrophy

- Nail matrix abnormalities
- Acrokeratosis
- Often seen in digit involved with DIP arthritis

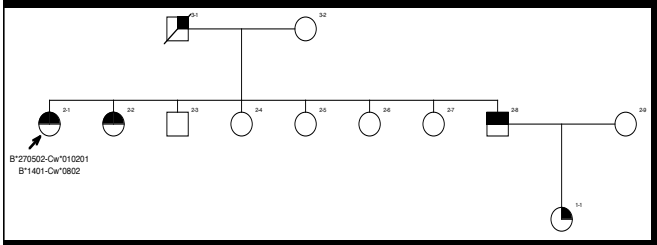


Psoriatic Arthritis Genetics





~60% strongly positive family histories, most often first degree relatives affected by psoriasis



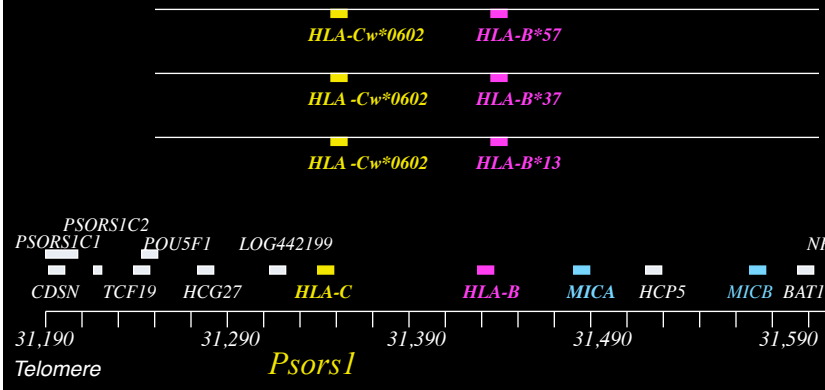
λ_R= 55 (assuming prevalence 0.1%)

Mode: mixed multifactorial pattern, partially dominant, incompletely penetrant

Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

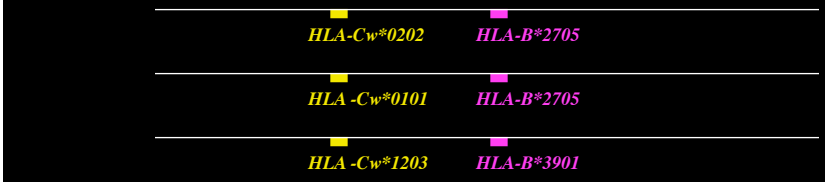
1. Psoriasis susceptibility HLAhaplotypes containing: *HLA-Cw*0602*, (*Psors 1*) Account for ~ 30% of PsA cases (and 70% psoriasis cases)



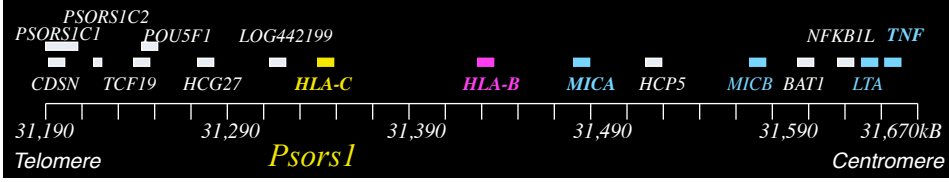
Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

2. Second group of *HLA-B* alleles, e.g. *HLA-B27* and *HLA-B39* Account for ~30% of psoriatic arthritis (not as strongly associated with psoriasis)



HLA-B39 molecules very similar to HLA-B27 in peptide binding
No common *HLA-C* alleles



Psoriatic arthritis genetics

Genetic Heterogeneity in MHC associations

Imply susceptibility governed by different interactions with genes outside MHC

e.g. genes encoding NK receptors expressed on memory-effector CD8 T cells (KIR system)

Imply different pathophysiologic mechanisms and the possibility of clinical differences

These are now being identified

Specific Spondyloarthritis Diseases

Reiter's syndrome /Reactive arthritis

Directly triggered by *specific pathogenic microorganisms* in genetically susceptible persons (*HLA-B27*)

First example of a MHC allele controlling an immune response in humans (1974 Brewerton)

Reiter's syndrome /Reactive arthritis

"On August 21, 1916 a lieutenant in the Prussian army developed abdominal pain and diarrhea. This episode last 48 hours and was followed by a latent period of 7 days at which time urethritis and conjunctivitis occurred.

"The following day he developed polyarthralgias and arthritis of the knees, ankles, elbows, wrists and several interphalangeal joints.

"Within a few days the symptoms remitted and the patient remained well for 3 weeks.

"A relapse followed with a recurrence of urethritis and uveitis"

H. Reiter (Andre Calin)

Triad of Reiter's syndrome

Reiter's syndrome-clinical features I

- Onset 7- 30 days after specific enteric or venereal infection

- Course-Initial episode completely regresses, occasionally returns as increasingly intense recrudescences becoming chronic

- Peripheral arthritis: acute, highly inflammatory asymmetric arthritis involving knees, ankles, toes, and fingers (2-4 joints)
  - All joints synchronous in abrupt fulminant onset

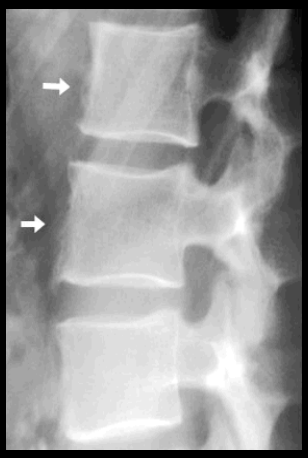
- Enthesitis - notably plantar fascia and Achilles tendon (40%)

- Dactylitis (Sausage digit) (40%)

- Sacroiliitis, stuttering spondyloarthritis

Reiter's syndrome
Spondyloarthritis

Sub periosteal new bone formation a major feature



Infiltration of T cells

Fluffy reactive new bone formation

"Square" vertebrae but minimal paravertebral ossification

Asymmetric involvement of only one or two vertebral units

Reiter's syndrome - Clinical features II

• Onychodystrophy: subungual hype and para-keratosis

• Conjunctivitis (often first manifestation). Uveitis in recurrent disease

• Non specific urethritis

• Painless circinate balanitis and mucosal ulcers, prostatitis

• Heart - 10% of chronic phase 1^{o} heart block from IV septum inflammation;
•Aortic valve insufficiency due to granulomatous aortitis at aortic ring, rarely aortic dissection

Reiter's syndrome- role of specific infection

Develops 7-30 days after enteric infection with certain Gram neg. rods

- *Salmonella typhimurium*, and occasionally *S. paratyphi* or *S. heidelbergii*
- *Shigella flexneri* 2a and 2b, but not *S. sonnei*
- *Yersinea enterocoliticas*
- *Campylobacter jejuni* or *C. fetus*

These organisms typically invade and kill intestinal M cells, perhaps arthritogenic peptides cross-presented in class I MHC

Develops 7-30 days after venereal infection with

- *Chlamydia trachomatis* or *C. psittaci*

Obligate intracellular eubacteria

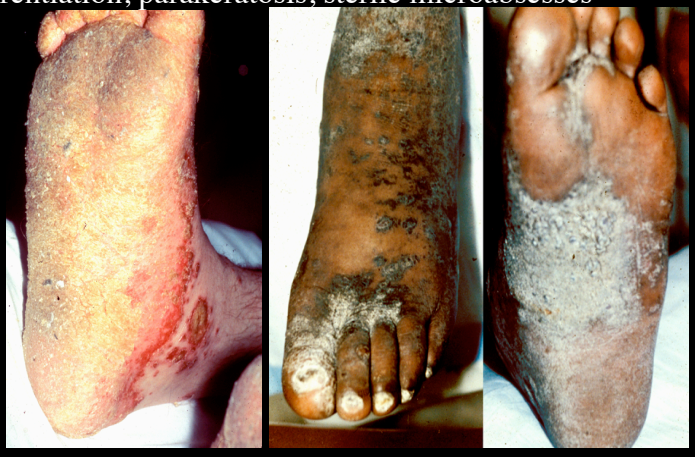
Psoriasis / Reiter's syndrome in the setting of AIDS

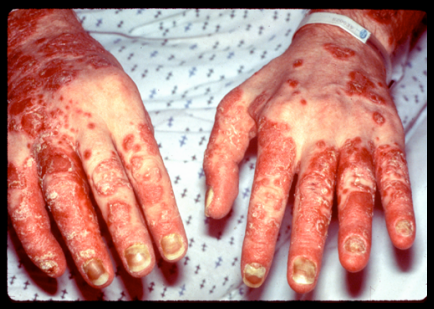
Provided major clue pointing to importance of CD8 T cells in pathogenesis

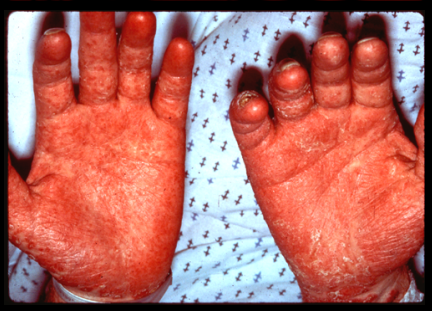
Major source of disability in otherwise relatively well HIV+ patients in developing countries where HIV therapy is inadequate

Psoriasis / Reiter's syndrome in the setting of AIDS

- Keratodermia blenorrhagicum- pustular psoriasis-like lesions of palms and soles
- Psoriasis - like lesions (T cell infiltration, keratinocytes HLA-DR $^{+}$ with delayed differentiation, parakeratosis, sterile microabsesses







Progression to psoriasis pattern of skin disease in AIDS