Collaborative Association Study of Psoriasis

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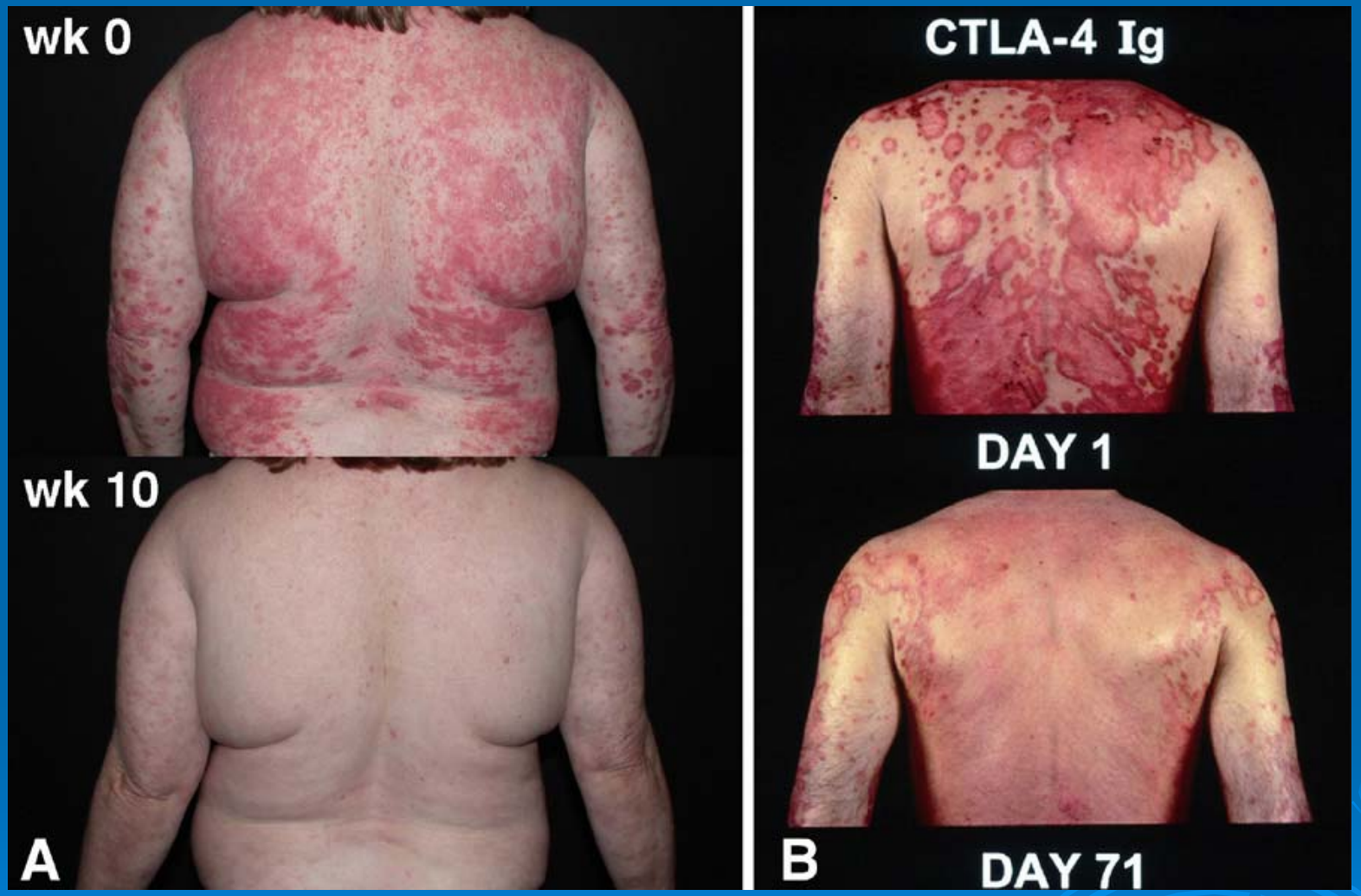
Psoriasis

- Chronic, inflammatory skin condition
  - Characteristic lesions, can affect substantial proportion of body surface
- Prevalence of 1-2% (U.S.), 0-3% (worldwide)
  - Peak age of onset ≈ 25 yrs old
- Inflammatory arthritis in 10-25% of patients
- Sex ratio ≈ 1
- Environmental “trigger factors”
  - Infections (esp. streptococcal pharyngitis)
  - Skin trauma (Koebner phenomenon)
  - Emotional stress
  - Medications (beta-blockers, lithium)



Cyclosporine A

CTLA4 Ig

Original Plan

- Case Control Association Study
  - 1000 cases / 1000 controls (GAIN, first phase)
  - 1000 cases / 1000 controls, follow-up
- Cases and controls drawn from 3 collections:
  - Anne Bowcock / Alan Menter (Wash U / Texas)
  - James Elder (Michigan)
  - Gerald Krueger (Utah)
- Objective
  - Identify genetic susceptibility factors, including modifiers of PSORS1
- Appears likely we'll examine more samples in initial scan

Case / Control Definitions

- Cases collected from Dermatology clinics
  - >90% participation rate in Utah, Michigan and Texas clinics
  - More severe disease spectrum
  - 11% of body surface area affected, on average
- Controls collected to match geographic and ethnic origin of cases
  - Free of psoriasis (Michigan, Texas)
  - To represent Utah Population (Mark Leppert, Utah)
- Initial round of genotyping will focus on individuals that are “White, not of Hispanic origin”

Information Provided to GAIN

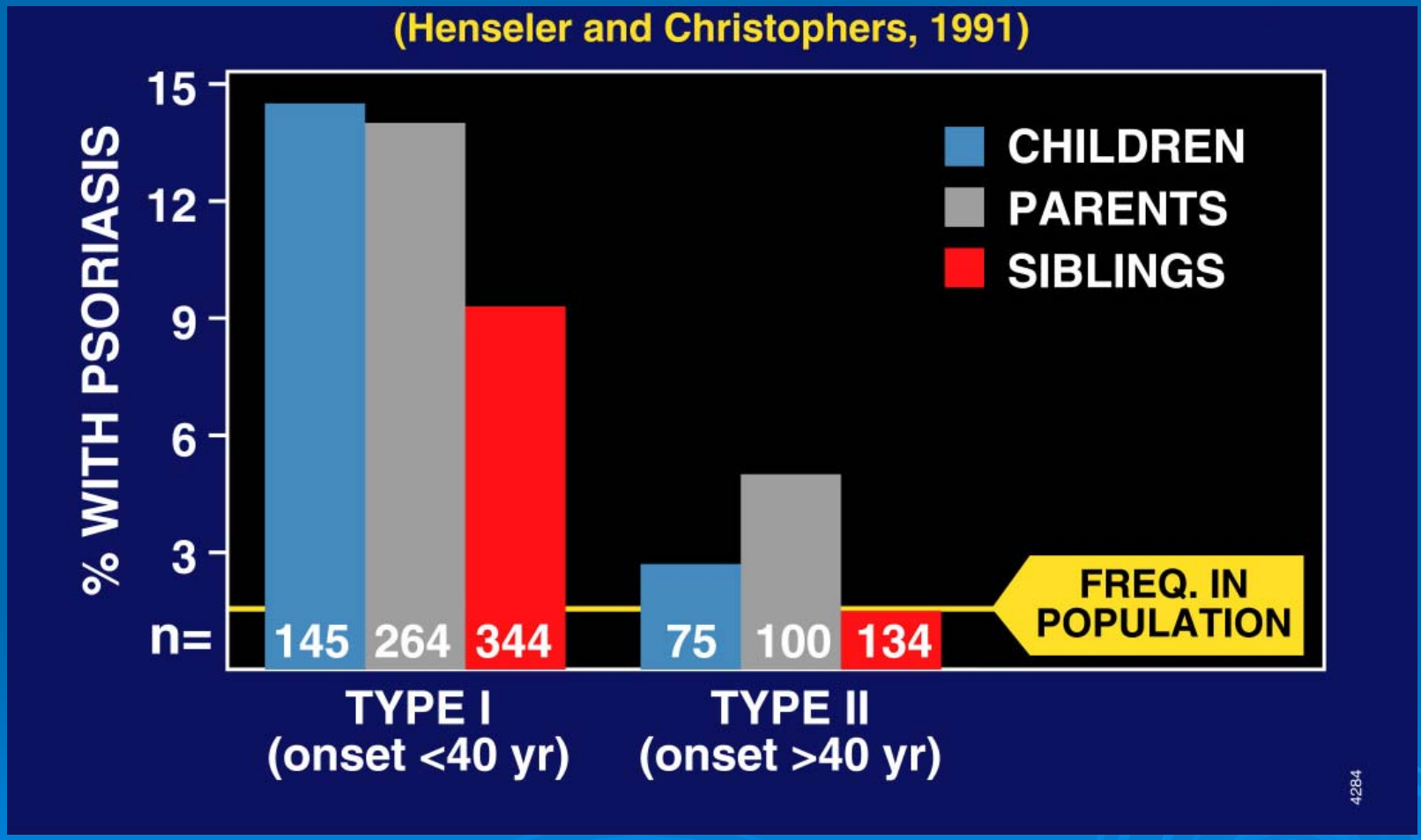
- Age of Onset
- Presence of affected first degree relative

- Body surface area affected (%)
- Sites of involvement
  - Head, upper limbs, lower limbs, trunk, nails

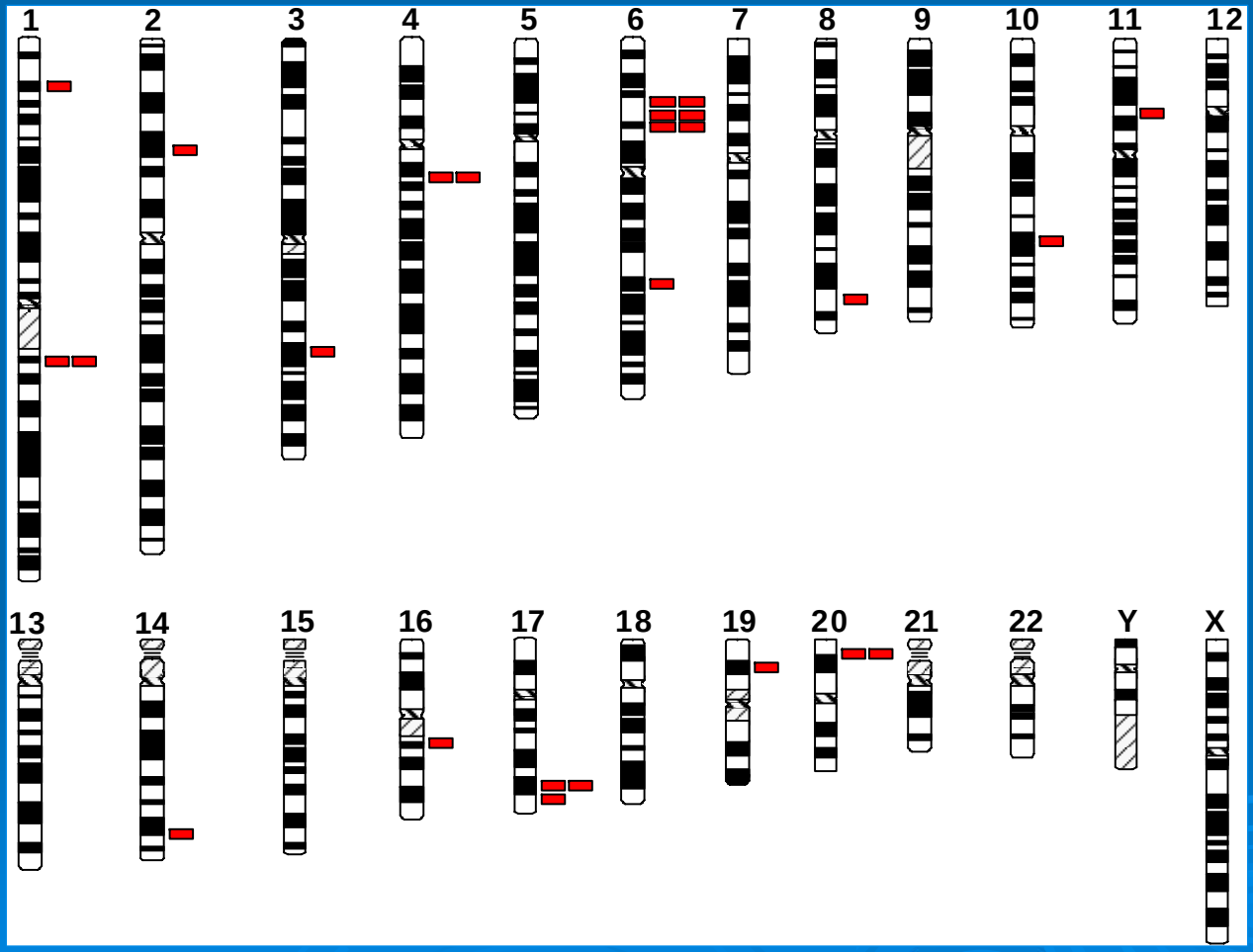
- Psoriatic arthritis status
- Disease severity rating (scaling, induration, erythema)

- Crohn's disease / autoimmune disorder status

Familial Clustering of Psoriasis



Summary of Linkage Studies



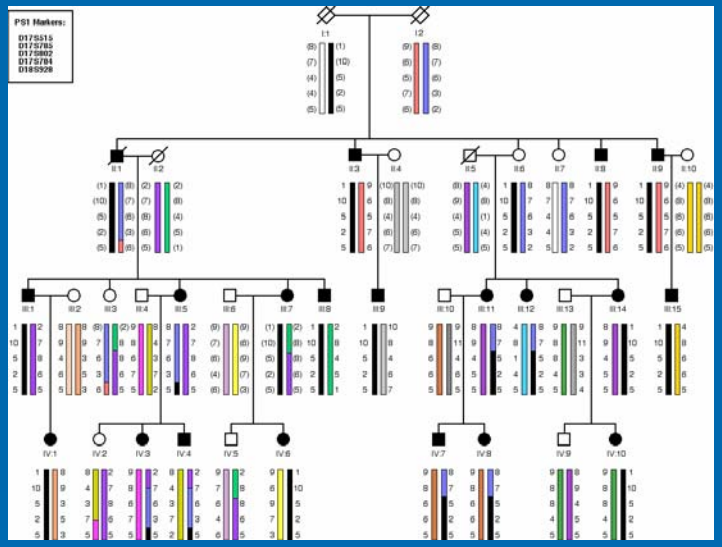
MHC Association

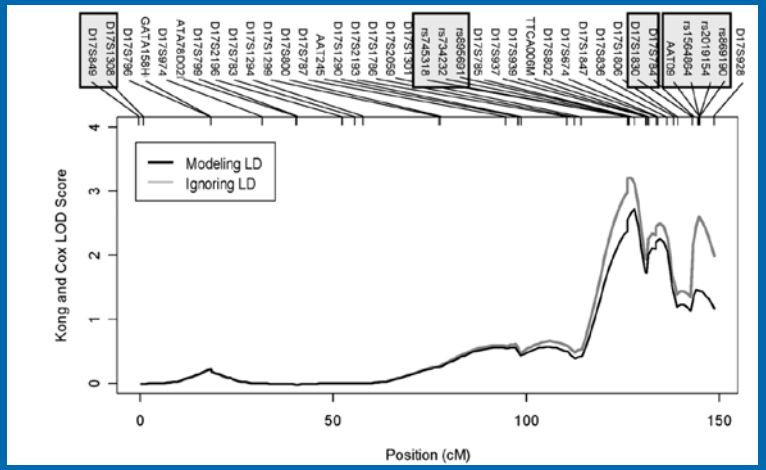
Major 36-Marker Haplotype Clusters: Consensus Alleles and Family-Based Tests of Association with Psoriasis

Category and Cluster[a]	Frequency[b]	Alleles at: D6S273	M6S2	TNFB	M6S5	MICA	M6S6	HLA-B	M6S1	M6S1	HLA-C	M6S7	M6S5	M6S8	M6S8	M6S2	M6S2	M6S7	M6S7	M6S4	M6S4	M6S1	M6S6	M6S9	M6S9	M6S7	M6S8	M6S8	M6S6	M6S6	M6S5	M6S3	T:NT (%T)[c]	P[d]
Risk:																																		
44	.0881	6	13	2	12	5	9	57	15	3	6	13	3	2	3	6	1	3	1	1	8	2	4	3	1	7	2	2	2	4	*20*	1	2	4	6	13	8	5	138:38 (78.4)	1.6×10^{-14}
47	.0615	3	6	7	7	3	5	13	16	3	6	*15*	3	2	3	6	1	3	1	1	9	2	4	3	1	1	2	2	2	4	*16*	1	2	7	9	9	3	*3*	84:37 (69.4)	2.3×10^{-5}
43	.0204	6	*6*	9	9	3	10	37	*15*	3	6	*13*	3	2	3	6	1	3	1	1	8	2	4	3	1	7	2	2	2	4	*26*	1	2	4	6	13	8	5	28:12 (70.0)	.017
41	.0141	2	6	*5*	3	4	6	*50*	16	3	6	9	3	2	3	6	1	3	1	1	9	3	4	3	1	3	2	2	2	4	8	2	1	4	3	*5*	3	9	20:8 (71.4)	.036
Nonrisk:																																								
37	.0926	*6*	6	11	6	3	*5*	7	9	3	7	1	7	...	*5*	1	3	3	1	1	4	4	6	3	2	2	2	2	2	4	23	2	2	*5*	3	*5*	3	*5*	66:104 (38.8)	.0044
49	.0904	*8*	4	2	16	3	12	8	7	3	7	15	3	*5*	3	6	1	3	1	1	10	2	4	3	6	5	2	1	2	4	1	1	2	7	3	6	3	*16*	69:80 (46.3)	.41
11	.0256	*5*	10	6	3	3	15	44	*4*	2	*5*	10	3	*13*	7	3	3	1	1	1	2	4	*5*	4	8	5	14	*13*	4	1	...	1	2	4	3	6	1	...	18:35 (34.0)	.027
60	.0252	*6*	*10*	2	*10*	2	*1*	*62*	14	2	3	*15*	3	8	6	6	*5*	2	2	4	2	1	6	3	8	4	2	2	2	4	11	2	1	6	3	6	4	*11*	20:33 (37.7)	.098
7	.0219	*5*	10	10	17	*5*	3	38	14	3	12	2	3	12	7	2	3	1	2	6	9	*5*	*5*	3	8	6	*21*	8	4	16	*8*	1	2	6	3	6	*8*	...	24:25 (49.0)	1.00
68	.0204	4	*5*	7	7	4	*5*	44	3	2	*16*	*15*	3	9	6	6	*5*	2	2	4	2	1	*5*	3	6	4	2	1	2	3	20	2	1	6	4	3	3	*5*	21:27 (43.8)	.47
51	.0189	4	6	2	3	4	3	65	*5*	2	8	*13*	3	2	3	6	1	3	1	1	9	2	4	3	8	4	3	10	4	16	...	1	2	6	4	6	2	*21*	26:13 (65.0)	.053
22	.0167	*5*	6	*5*	12	*5*	13	35	*19*	2	4	10	3	1	3	6	*5*	2	2	2	2	4	4	3	6	2	15	8	4	1	*19*	1	1	6	3	6	1	*10*	11:18 (37.9)	.27
57	.0148	3	*5*	4	16	3	13	60	12	2	3	15	3	*7*	6	6	*5*	2	2	4	2	1	6	3	8	4	2	3	2	4	11	2	1	6	*3*	8	4	*9*	6:19 (24.0)	.015
29	.0133	4	*5*	7	7	4	*5*	44	11	2	4	8	8	1	3	6	*5*	2	1	1	4	4	6	4	6	6	7	8	4	16	*18*	1	2	*5*	3	6	3	*15*	10:15 (40.0)	.42
5	.0104	*5*	9	10	10	1	12	*18*	14	3	12	2	3	*13*	7	2	3	1	2	*5*	9	*5*	*5*	3	9	6	18	9	4	14	*10*	1	2	6	3	*8*	3	*11*	8:10 (44.4)	.82

- Strongest genetic influence on psoriasis is in the MHC
  - First HLA association described in 1972 (Russell et al)
- Systematic comparisons, evaluation and resequencing of MHC haplotypes suggest HLA-Cw6 is responsible
  - In Caucasians, haplotypes without Cw6 but with risk alleles at other nearby genes (e.g. CDSN) do not show association

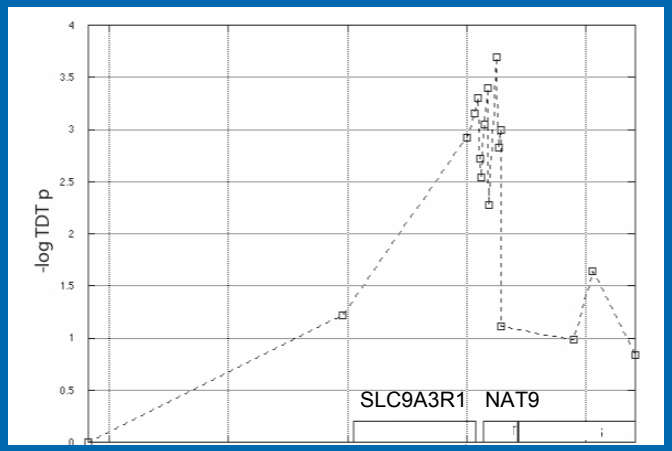
PSOR2 (17q25)





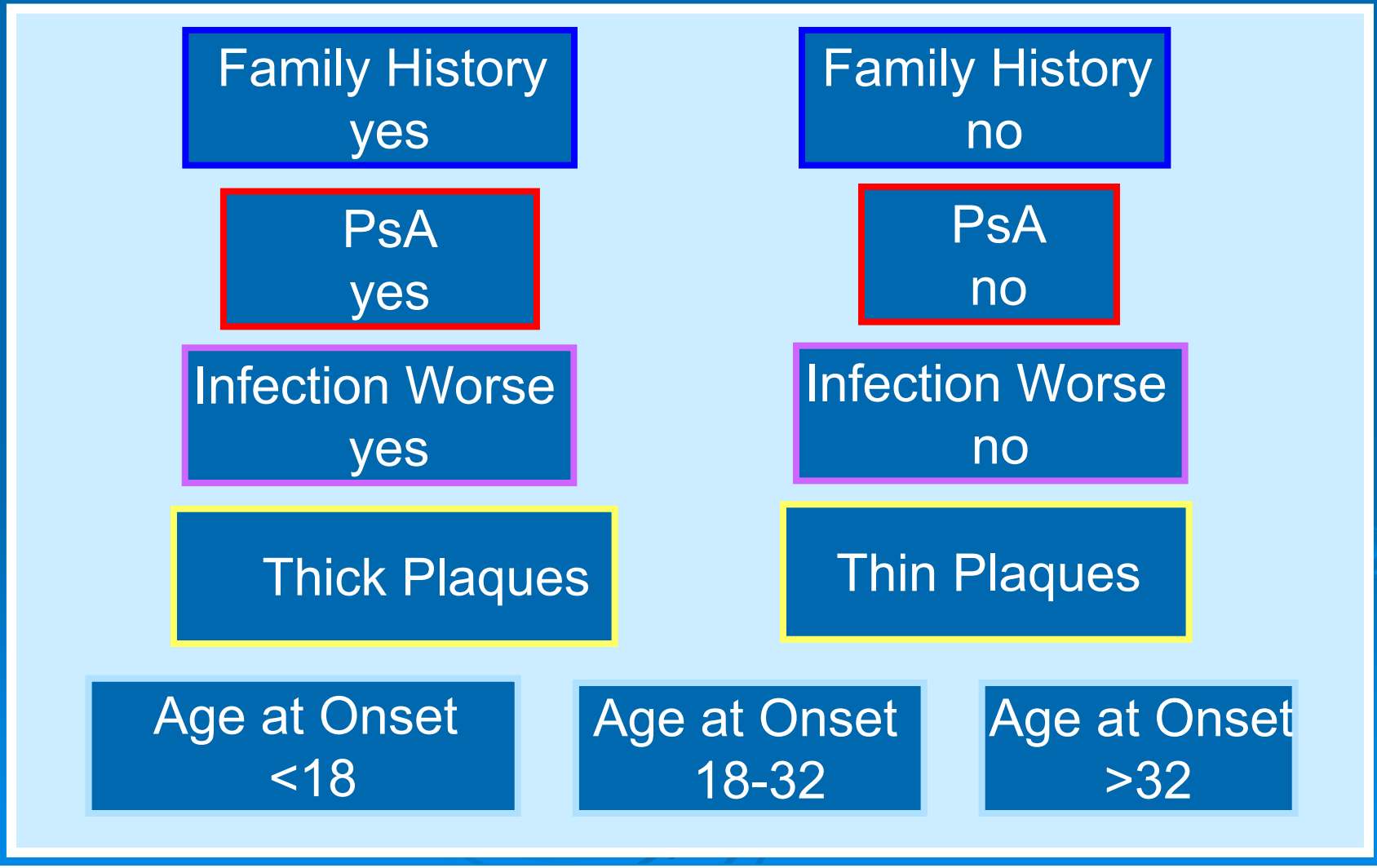
- First mapped susceptibility locus (Tohmforde et al, 1994)
  - 8 large pedigrees; segregates in Mendelian fashion
- Linkage widely replicated
  - Plot shows LOD score curve for 278 families (2518 individuals)

Association Mapping within 17q25



- RUNX1 binding site, between SLC9A3R1 and NAT9 associated with psoriasis (Helms et al. 2003)
  - Association does not always replicate
- Given strength of linkage peak, other susceptibility alleles likely exist in the region

Utah Psoriasis Initiative Pooled Genotype Study



Utah Psoriasis Initiative

SNP	Chr	Mb	P-value	Trait	Gene
rs1265053	6	31.19	$1.8*10^{-14}$	Psoriasis Age of Onset	C6orf15
rs713031	6	31.43	$5.5*10^{-9}$	Family History	HLA-C
rs2271233	17	6.64	$3.9*10^{-7}$	Psoriasis Age of Onset	TEKT1
rs15574	6	31.79	$5.5*10^{-7}$	Percent BSA at Worst	LY6G6E
rs9905086	17	3.16	$2.7*10^{-6}$	Infection Worsens	
rs2857693	6	31.70	$2.8*10^{-6}$	Percent BSA at Worst	
rs1003645	17	31.36	$8.6*10^{-6}$	Psoriatic Arhtritis	CCL23
rs437179	6	32.04	$1.9*10^{-5}$	Percent BSA at Worst	SKIV2L
rs388685	19	49.11	$2.0*10^{-5}$	Psoriasis Age of Onset	ZNF45
rs981684	17	36.19	$5.5*10^{-5}$	Family History	KRT25C
rs11944159	4	38.70	$5.5*10^{-5}$	Psoriasis Age of Onset	LOC92689
rs1475563	1	62.29	$6.3*10^{-5}$	Family History	
rs2853941	6	31.36	$6.9*10^{-5}$	Family History	HLA-C
rs2523733	6	30.24	$7.4*10^{-5}$	Psoriatic Arhtritis	TRIM26
rs1800629	6	31.65	$8.8*10^{-5}$	Family History	
rs2844749	6	30.42	$1.2*10^{-4}$	Psoriatic Arhtritis	RPP21
rs707936	6	31.84	$1.5*10^{-4}$	Percent BSA at Worst	C6orf27
rs2121133	19	8.93	$1.7*10^{-4}$	Family History	
rs9267532	6	31.75	$1.9*10^{-4}$	Percent BSA at Worst	LY6G5B
rs9911226	17	3.16	$1.9*10^{-4}$	Infection Worsens	OR3A2
rs2074890	17	15.50	$2.1*10^{-4}$	Infection Worsens	
rs3744108	17	53.94	$2.5*10^{-4}$	Psoriasis Age of Onset	MTMR4
rs707936	6	31.84	$2.5*10^{-4}$	Infection Worsens	C6orf27
rs11655759	17	76.82	$2.6*10^{-4}$	Family History	FLJ44861
rs9386620	6	107.61	$2.7*10^{-4}$	Psoriatic Arhtritis	C6orf210
rs2318789	17	46.71	$2.8*10^{-4}$	Percent BSA at Worst	CGI-48
rs713031	6	31.43	$2.8*10^{-4}$	Family History	HLA-C
rs2782641	1	43.68	$2.9*10^{-4}$	Thick Plaques	
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Additional Phenotype Information

- Evaluation of gene expression for ~50,000 transcripts
  - Affymetrix U133 Plus 2.0 Arrays
- Skin biopsies
  - 40 control biopsies (buttock)
  - 40 biopsies of unaffected skin from cases (buttock)
  - 40 biopsies of affected skin from cases (plaque)
- Early assessment of the impact of any associated variants we identify
  - Comparison of control and unaffected skin biopsies particularly interesting

Overall Analysis Plan

- Primary interest is to identify risk alleles for psoriasis
  - Compare genotypes in cases and controls
- Things on our mind:
  - Correlating genes with subphenotypes
    - Can we predict disease manifestations based on genes?
  - Allowing for known MHC effect
    - Can we increase power to map secondary or interacting alleles?
  - Ensuring matching of cases and controls
    - Can we expand our control pool? Would it help?
  - Evaluating the effects of unobserved alleles
    - Can we use HapMap information effectively to do this?
  - Incorporating family information into analysis
    - Can we increase power by using phenotypes of relatives?

Restrictions on Data Use

- Data can be used to study psoriasis and other genetic diseases

- Proviso:
  - Original consent (Washington U - St. Louis) states that data will be used to study psoriasis and other auto-immune diseases

  - IRB has approved use of de-identified samples (such as provided to GAIN) to study other diseases

Credits

- University of Utah
  - Gerald Krueger
  - Kristina Callis
  - David Goldgar
- University of Michigan
  - JT Elder
  - Rajan Nair
  - Phil Stuart
  - Johann Gudjonsson
  - John Voorhees
- Washington University
  - Anne Bowcock
  - Alan Menter
  - Justin Paschall
  - Cindy Helms
  - Gonçalo Abecasis
  - Jun Ding