HISTORY, GENES AND AUTOIMMUNITY
WE CHANGE THE SCENERY, THE SCRIPT STAYS THE SAME

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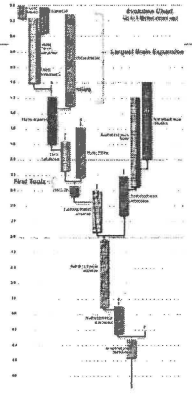
I. HISTORY

- The Epic of Gilgamesh depicts the adventures of the historical King Gilgamesh of Uruk in Babylonia. It dates to about 2700 BC and was originally written on 12 clay tablets in the cuneiform script of ancient Sumeria.
- Gilgamesh's ancestor Ut-napishtim (who with his wife had been the only survivor of a great flood similar in many ways to the biblical account in Genesis) told him of a plant that gave eternal life. After obtaining the plant, however, Gilgamesh left it unguarded and a serpent carried it off.



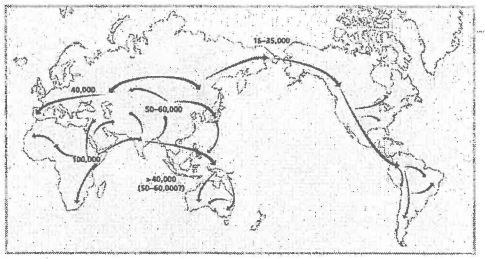
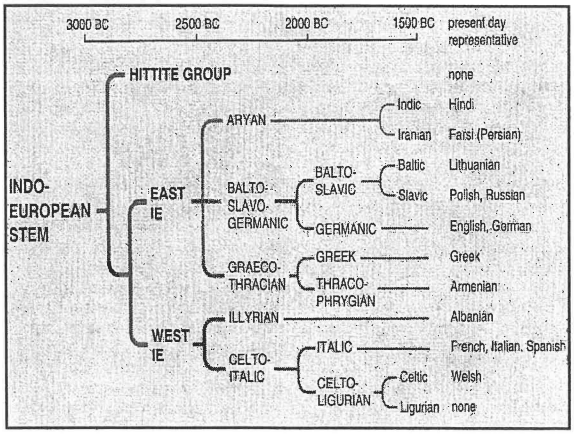
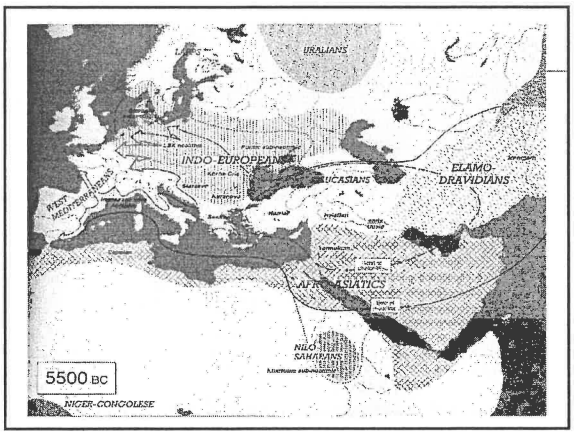


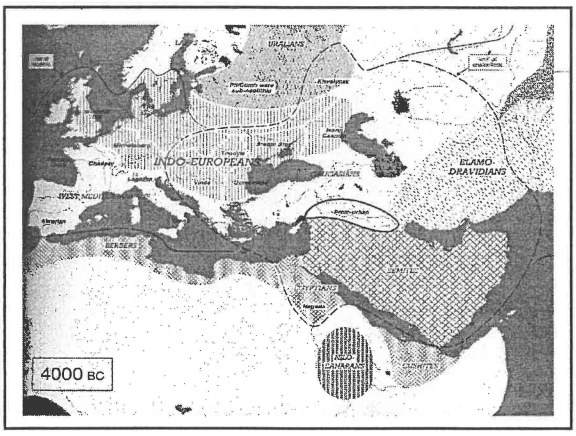
FIGURE 3. THE MIGRATION OF MODERN *HOMO SAPIENS*.
THE SCHEME OUTLINED ABOVE BEGINS WITH A RADIATION FROM EAST AFRICA TO THE REST OF AFRICA ABOUT 100 KYA AND IS FOLLOWED BY AN EXPANSION FROM THE SAME AREA TO ASIA, PROBABLY BY TWO ROUTES, SOUTHERN AND NORTHERN BETWEEN 60 AND 40 KYA. OCEANIA, EUROPE AND AMERICA WERE SETTLED FROM ASIA IN THAT ORDER.

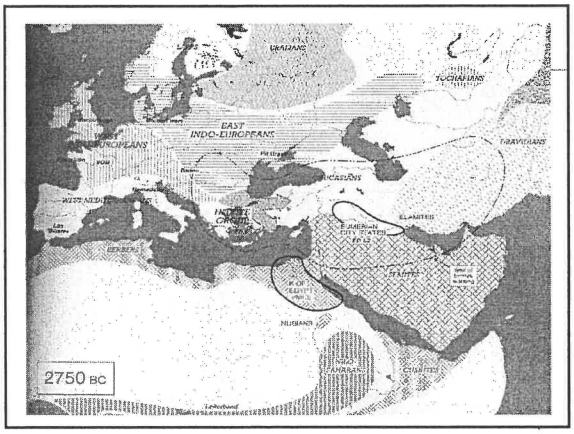
The LORD came down to see the city and the tower that the men had built. Then the LORD said: "if now, while they are one people, all speaking the same language, they have started to do this, nothing will stop them later from whatever they presume to do. Let us go down and there confuse their language, so that one will not understand what the other says". Thus the LORD scattered them from there all over the earth, and they stopped building the city. That is why it was called Babel..."

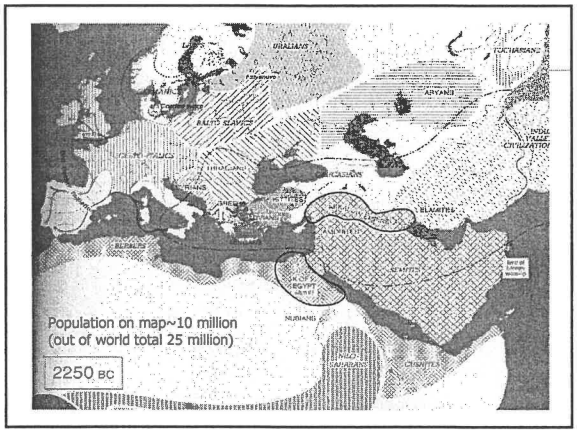
Genesis 11: 5-9

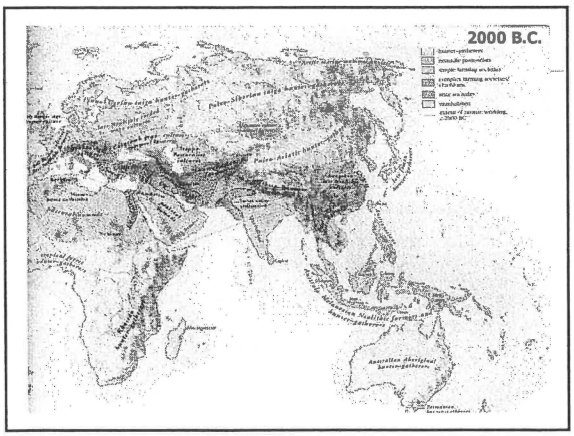


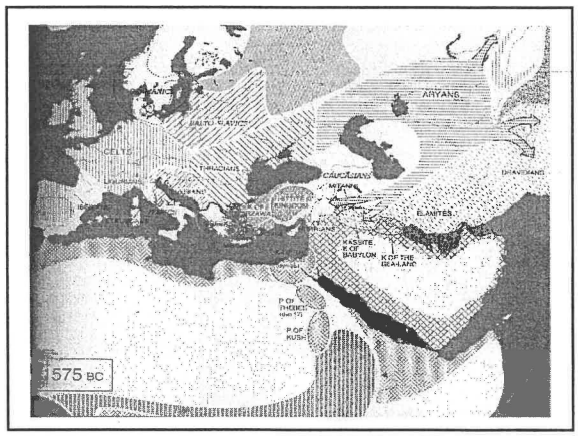

URALIANS
INDO-EUROPEANS
CAUCASIANS
ELAMO-DRAVIDIANS
AFRO-ASIATICS
NILO-SAHARANS
5500 BC
NIGER-CONGOLESE

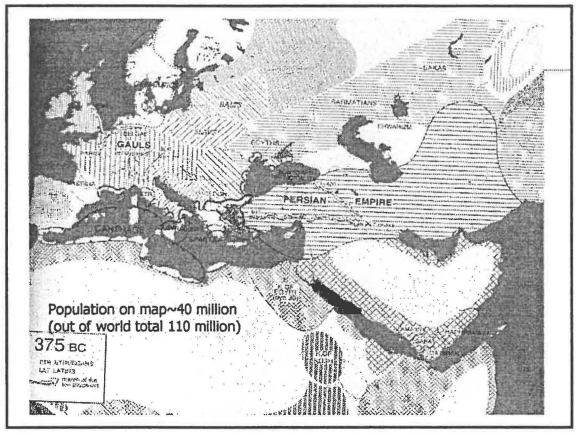

URALIANS
INDO-EUROPEANS
CAUCASIANS
ELAMO-DRAVIDIANS
BERBERS
CHADIANS
NILO-SAHARANS
4000 BC

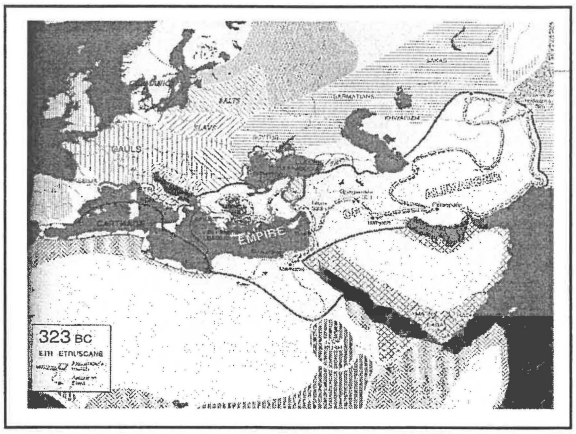

URALIANS
EAST INDO-EUROPEANS
DRAVIDIANS
CAUCASIANS
ELAMITES
NUBIANS
2750 BC

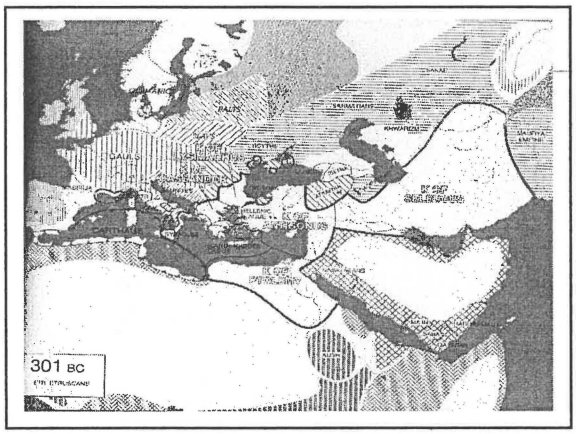

URALIANS
ARYANS
CAUCASIANS
ELAMITES
NUBIANS
Population on map~10 million
(out of world total 25 million)
2250 BC

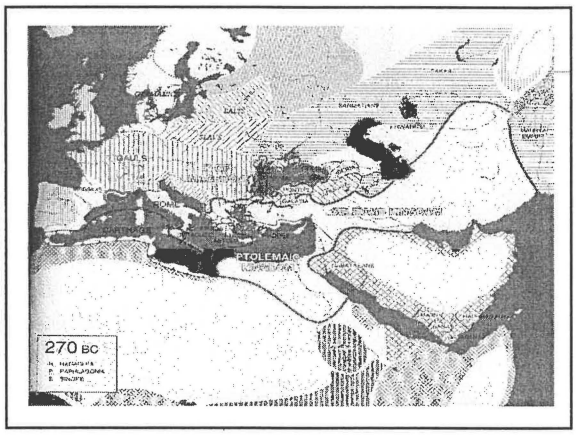

2000 B.C.

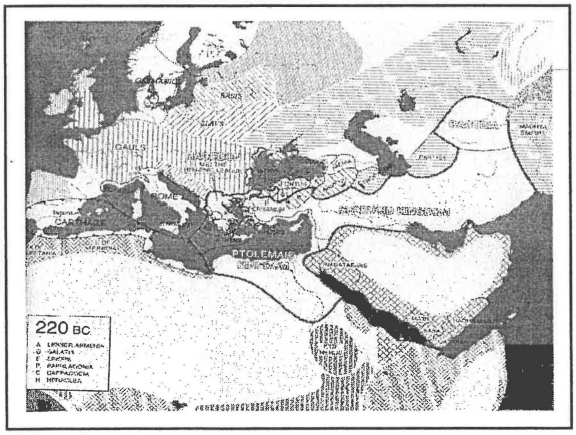

ARYANS
CAUCASIANS
ELAMITES
575 BC

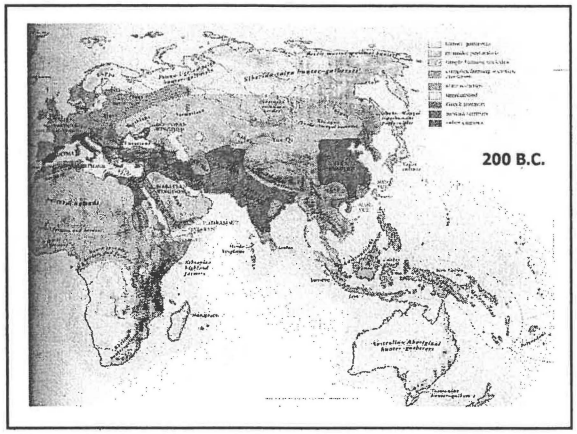

GAULS
PERSIAN EMPIRE
Population on map~40 million
(out of world total 110 million)
375 BC

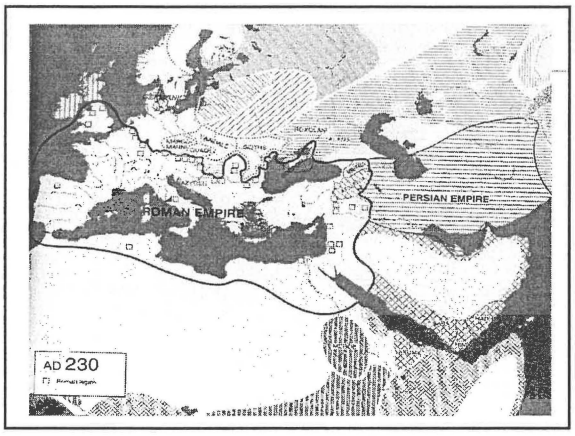

GAULS
EMPIRE
323 BC

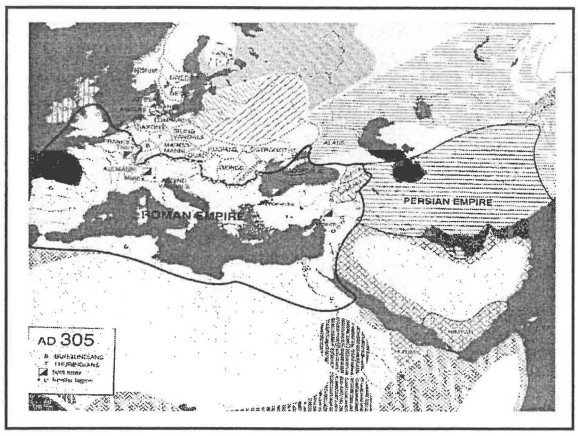

301 BC

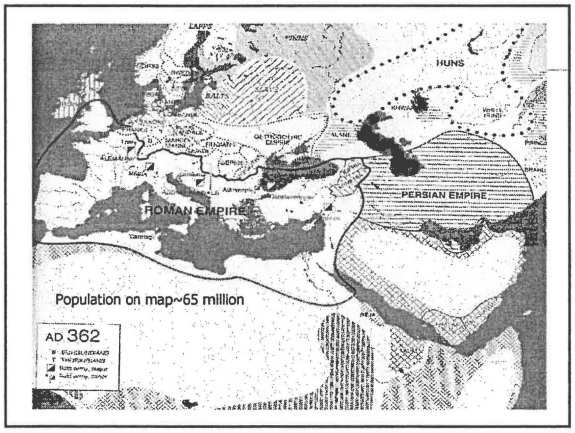

PTOLEMAIC
270 BC

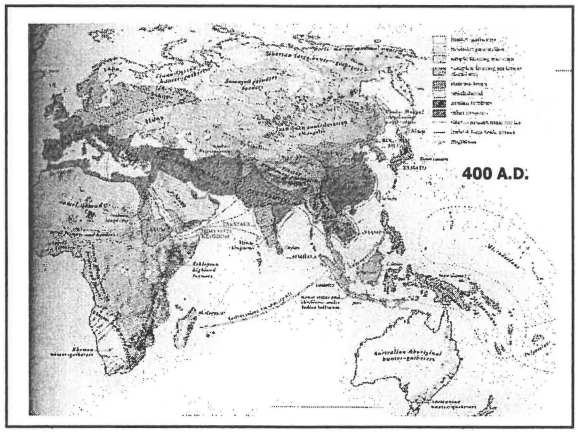

GAULS
PTOLEMAIC
220 BC

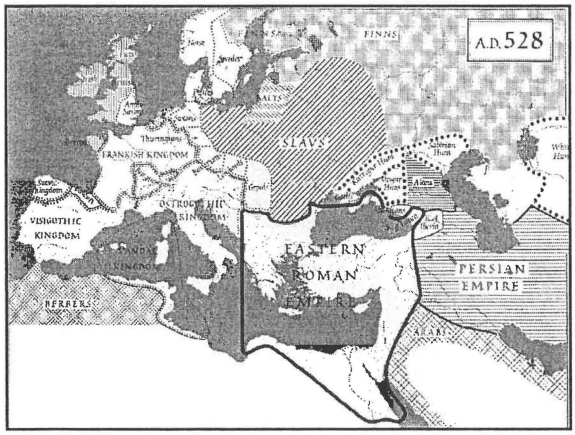

200 B.C.

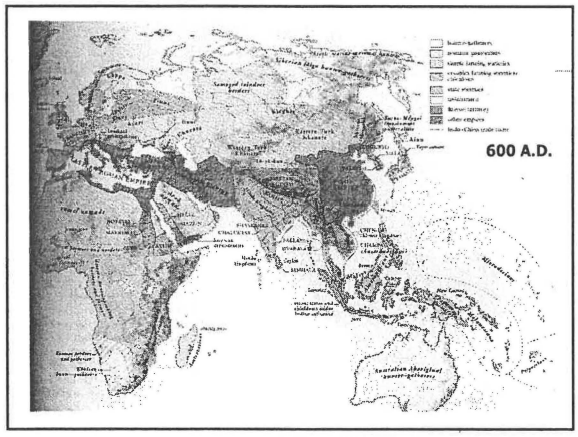

ROMAN EMPIRE
PERSIAN EMPIRE
AD 230

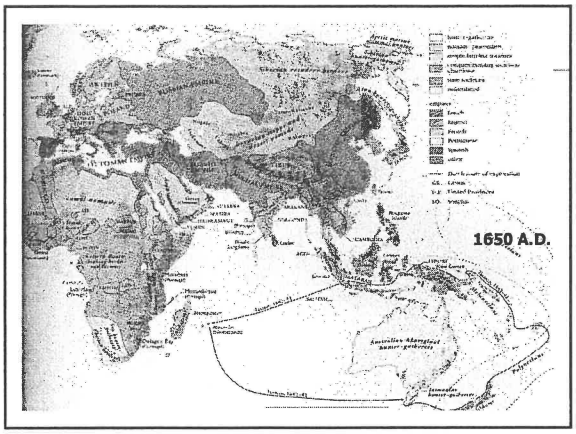

ROMAN EMPIRE
PERSIAN EMPIRE
AD 305

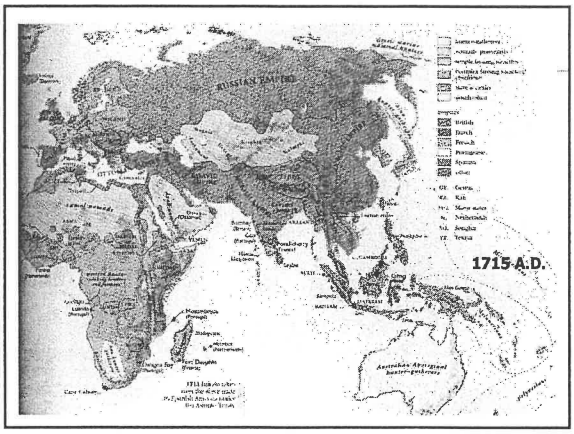

HUNS
ROMAN EMPIRE
PERSIAN EMPIRE
Population on map~65 million
AD 362


400 A.D.


A.D. 528
FINNS
SLAVS
FRANKISH KINGDOM
VISIGOTHIC KINGDOM
BERBERS
EASTERN ROMAN EMPIRE
PERSIAN EMPIRE


600 A.D.

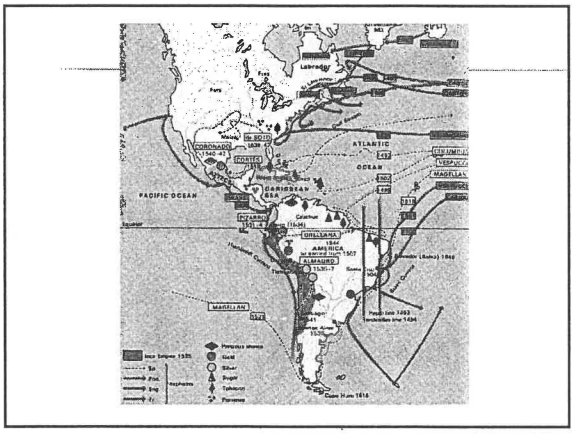


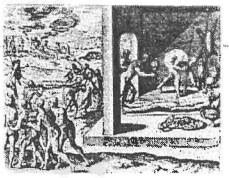


The Peopling of America

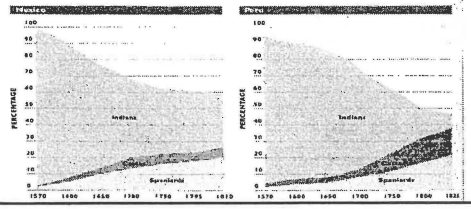
Current DNA studies support two, and possible three genetically distinct groups that settled the Americas:

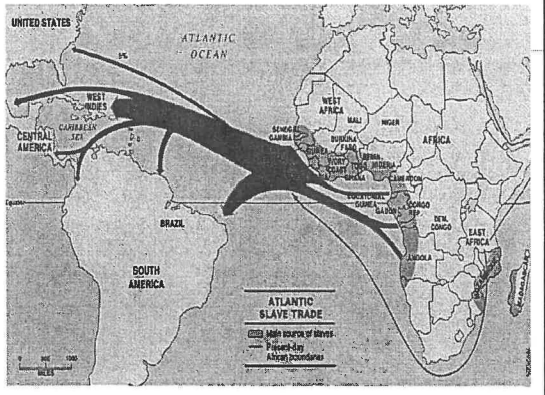
1. the first, occurring up to 30,000 years ago (the Amerinds) comprised the groups in South and Central America and Eastern North America
2. The second, occurring later, comprised the Pacific Northwest and Southwest tribes (Pima, Navajo)-the NaDenes.
3. A third group comprised the Eskimos



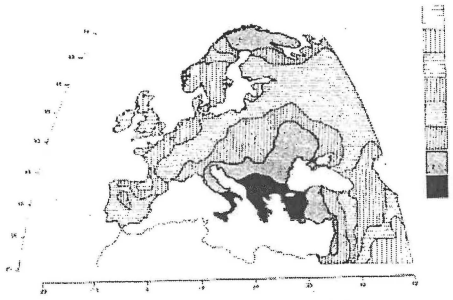


Changes in the Ethnic Composition of Latin American Populations

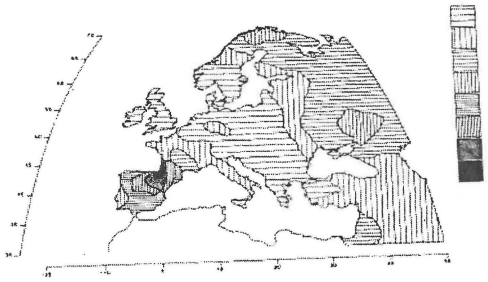




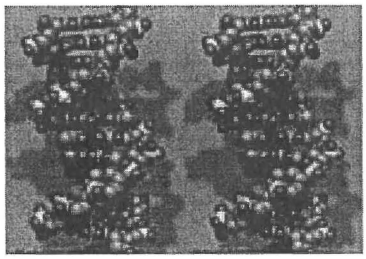
PRINCIPAL COMPONENT 4: REFLECTING THE GREEK COLONIZATION OF EUROPE



PRINCIPAL COMPONENT 5:REFLECTING THE INFLUENCE OF THE BASQUES-I.E. MESOLITHIC MAN



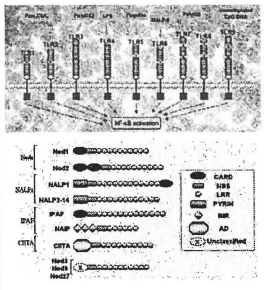
II. GENES



DIFFERENCES BETWEEN ADAPTIVE AND INNATE IMMUNITY

	Innate	Adaptive
Action time	Early (hours)	Late (days)
Cell types	Macrophages, dendritic cells, neutrophils	B, T lymphocytes
Receptors	Fixed in genome (i.e. toll receptors)	Gene rearrangement necessary (i.e. B cell receptor, T cell receptor)
Recognition	Conserved molecular pattern (i.e.LPS)	Wide variety of molecular structures (i.e. proteins, peptides-over 1 x 10^{18})
Evolution	Evolutionarily conserved (plants, animals)	Only vertebrates

COMPONENTS OF THE INNATE IMMUNE SYSTEM



- Toll receptors
- NOD proteins
- Complement system
- Phagocytosis
- Cytoplasmic viral receptors
- Antimicrobial peptides
- Apoptosis

THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

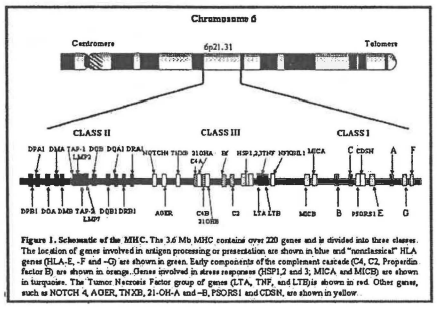


Figure 1. Schematic of the MHC. The 3.6 Mb MHC contains over 220 genes and is divided into three classes. The location of genes involved in antigen processing or presentation are shown in blue and "nonclassical" HLA genes (HLA-E, -F and -G) are shown in green. Early components of the complement cascade (C4, C2, Properdin factor B) are shown in orange. Genes involved in stress responses (HSP1,2 and 3; MICA and MICB) are shown in turquoise. The Tumor Necrosis Factor group of genes (LTA, TNF, and LTB)is shown in red. Other genes, such as NOTCH 4, AGER, TNXB, 21-OH-A and -B, PSORS1 and CDSN, are shown in yellow.

WHAT WAS ONCE AN ADVANTAGE MAY NO LONGER BE SO

Group	HLA-haplotype	Advantage	Disadvantage
Caucasians (Celts)	*B*08, C4A*Q0, DRB1*0301, DQB1*0201*	?protection against infection	autoimmunity
Caucasians (Germanics)	*B*07, DRB1*1501, DQB1*0602*	?protection against infection	SLE, Multiple sclerosis, narcolepsy
Caucasians	*B*2705, DRB1*0101, DQB1*0501*	Protection against viral infections (HIV, influenza)	Ankylosing spondylitis
Africans	*B*53, DRB1*1304*	Protection against severe malaria	?
East Asians	*DRB1*0405, DQB1*0401*	?protection against infection	autoimmunity

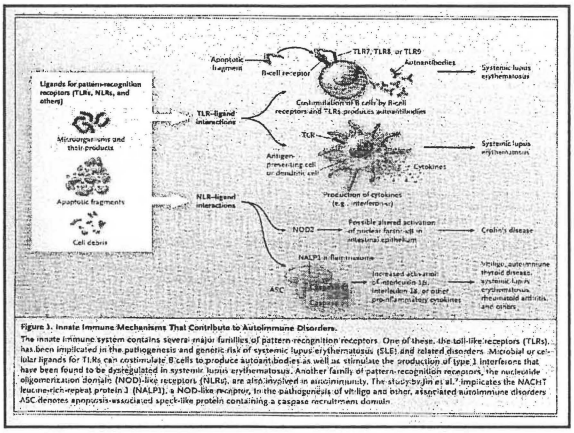


Figure 1. Innate Immune Mechanisms That Contribute to Autoimmune Disorders.

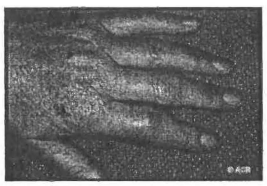
The innate immune system contains several major families of pattern-recognition receptors. One of these, the toll-like receptors (TLRs), has been implicated in the pathogenesis and genetic risk of systemic lupus erythematosus (SLE) and related disorders. Microbial or cellular ligands for TLRs can costimulate B cells to produce autoantibodies as well as stimulate the production of type 1 interferons that have been found to be dysregulated in systemic lupus erythematosus. Another family of pattern-recognition receptors, the nucleotide oligomerization domain (NOD)–like receptors (NLRs), are also involved in autoimmunity. The study by Jin et al.[9] implicates the NACHT leucine-rich-repeat protein 1 (NALP1), a NOD-like receptor, in the pathogenesis of vitiligo and other, associated autoimmune disorders. ASC denotes apoptosis-associated speck-like protein containing a caspase recruitment domain.

III. CLINICAL PRACTICE

ASSOCIATIONS OF MHC ALLELES AND AUTOIMMUNE DISEASE

Subspecialty	Disease	MHC Association
Rheumatology	Rheumatoid Arthritis	*DRB1*04, *01, *1001*
	Systemic lupus erythematosus	*DRB1*0301,*1501, C4A*Q0*
	Scleroderma	*DRB1*11, DRB1*1502*
	Ankylosing spondylitis	*B*27*
Pulmonary	Narcolepsy	*DQB1*0602*
Endocrinology	Type I Diabetes Mellitus	*DQB1*0201, DQB1*0302*
	Autoimmune thyroid Disease	*DRB1*0301, DQB1*0201*
Gastroenterology	Celiac Disease	*DQB1*02, DQB1*0302*
Neurology	Multiple Sclerosis	*DRB1*1501, DQB1*0602*
	Myasthenia Gravis	*B*08, DRB1*0301*
Dermatology	Dermatitis herpetiformis	*DRB1*0301, DQB1*0201*

RHEUMATOID ARTHRITIS



*HLA-DRB1*04* AND RA AROUND THE WORLD

	DR4 subtype	Linked DQB1 allele	Associated with RA?
Northern European Caucasians	**0401, *0404*	**0301, *0302*	Yes
Eastern European Caucasians	**0402*	**0302*	No
Spanish, Basques	**0405*	**0302*	Yes
North Africans	**0404*	**0202*	Yes
East Asians	**0405*	**0401*	Yes
East Asians	**0406*	**0302*	No
Native Americans (Hispanics)	**0407, *0411*	**0302*	No

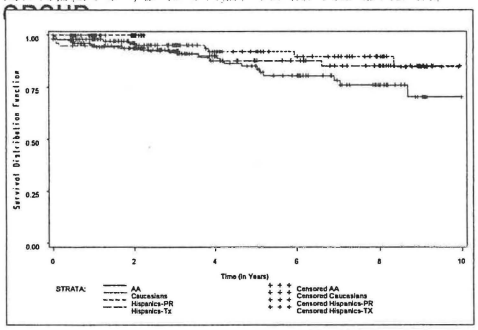
ETHNIC DIFFERENCES IN SLE-ASSOCIATED AUTOANTIBODIES: THE LUMINA COHORT

Autoantibody	Hispanic (n=205)		African-American (n=208)	Caucasian (n=163)	P Value
	Texas N=110	Puerto Rico N=95			
ANA	100	95	99	99	0.020
Anti-dsDNA nephritis	71	51	60	38	<0.0001
Anti-Sm	8	13	25	9	<0.0001
Anti-RNP Raynaud's, myositis	32	25	50	30	<0.0001
aPL-thrombosis	19	2	17	18	0.0014

CLINICAL MANIFESTATIONS OF SLE IN THE PROFILE STUDY BY ETHNIC GROUP

Criterion	Hispanic (N=109)	Afr American (N=339)	Caucasian (N=467)	P Value
Malar rash	64%	45%	67%	<0.0001
Discoid rash	6%	33%	12%	<0.0001
Photosensitivity	59%	46%	72%	<0.0001
Renal involvement	59%	54%	23%	<0.0001
Serositis	64%	60%	42%	<0.0001
Cytopenias	85%	82%	62%	<0.0001
Immunologic	83%	79%	65%	0.0003

10-YEAR SURVIVAL IN LUMINA PATIENTS AS A FUNCTION OF ETHNIC GROUP



MHC GENES IMPLICATED IN PREDISPOSITION TO SLE

- HLA-DRB1
  - + *HLA-DRB1*0301* in Caucasians
  - + *HLA-DRB1*1501/*1503* implicated in Africans, Chinese, Japanese and some Caucasian cohorts
  - + HLA-DRB1*08 in Hispanics, secondary association in Caucacasians
- HLA-DQA1, DQB1
  - + Associated primarily with autoantibody subsets of SLE
- C4 null alleles (*C4A*Q0, C4BQ*0*)

NON-MHC GENES ASSOCIATED WITH SLE

- FcγRIIa, IIIa
- PTPN22
  - + R620W polymorphism-not seen in Asians and Afr. Americans
- FCRL3
- CR2
- B lymphoid tyrosine kinase (*BLK*) and *C8orf13*
  - Hom et al. N Engl J Med. 2008 Feb 28;358(9):900-9.
- BANK1
- STAT4
- IRF5-seen in all ethnic groups
- CD11b-
  - identified in 3,818 individuals of European descent and replicated in two independent samples of individuals of African descent

IMPACT OF GENETICS AND DISEASE

- Susceptibility
- Profiling severity and outcome
- Identification of new targets for drug discovery
- Pharmacogenomic profiling to predict response to therapy