Disease Genes of Population: Example of Finland

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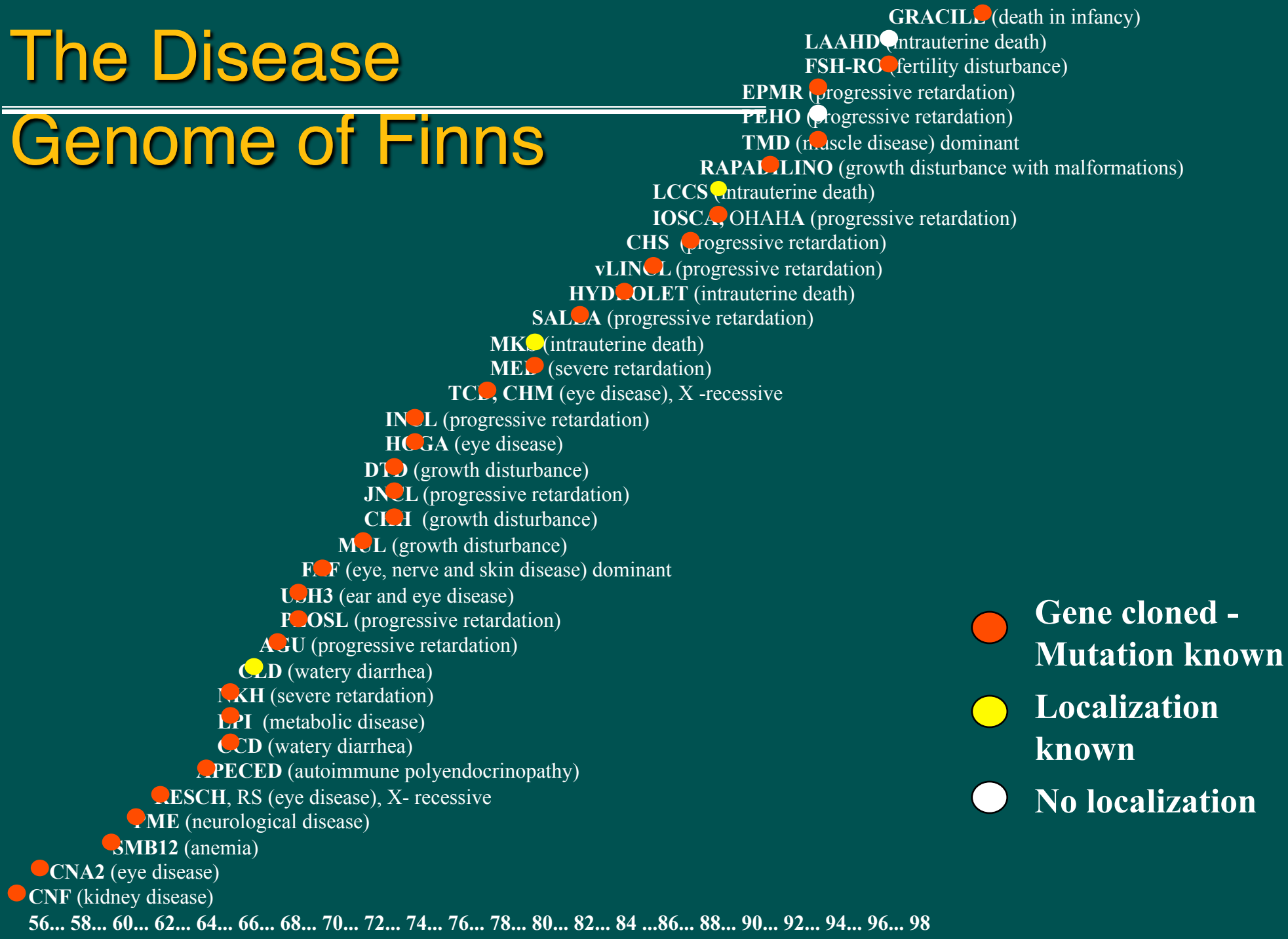
Finland - The Promised Land of Disease Genetics

- Founder Effect
- Genetic Drift
- Isolation
- Regional Expansion

- Enrichment of Rare Diseases
- Fin-Major mutation
- Lack of CF, PKU
- Population records since 1634
- Epidemiological registers

- Inbred training of clinicians
- Favorable attitudes by public
- Traditions in public health interventions

The Disease Genome of Finns



Finnish Disease Database

1980: 60 patients born annually, regional differences

Clinical Picture highly variable

Severe or Progressive Mental Retardation:

- ✓ INCL, vLINCL, JNCL, AGU, SALLA,

Intrauterine Death or Death in Infancy

- ✓ GRACILE, LCCS, HYDROLET, MECKEL, Cong.nefrosis

Problems Later in Life

Dementia (PLO-SL), Autoimmune disease (APECED)

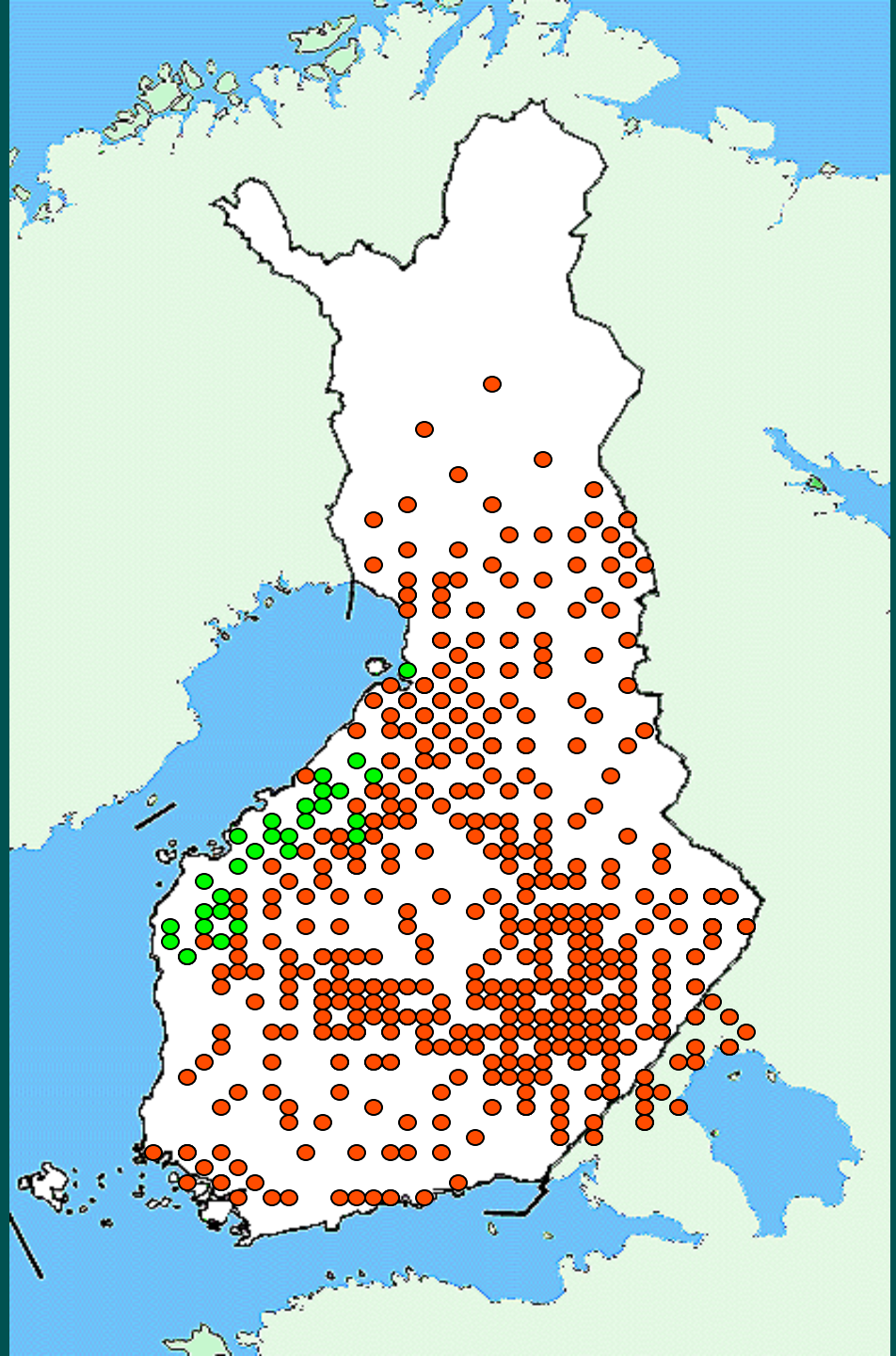
Eye or ear disease, Fertility disturbance

Growth disturbance, Metabolic disease

Muscle disease, Watery diarrhea

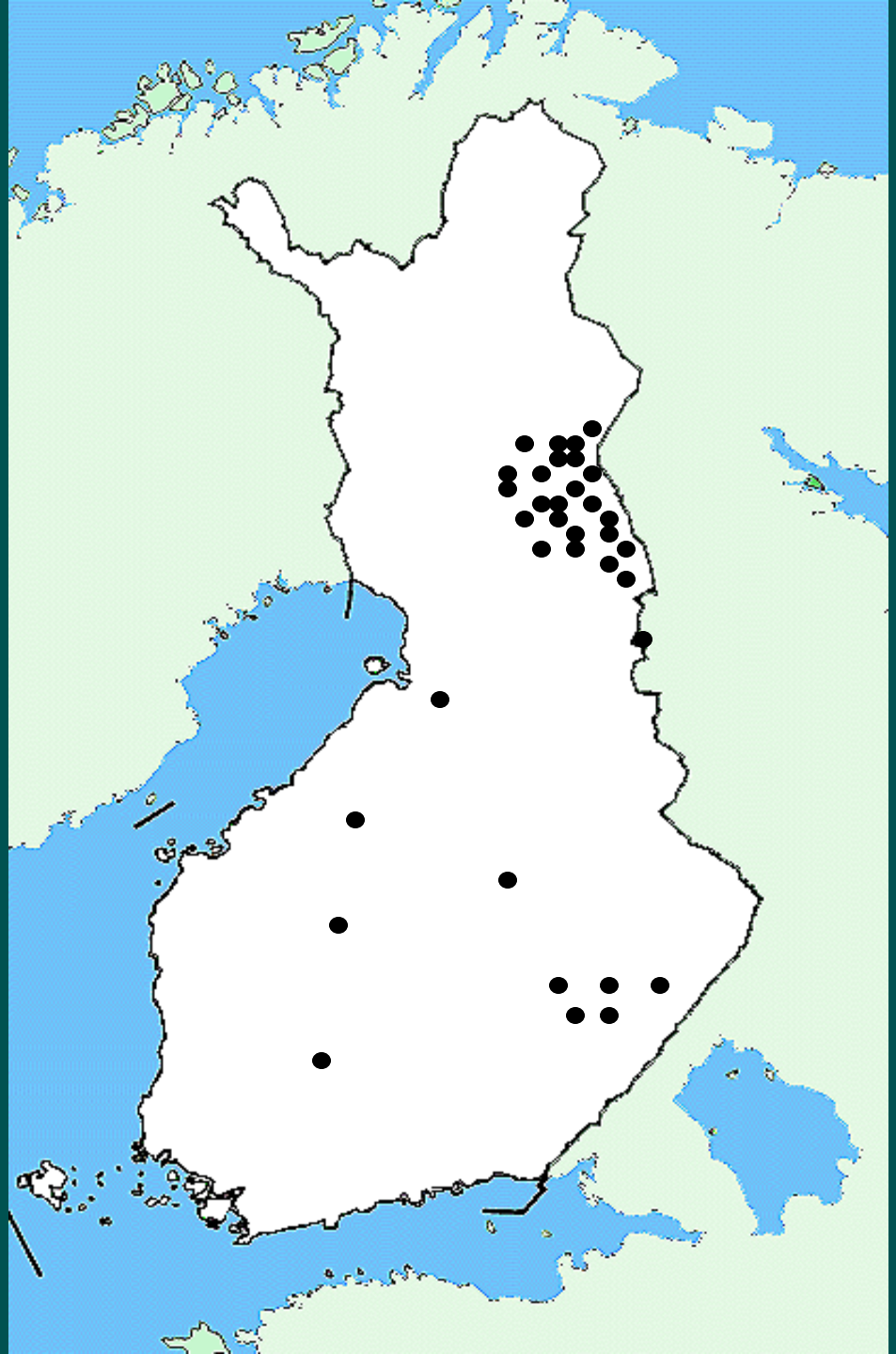
Congenital Nephrosis

- BirthPlaces of GreatGrandParents
- Fin-major 78 %
- Fin-minor 16 %
- Incidence 1:8000
- Carrier Frequency 1:45



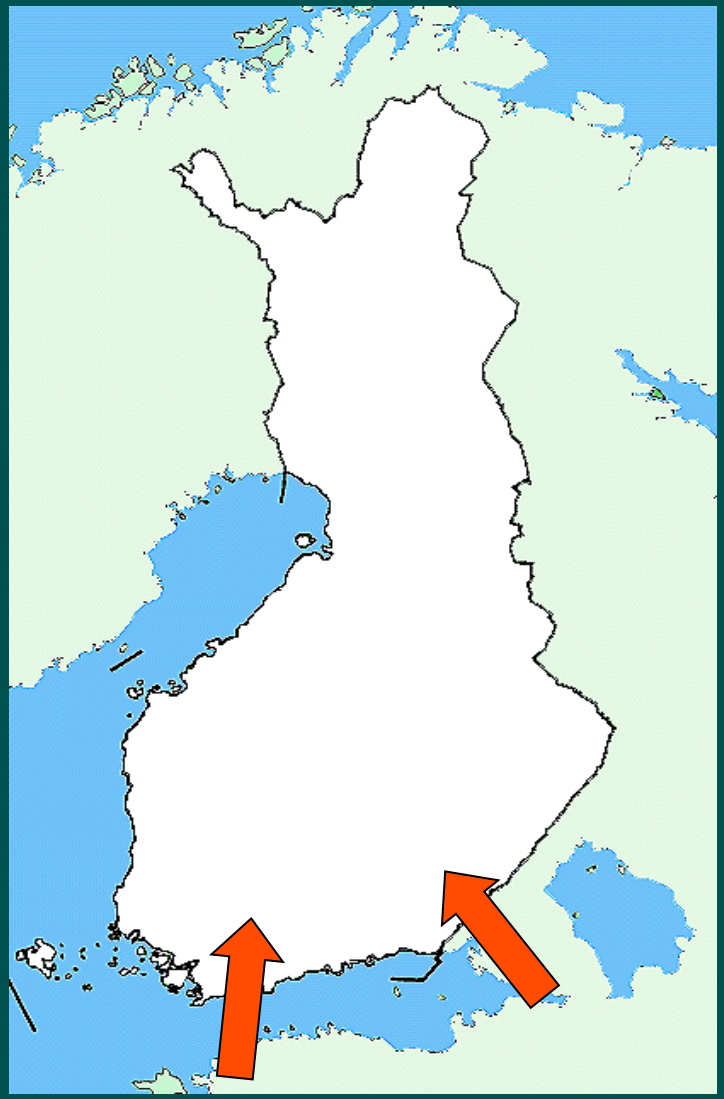
SALLA disease

- BirthPlaces of GreatGrandParents
- Fin-Major 95 %
- Incidence 1:40 000
- Carrier Frequency 1:100 much higher in Salla



Population History

- Small Number of Founders
- No Immigration
- Isolation
  - Geographical
  - Linguistic, cultural
- Rapid Expansion



Early Settlement

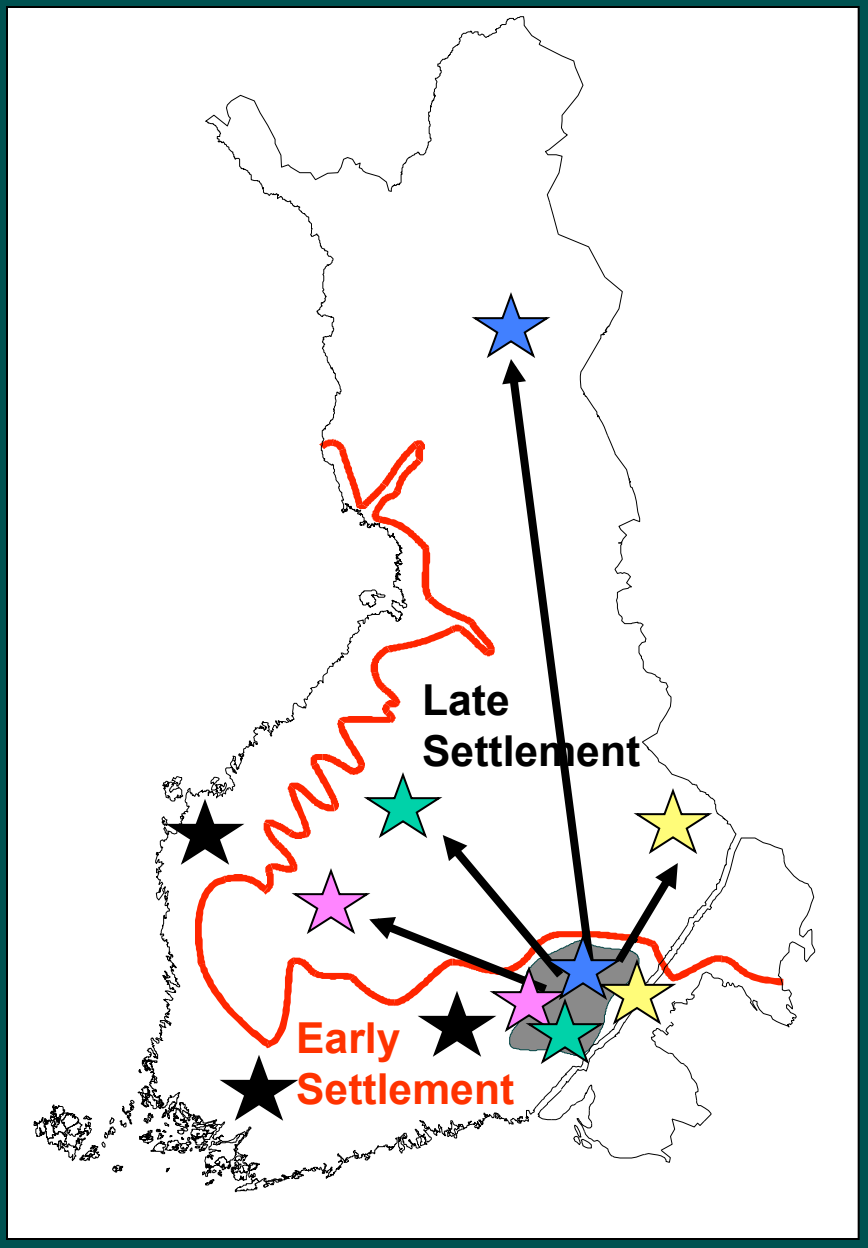
- 2000 years ago
- South and Coast

Late Settlement

- 16th century
- multiple bottle necks

Expansion

- 18th century -
  population 250 000
- Today -
  population 5.1 million



Benefits of the limited number of ancestral disease chromosomes in disease gene hunt

- A sparse marker map sufficient to detect the disease locus
- Association studies or “homozygosity scanning” of affecteds only can be used instead of linkage analyses

- More cost-effective disease gene mapping and identification

More cost/time-effective?

Mixed populations

- 15 families with two affected children genotyped
- 400 markers for linkage analyses

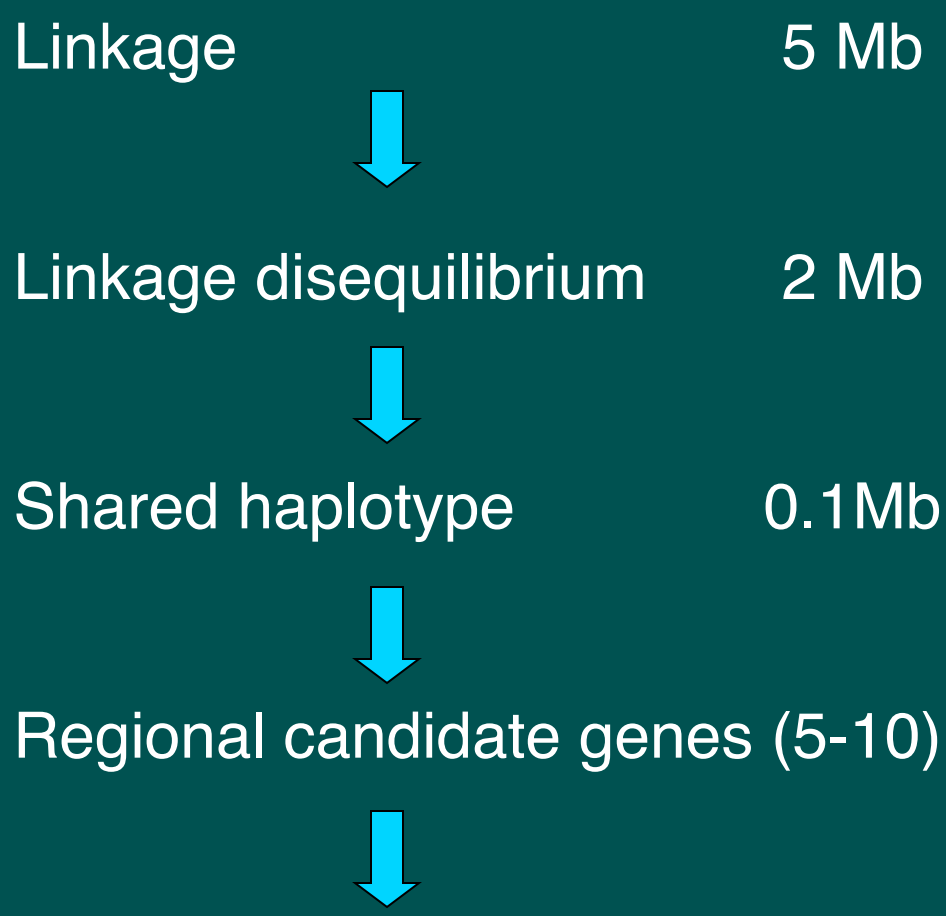
30 000 genotypes

Isolates

- 5 affected individuals genotyped
- 200 markers scanned for allele sharing

1000 genotypes

Genome Project and Identification of Disease Genes



PLO

Polycystic
Lipomembranous
Osteodysplasia
Sclerosing
Leucoencephalopathy

- Progressive presenile dementia
- Bone cysts
- Recessive, age of onset 20-40

Neuropathological findings

- Frontally accentuated loss of myelin
- Astrocytic gliosis
- Enlarged ventricles
- Calcifications and atrophy of basal ganglia
- Atrophy of corpus callosum
- Activation of microglia
- Vascular alterations

Short History of PLO SL

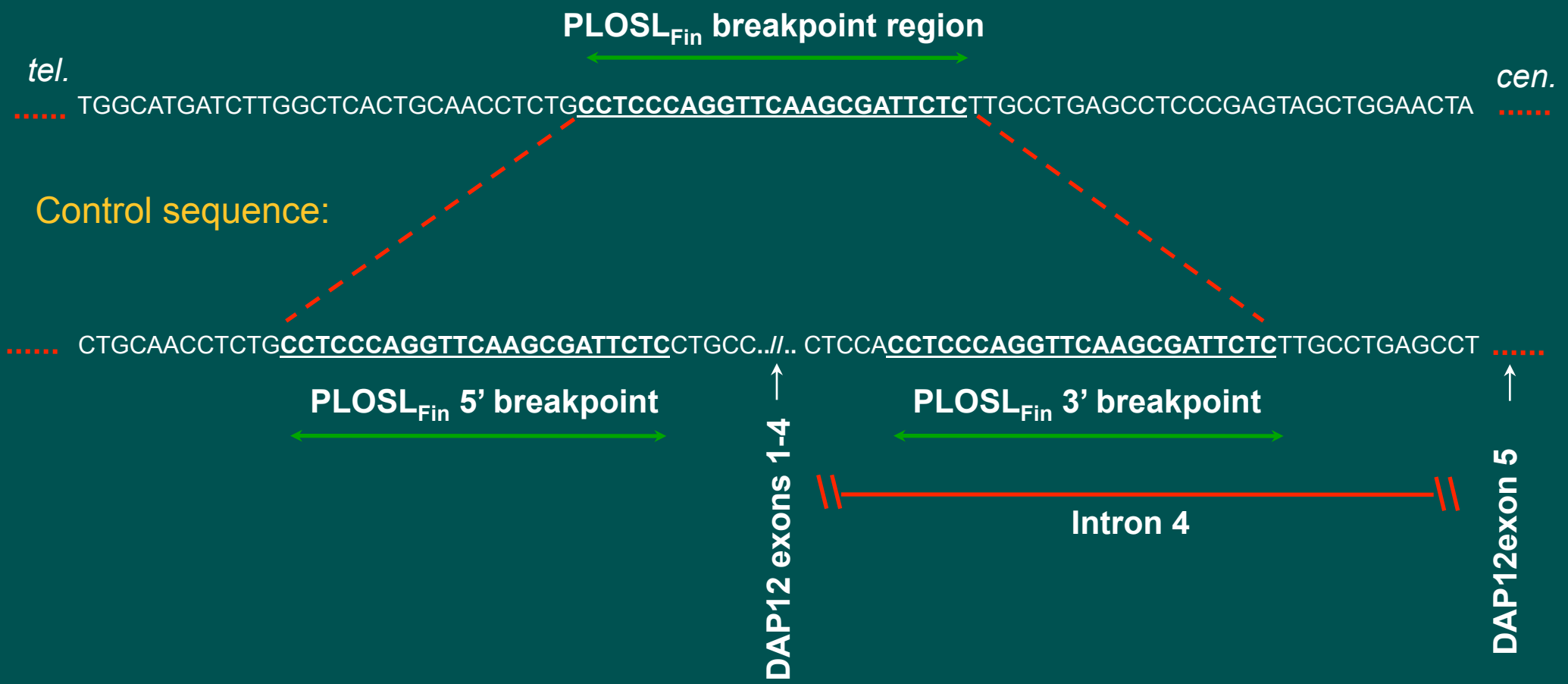
- Clinical phenotype described 1961 (Nasu and Hakola)
- Histopathology defined 1973-89
- Assignment of disease locus by genome-wide scan to 19q13 to 153 kb region 1998 (Pekkarinen et al.)
- Gene identified 1999 (Paloneva et al.)

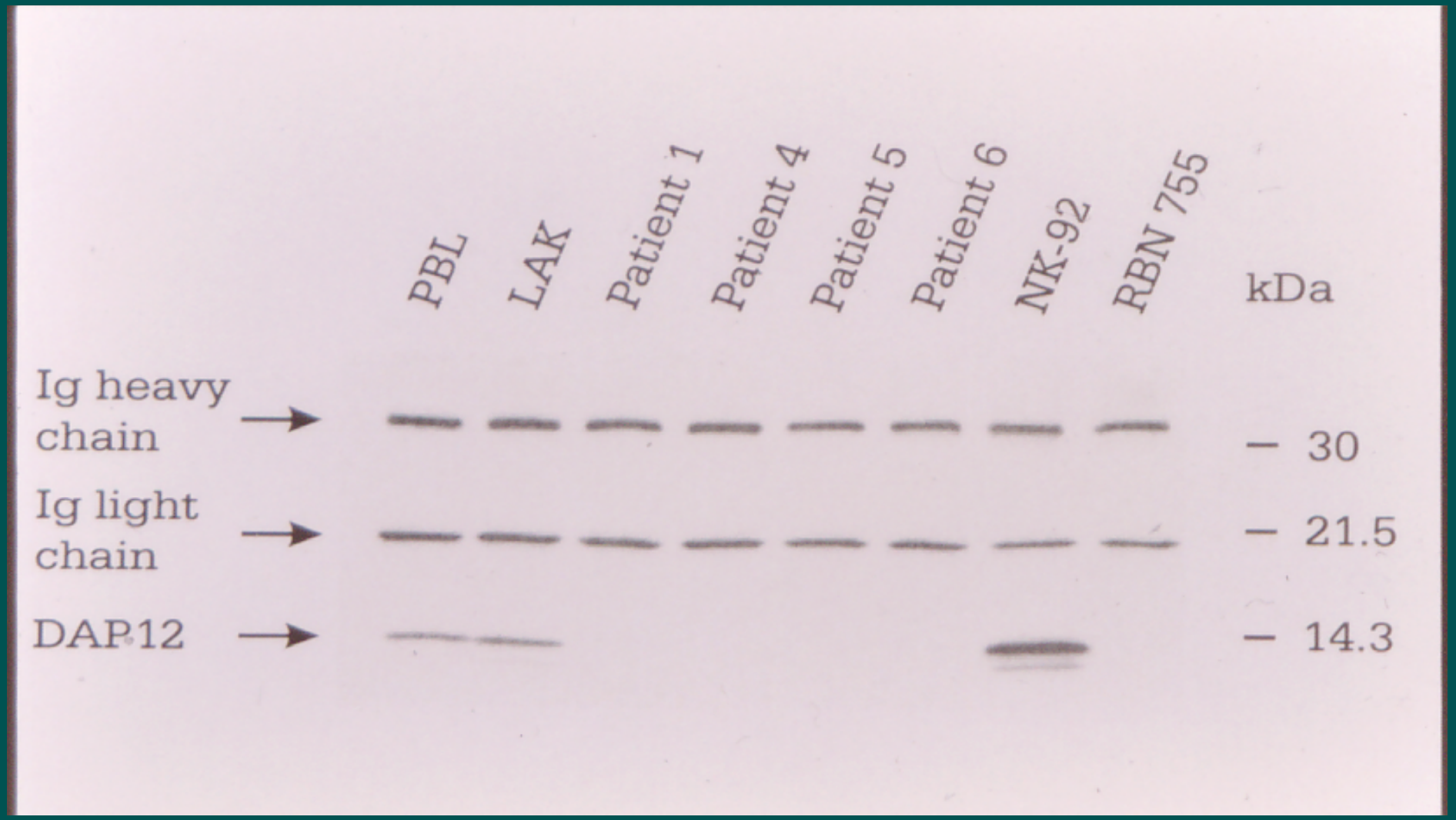
DAP 12

- NK cell membrane protein
- Crucial role in NK-cell activation and NK-cell-mediated lysis
- Transmits activating signals via association with activating receptors recognizing MHC class 1 molecules

$PLOSL_{Fin}$ deletion

$PLOSL_{Fin}$ mutant allele:




PBL
LAK
Patient 1
Patient 4
Patient 5
Patient 6
NK-92
RBN 755
kDa
Ig heavy chain
Ig light chain
DAP12
30
21.5
14.3

PLO patients

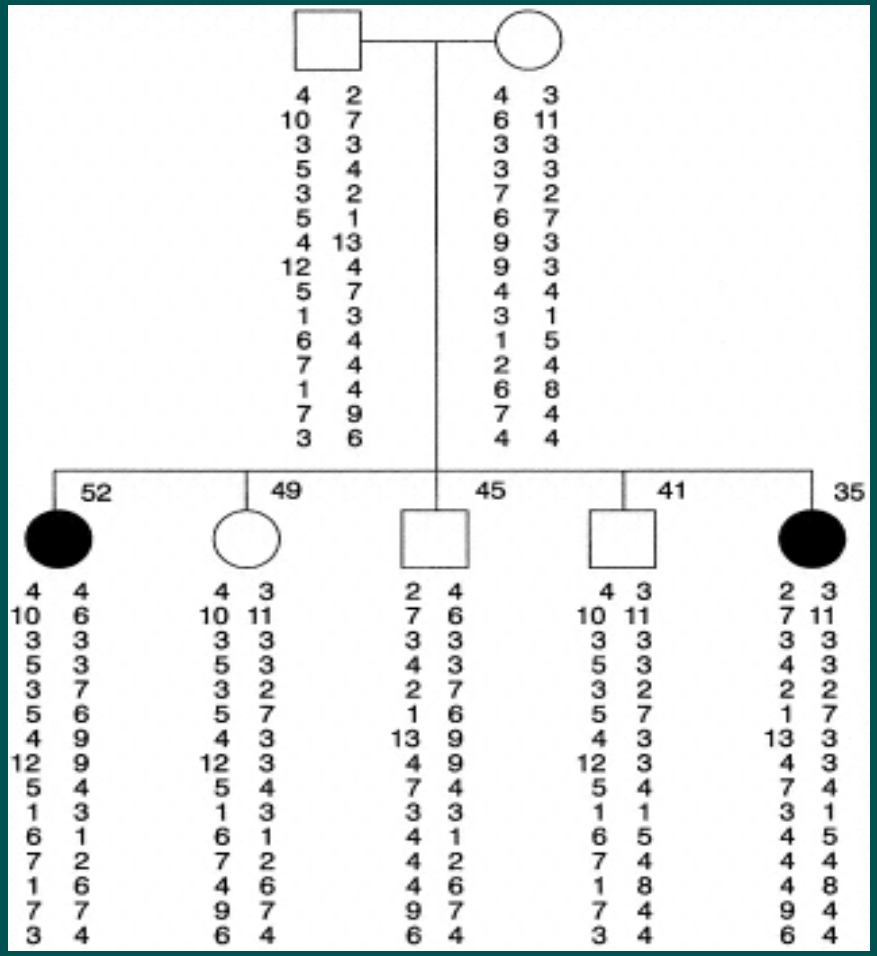
- Both Finnish and Japanese mutations represent functional ‘knock-out’s for DAP12
- No abnormality in the number or cytotoxic activity of NK cells
- No clinical problems arising from defective NK cell function

PLO shows locus heterogeneity

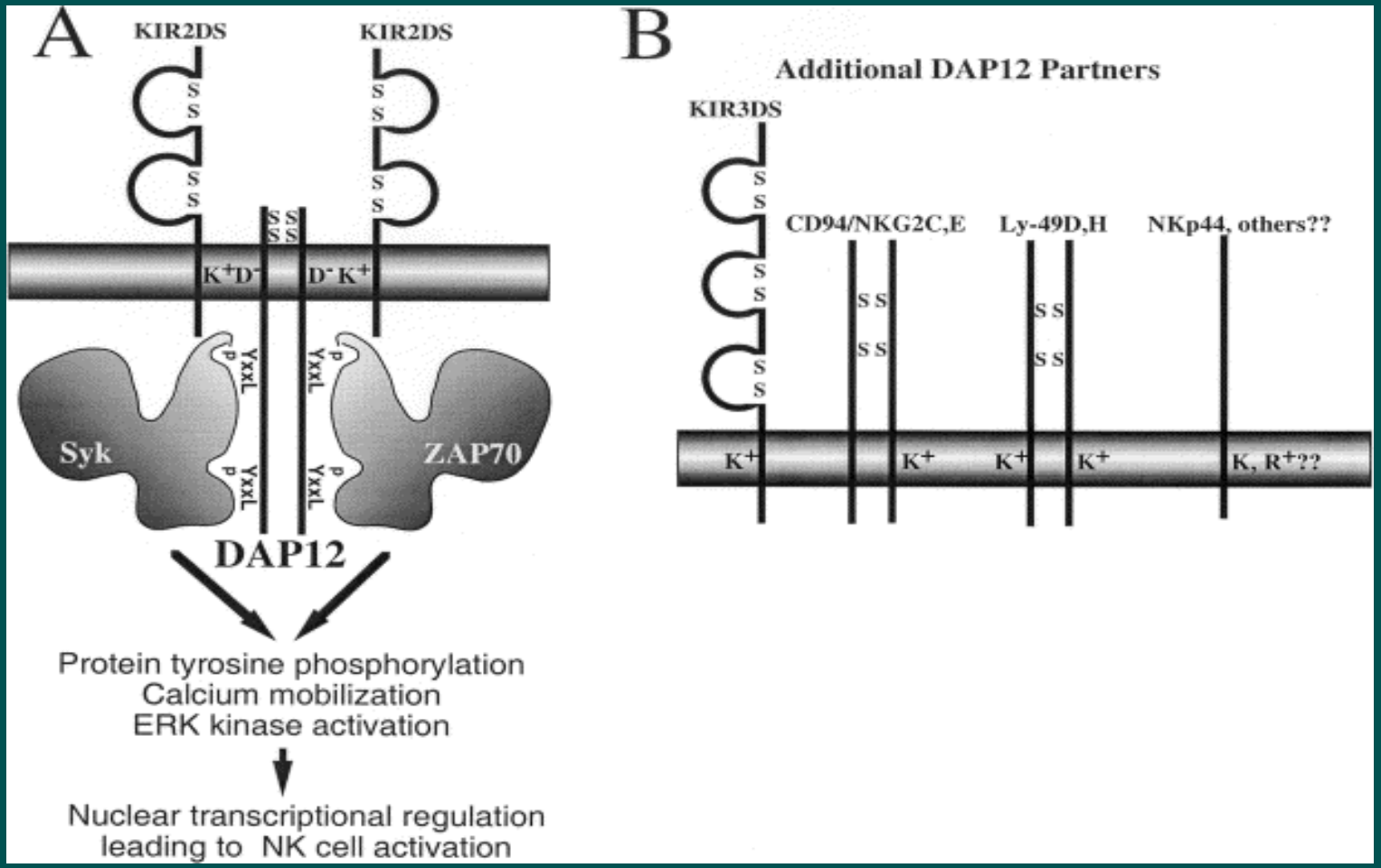
- Some families don’t show linkage to chromosome 19 and have no mutations of DAP 12

- What are the mutated gene(s) ?

Chromosome 19 haplotypes for Norwegian PLO-SL family



Am. J. Hum. Genet. 62:362-372 Pekkarinen et. al.



IJBCB, Kerry S. Campbell et. al., 1999

Genes of DAP12-ligands

Protein /gene	Chr	Haplotype segregation
KIR2DS2	19	-
MDL-1	7	-
TREM-1	6	+
TREM-2	6	+
NKG2C/CD94	12	-
SIRP-BETA-1	20	-
CD49	12	-
SYK	9	-
ZAP70	2	-

Sequence analyses of TREM 2

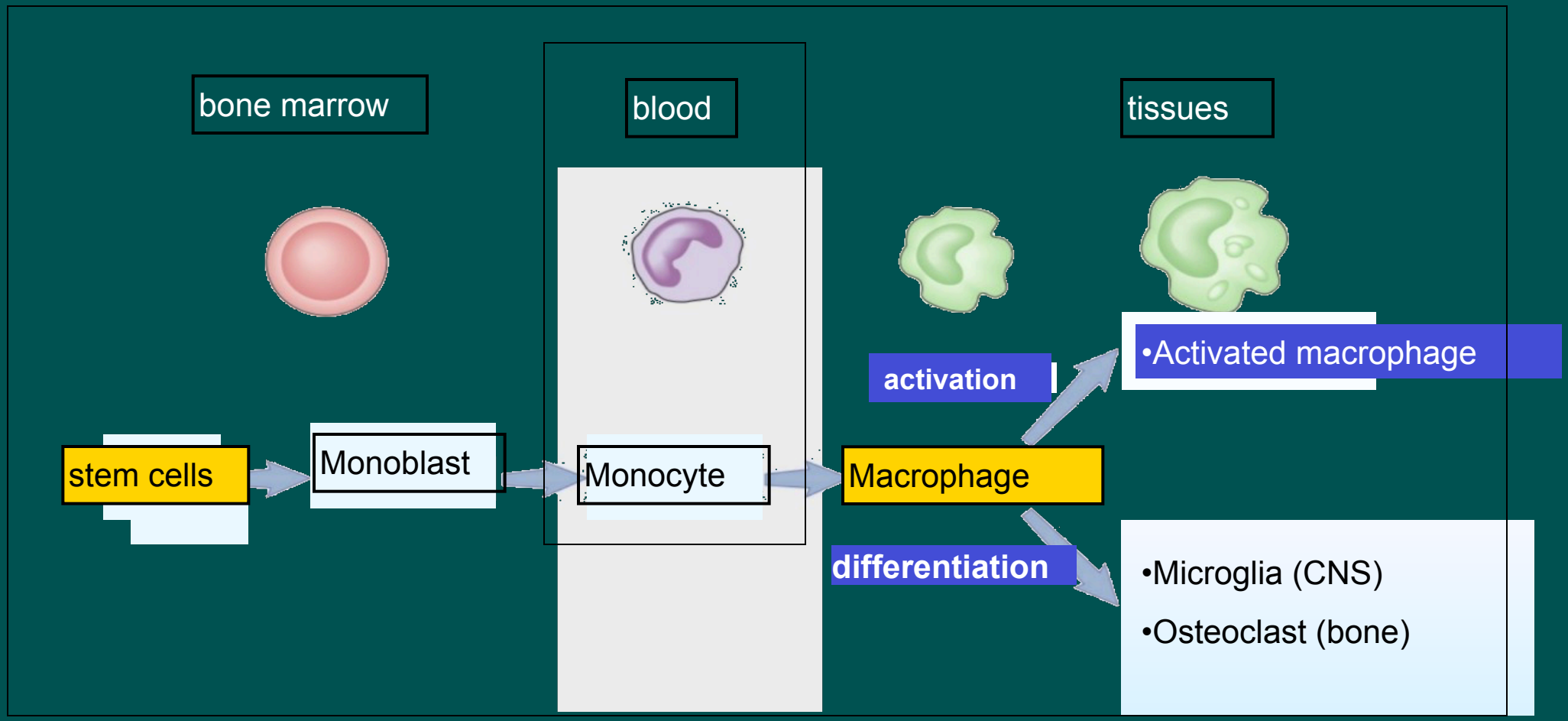
- Norwegian family: a Lys to Arg
- Swedish family: Trp to STOP
- US family: Asp to Gly
- Bolivian family: Trp to STOP
- Italian family: Splicing donator mutation

DAP 12 and TREM 2

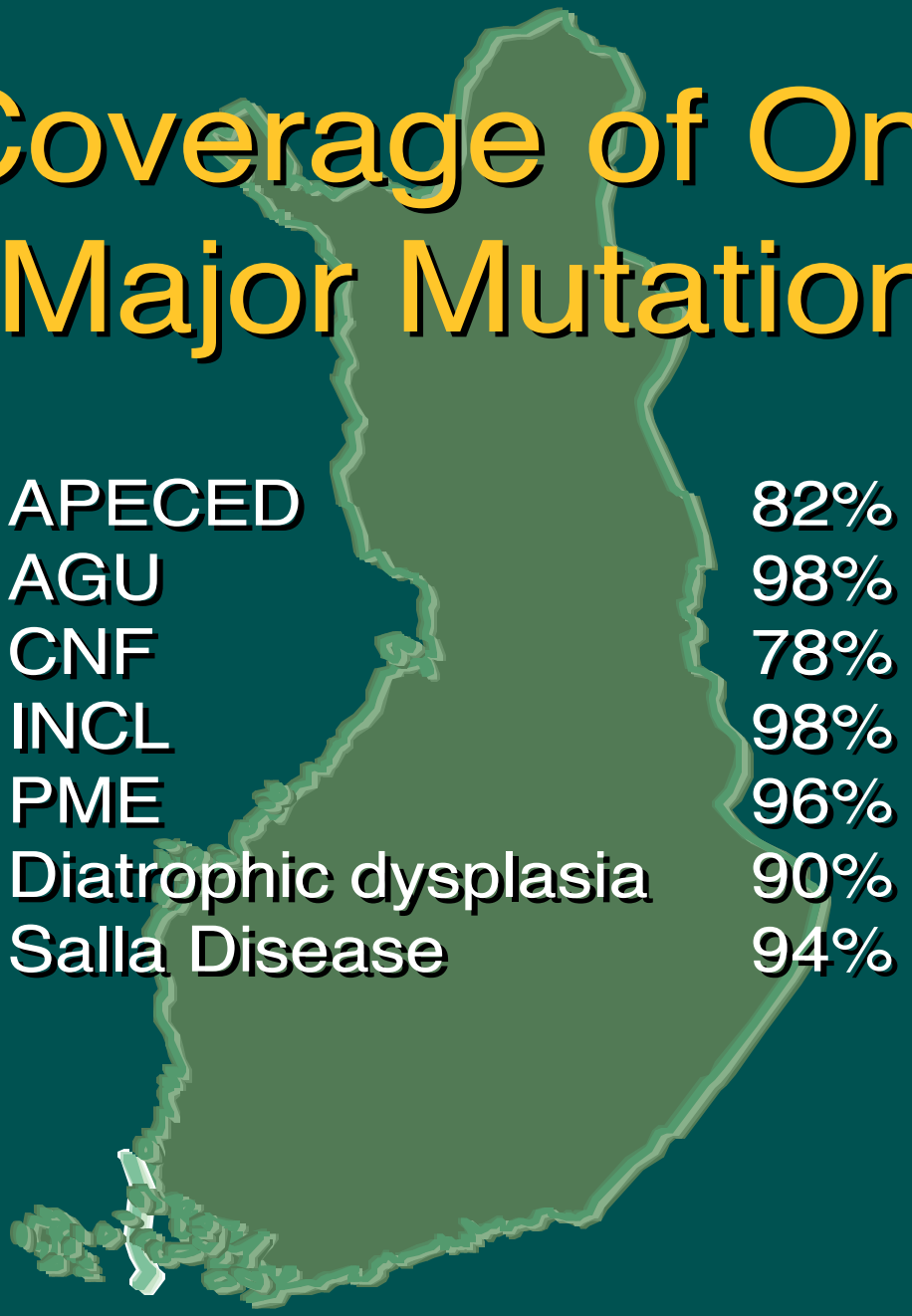
- Mutations in two separate subunits of multi-subunit receptor signaling complex result in the same human disease
- Relationship of functional defect with dementia and bone cysts??

Molecular pathogenesis of PLO?

-cells with functional defect represent the same lineage

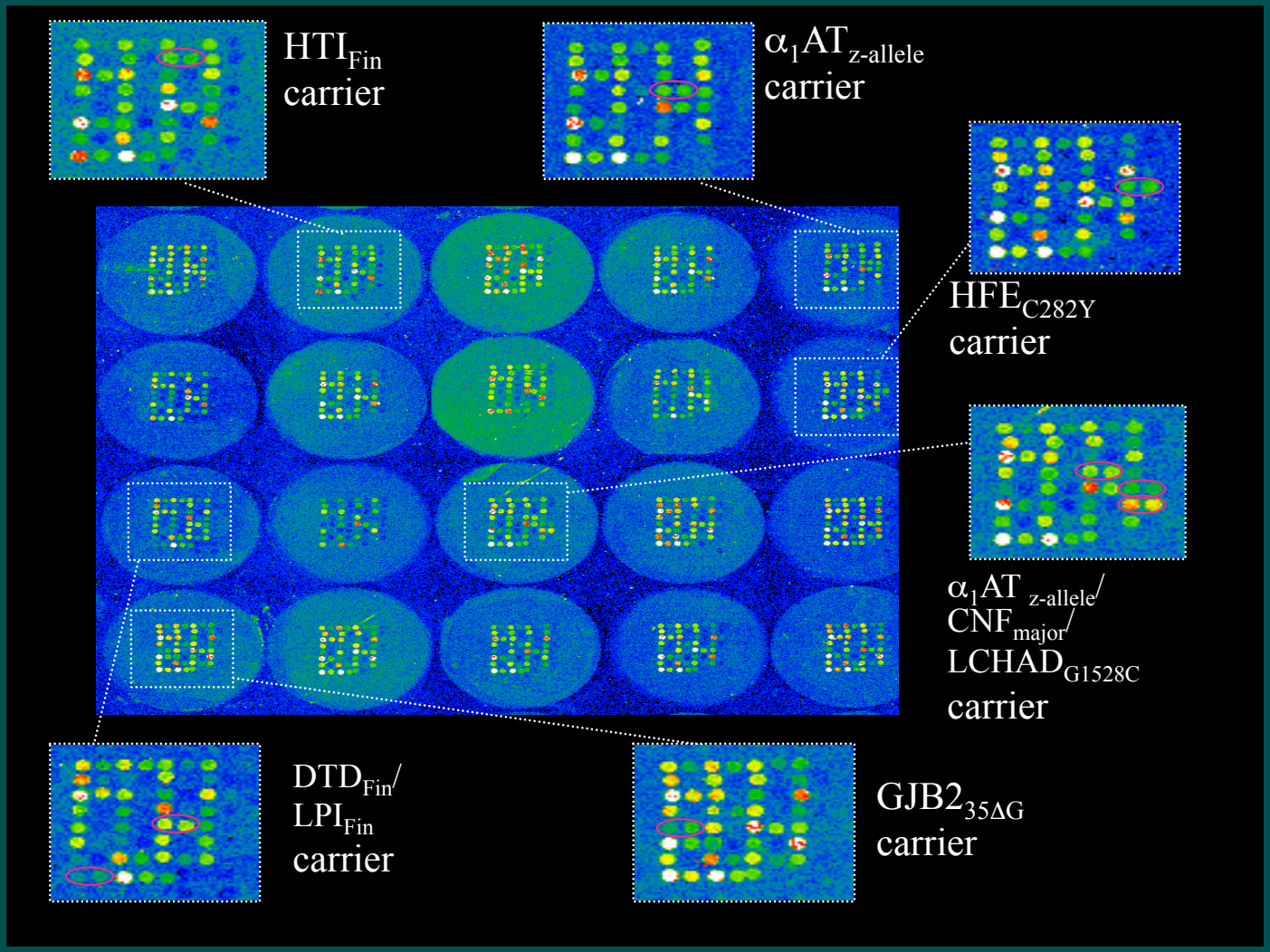


Coverage of One Major Mutation



APECED	82%
AGU	98%
CNF	78%
INCL	98%
PME	96%
Diatrophic dysplasia	90%
Salla Disease	94%

Finland Array

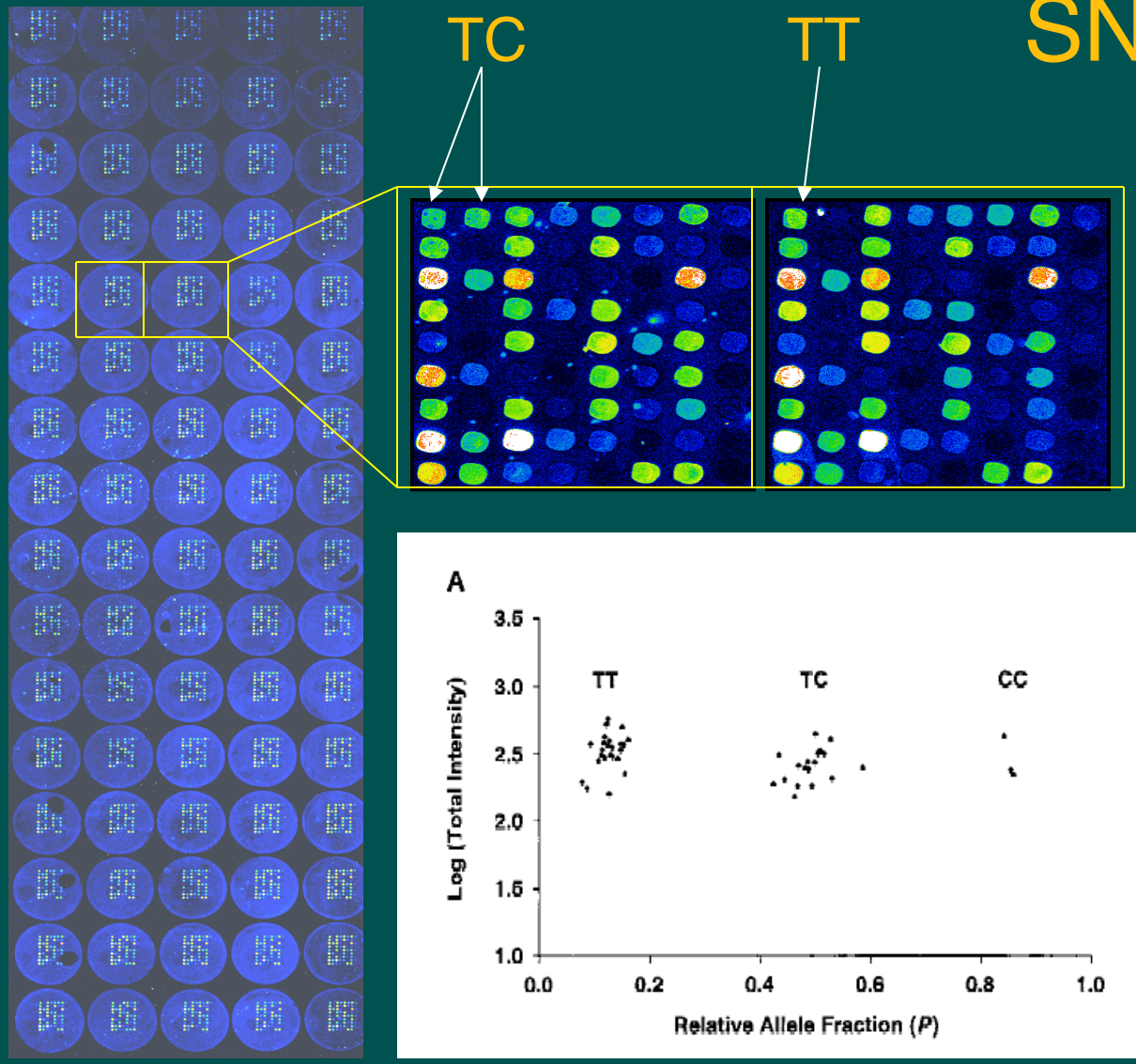


DNA-Chip for population screening

2400 DNA-samples analyzed for 31 disease mutations on the chip

- Prevalence of recessive mutations
- Regional variations
- Feasibility for large screening programs

SNP genotyping

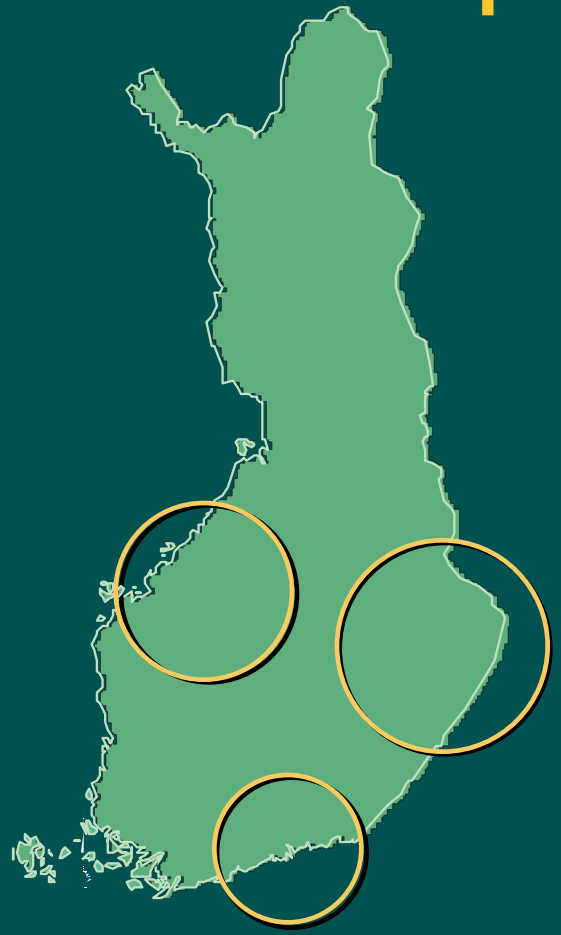


Genotype-calling software developed by Juha Saharinen

Y= LOG (signal A1+A2)

X= (signal A1)
(signalA1+A2)

Carrier Frequencies

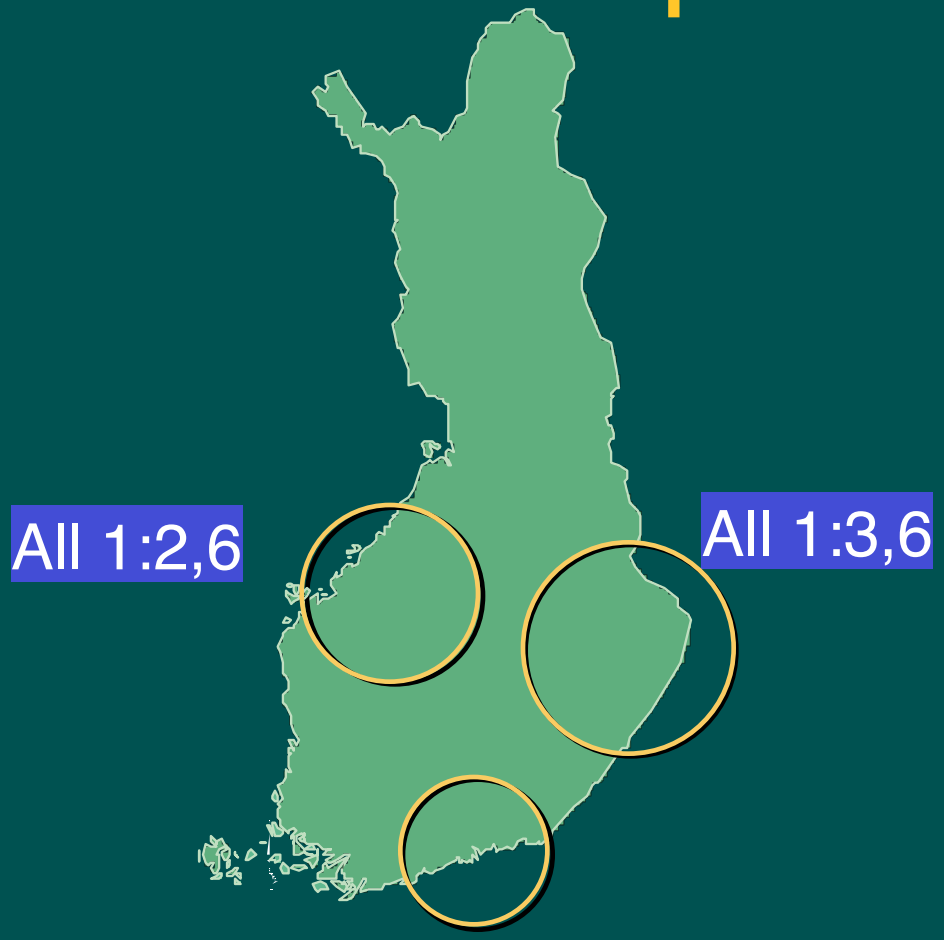


early settlement

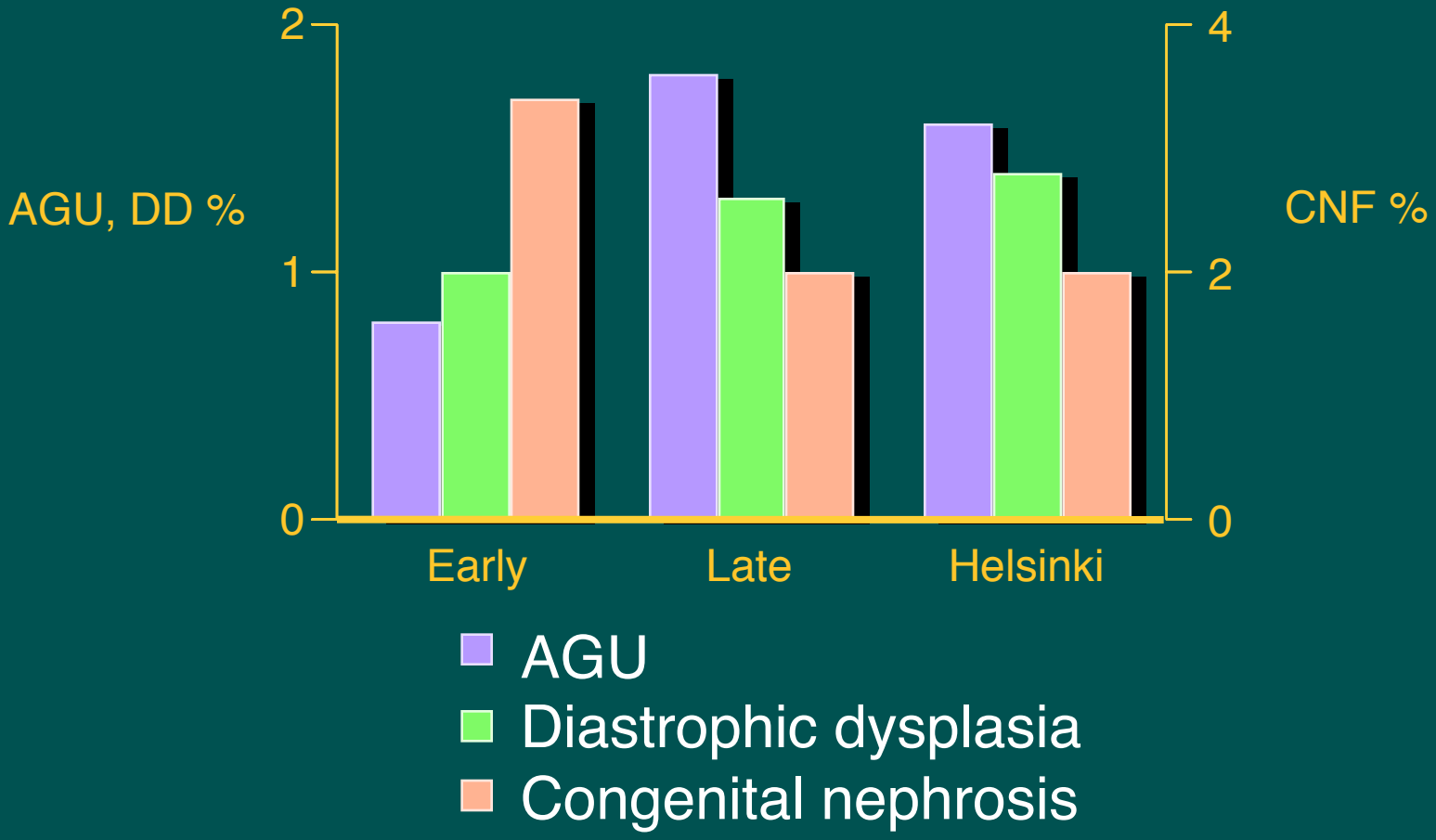
late settlement

Helsinki

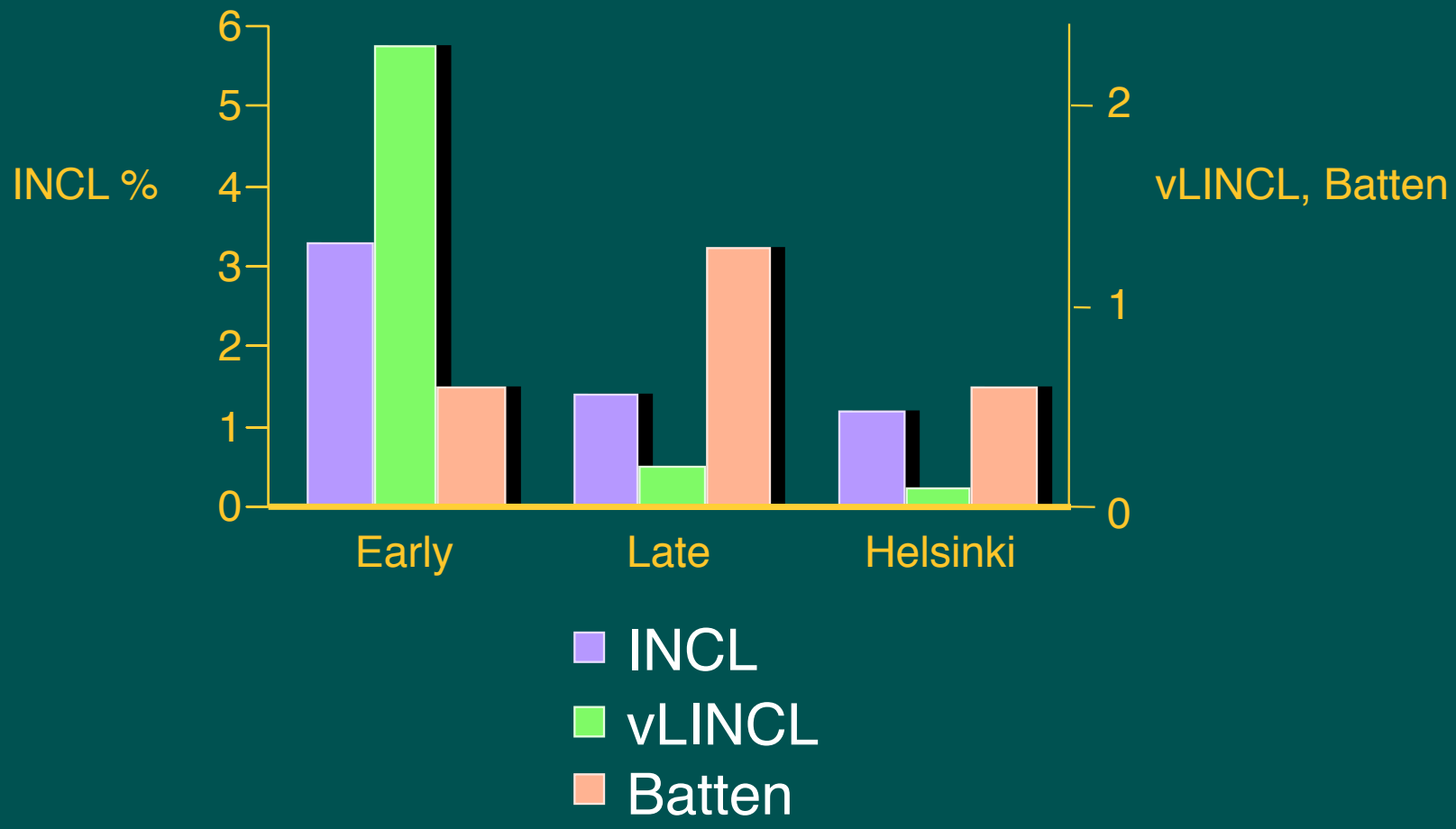
Carrier Frequencies



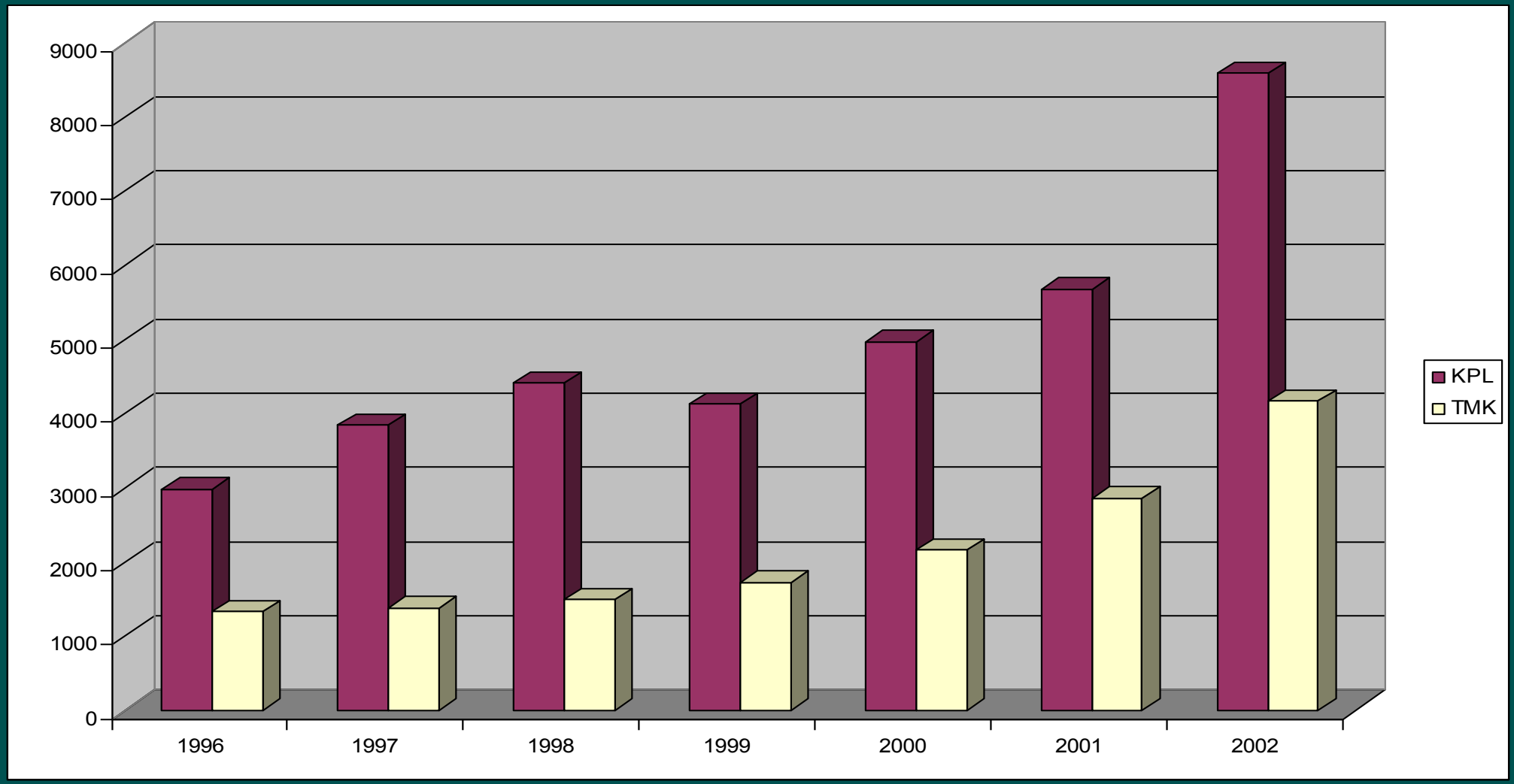
"Old" Finnish Mutations



NCL-diseases



Diagnostic DNA tests in the University of Helsinki laboratory



Genome Studies

- Accurate diagnosis / carrier detection of rare diseases (1500 currently)
- New metabolic pathways, critical for human cells and tissues, identified
- New molecular classification of diseases
- Avenues for drug development

Where we fall short

We are not competent to infer from the accumulated genome information

- Physiological function of molecules
- Understanding how molecules work together

We are unaware of the biochemical function of most proteins

We lack the knowledge of most interactions between cellular components

Function of the proteins

- Three dimensional structure of 1540 human proteins determined experimentally (www.rcsb.org.pdb)
- The function of 6000 human proteins is known

Ultimately it should be possible

- Examine individual's genetic make-up at any position of the sequence

- Deduce functional consequences

- Make a well-informed choice of medical actions

Slowly discovering functional information of the genome

- Alternative splicing produces cell or tissue specific products
- Multiple promoters confer diversity of substrate specificity or inducible response
- Only 2/3 of the genes have canonical structure with ORF
- New classes of RNA genes
- Genome landscape complexities

Treatment and Cure

- Drug discovery : target identification
- Biology-based stratification of diseases and syndromes
- Better targeted treatment trials
- Prevention versus treatment

”We finished the genome map
but we don't know how to fold it”