Institute of Human Genetics
Sheba Medical Center

- **Main Goal: Help people bring healthy babies**
- **55 workers**
- **60,000 tests every year**
- **More than 2,000 invasive prenatal diagnosis every year**

Pre Conception Genetic Screening

- **Thousands of genetic diseases**
- **A couple of dozens relatively common**
- **Most autosomal recessive**
- **One X-linked (fragile X syndrome)**

בדיקות גנטיות

סמנו את הבדיקות שברצונכם לבצע

☐ **הפקת דנ"א בלבד**

כל העדות:

☐ X שביר (אם בוצעה לפני 2011, ניתן לבצע שוב בטכנולוגיה מתקדמת יותר)

הסיכון לטעות בשיטה הקודמת היו קטן מ 1:30000. ביצוע בדיקה במימון פרטי

☐ CF

☐ SMA

☐ חירשות (קונקסין)

אשכנזים *

☐ גושה

☐ קנוואן

☐ פנקוני

*** מוצא אשכנזי כולל גם יוצאי בלקן ומצרים**

אשכנזים (המשך)

☐ בלום

☐ דיסאוטונומיה משפחתית

☐ ML4

☐ נימרפיק

☐ אשר

☐ אגירת גליקוגן 1

☐ מייפל סירופ

☐ נמליין

☐ גלקטוזמיה

☐ זיברט 2

☐ LDD

☐ אשר 3A

☐ טירוזינמיה

☐ ווקר ורבורג

**רוסיה האסיאתית

☐ ICCA

☐ MTHFR

**קווקז, גרוזיה,אזרביגאן, ארמניה, קז'חסטאן,אוזבקיסטן וטורקמיניסטאן

יוצאי צפון אפריקה

☐ AT

☐ אגירת גליקוגן 3

☐ פנקוני A

☐ ניוון שרירים LGMDIIb :

☐ MLC1

☐ CTX

☐ PCCA

☐ חירשות (TMC1)

יוצאי תימן

☐ MLD

☐ PKU

☐ RP26

כל זוג שאינו אשכנזי צריך לבדוק תלסמיה דרך הרופא המטפל בקופ"ח

יוצאי עירק כורדיסטאן

☐ קוסטף

☐ PCCA

אשכנזים/צ. אפריקה

☐ טאי זקס

☐ סרום ☐ לויקו)

☐ מולקולרי)

ערבי נוצרי

☐ קוקיין

איראן

☐ אשר 2A

☐ HIBM

אחר: _____

Pre Conception Genetic Screening

- Usually the female is first screened
- If found a carrier her mate is checked
- If both are carriers: PND or PGD
- 1% are saved from serious problems
- New microarray chips 200-500 diseases

Genetic diseases not in the screening program

- **First: clinical diagnosis**
- **Identification of the gene and the disease causing mutation (dominant and recessive)**
- **PND or PGD**
- **What happens when we encounter a disease with no known causative gene**

Clinical Symptoms and Initial Evaluation

⇨ Episodes of syncope

Normal ECG

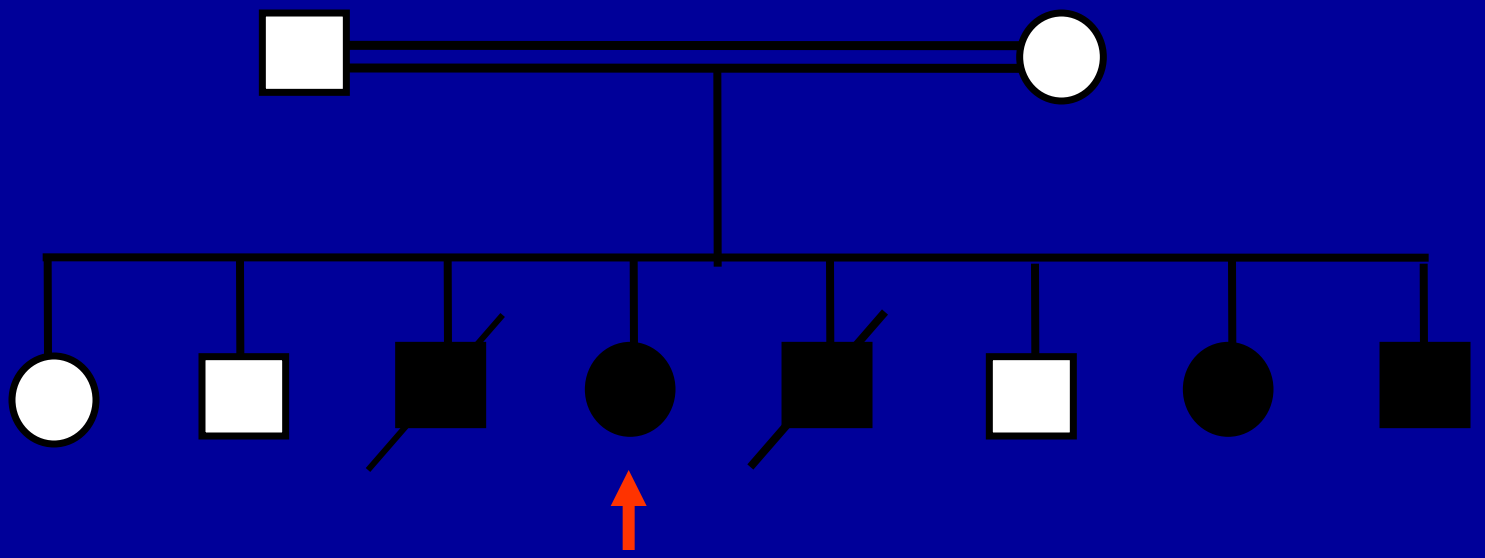
Normal Holter

Normal EEG

Normal CT

Normal Ecocardiography

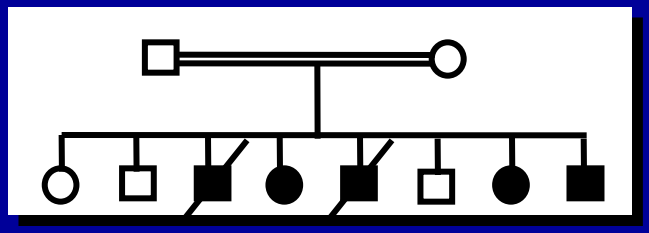
Bedouin family

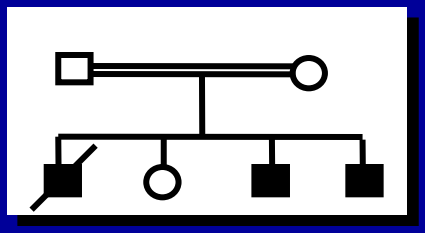


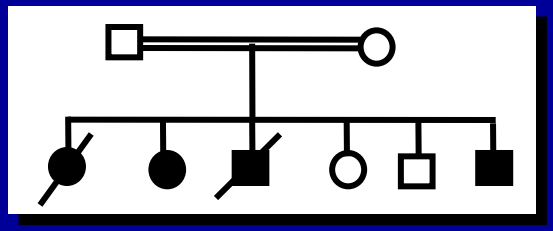
Candidate Gene Approach

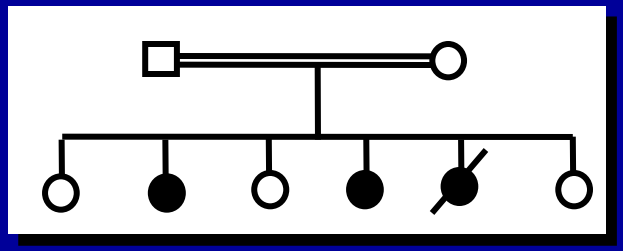
(Chromosome 3)	SCN5A
(Chromosome 7)	HERG
(Chromosome 11)	KVLQT1
(Chromosome 21)	KCNE
(Chromosome 4)	Long QT 4

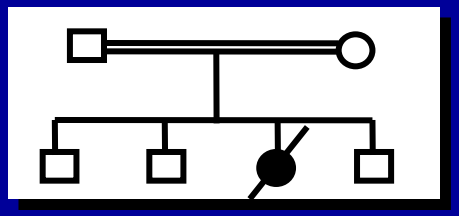
Bedouin families

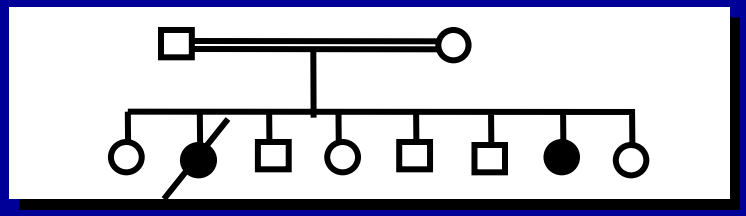


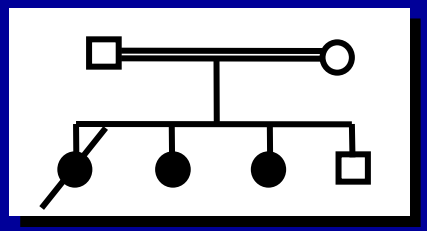






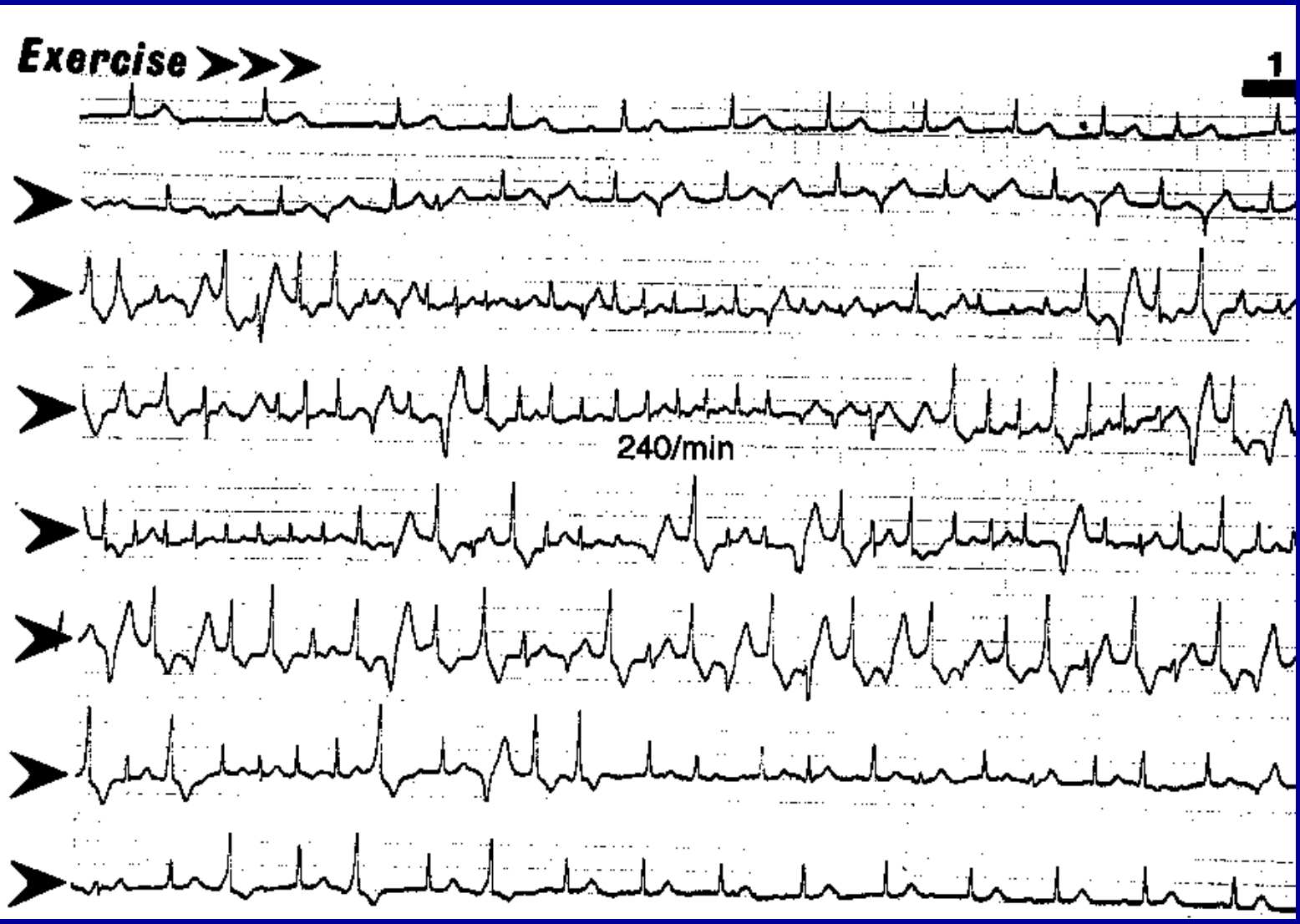






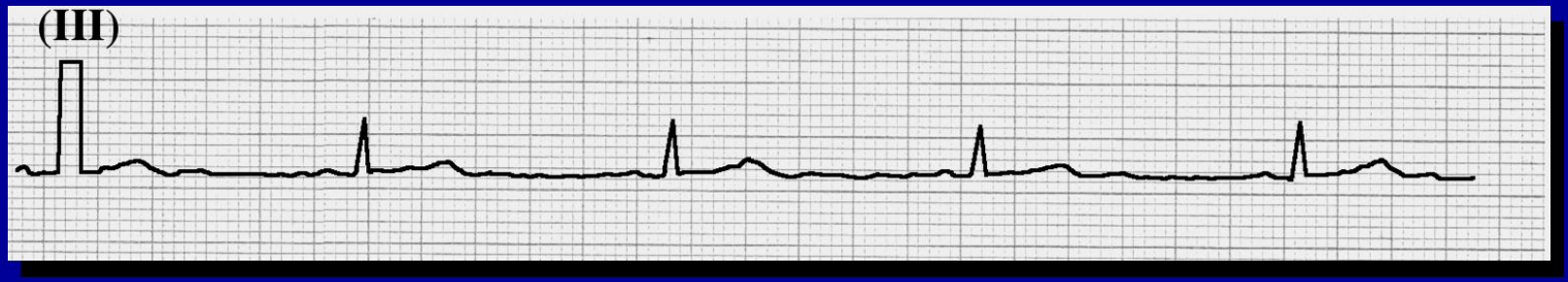
Catecholamine induced polymorphic ventricular tachycardia

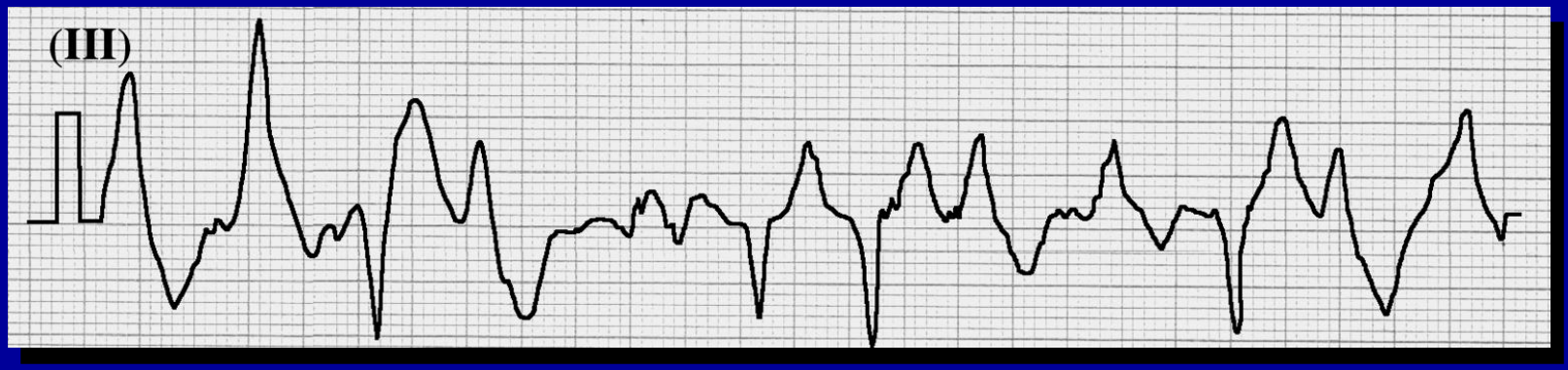
- Average age of onset 7.8 years
- Familial aggregation but no clear pattern of inheritance
- Reproducible form of PVT without QT prolongation, which appears during exercise test, or isoproteranol infusion



Leenhardt A, Circ. 1995; 91:1514

Patient's ECG





Overview of Positional Cloning

⇨ **Chromosomal Identification**

Genome-wide search for a marker that co-segregates with the disease in families

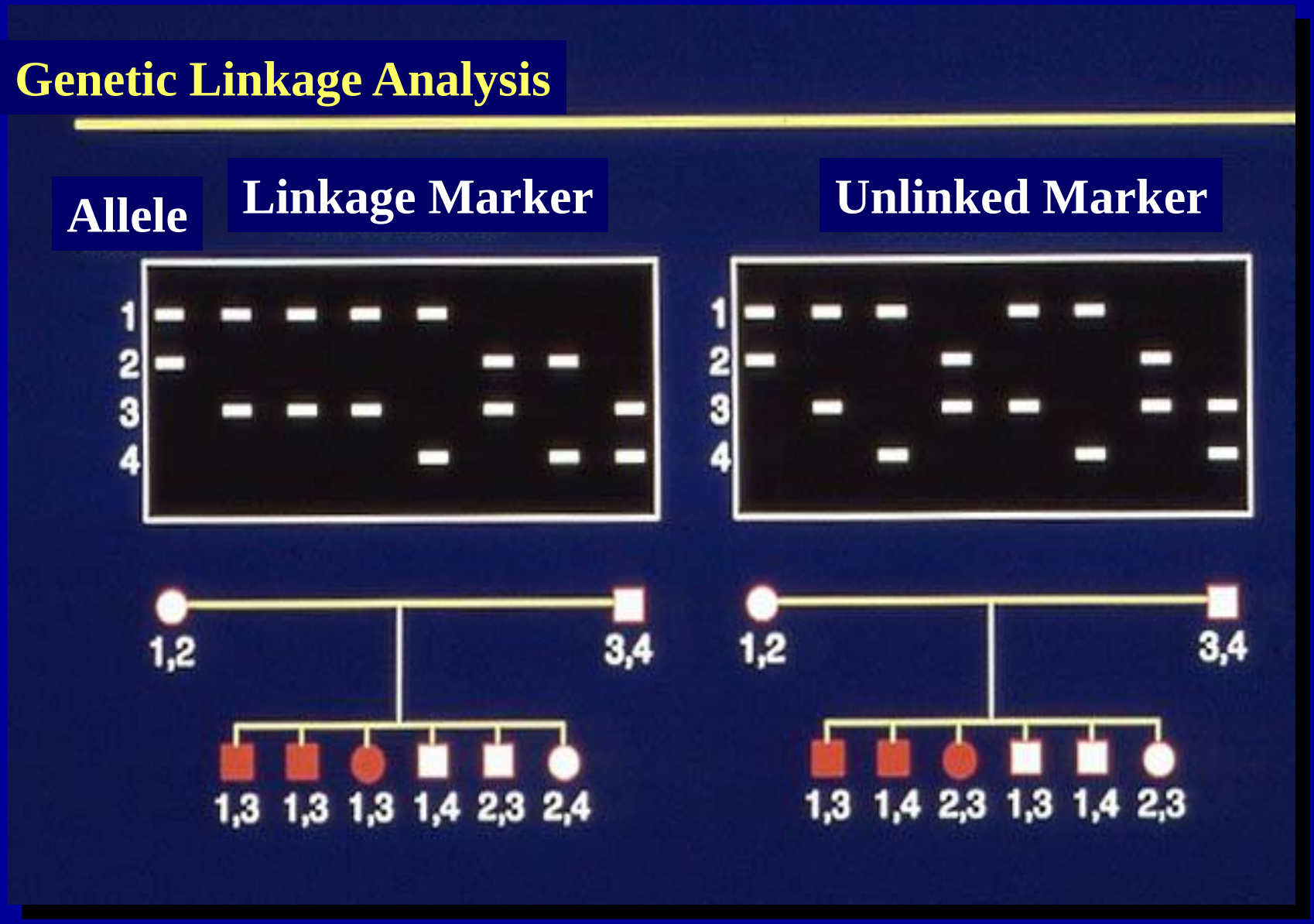
⇨ **Fine Genetic Localization**

Analysis of recombinations in families and linkage disequilibrium in populations to narrow narrow the candidate interval

⇨ **Gene Identification**

Screening of genes from the intervals for mutations

Genetic Linkage Analysis



Linkage Disequilibrium

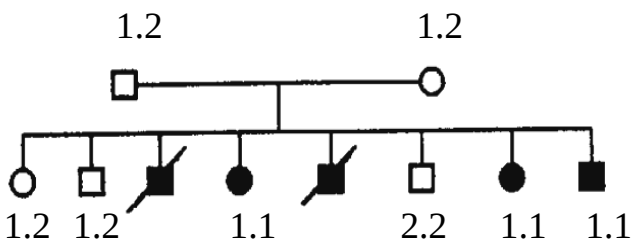
A. Linkage Without Linkage Disequilibrium

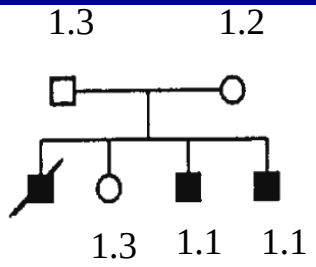
B. Linkage With Linkage Disequilibrium

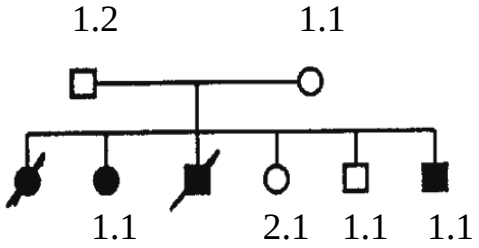
Genome wide search

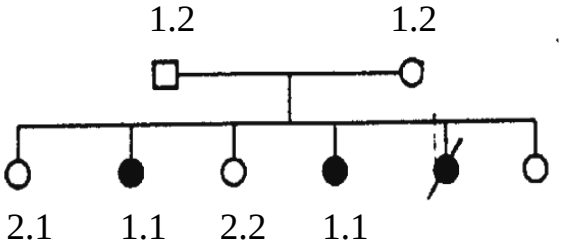
D1S468	D2S405	D3S4523	D5S2505	D6S474	D8S1145	D10S189
D1S1612	D2S1788	D3S1764	D5S807	D6S1040	D8S136	D10S1412
D1S1597	D2S1356	D3S1744	D5S817	D6S1009	D8S1477	D10S1430
D1S3669	D2S2739	D3S1763	D5S2845	NADA	D8S1110	D10S1423
D1S552	D2S441	D3S3053	D5S2848	D6S2436	D8S1113	D10S1426
D1S1622	D2S1777	D3S2427	D5S1470	D6S305	D8S1136	D10S1208
D1S3721	D2S297 2	D3S1262	D5S1457	D6S1277	D8S2324	D10S1221
D1S2134	D2S410	D3S2398	D5S2500	D6S1027	D8S1119	D10S1225
D1S3728	D2S1328	D3S2418	D5S1501	D7S3056	Gaat1a4	Gata121a08
D1S1665	D2S1334	D3S1311	GATA89G8	D7S513	D8S1132	D10S1432
D1S1728	D2S442	D4S2366	D5S1462	D7S3051	D8S592	D10S2327
D1S551	D2S1399	D4S403	D5S1453	D7S1802	D8S1179	D10S2470
D1S1588	D2S1353	D4S2639	D5S2501	D7S1808	D8S1128	D10S677
D1S1631	D2S1776	D4S2397	D5S1505	D7S817	D8S256	D10S1239
D1S3723	D2S1391	D4S2632	D5S816	D7S2846	D8S373	D10S1237
D1S534	D2S1384	D4S1627	D5S1480	D7S1818	GATA62F3	D10S1230
D1S1653	D2S434	D4S3248	D5S820	D7S3046	D9S921	D10S1248
D1S1679	D2S427	D4S2367	D5S1471	D7S2204	D9S925	D10S212
D1S1677	D2S2968	D4S3243	D5S1456	D7S2212	D9S1121	D11S1984
D1S1589	D2S125	D4S2361	D5S211	D7S821	D9S1118	D11S2362
D1S518	D3S2387	D4S1647	D5S408	D7S1799	D9S301	D11S1999
D1S160	D3S1304	D4S2623	F13A1	D7S3061	D9S1122	D11S1981
D1S1678	D3S4545	D4S2394	D6S2434	D7S1804	D9S922	ATA34E08
N/A	D3S1259	D4S1644	D6S1959	D7S1824	D9S257	D11S1392
D1S2141	D3S2432	D4S1625	D6S2439	D7S2195	D9S910	D11S1985
D1S549	D3S1768	D4S1629	D6S2427	D7S1826	D9S938	D11S2371
D1S3462	D3S2409	D4S2368	D6S1017	D7S3070	D9S930	D11S2002
D1S235	D3S1766	D4S2431	D6S2410	D7S3058	D9S934	D11S2000
D1S547	D3S4542	D4S2417	D6S1053	D7S559	D9S1825	D11S1986
D1S1609	D3S4529	D4S408	D6S1031	D8264	D9S2157	D11S1998
D2S2952	D3S2459	D4S1652	D6S1043	D8S277	D9S1838	D11S4464
D2S1400	D3S3045	D5S2488	D6S1056	D8S1130	D10S1435	D11S912
D2S1360	D3S2460	D5S2849	D6S1021	D8S1106		

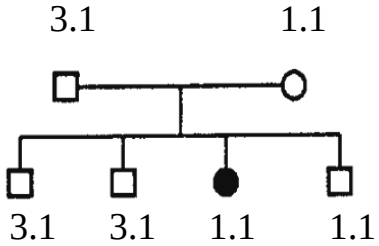
Typing results for D1S2784

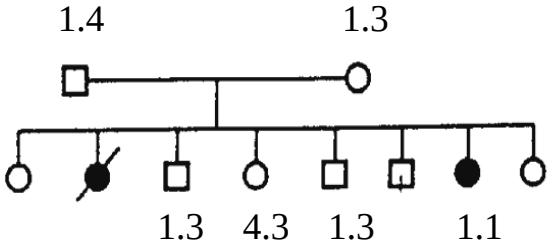


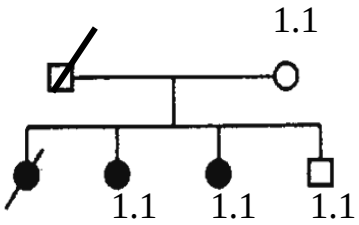






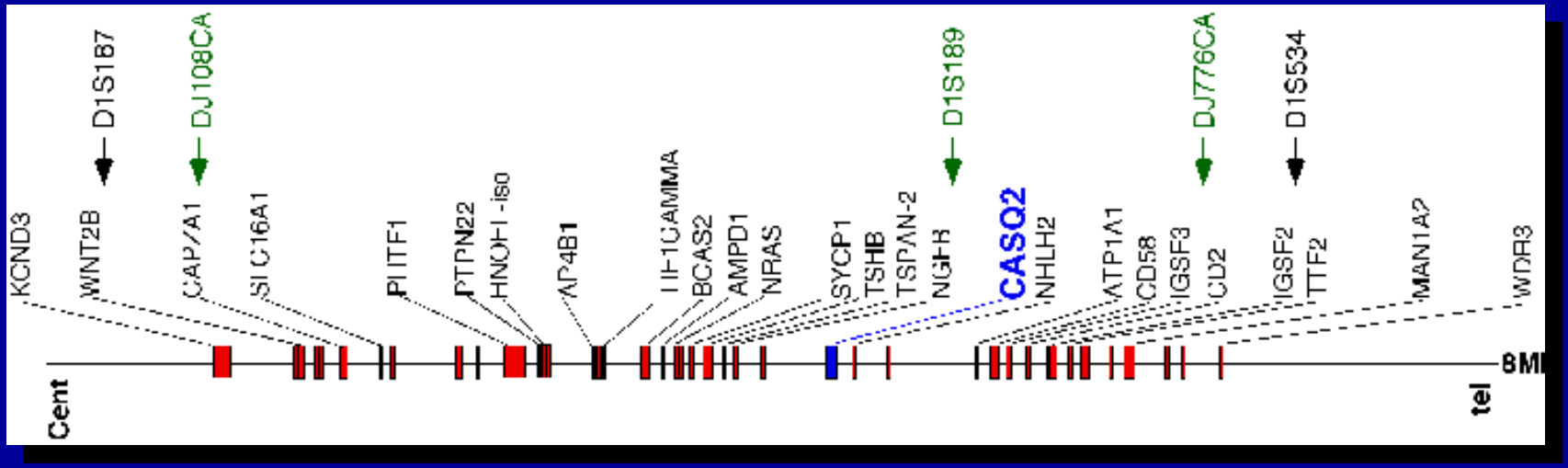




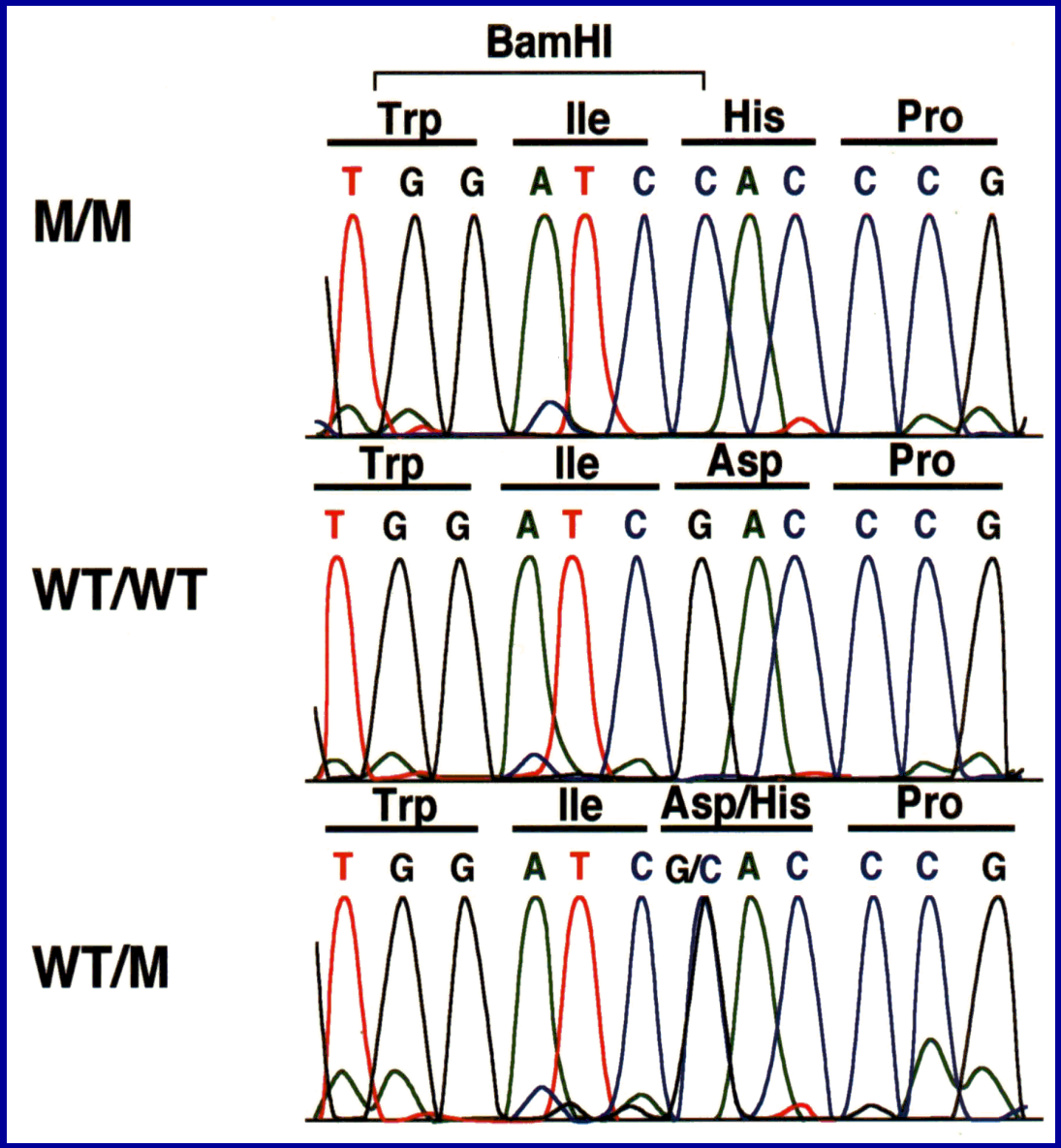


PVT linkage interval 1P (13-21)

8 Mb



CASQ2 Mutation



Beta-Blockers Treatment

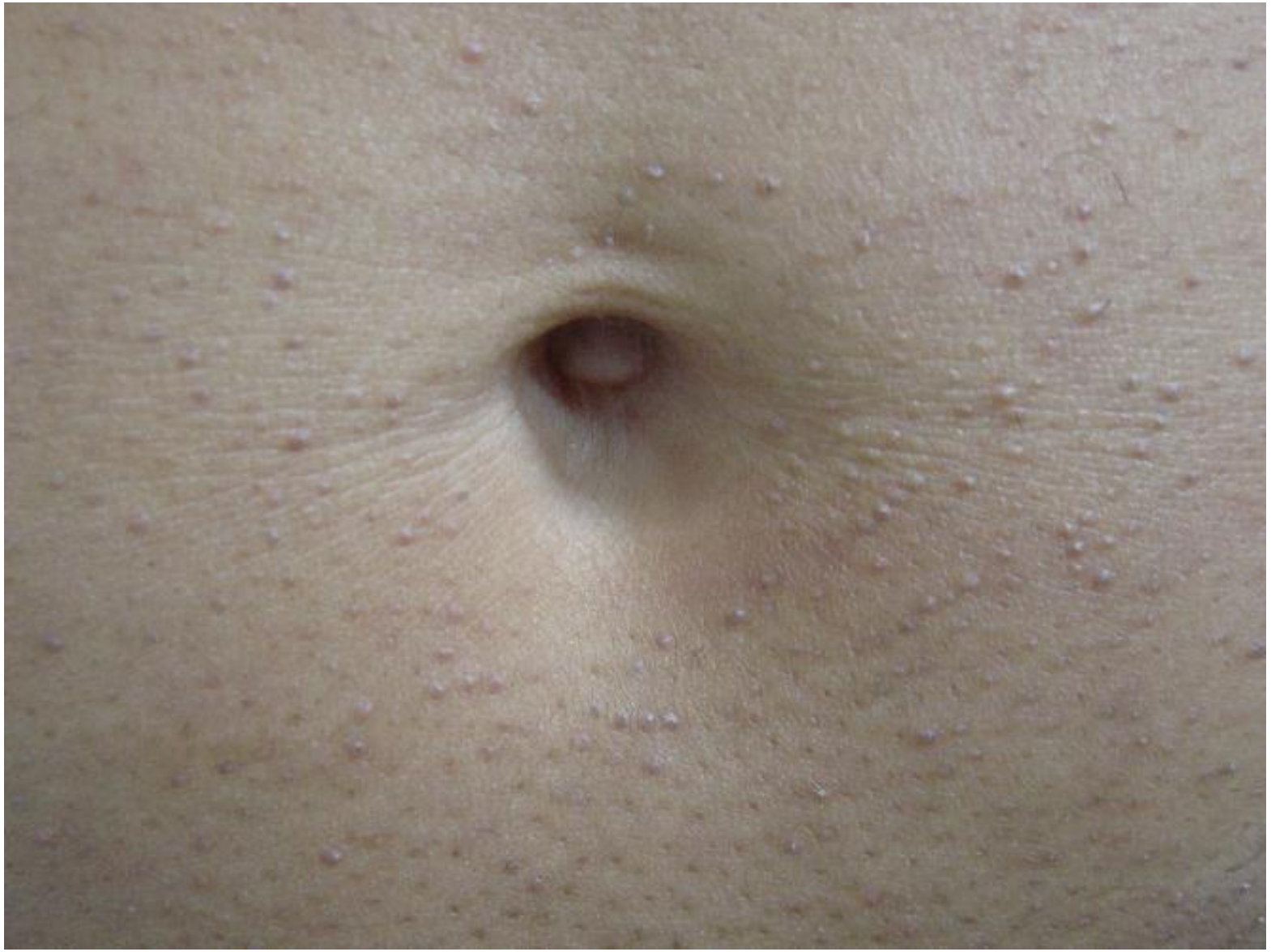
- **Propranolol 20 mg TID to all the patients**
- **Significant reduction in the number of syncope episodes**
- **One case of death in 5 years of treatment compared to 9 cases in the last decade**

Prenatal Diagnosis

CVS
Amniocynthesis

Costs!!!!!

$40,000



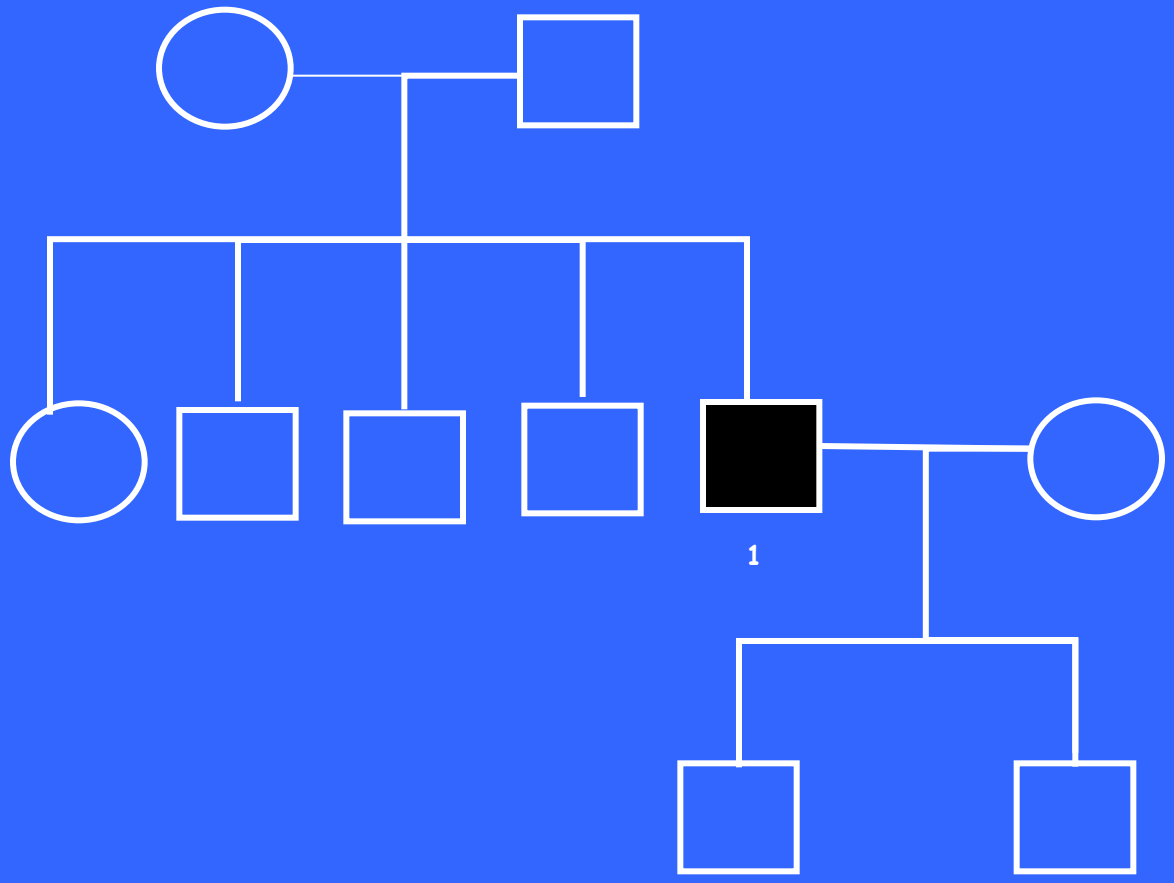
Monilethrix

- Light microscopy of the hair shaft

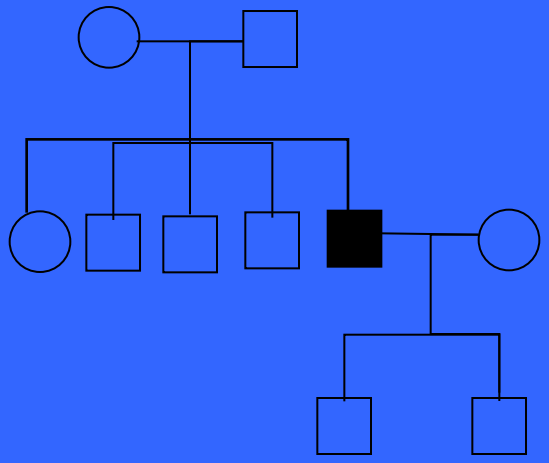
Monilethrix

- Autosomal dominant inheritance
- Caused by three genes:
- KRT81, KRT86, KRT83 (Chromosome 12q)

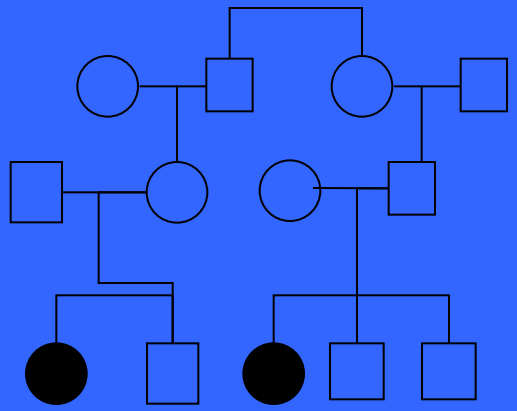
Family 1



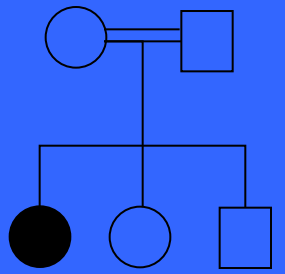
Pedigrees of Iraqi Families



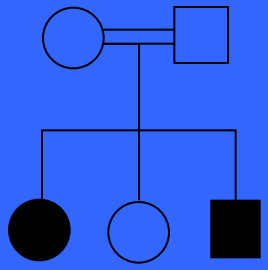
Family 1



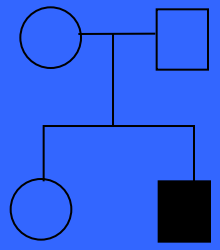
Family 2



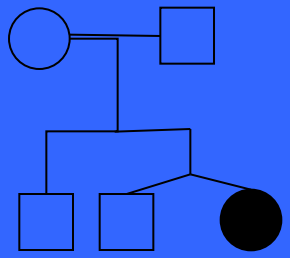
Family 3



Family 4



Family 5



Family 6

Monilethrix

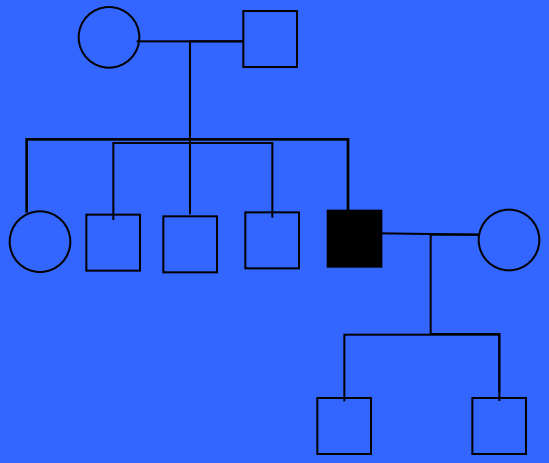
- Autosomal recessive inheritance
- Most likely a common founder
- Skin and hair genes are located in clusters

Cluster name	No. of genes	Genomic location	Accession no. genomic DNA	PCR primer sequence	Annealing temp (°C)	PCR product
Type II hair keratin	6	12q13	AC021066	5’ctgctgaagatctgcctccagt3’ 5’ gtgggtgtgacatgcagctta3’	58	229
			ACO55736	5’atctagacatctagcaggctcacag3’ 5’acttttggaccagcttggaagt3’	56	239
Type I hair keratin	9	17q12-q21	AC019349	5’gtactgagctccttggtggttc3’ 5’catgacattccctctcaacaaa3’	56	235
			AC006070	5cccatacttcttcatggttgtt3’ 5’gatggggcacagcatgtgacaaaa3’	56	228
HS[a] /UHS[b] KAP	37	17q12-q21	AC037482	5’caagtggcgaacacctgtagt3’ 5’gcaatttgatgtagaggtcagc3’	56	238
HGT[c]/ UHS KAP	24	21q22.11	AP001069	5’gcctcccatatttagagcacac3’ 5’ggctgatgtttcttcaatcctt3’	56	240
HS KAP	11	11p15.5	AC130310	5’tcccattgtggttgtatatgga3’ 5'ctttcccactctttgctcaca3’	56	243
UHS KAP	11	11q13.5	AP000867	5’attaaggggtgttaggagctga3’ 5’tattctgaccaatcatggtgga3’	56	267
HS KAP pseudogene	16	21q22.3	AL773602	5'cacctgagctctgcctttatct3’ 5’ctgaccgctggtacatgtgaat3’	58	216
Netherton	1	5q32	AC116334	5’acccttgccaaaacttgttact3’ 5’aatgagccatgattgtgtcact3’	56	218
Desmosomal Cadherins	7	18q12.1	AC079096	5’tcttccatttatcccaaaatgc3’ 5’aggaggggtaggagcagttcta3’	56	220
			AC012417	5’atctacattccagggccgta3’ 5’tcatccaggaataatcatgagc3’	58	203
			AC009717	5’ctttcactgtagcctcgacctt3’ 5’taaggcgggtgaatctcttg3’	56	202

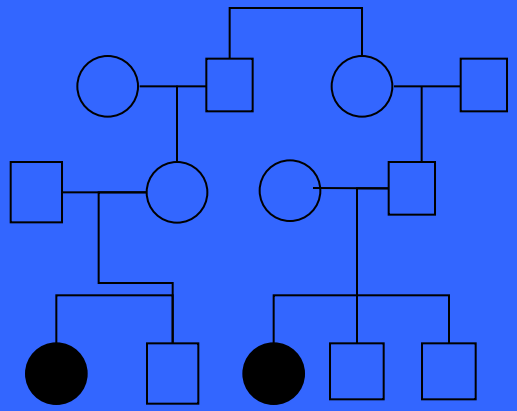
Linkage Disequilibrium Mapping

Since all patients are derived from a common founder they will show homozygosity for a common haplotype comprised of polymorphic markers very close to the gene

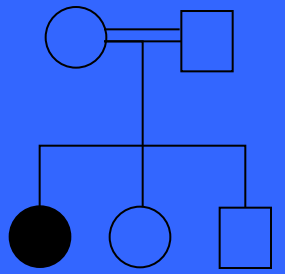
Pedigrees of Iraqi Families



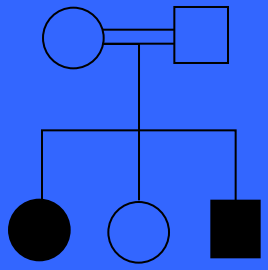
Family 1



Family 2



Family 3



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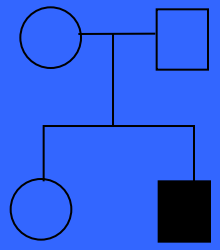
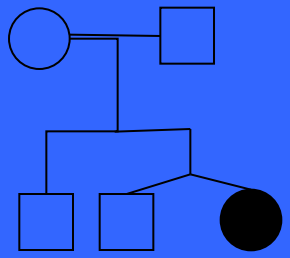


Family 5



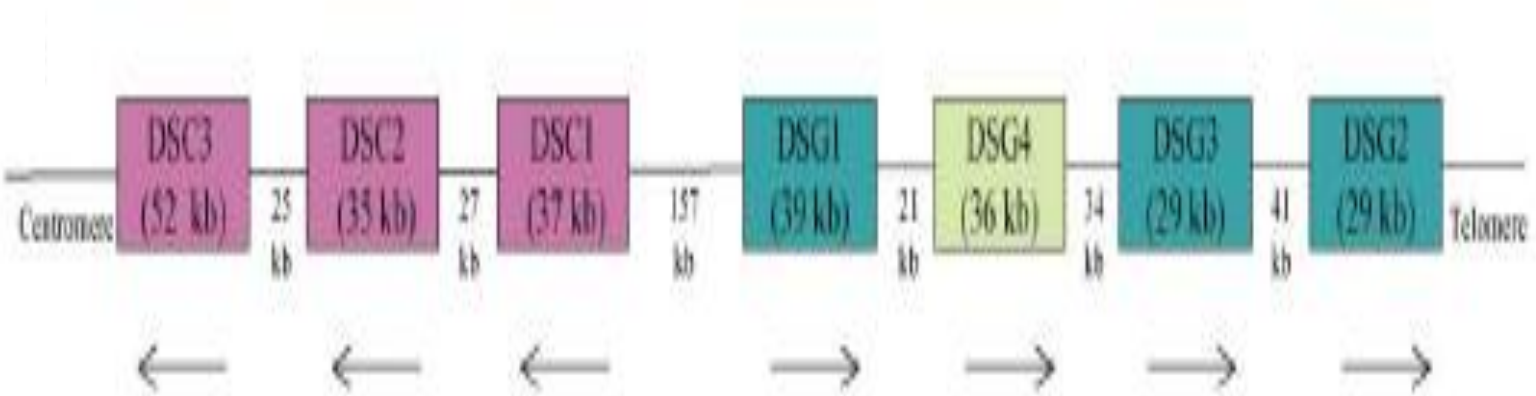
Family 6

Linkage Disequilibrium Mapping-Results

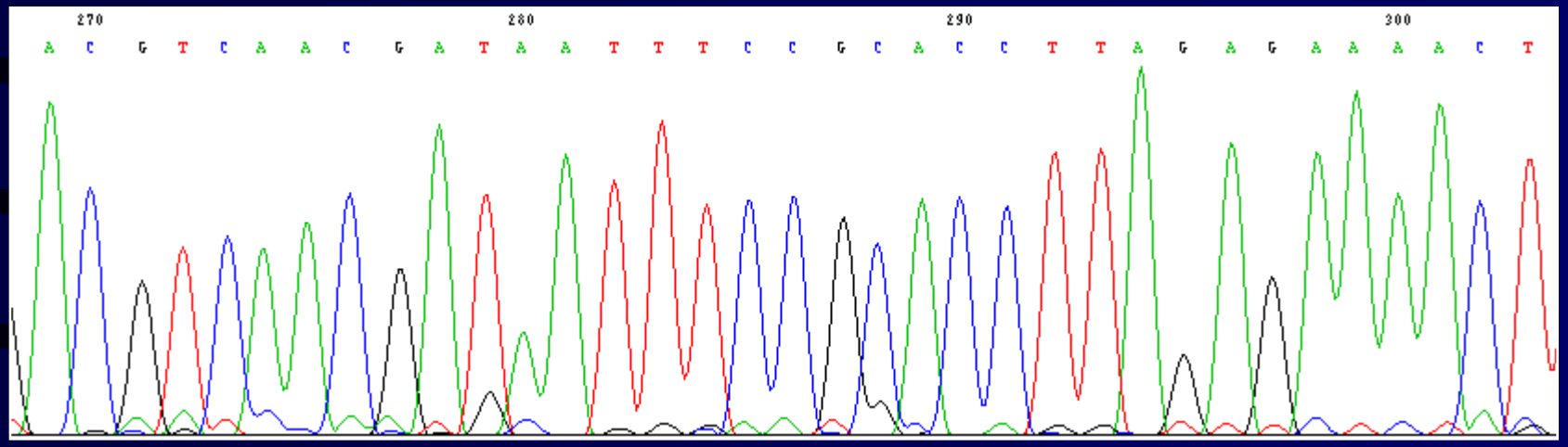
For a polymorphic marker derived from clone AC012417 (chromosome 18q) all patients were homozygous for the 219 bp allele, while only 3 of 20 controls were heterozygous for it ($p<0.001$)

Desmosomal Cadherin divides into two different groups: Desmogleins and Desmocollines

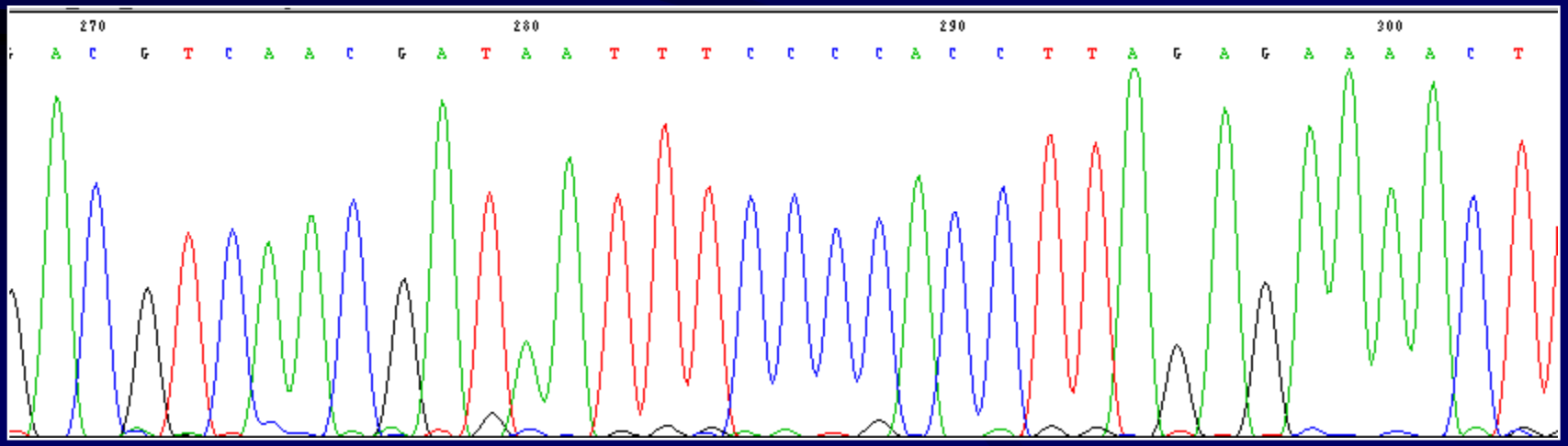
Desmosomal Cadherin is located in a small region on chromosome 18q12.

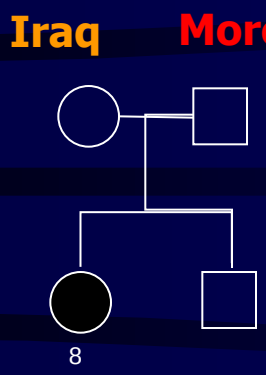


P267R-Iraq

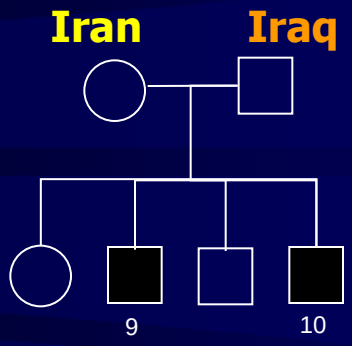


Cac → gac

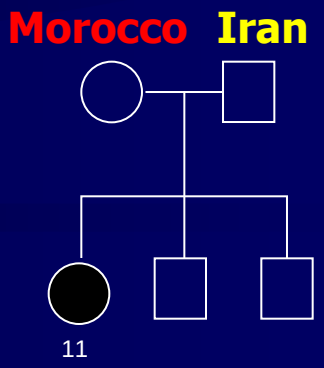




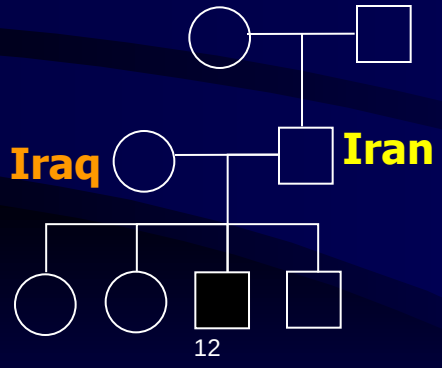
Family 7



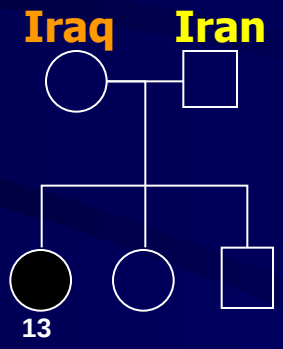
Family 8



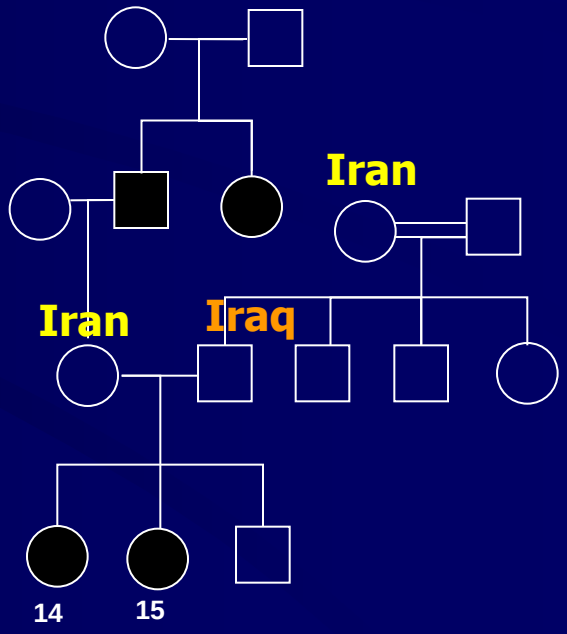
Family 9



Family 10

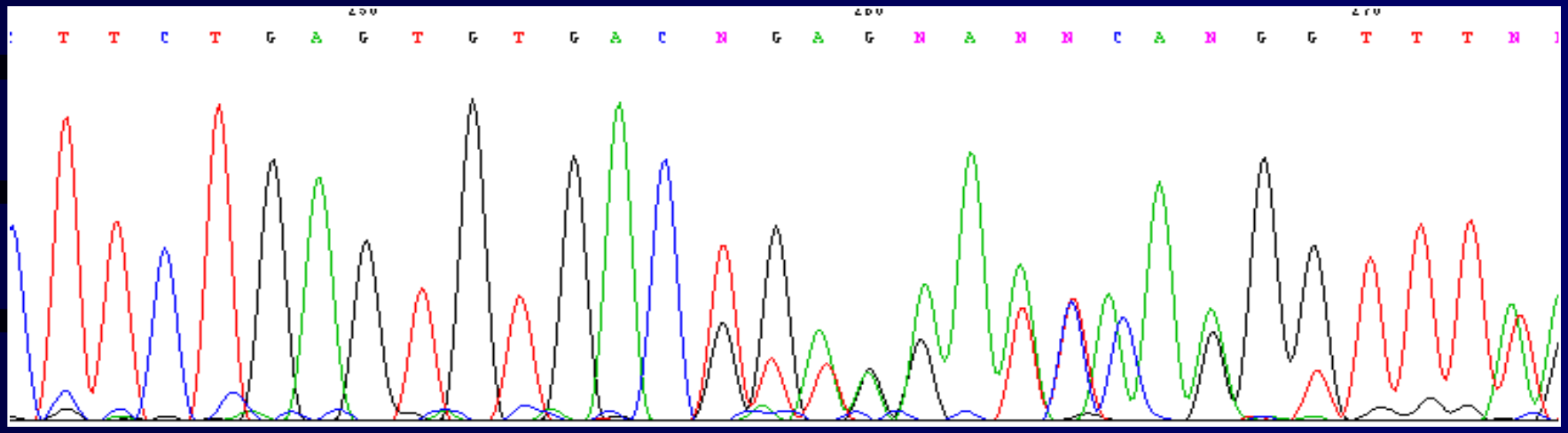


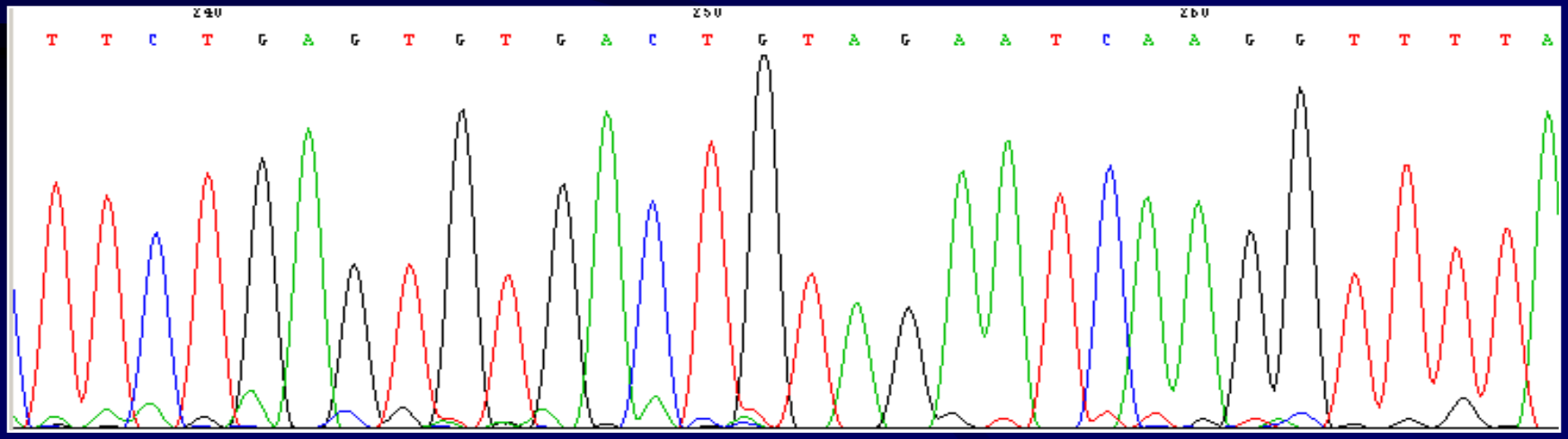
Family 11



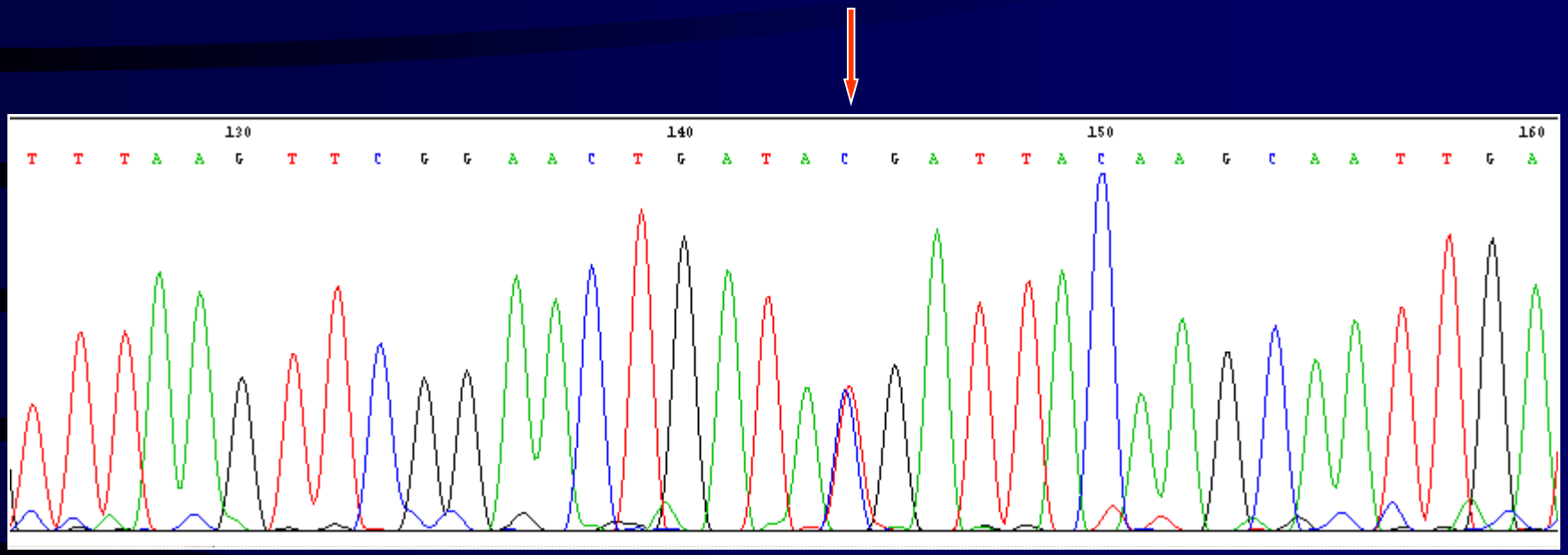
Family 12

763 del T-Iran

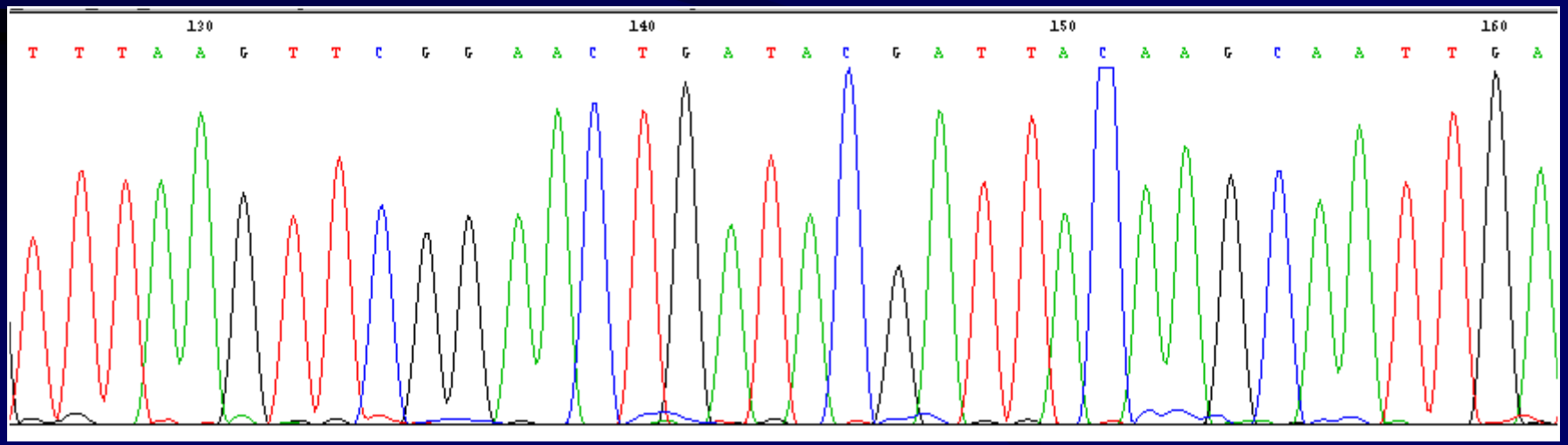


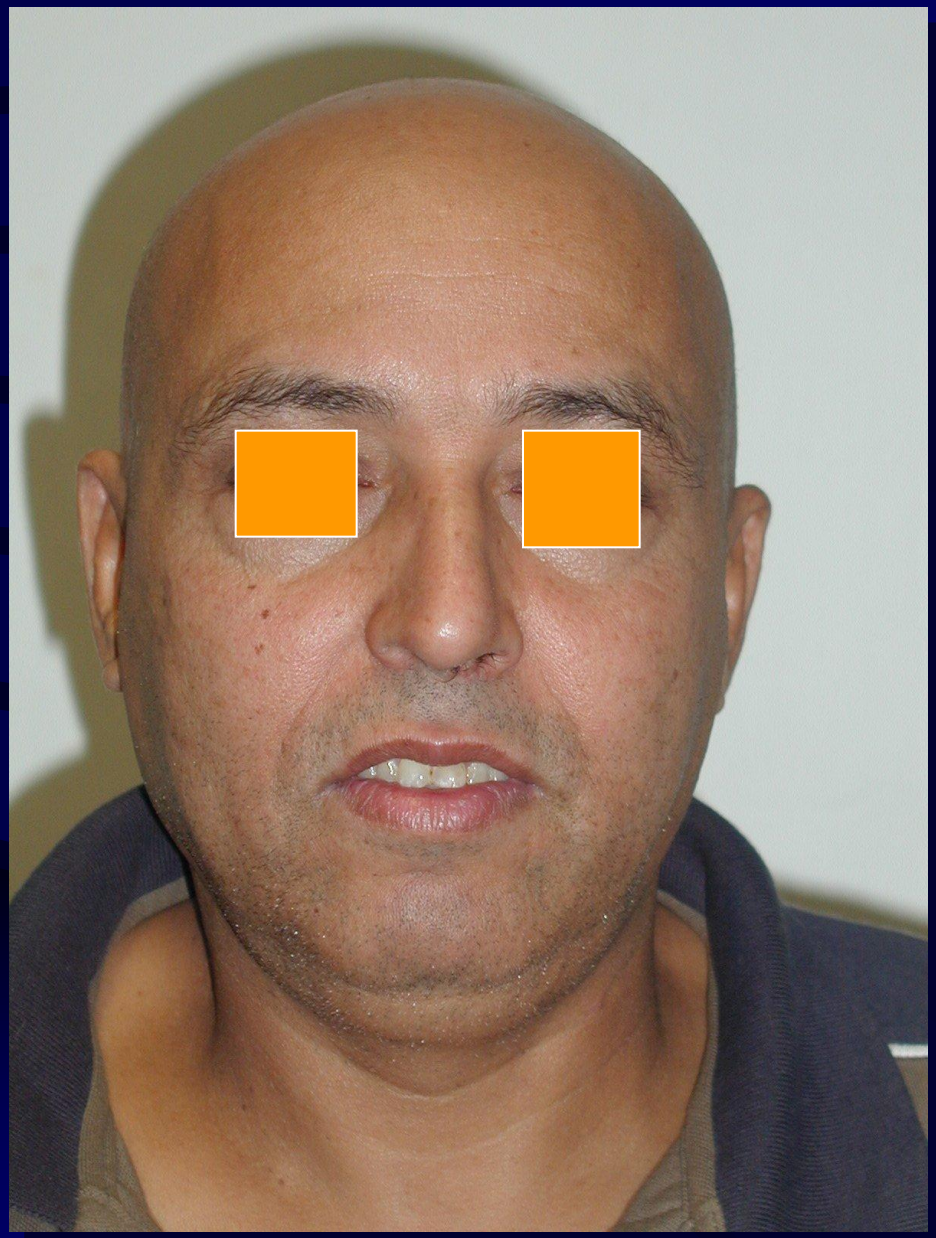


R289X-Morocco



cga → tga





In a perfect world (March 2014)

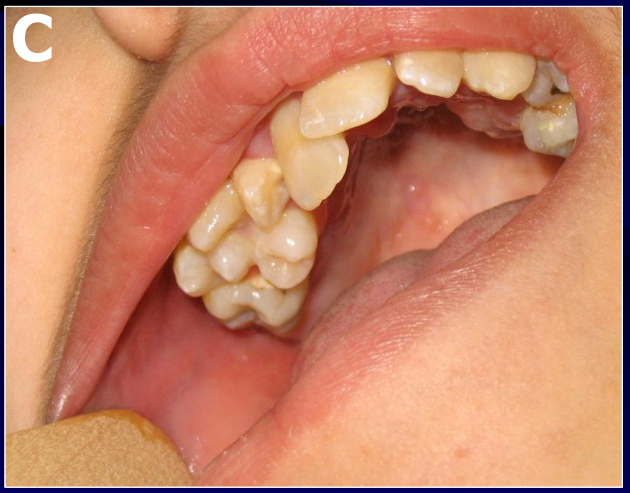
In a perfect world (March 2014)

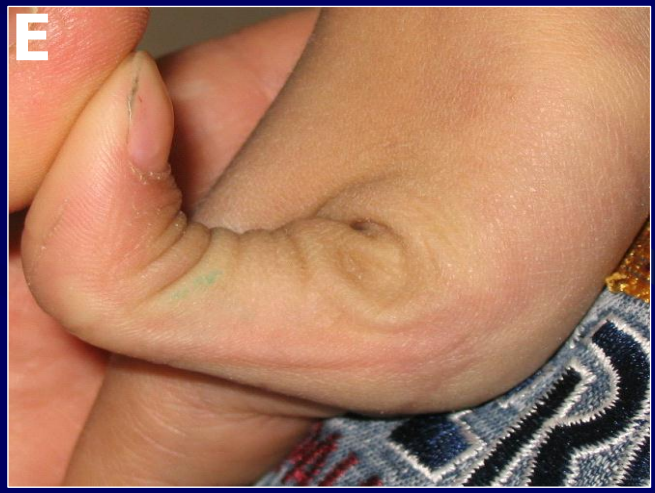
Prenatal Diagnosis

CVS
Amniocynthesis

Brittle Cornea Syndrome

Clinical Features:

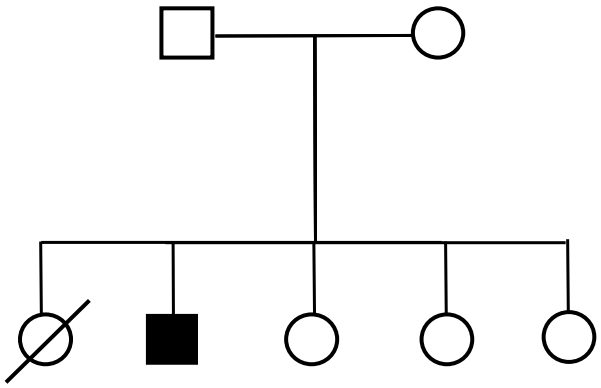




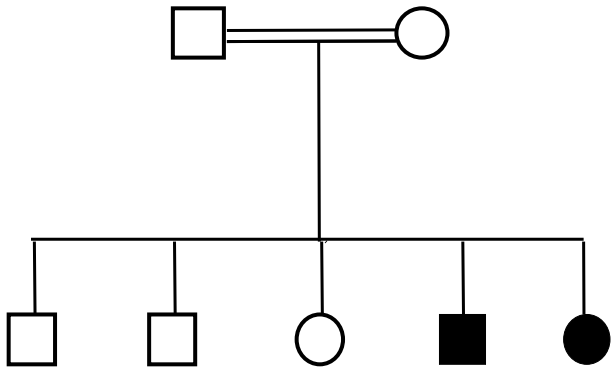
BCS is a rare generalized connective tissue disorder.


2008 © Tsur Richter-Levin

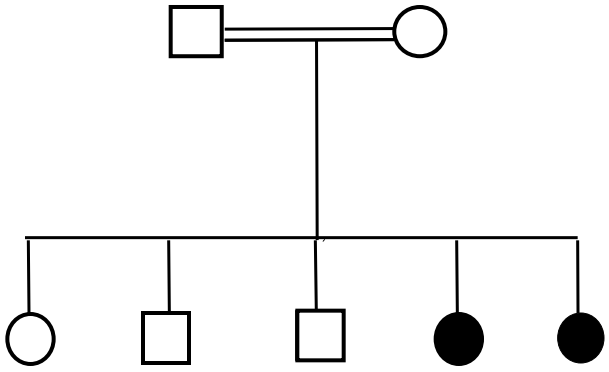
Tunisian Families



Family A



Family B

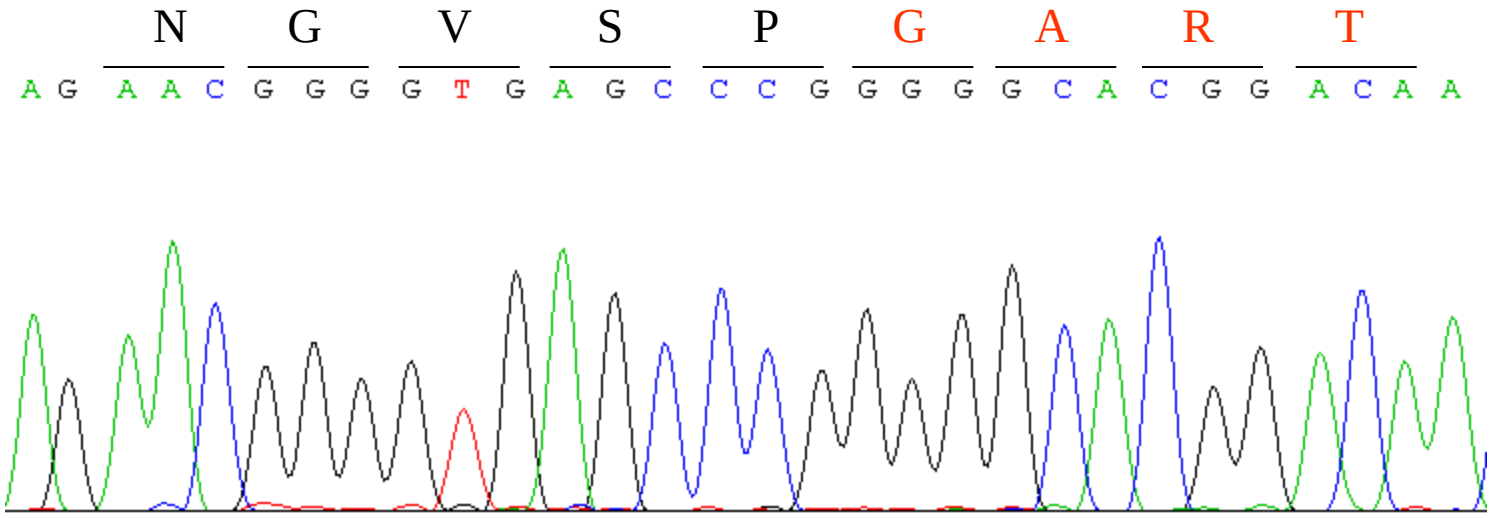


Family C *

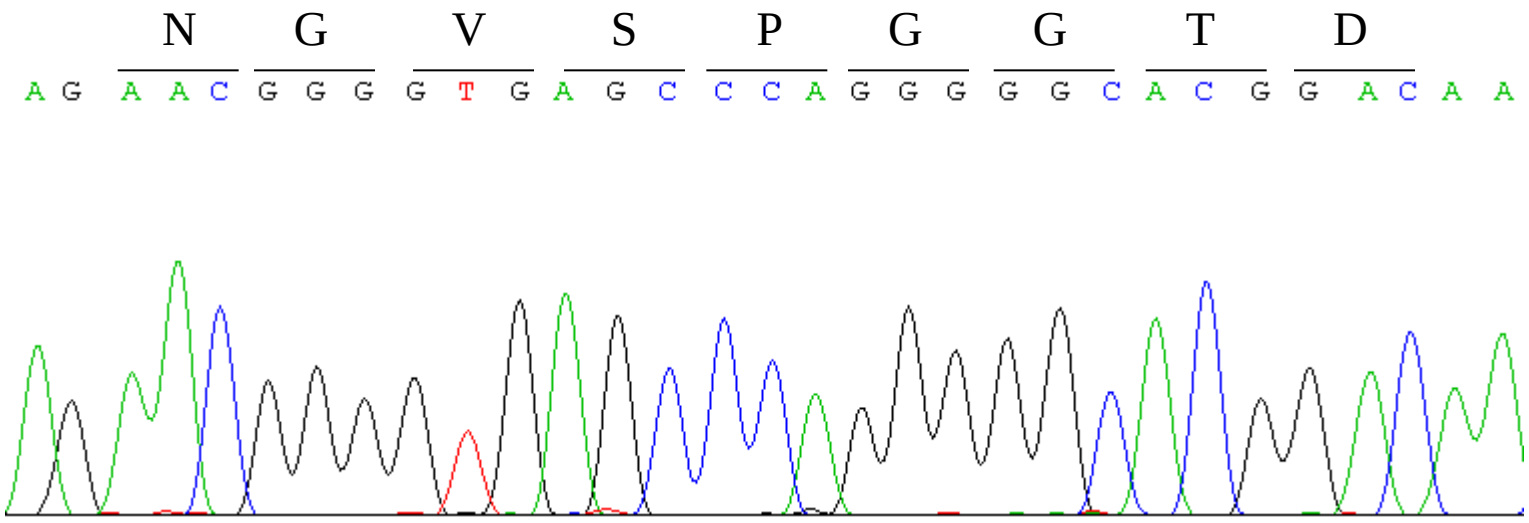
	cen.								tel.
Location	83.8	84.7	85.7	86.5	87.6	88.1	88.3	88.5	88.7
Markers	*AC092275*	*AC135012*	*AC136285*	*AC133539*	*AC135782*	*AC092123*	*AC005360*	*AC092143*	*AC137933*
		3	**2**	**1**	**1**	**1**	**1**		
A.S.-allele 1	2	3	2	1	1	1	1	2	2
A.S.-allele 2	2	3	2	1	1	1	1	2	2
T.F.-allele 1	3	3	2	1	1	1	1	2	1
T.F.-allele 2	4	3	2	1	1	1	1	2	2
J.F.-allele 1	3	3	2	1	1	1	1	2	1
J.F.-allele 2	4	3	2	1	1	1	1	2	2
O.R.-allele 1	2	3	2	1	1	1	1	2	1
O.R.-allele 2	2	3	2	2	1	1	1	2	2
N.M.-allele 1	2	3	2	1	1	1	1	4	1
N.M.-allele 2	2	3	2	1	1	1	1	4	2

5943 del A - Tunisian Jews

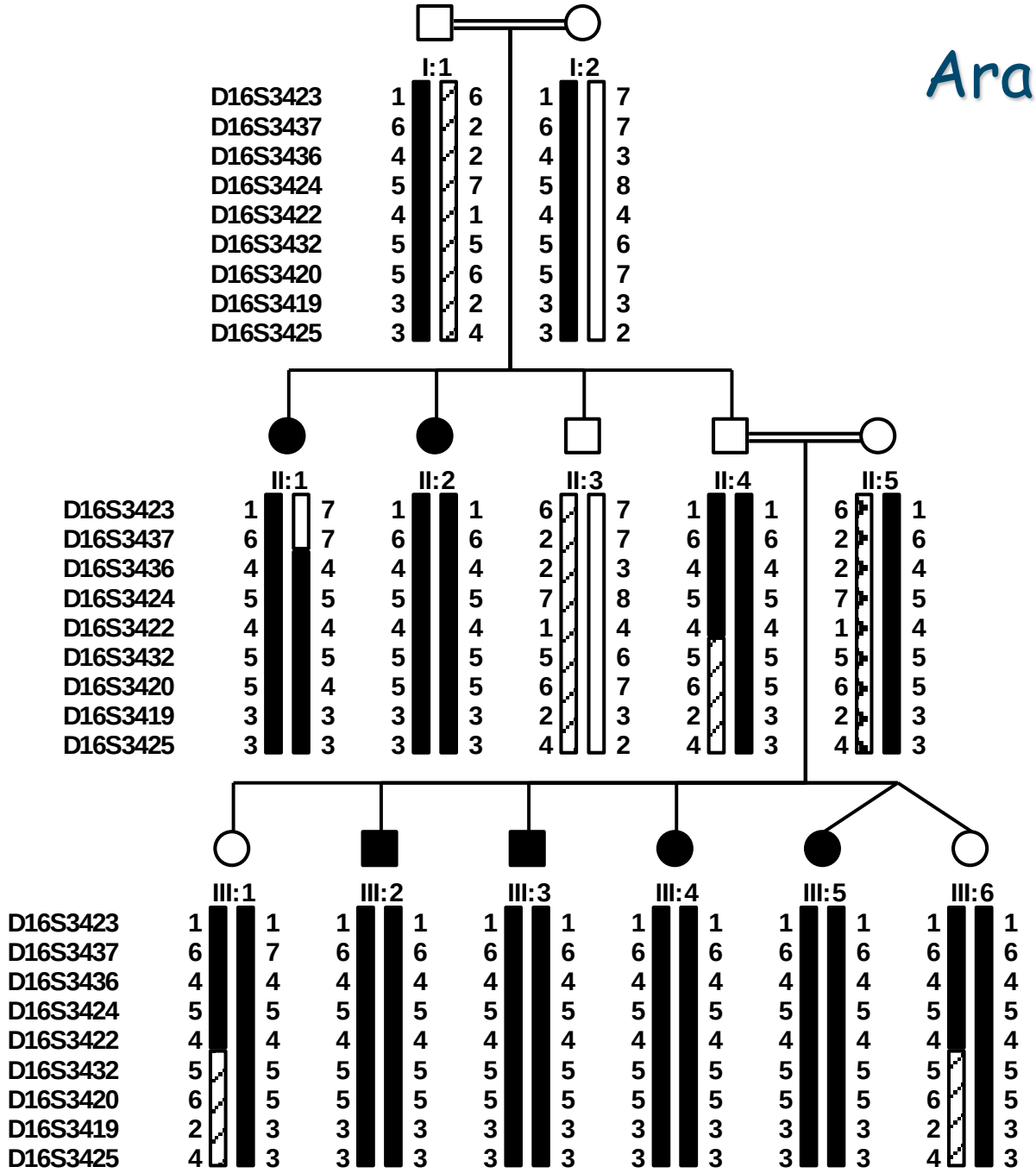
Patient

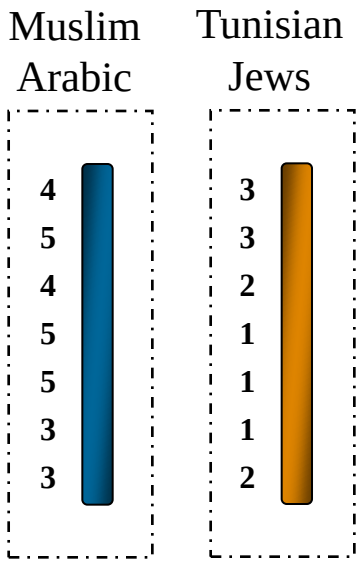


WT



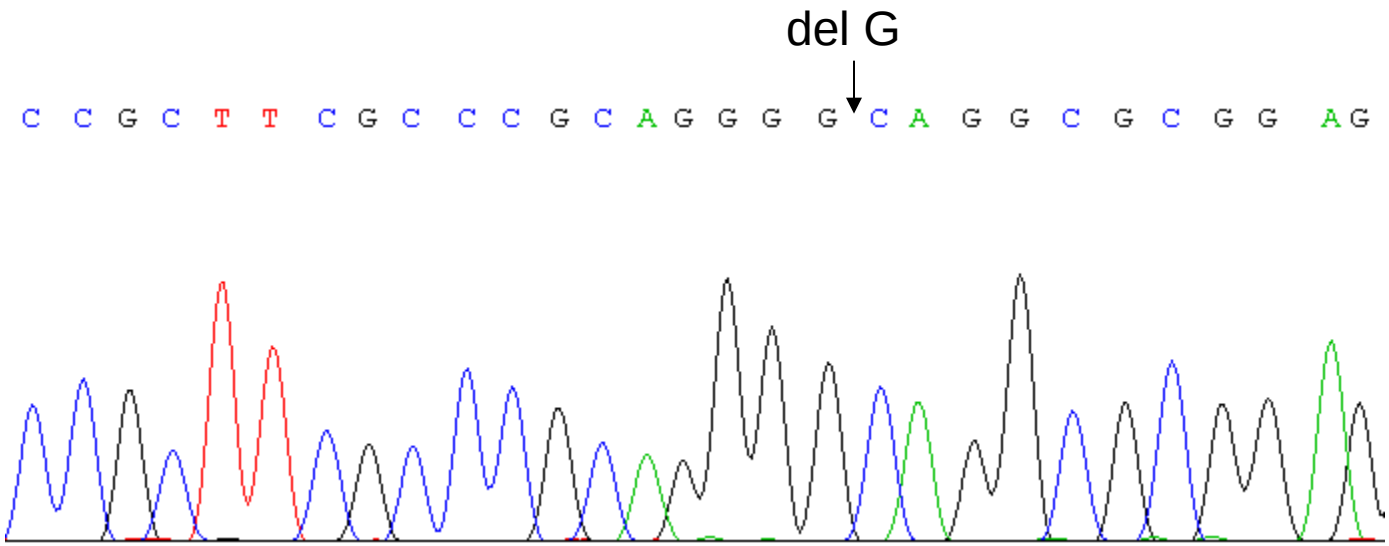
Arab Muslim Family



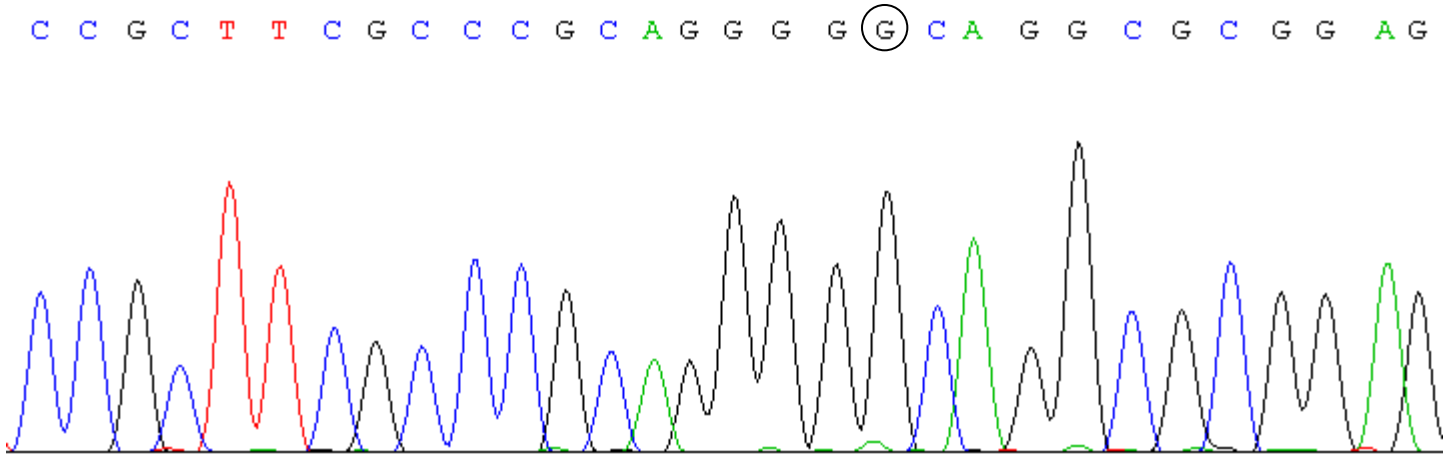


9527 del G - Muslim Arabic

Patient

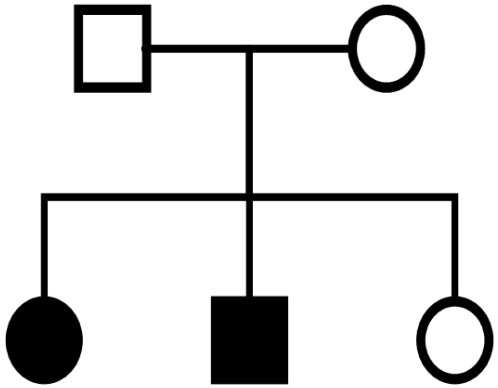


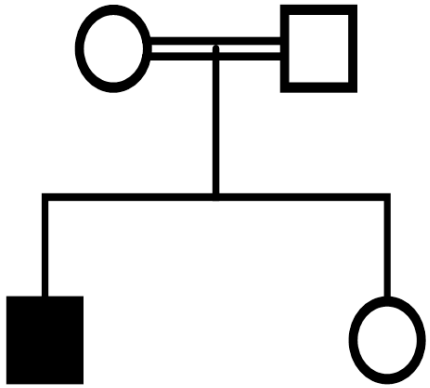
WT



ZNF 369

Involved in polygenic keratoconus diseases





Clinical Features

- Persian Jewish origin
- Microcephaly from birth
- Feeding difficulties
- Increased spastic tone
- Intractable infantile spasms
- Profound mental retardation
- Cortical blindness
- Progressive cortical and subcortical atrophy with delayed myelination (MRI)
- Metabolic workup – unremarkable

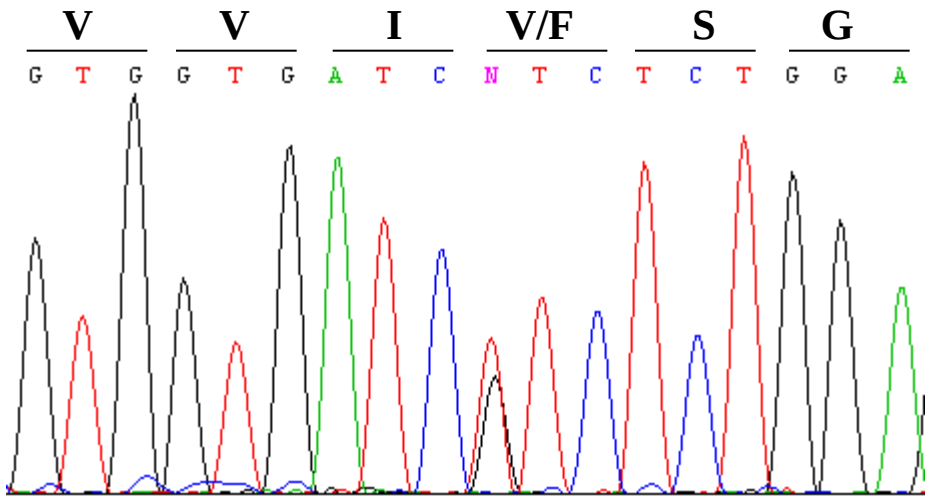
Whole Exome Sequencing

A new method for identifying genes that cause monogenic disorders

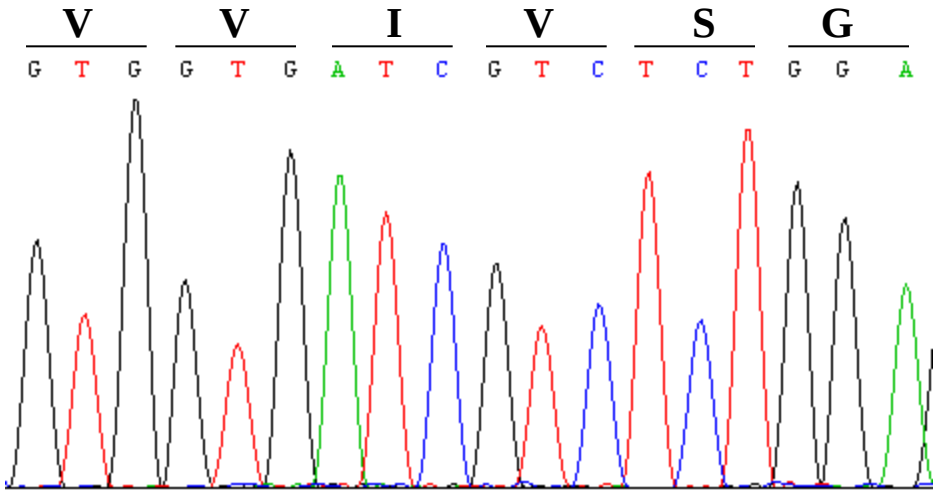
Elon Pras

ASNS

Hetero.



Patient



Microcephaly and Mental Retardation

- The mutation is in a conserved region
- It was found in full segregation in the families
- It was not found in Caucasian 1160 controls
- It was found in the heterozygous state in 1:80 Persian Jews
- It is linked to Alanin and Aspartate/ nitrogen metabolism
- The mutation causes an unstable protein

Costs!!!!!

$4,000

Take home message

Thank You