Research seminar Genetic Epidemiology

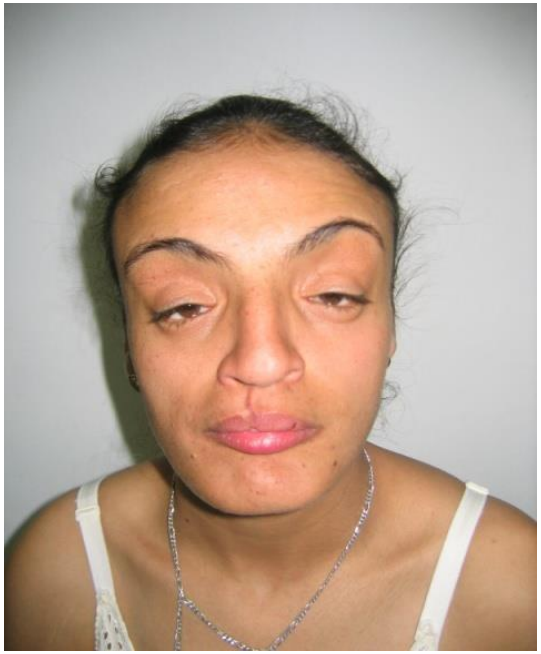
- **Genetic epidemiology** is the study of the role of genetic factors in determining health and disease in families and in populations, and the interplay of such genetic factors with environmental factors. In slightly more formal language, genetic epidemiology was defined by Morton as "a science which deals with the etiology, distribution, and control of disease in groups of relatives and with inherited causes of disease in populations". It is closely allied to both molecular epidemiology and statistical genetics, but these overlapping fields each have distinct emphases, societies and journals.
- Traditionally, the study of the role of genetics in disease progresses through the following study designs, each answering a slightly different question:
- Familial aggregation studies: Is there a genetic component to the disease, and what are the relative contributions of genes and environment?
- Segregation studies: What is the pattern of inheritance of the disease (e.g. dominant or recessive)?
- Linkage studies: On which part of which chromosome is the disease gene located?
- Association studies: Which allele of which gene is associated with the disease?

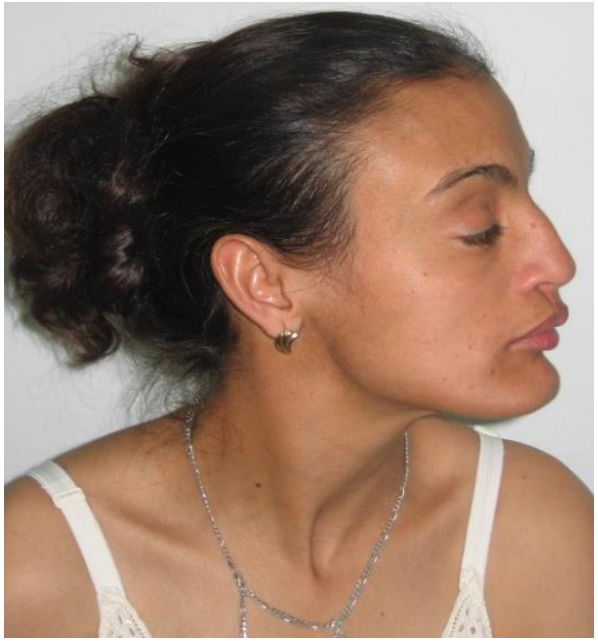
Is er een gen voor 3MC syndroom ?

Genoomwijd koppelingsonderzoek als strategie om nieuwe genen te identificeren

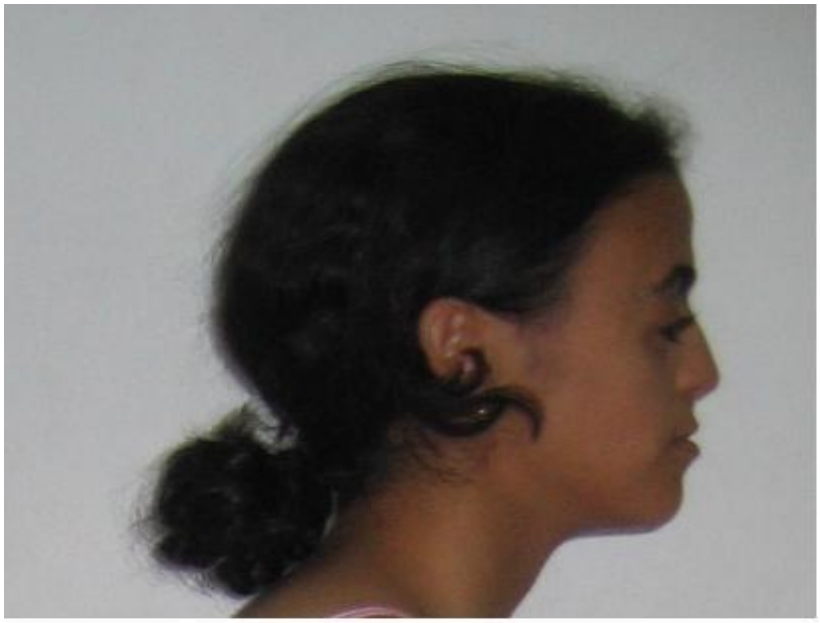
Hilde Peeters

Seloua



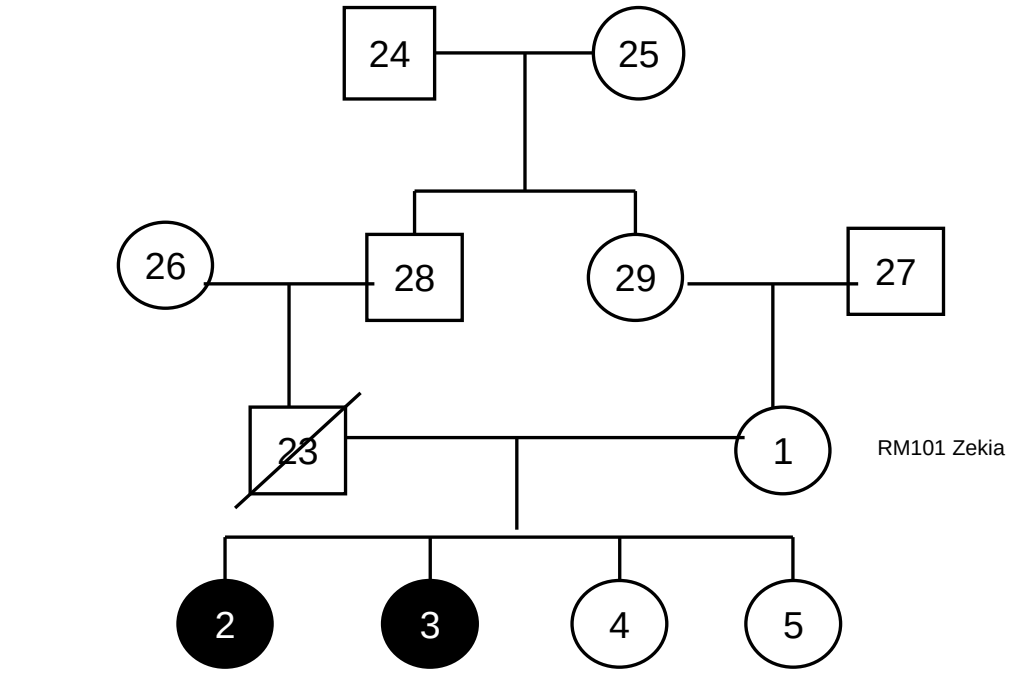


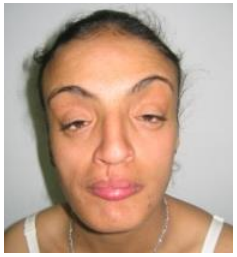
Meyda

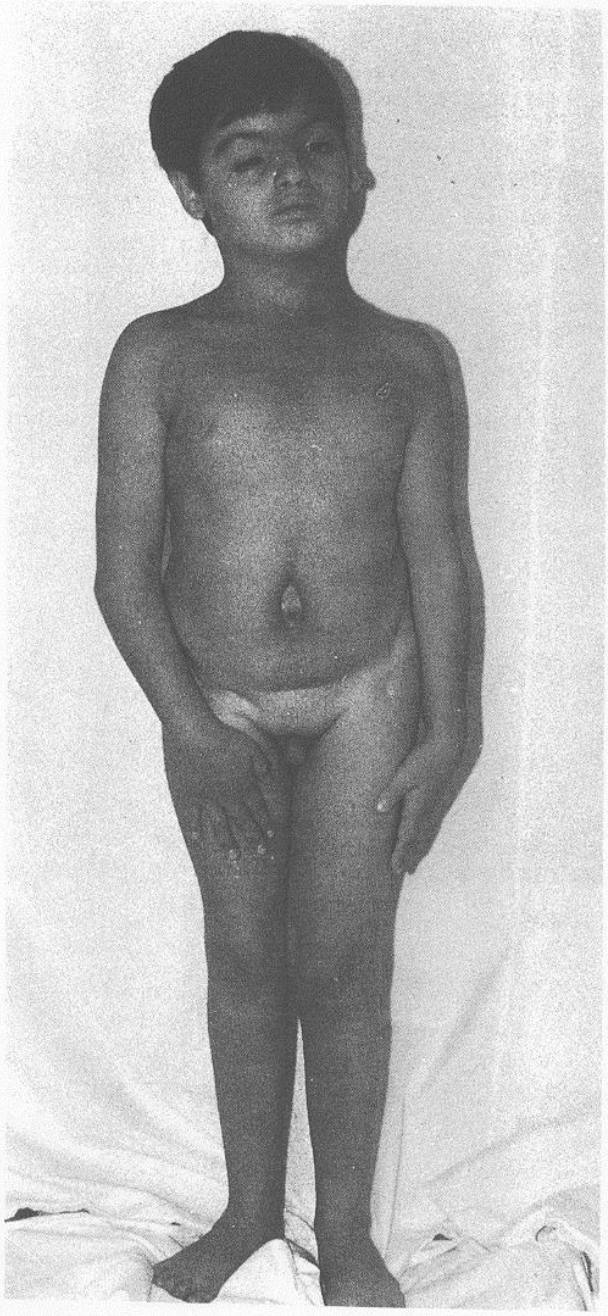


Ped.1

Tunisia







Patient 1 at 9½ years. Note defect of the abdominal muscles from surgery for hip dislocation.

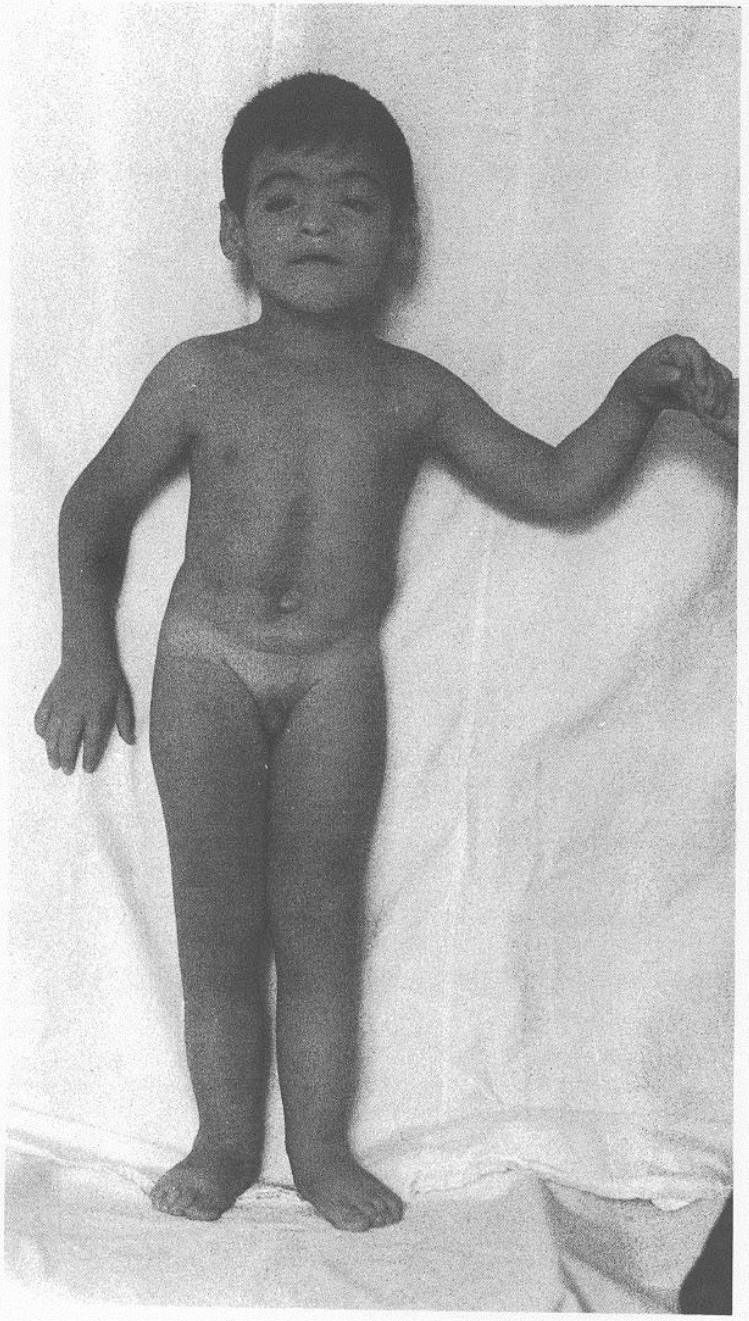


Fig. 4. Patient 2 at 6½ years. Note defect of the abdomi and laterally rotated feet.

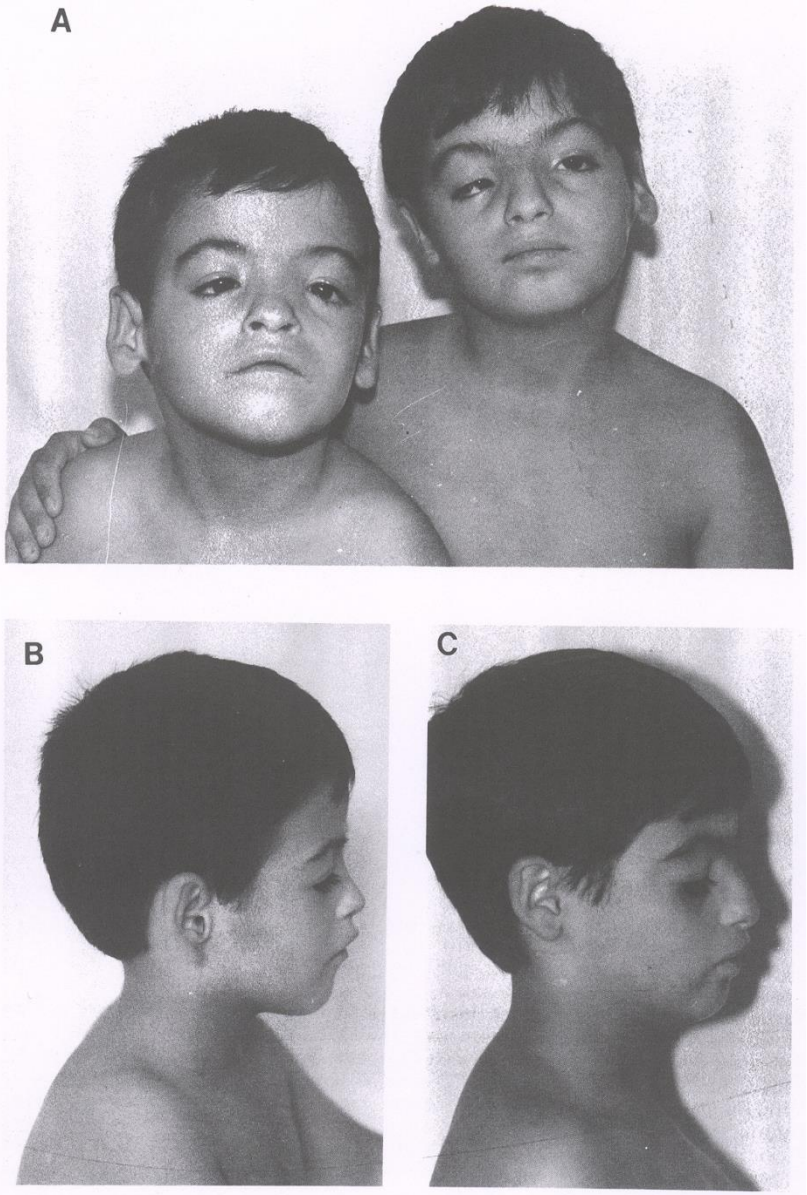
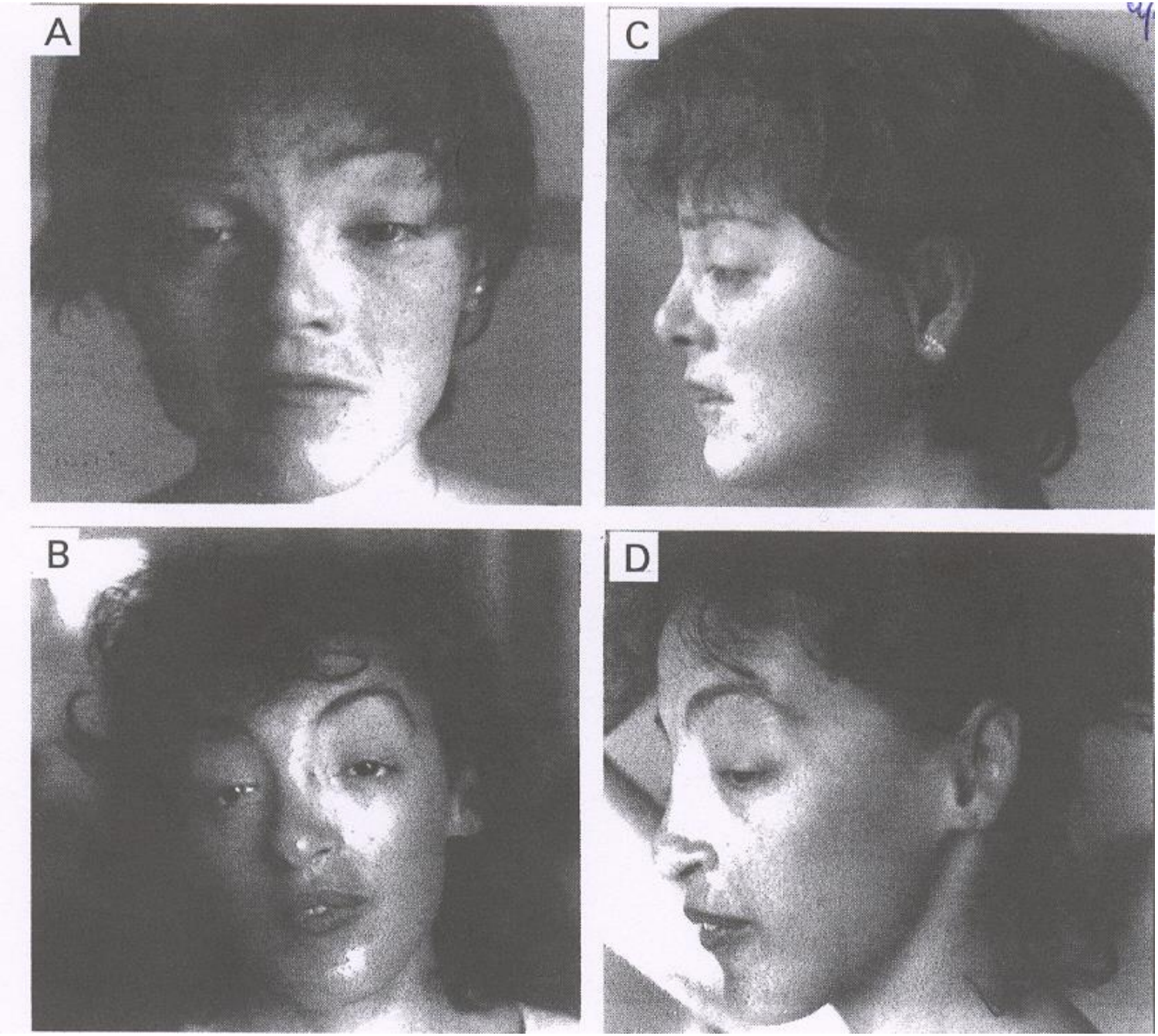
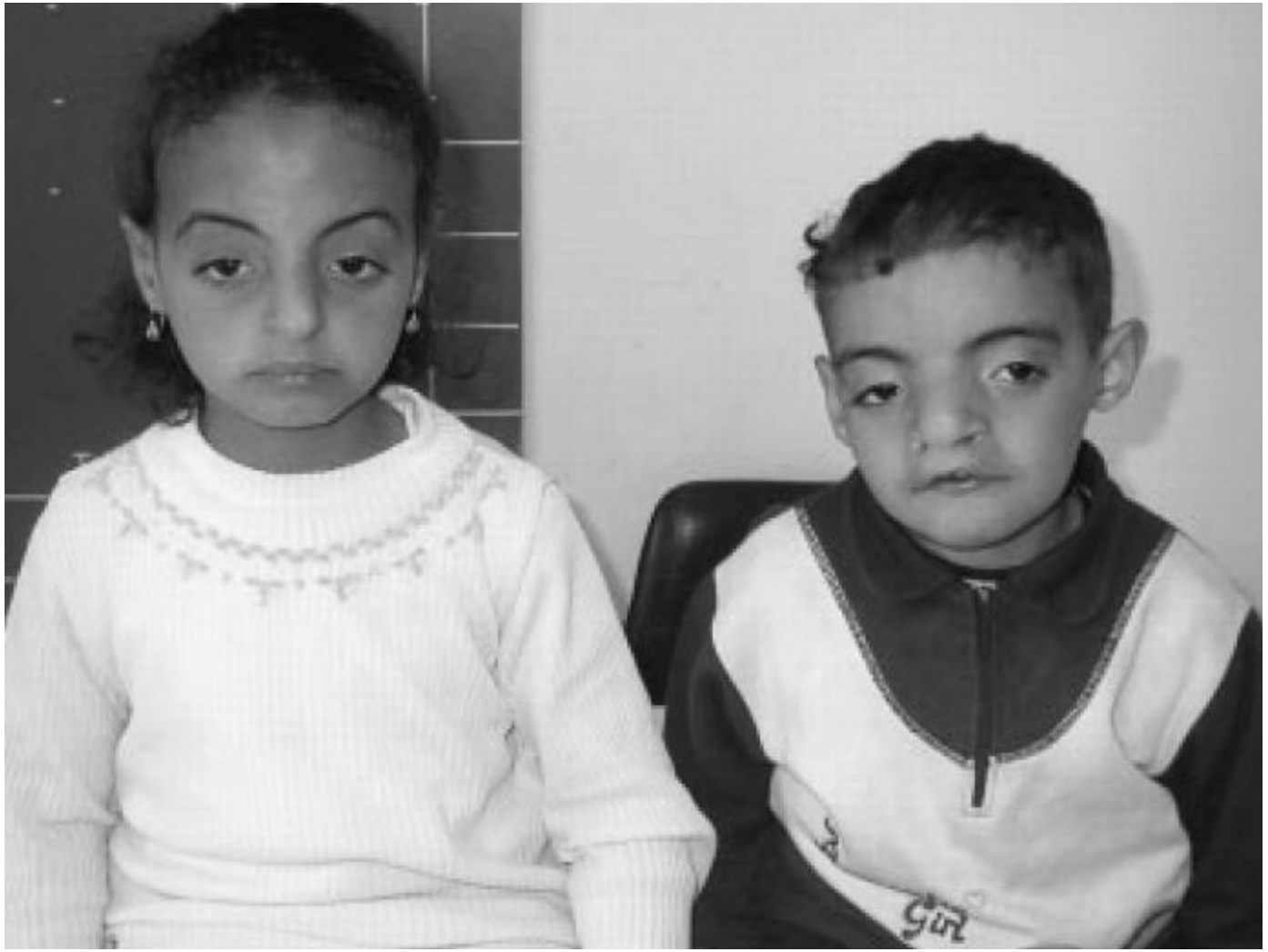
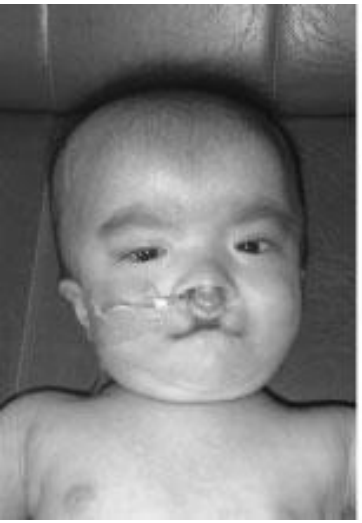
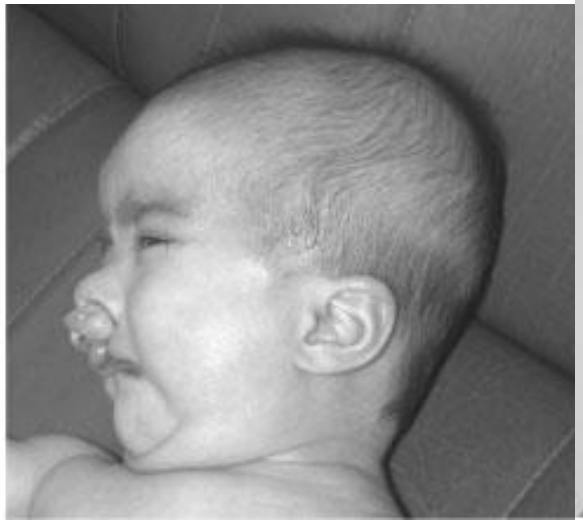
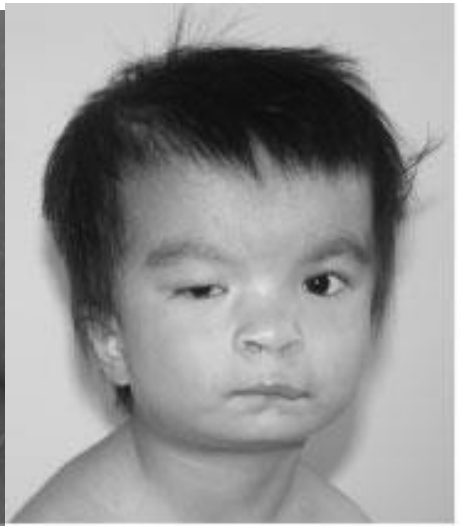
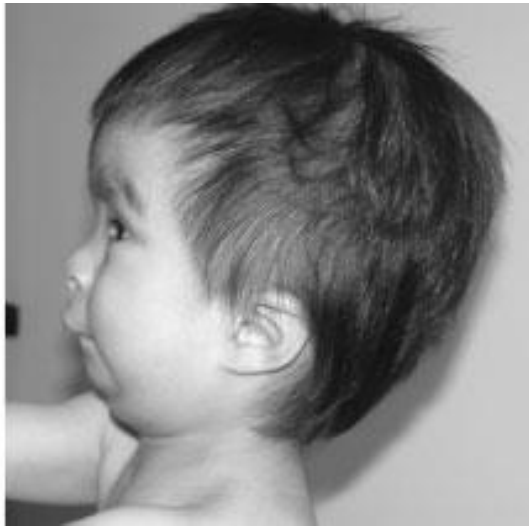


Fig. 2. Patients 1 and 2 at years 6½ and 9½, respectively. **a:** Note ptosis of the eyelids, convergent strabismus, depressed bridge of the nose, smooth philtrum, downturning corners of the mouth. **b,c:** Note malformed helices and micrognathia.


A
C
B
D



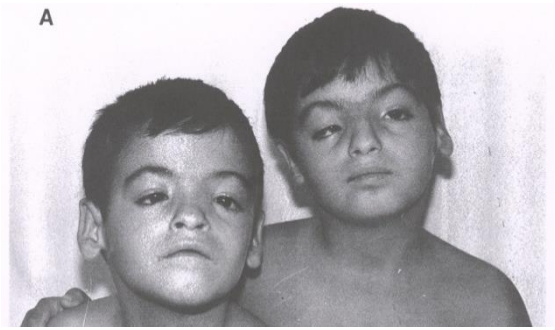





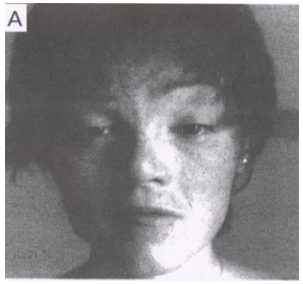
1. Carnevale F et al. 1989. Ptosis of eyelids, strabismus, diastasis recti, hip defect, cryptorchidism, and developmental delay in two sibs. Am J Med Genet 33: 186-189.

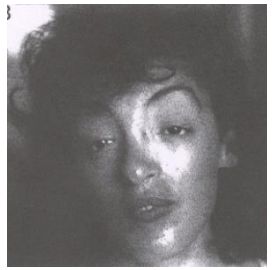
2. Mingarelli R et al. 1996. Two sisters with a syndrome of ocular, skeletal, and abdominal abnormalities (OSA syndrome). *J Med Genet* **33**: 884-886

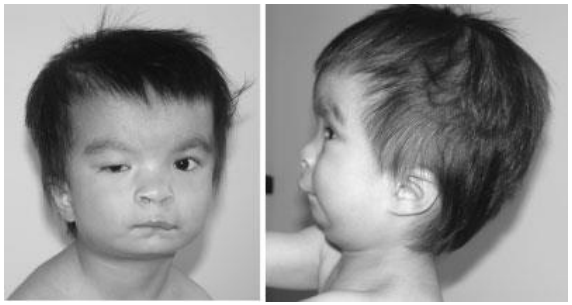
3. Verloes A et al. 2005. Michels syndrome, Carnevale syndrome, OSA syndrome, and Malpuech syndrome: variable expression of a single disorder (3MC syndrome)? *Am J Med Genet 137:332-335*.

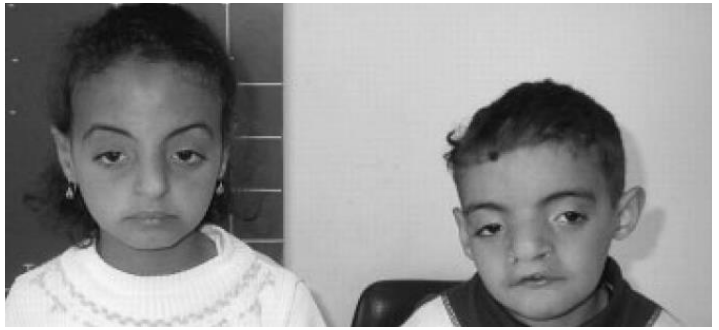
4. Al Kaissi A, Klaushofer K, Safi H, Chehida FB, Ghachem MB, Chaabounni M, Hennekam RC. Asymmetrical skull, ptosis, hypertelorism, high nasal bridge, clefting, umbilical anomalies, and skeletal anomalies in sibs: is Carnevale syndrome a separate entity? Am J Med Genet A. 2007 Feb 15;143(4):349-54.

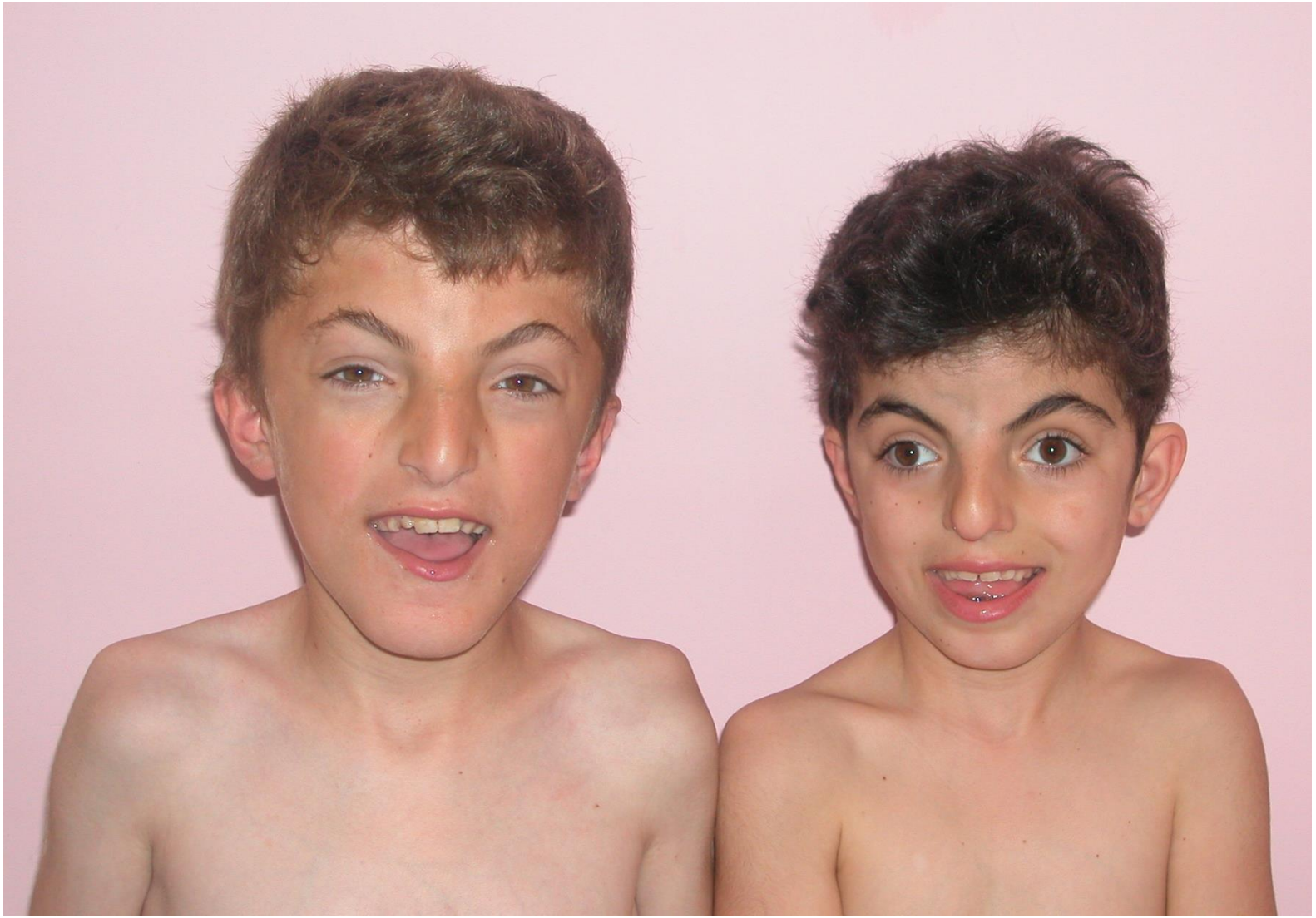


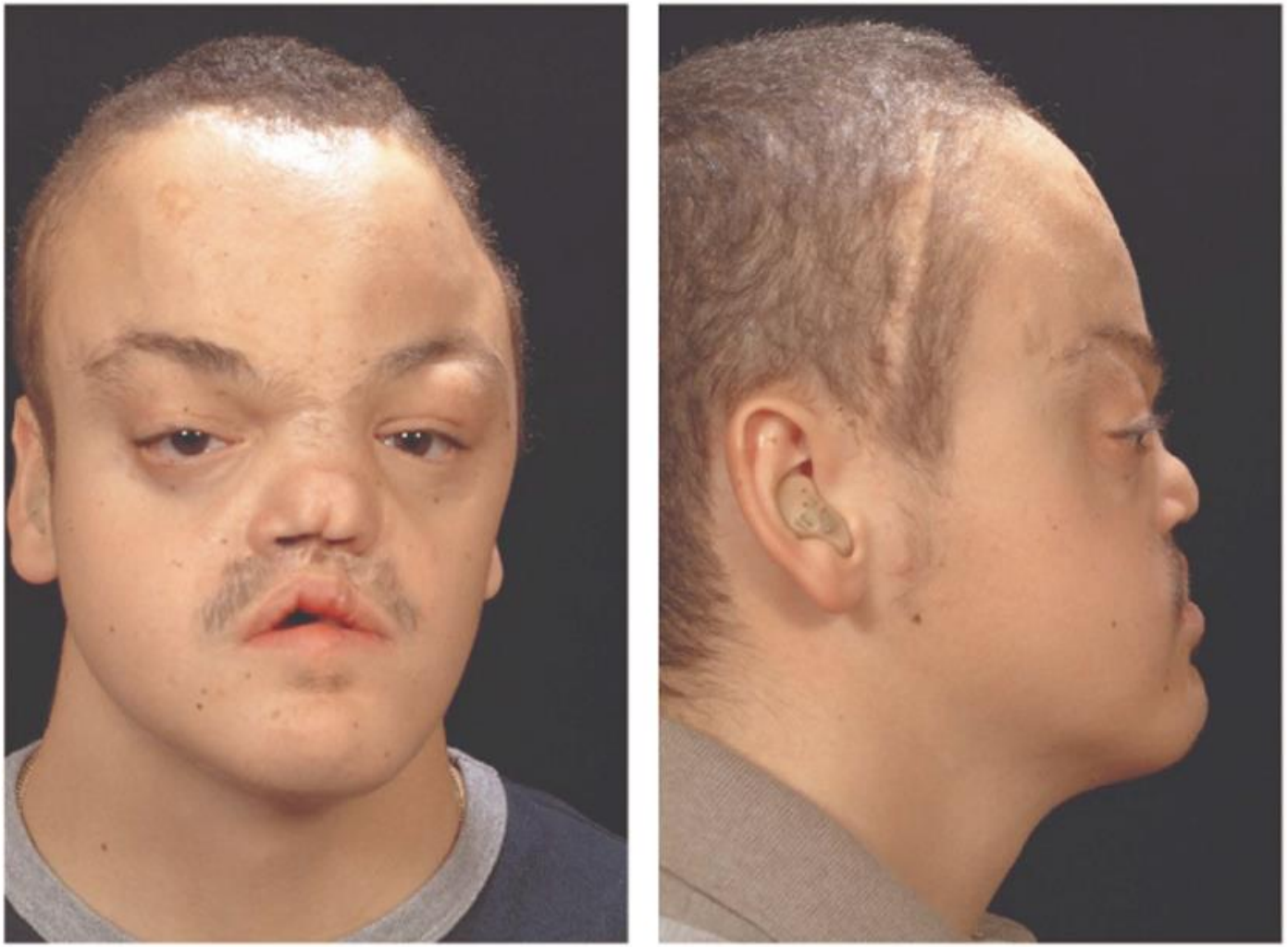










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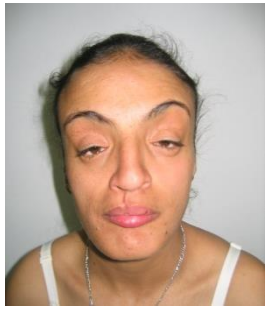

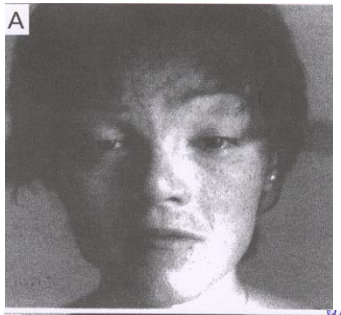
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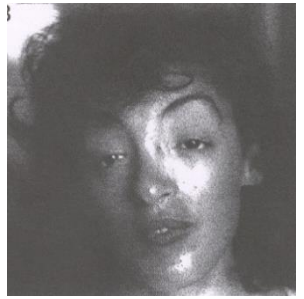

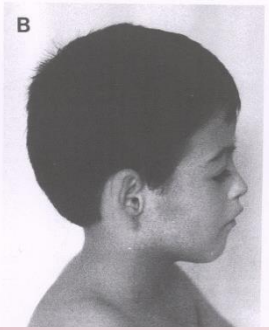
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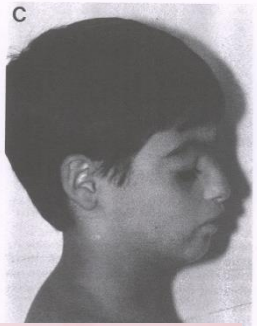
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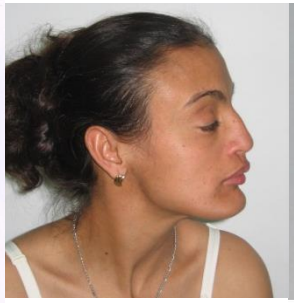

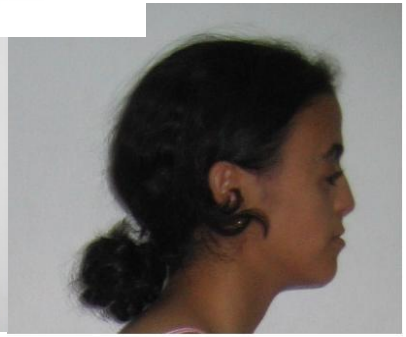

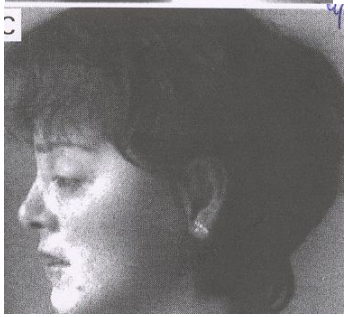
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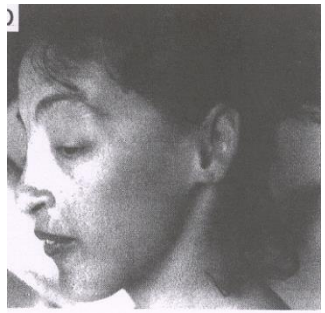
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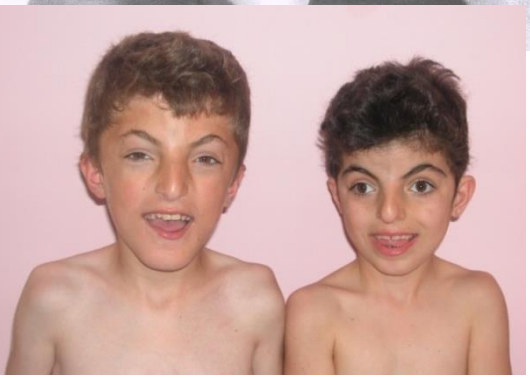
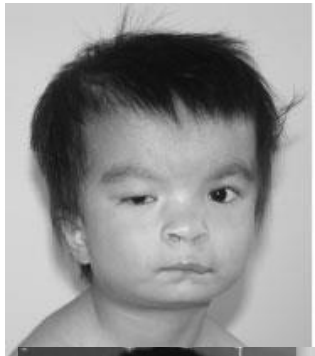
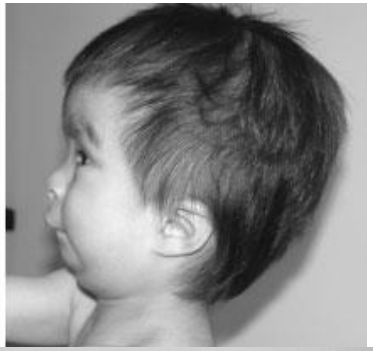
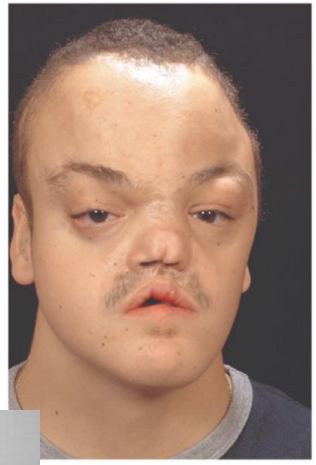
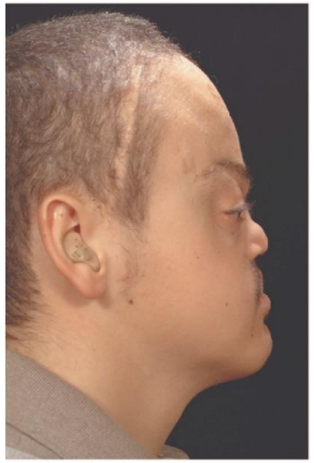










Family	Subject	Diagnosis	Origin
MC1	1.1	Carnevale	Tunisia
	1.2	Carnevale	Tunisia
MC2	2.1	Malpuech	Bangladesh
	2.2	Malpuech	Bangladesh
MC4	4.1	Malpuech or Michels	Afghanistan
	4.2	Malpuech or Michels	Afghanistan
MC8	8.1	Carnevale	Saudi Arabia
MC9	9.1	Malpuech	Pakistan
MC10	10	Mingarelli	Italy
MC11	11	Carnevale	Italy
MC3	3.1	Carnevale	Greece
MC5	5.1	Malpuech	Italy
	5.2	Malpuech	Italy
MC6	6.1	3MC	Brazil
	6.2	3MC	Brazil
MC7	7.1	Michels	Brazil

* **M**ingarelli (OSA) sd
* **M**alpuech sd
* **M**ichels sd
* **C**arnevale sd

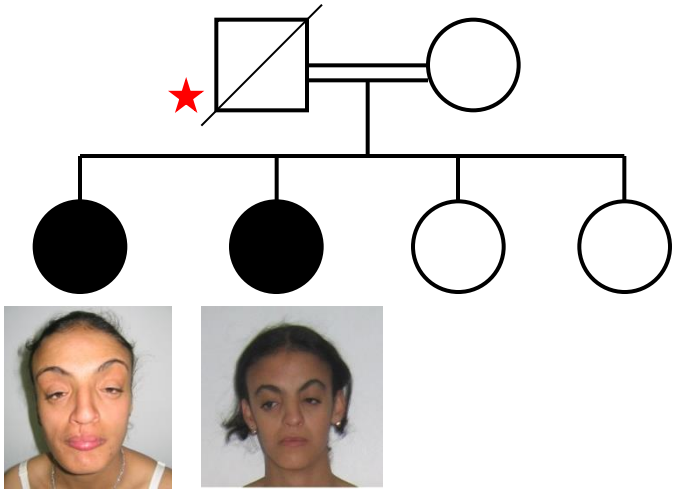
3MC syndrome

→ genetically heterogenous?
Locus heterogeneity?

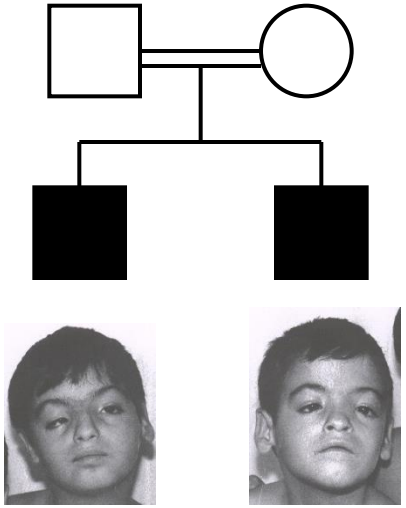
3MC syndrome

- Eyes Anomalies :
  - Eyelid triad (blepharophimosis, blepharoptosis, epicanthus inversus)
  - Hypertelorism
  - Arched eyebrowses
- Cleft lip /palate
- Abdominal muscular defect:
  - Umbilical depression
  - Umbilical hernia
  - Diastasis recti
- Limbal anomalies:
  - Limited supination-pronation/radioulnar synostosis
  - Short/clinodactily fifth finger
- Craniosynostosis

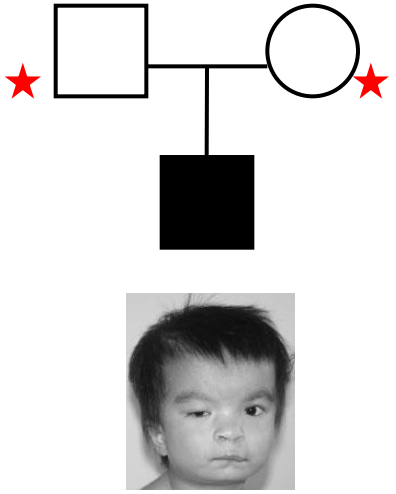
Families Available



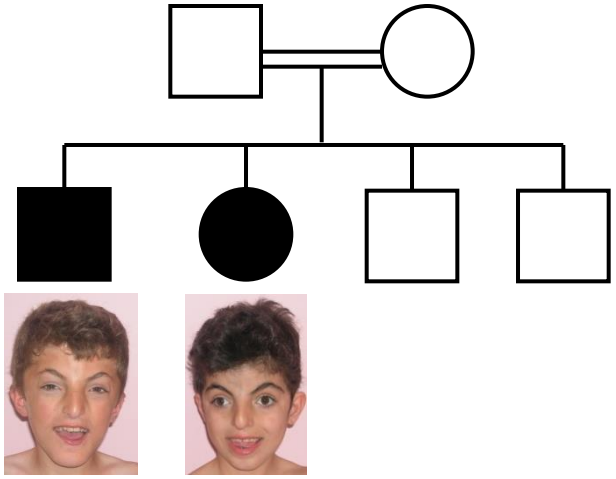
Ped.1 Tunisia



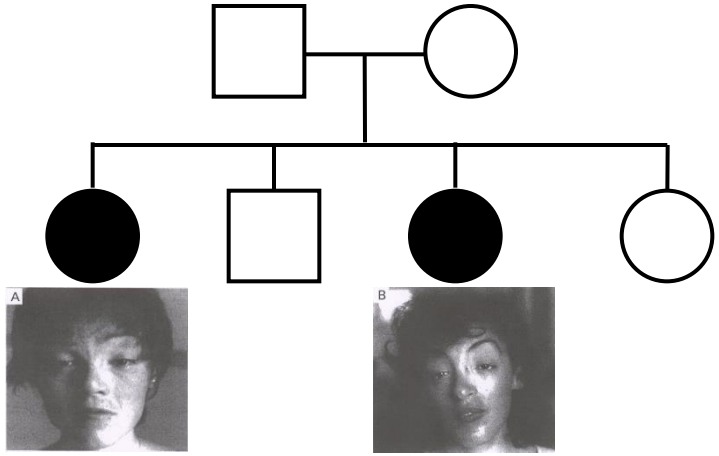
Ped.2 Italy: original Carnevale



Ped.3 China: A Verloes

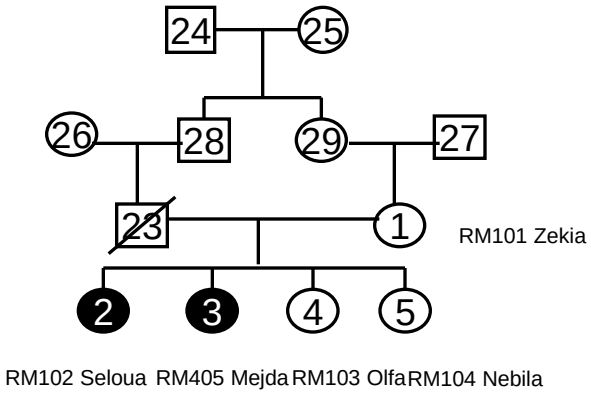


Ped.4 Turkey

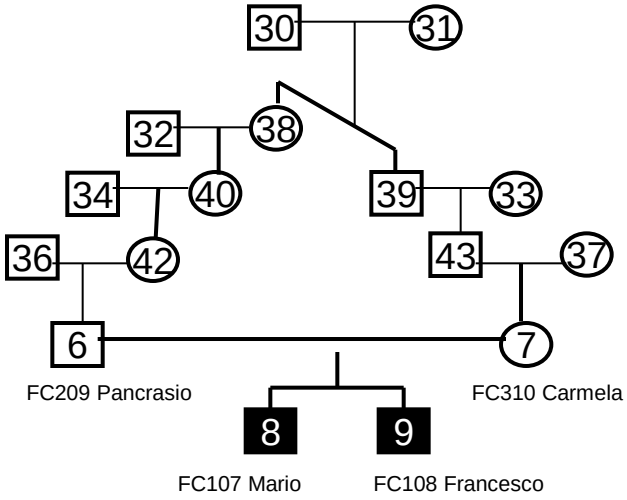


Ped.5 Italy: original Mignarelli

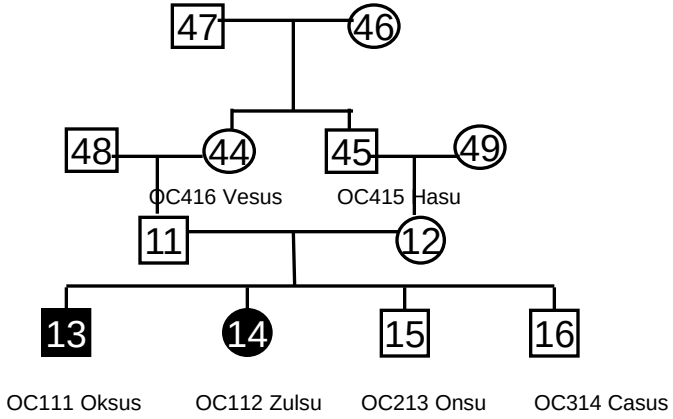
★ DNA not available



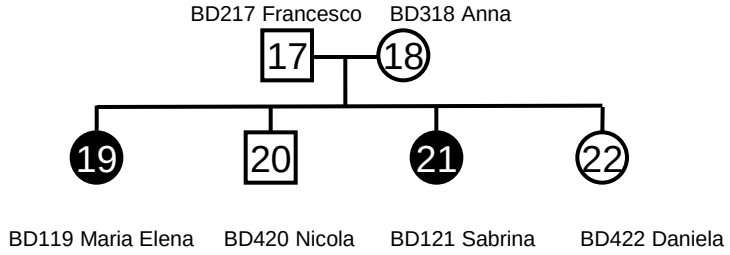
Ped.1 *Tunisia*



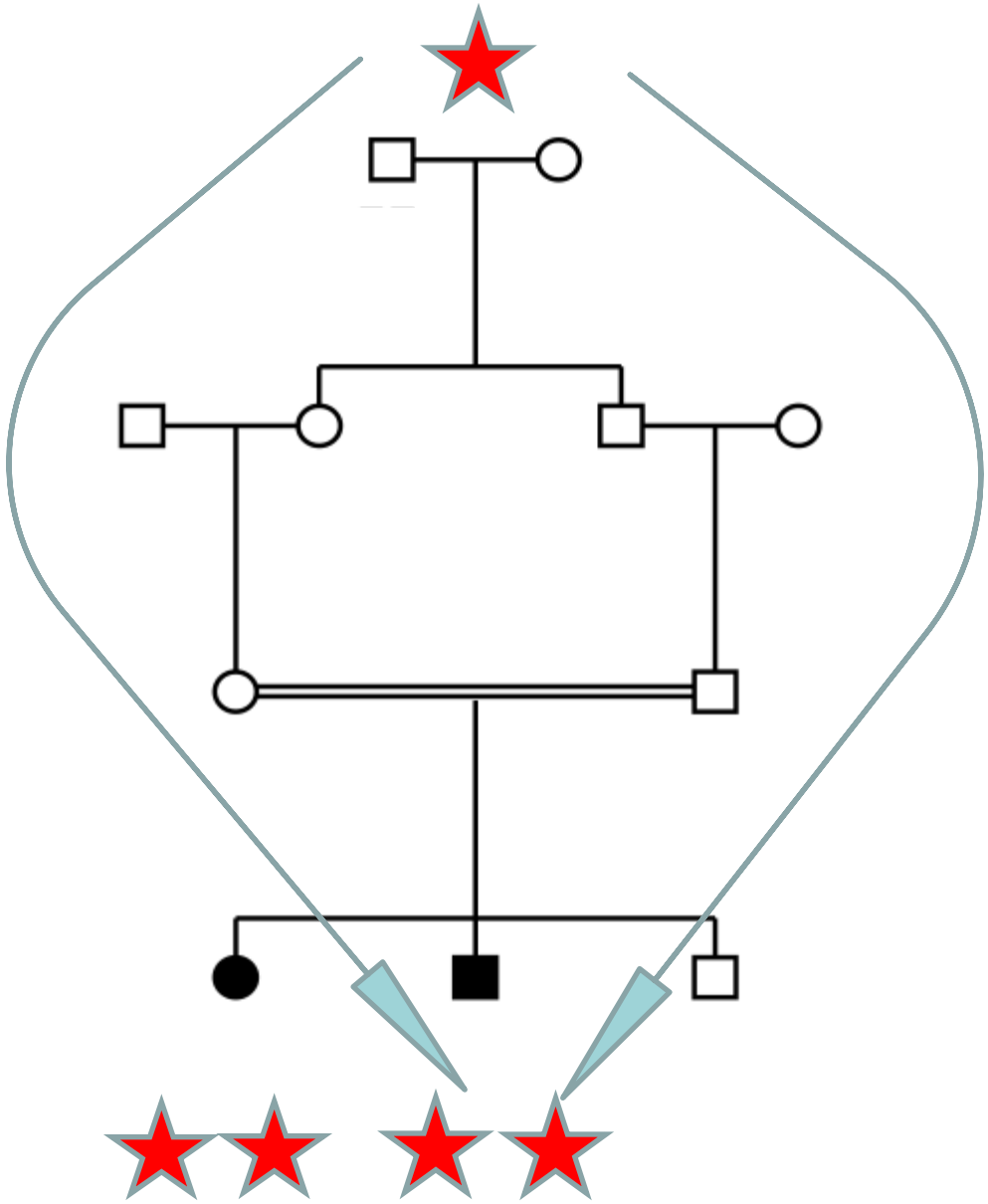
Ped.2 *Italy*



Ped.4 *Turkey*

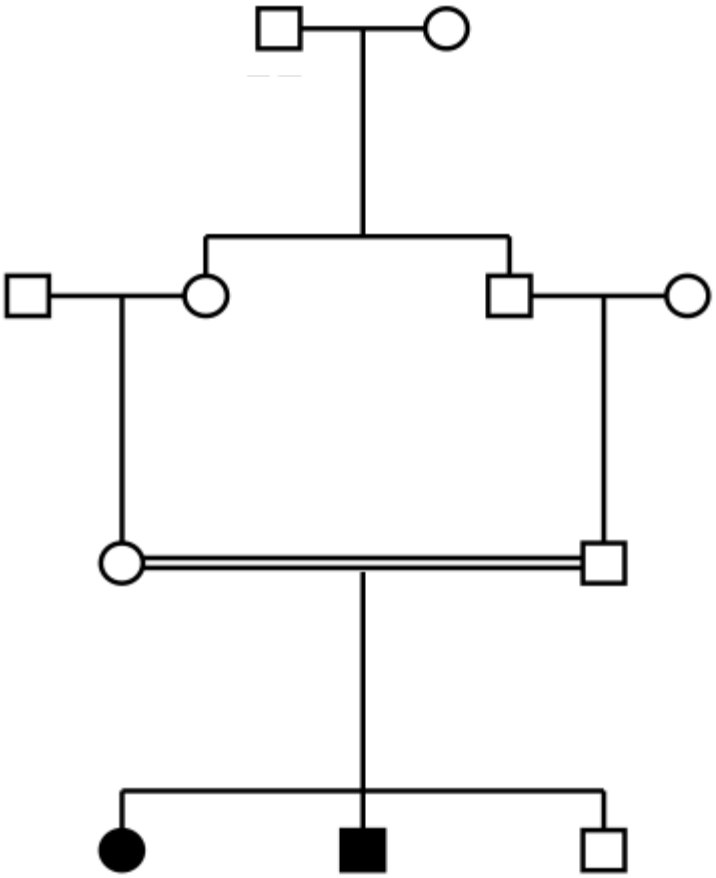


Ped.5 *Italy*



Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor



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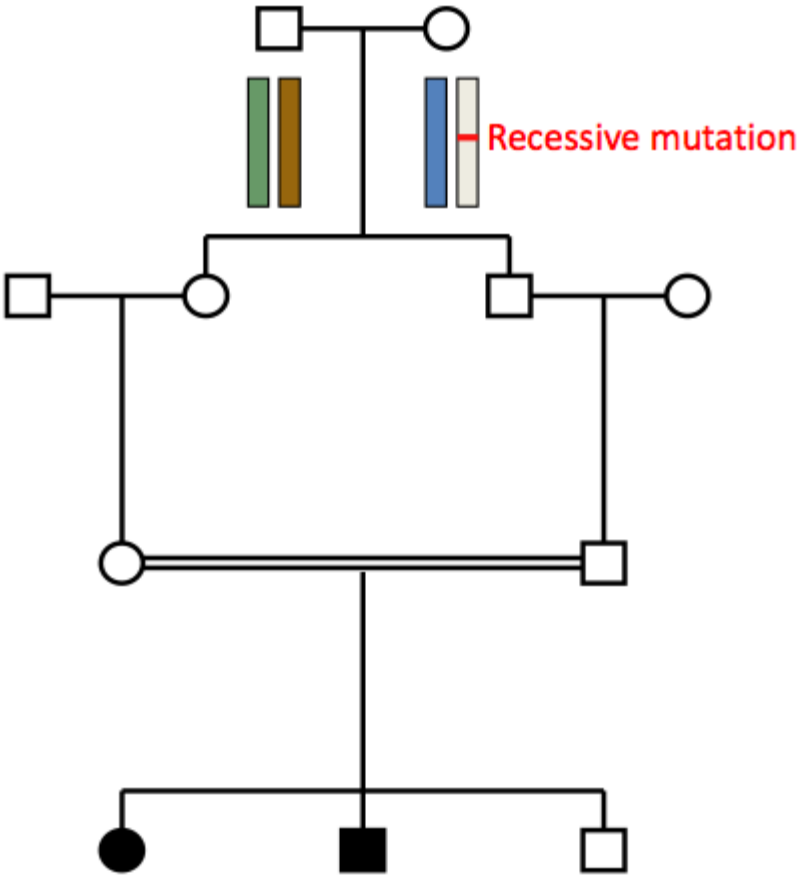

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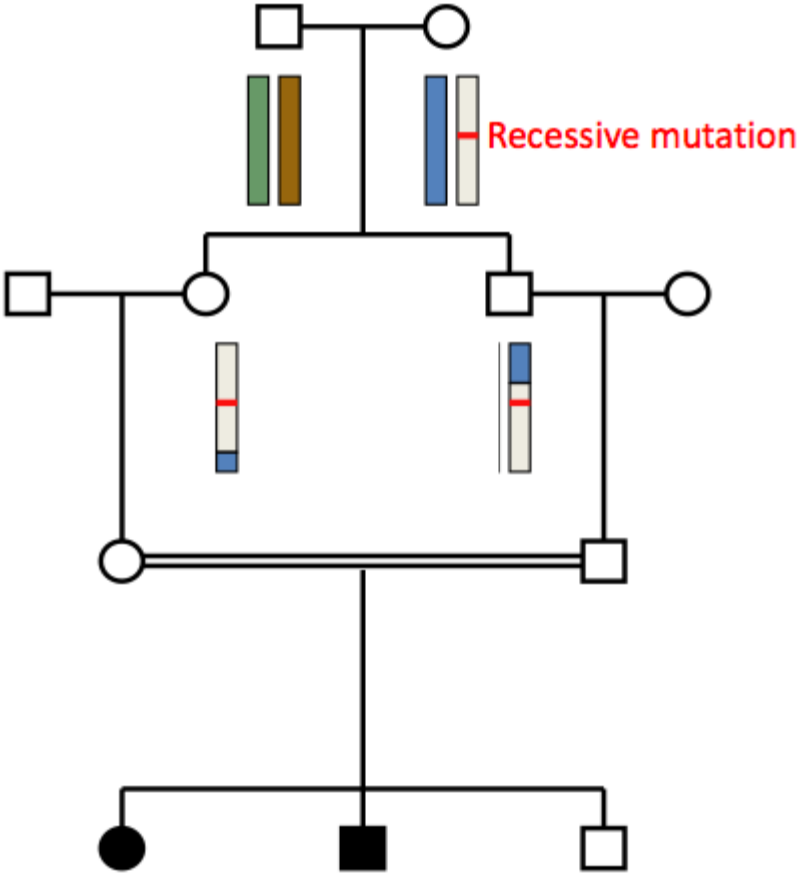

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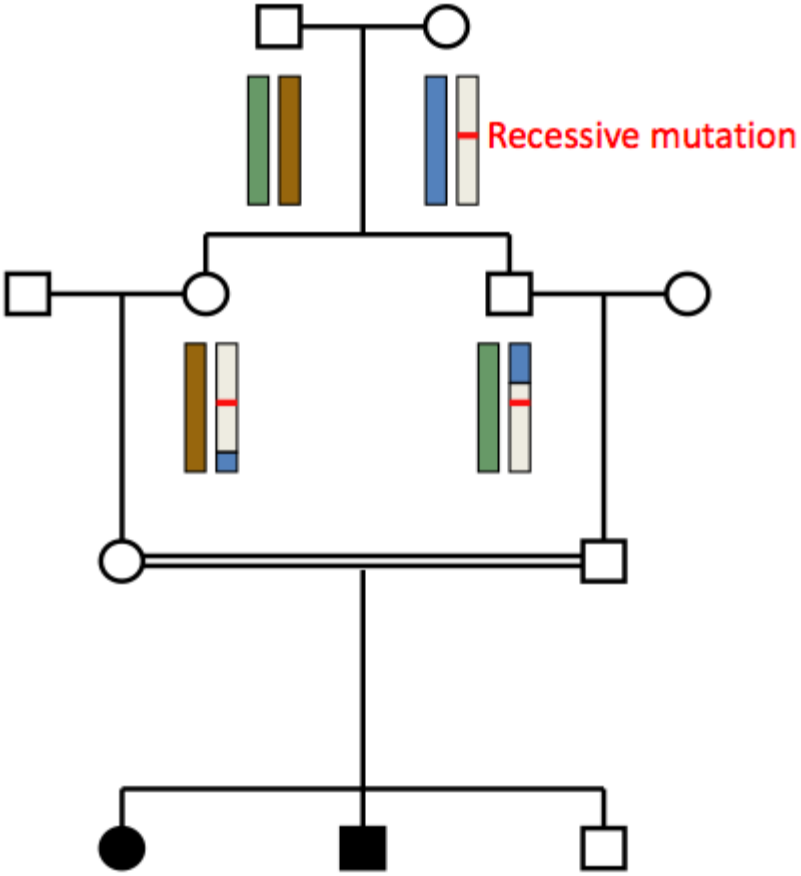

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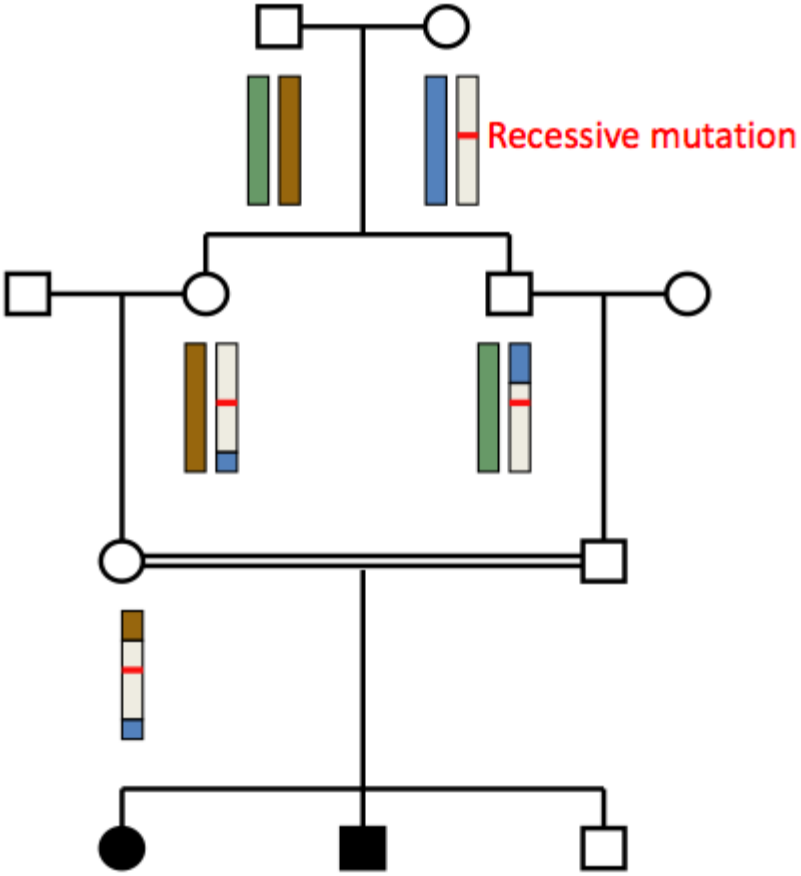
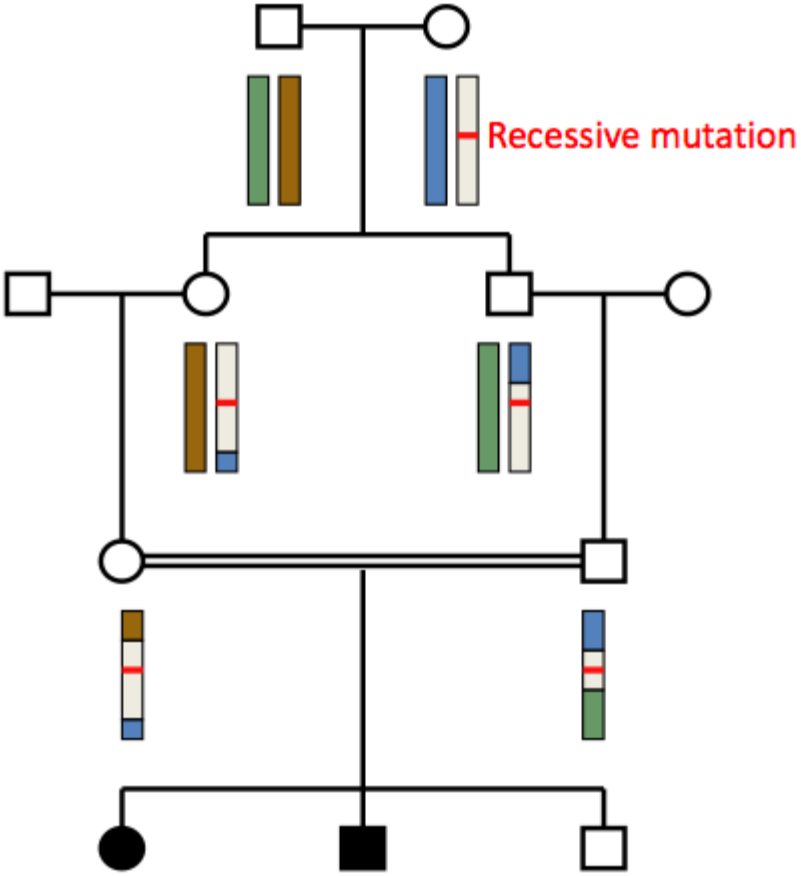


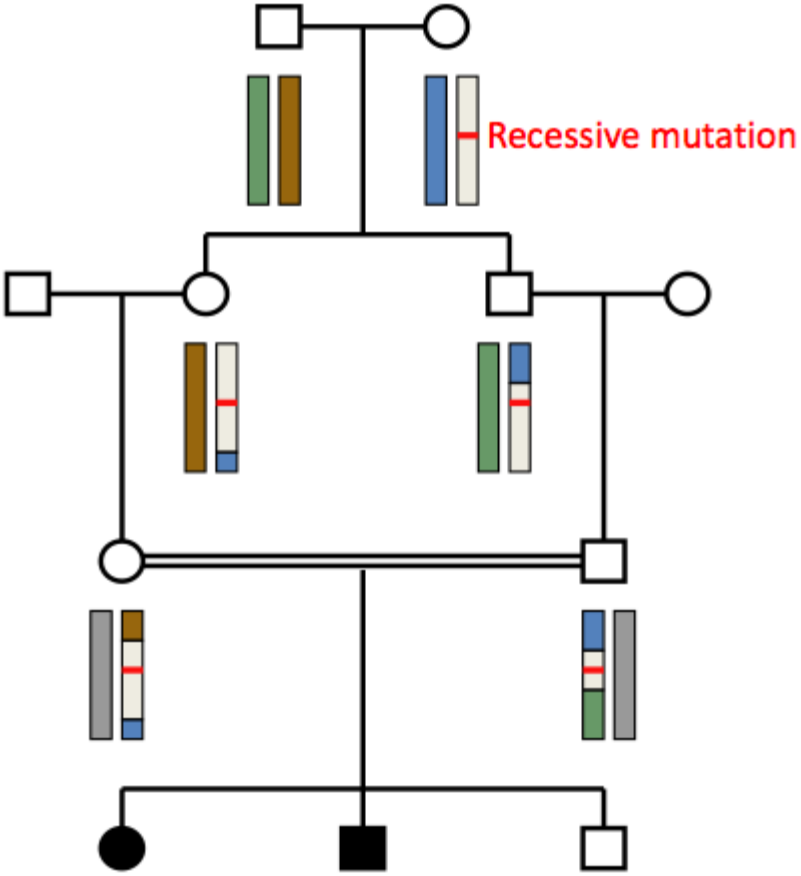
Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor



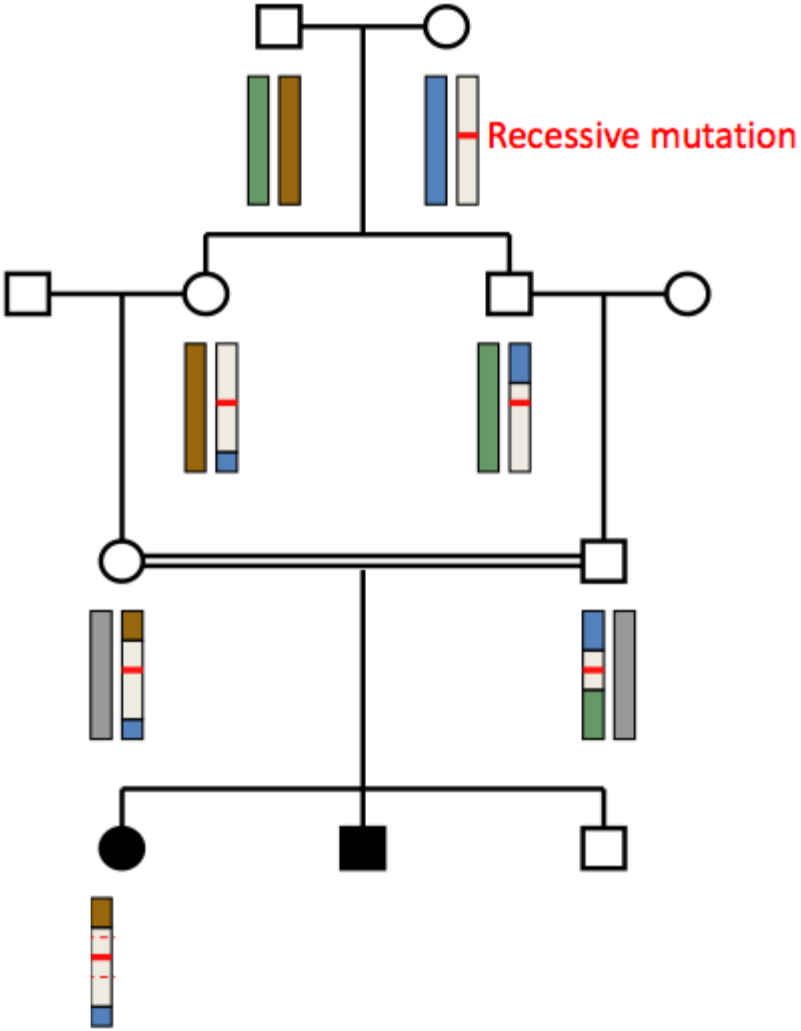
Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor



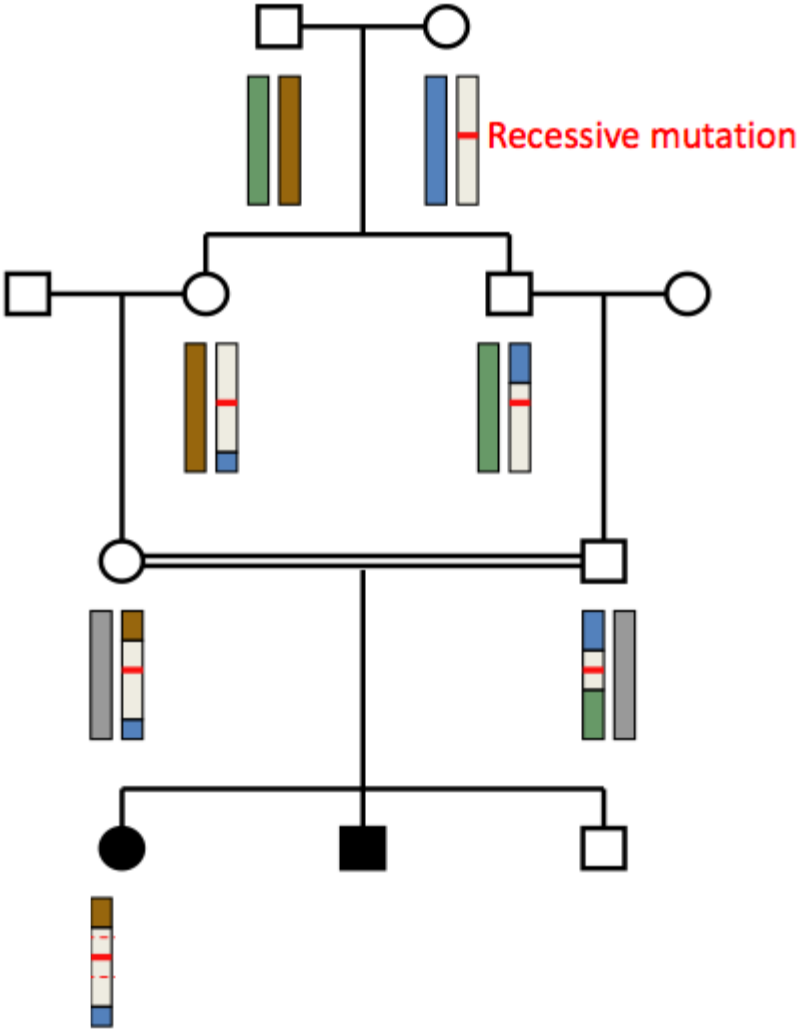
Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor



Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor



Hypothesis: 1) autosomal recessive ★★

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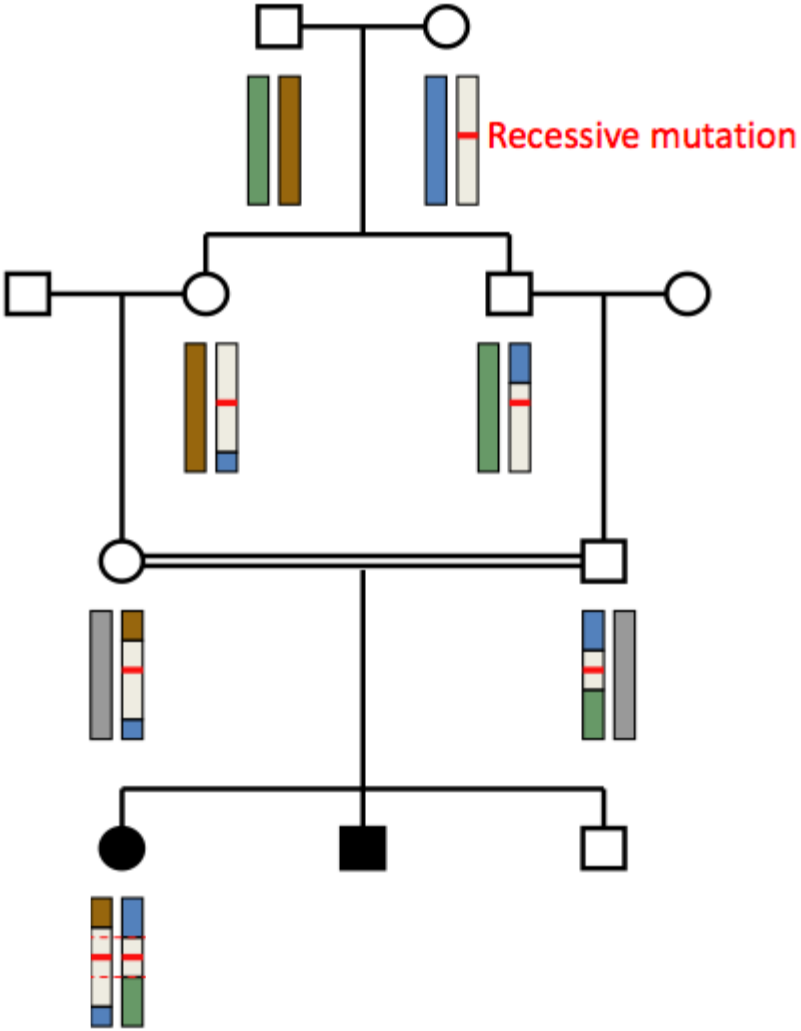
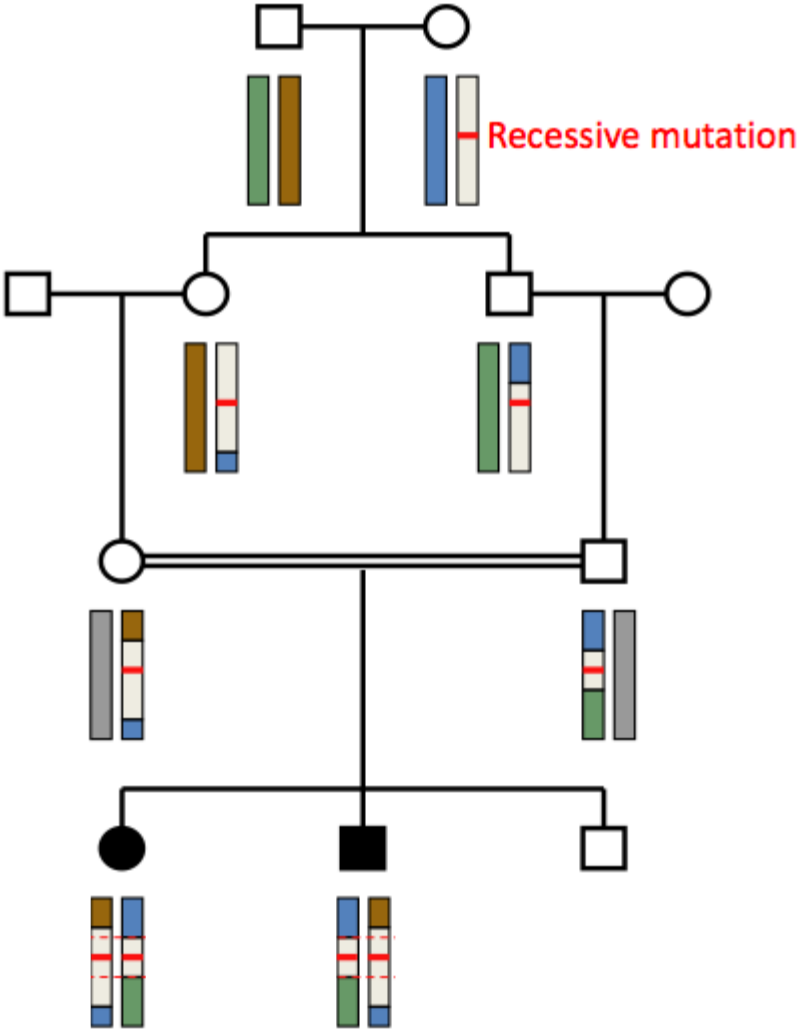


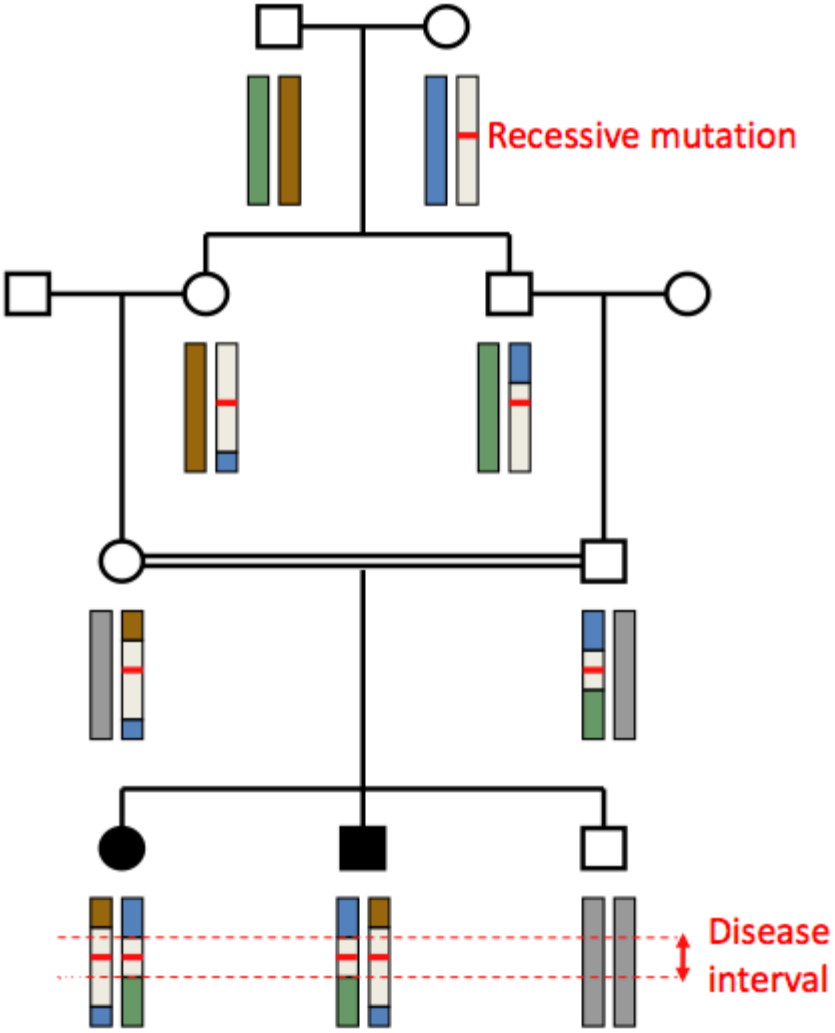
Hypothesis: 1) autosomal recessive ★★

2) homozygous mutation: one single mutation from one ancestor

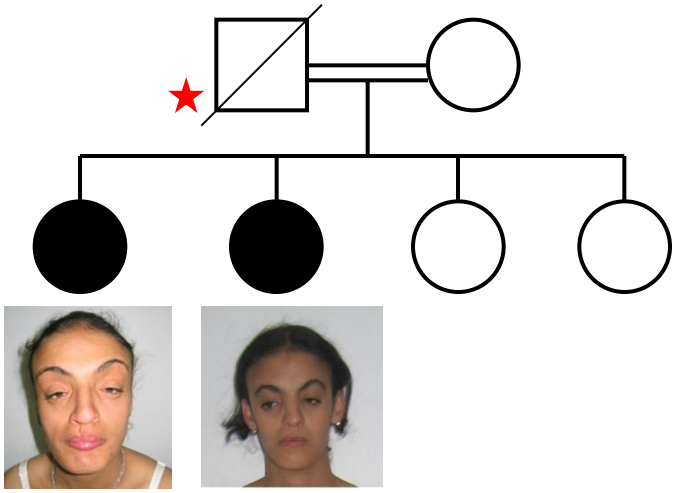


Hypothesis: 1) autosomal recessive ★★

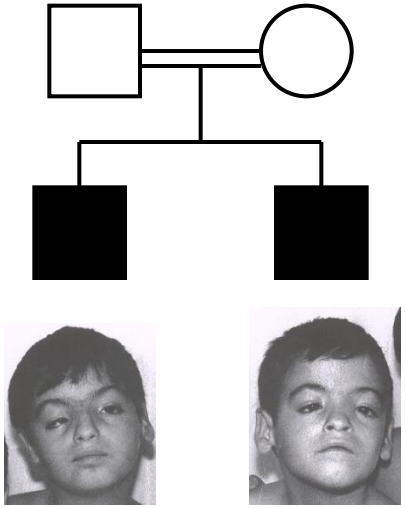
2) homozygous mutation: one single mutation from one ancestor



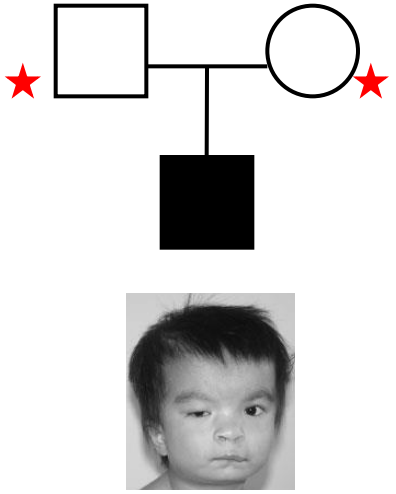
Families Available



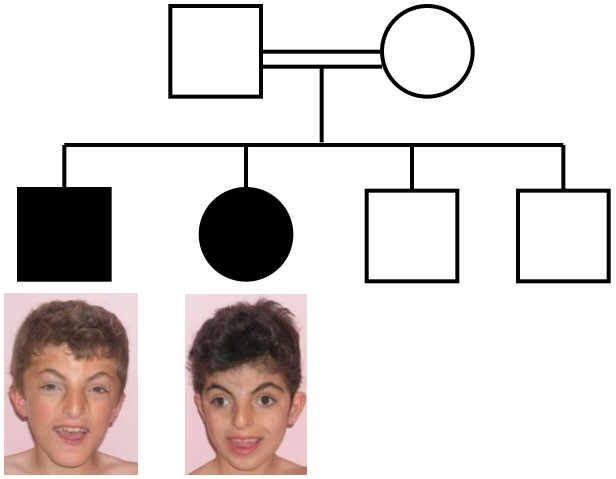
Ped.1 Tunisia



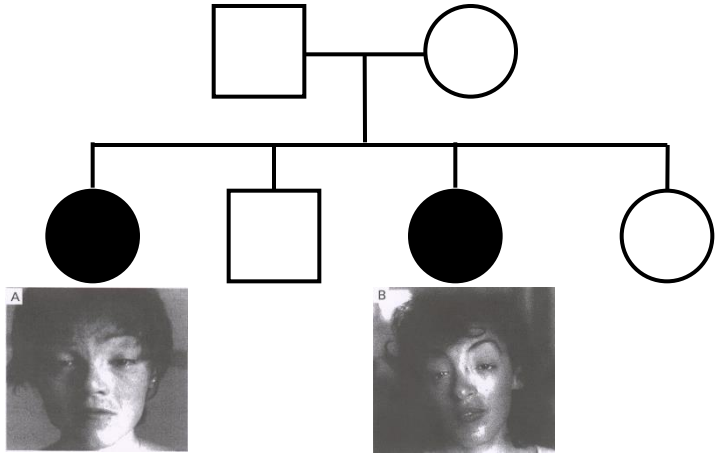
Ped.2 Italy: original Carnevale



Ped.3 China: A Verloes

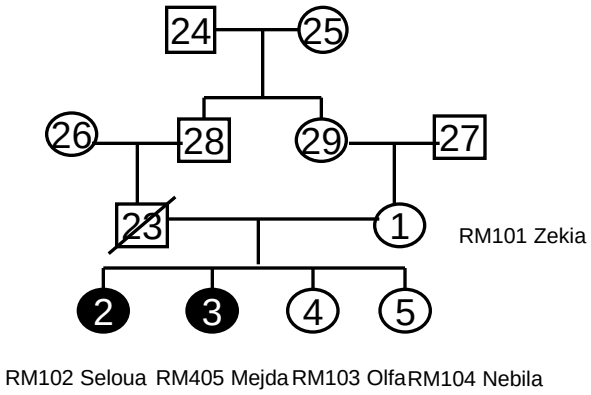


Ped.4 Turkey

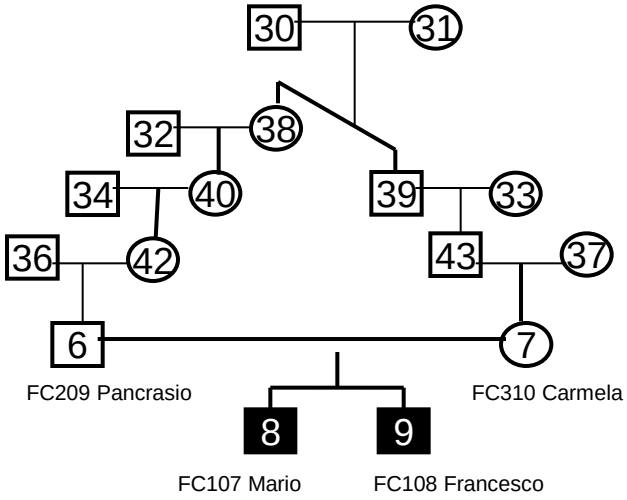


Ped.5 Italy: original Mignarelli

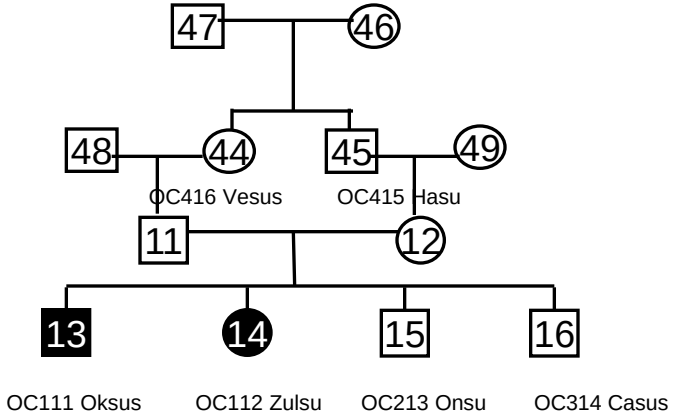
★ DNA not available



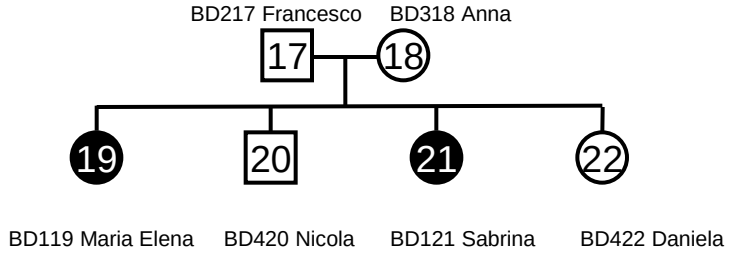
Ped.1 *Tunisia*



Ped.2 *Italy*



Ped.4 *Turkey*



Ped.5 *Italy*

- 22 chp files txt format: filename.brlmm.txt : 12MB per file: 5000 A4 pages per patient

#CHP File=\\UZ\data\Admin\affymetrix\Batch Genotype Result folder\Thierry Voet\CHP file results\Homozygosity mapping Elyes\20080321_164500_homozygosity mapping_score threshold 0_1\P162 RM 101 Zekia.brlmm.chp
#Exec GUID=0000008133-1206114365-0000018369-0000022030-0000013986

SNPID	Call	Confidence	Forced Call	Contrast	Strength	
AFFX-2315060	AB	0.01509365	AB	-0.06984246		11.69507
AFFX-2315061	BB	0.01683226	BB	-0.822069	11.10029	
AFFX-2315062	AB	0.01504767	AB	-0.09716111		10.45533
AFFX-2315057	AB	0.01815814	AB	-0.192368	10.19673	
AFFX-2315058	AA	0.0006541961	AA	0.6871254	11.40688	
AFFX-2315059	AA	0.004756276	AA	0.7620469	10.33798	
AFFX-2315063	AB	0.006349149	AB	-0.04977954		10.34123
AFFX-2315064	AB	0.04271883	AB	0.1842863	10.26872	
AFFX-2315065	AA	0.04382166	AA	0.4789254	9.836063	
AFFX-2315066	BB	0.008553362	BB	-0.673949	10.28233	
AFFX-2315067	AB	0.002479254	AB	0.05865324		10.80329

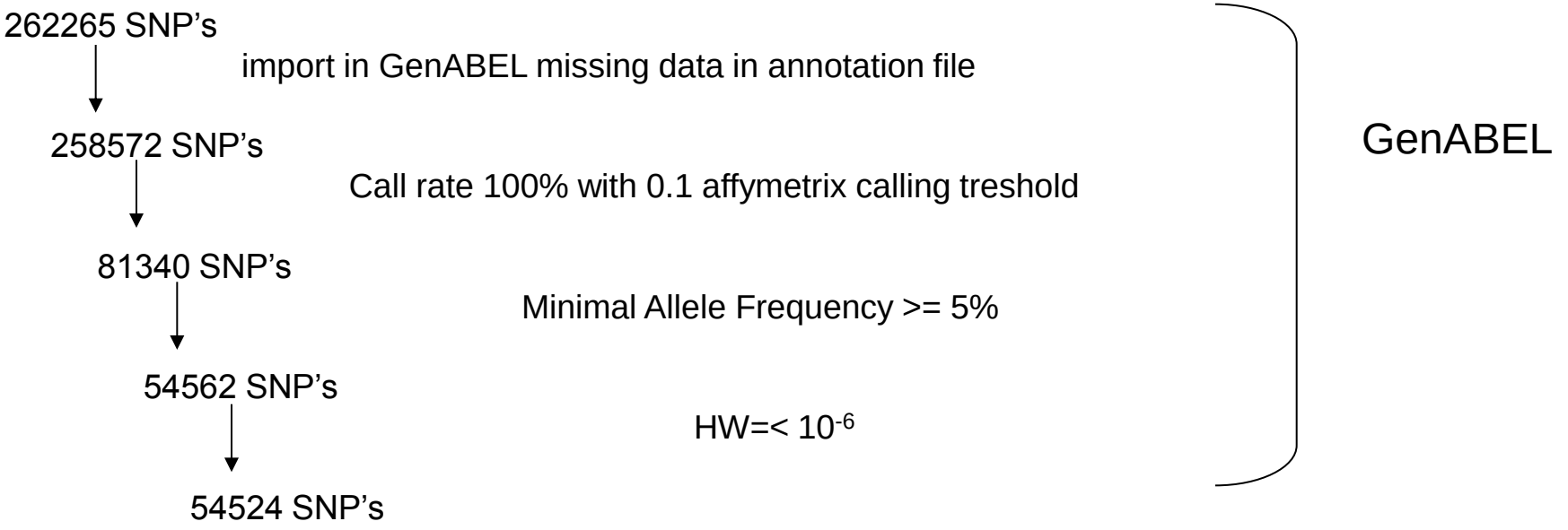
- 1 affymetrix annotation file: **Mapping250K_Nsp.na24.annot.csv : 348,5 MB**

##For information about the Annotation file content, please see the bundled README file.
"Probe Set ID","Affy SNP ID","dbSNP RS ID","Chromosome","Physical Position","Strand","ChrX pseudo-autosomal region 1","Cytoband","Flank","Allele A","Allele B","Associated Gene","Genetic Map","Microsatellite","Fragment Enzyme Length Start Stop","Allele Frequencies","Heterozygous Allele Frequencies","Number of individuals/Number of chromosomes","In Hapmap","Strand Versus dbSNP","Copy Number Variation","Probe Count","ChrX pseudo-autosomal region 2","In Final List","Minor Allele","Minor Allele Frequency"
"SNP_A-1780619","10004759","rs17106009","1","50433725","-","0","p33","ggatattgtgtgagga[A/G]taagcccacctgtggt","A","G","NM_021952 // intron // 0 // Hs.213050 // ELAVL4 // 1996 // Homo sapiens ELAV (embryonic lethal, abnormal vision, Drosophila)-like 4 (Hu antigen D) (ELAVL4), mRNA. /// ENST00000371827 // intron // 0 // --- // --- // --- // --- /// ENST00000357083 // intron // 0 // --- // --- // --- // --- /// ENST00000323186 // intron // 0 // --- // --- // --- // --- /// ENST00000371824 // intron // 0 // --- // --- // --- // --- /// ENST00000371823 // intron // 0 // --- // --- // --- // --- /// ENST00000361667 // intron // 0 // --- // --- // --- // --- /// ENST00000371821 // intron // 0 // --- // --- // --- // --- /// ENST00000371819 // intron // 0 // --- // --- // --- // ---","72.030224900657 // D1S2824 // D1S197 // --- // --- /// 76.2778636775225 // D1S2706 // D1S2661 // AFMA337WC1 // AFMA203YE9 /// 68.1611616801535 // --- // --- // 59969 // 770243","D1S1559 // downstream // 51841 /// D1S2299E // upstream // 6915","--- // 574 // 50433477 // 50434050","0.0 // 1.0 // Japanese /// 0.0 // 1.0 // Han Chinese /// 0.010204 // 0.989796 // CEPH /// 0.022222 // 0.977778 // Yoruba","0.0 // Japanese /// 0.0 // Han Chinese /// 0.0202 // CEPH /// 0.043457 // Yoruba","45.0 // Japanese /// 45.0 // Han Chinese /// 49.0 // CEPH /// 45.0 // Yoruba","YES","reverse","---","12","---","---","--- // Japanese /// --- // Han Chinese /// --- // CEPH /// --- // Yoruba","0.0 // Japanese /// 0.0 // Han Chinese /// 0.010204 // CEPH /// 0.022222 // Yoruba"
"SNP_A-1780618","10004754","

Putting files together and thinning the marker map

GenABEL from http://mga.bionet.nsc.ru/nlru/GenABEL/. = R-library (Unix version)

C++ function: convert.snp.affymetrix.tar.gz (Maksim Struchalin)
convert.snp.affymetrix(dir="last_data", map="annotation.csv", outfile="out1.raw", skipaffym=4)



Transfer data from GenABEL to merlin files: R

Change physical map for genetic map: DECODE: SAS

Merlin: Abecasis lab *Center for Statistical Genetics, Dept. of Biostatistics Washington Heights*: developing the computational and statistical tools required for understanding human genetic variation, with a particular focus on complex human disease.

ped file

```
1 1 27 29 2 1 G/T C/T A/G A/A
2 8 6 7 1 2 G/G T/T A/A A/A
2 9 6 7 1 2 G/G T/T A/A A/A
1 2 23 1 2 2 G/G C/C A/G A/T
1 4 23 1 2 1 G/G C/C G/G A/A
1 5 23 1 2 1 G/G C/C A/G A/T
1 3 23 1 2 2 G/T C/T A/A A/T
2 6 36 42 1 1 G/T T/T A/A A/T
2 7 43 37 2 1 G/G C/T A/A A/T
4 13 11 12 1 2 G/T C/T A/A T/T
4 14 11 12 2 2 G/T C/T A/A T/T
4 15 11 12 1 1 G/G C/C A/A T/T
4 16 11 12 1 1 G/G C/C A/A T/T
4 12 45 49 2 1 G/T C/T A/A T/T
4 11 48 44 1 1 G/G C/C A/A T/T
5 17 0 0 1 1 G/T C/T A/A T/T
5 18 0 0 2 1 G/G C/C A/G A/T C/T
5 19 17 18 2 2 G/G C/C A/A T/T
5 20 17 18 1 1 G/G C/C A/G A/T
5 21 17 18 2 2 G/G C/C A/A T/T
5 22 17 18 2 1 G/T C/T A/G A/T
2 42 34 40 2 1 0/0 0/0 0/0 0/0
2 43 39 33 1 1 0/0 0/0 0/0 0/0
1 23 28 26 1 1 0/0 0/0 0/0 0/0
```

map file

```
chromosome markername position
2 rs7574941 151.877972346097
2 rs4663384 243.172436792518
2 rs4848641 131.974567656034
2 rs1948267 88.0749332963866
2 rs4538203 136.000686707565
2 rs16865535 184.30320917144
2 rs7420849 214.423223863834
2 rs17032570 89.1668663988328
2 rs6730054 162.52826477965
2 rs2600672 83.7731695237487
2 rs1393823 90.8794214223852
2 rs9653477 118.842106243848
2 rs972513 244.487259345634
2 rs10181222 187.618330107824
2 rs6543868 58.4970660512621
2 rs934265 146.418183903651
2 rs747834 129.190824194869
2 rs929937 216.500836248827
2 rs13022815 214.88660391853
2 rs7572152 149.094665263571
2 rs13398994 185.811924096904
2 rs1317761 28.0252354409538
2 rs4852549 104.031481221753
```

dat file

```
A affected
M rs300774
M rs300710
M rs385272
M rs1474053
M rs7609512
M rs4241316
M rs10188763
M rs7605824
M rs4854302
M rs9309730
M rs3961050
M rs2685263
M rs1317881
M rs1320362
M rs6712649
M rs2683986
M rs17728164
M rs12468153
M rs11127484
M rs2867123
M rs2867122
M rs2903492
M rs6548247
```

model file

```
affected 0.0001
0.000,0.000,1.000
Recessive
```

Merlin (Unix version) =

Inputfiles: 3 filetypes per chromosome
Change per chromosome physical map to DECODE genetic map

C++, R and SAS programming

run Merlin per chromosome and per family

MODEL	FAMILY	POSITION	LOD
Recessive	1	rs300774	-INF
Recessive	1	rs300710	-INF
Recessive	1	rs385272	-INF
Recessive	1	rs1474053	-8.3735
Recessive	1	rs7609512	-9.9515
Recessive	1	rs4241316	-INF
Recessive	1	rs10188763	-8.2527
Recessive	1	rs7605824	-7.7558
Recessive	1	rs4854302	-7.5256
Recessive	1	rs9309730	-7.4839
Recessive	1	rs3961050	-7.3639
Recessive	1	rs2685263	-INF
Recessive	1	rs1317881	-11.3389
Recessive	1	rs1320362	-INF
Recessive	1	rs6712649	-INF
Recessive	1	rs2683986	-INF
Recessive	1	rs17728164	-INF
Recessive	1	rs12468153	-INF
Recessive	1	rs11127484	-10.7619
Recessive	1	rs2867123	-10.1216
Recessive	1	rs2867122	-10.0966

Parametric Analysis, Model Recessive

==========

POSITION	LOD	ALPHA	HLOD
rs300774	-INFINITY	0.466	2.393
rs300710	-INFINITY	0.467	2.405
rs385272	-INFINITY	0.467	2.417
rs1474053	-6.765	0.467	2.418
rs7609512	-8.342	0.467	2.418
rs4241316	-INFINITY	0.467	2.418
rs10188763	-6.644	0.467	2.418
rs7605824	-6.146	0.467	2.418
rs4854302	-5.916	0.467	2.418
rs9309730	-5.874	0.467	2.418
rs3961050	-5.752	0.467	2.418
rs2685263	-INFINITY	0.467	2.418
rs1317881	-9.727	0.467	2.418
rs1320362	-INFINITY	0.467	2.418
rs6712649	-INFINITY	0.467	2.418
rs2683986	-INFINITY	0.467	2.418
rs17728164	-INFINITY	0.467	2.418
rs12468153	-INFINITY	0.467	2.418
rs11127484	-9.150	0.467	2.418

54524 SNP's x 4 families = 218096 output lines = 2947 A4 pages

54524 SNP's = 54524 output lines = 736 A4 pages

Output to Excel to visualise LOD scores and genotype: looking for region

1 with linkage (recessive model, ful penetrance)

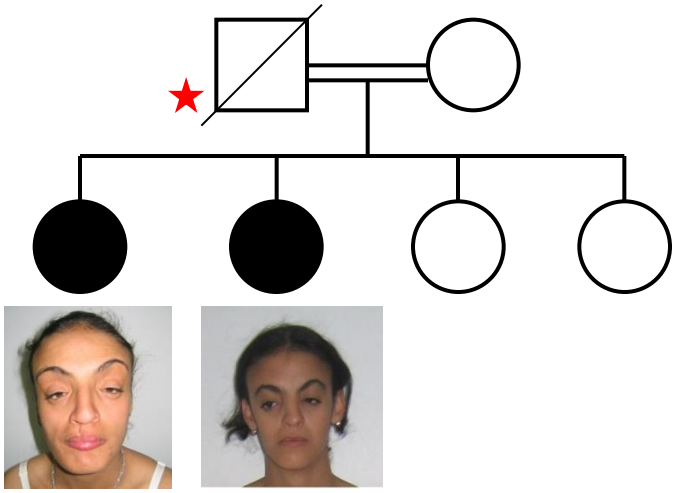
2 homozygous in affected

3 overlapping between families?

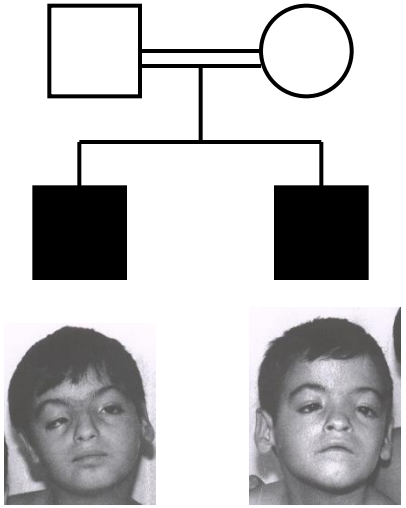
Results

- No single region fitting the data of 4 or 3 families: heterogeneous disorder
- Need for criteria to prioritise the regions.
  - Per family or per combination of families
  - Phenotypes across families? Suggestion R Hennekam: Ped2 and Ped5 = one entity
  - In one family: lengt of homozygous region given a certain degree of consanguinity
    - » 33 crossovers per genome per meiosis * 6 meiosis = 200 meiosis for family 1 and 4 *9 meiosis = 297 meiosis for family 4
    - » 3 bilion basepairs/200 crossovers = 15 MB and 3 bilion basepairs/297 crossovers = 10.1 MB
    - » Short stretches are coincidence or result of recombination hotspots?

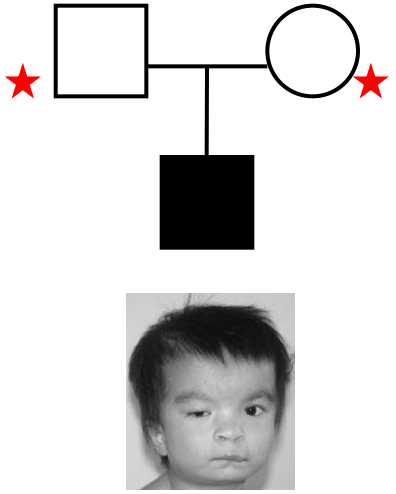
Families Available



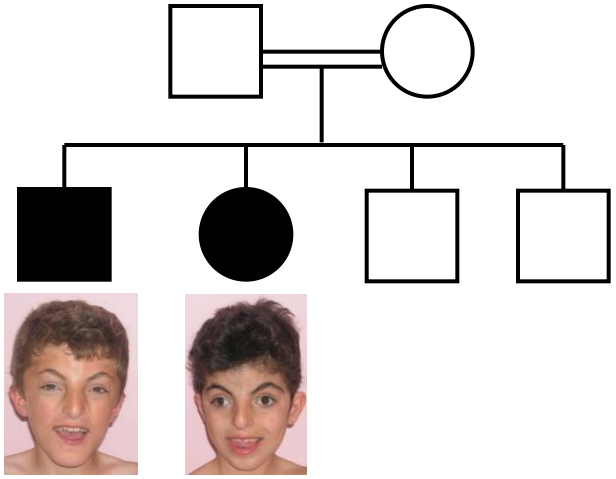
Ped.1 Tunisia



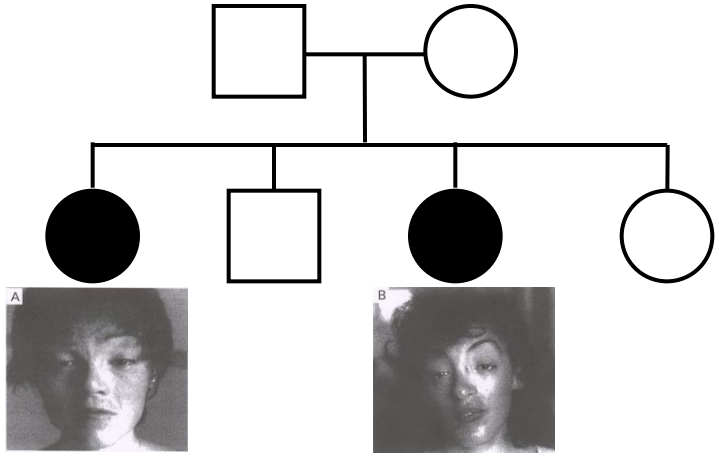
Ped.2 Italy: original Carnevale



Ped.3 China: A Verloes



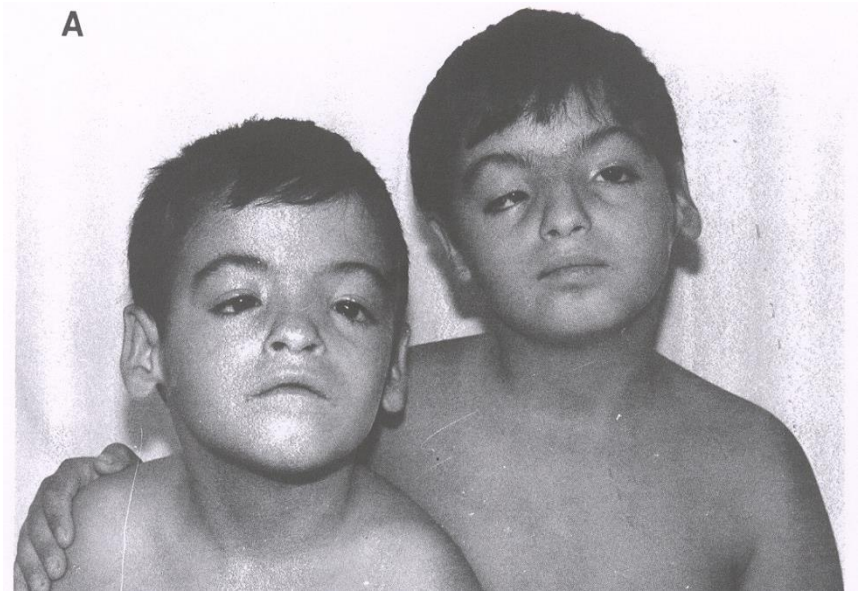
Ped.4 Turkey

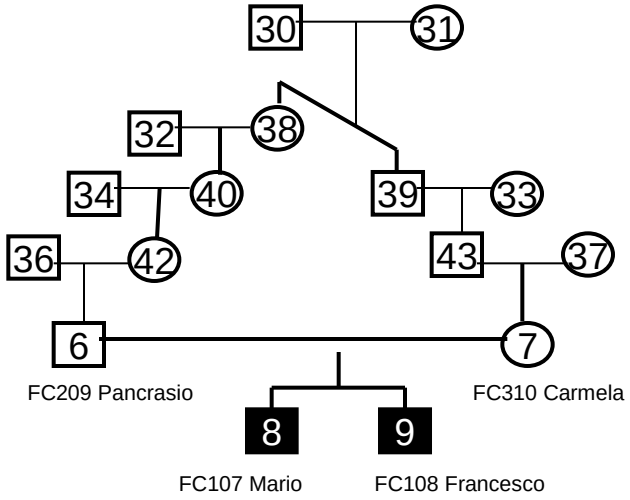


Ped.5 Italy: original Mignarelli

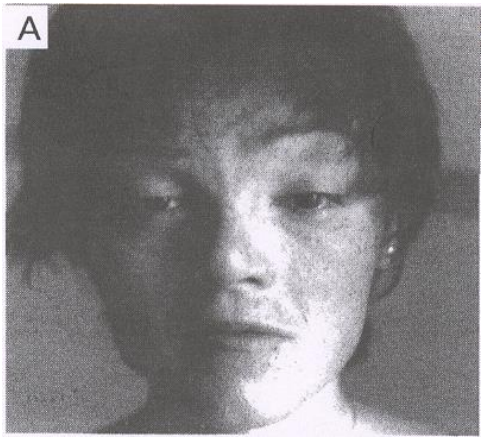
★ DNA not available

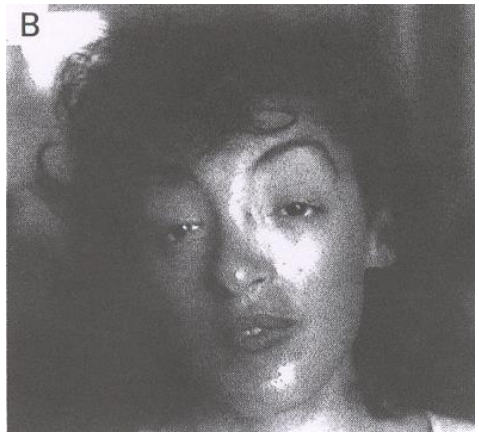
Ped 2 (Italy)

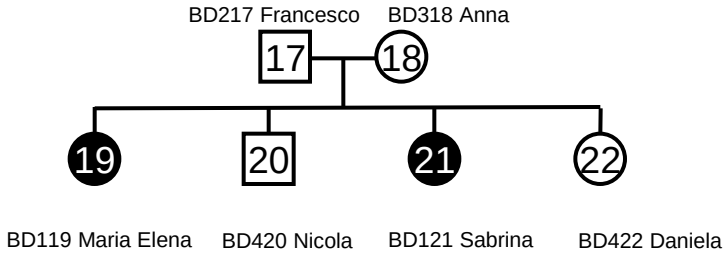


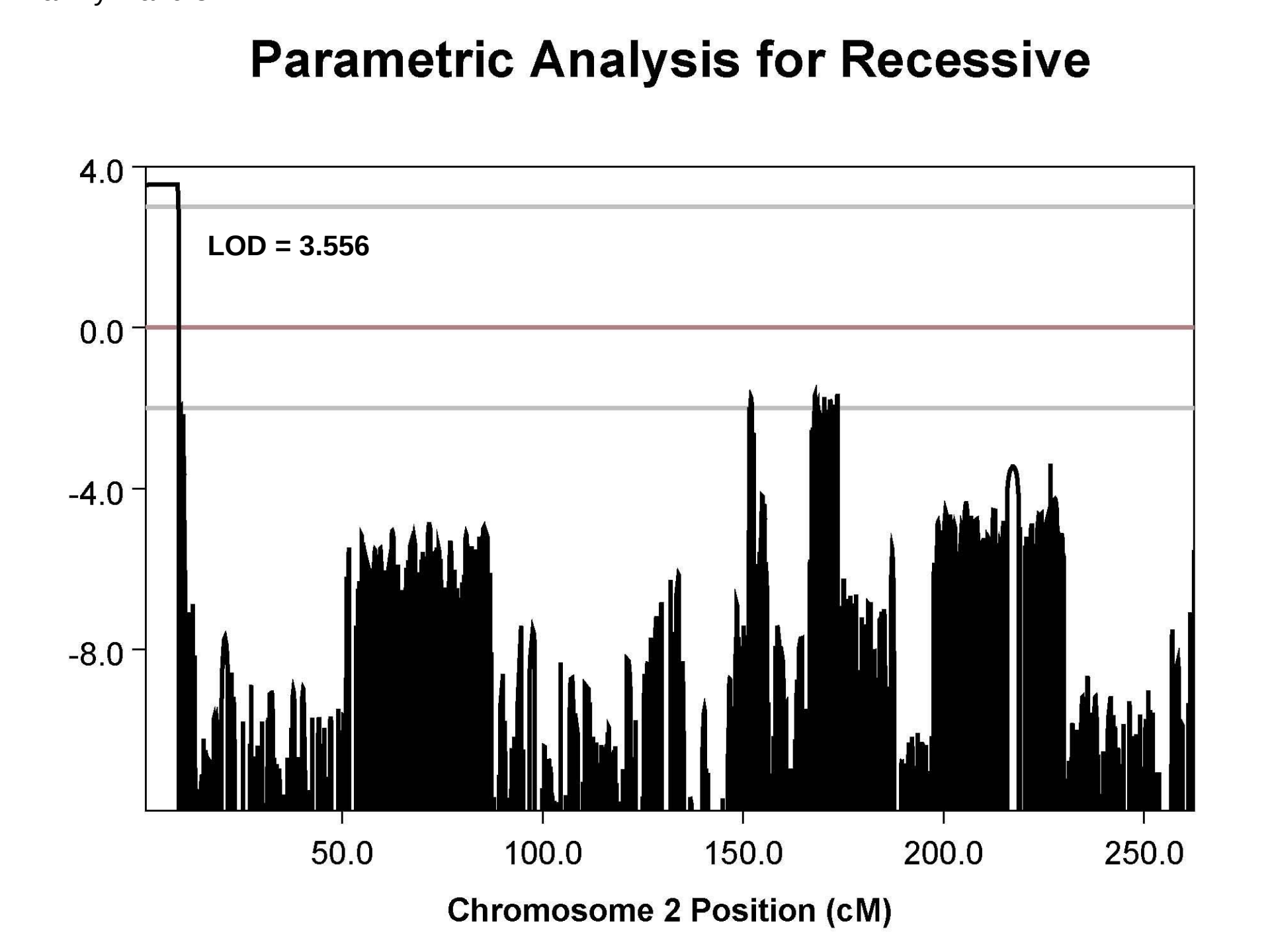


Ped 5 (Italy)



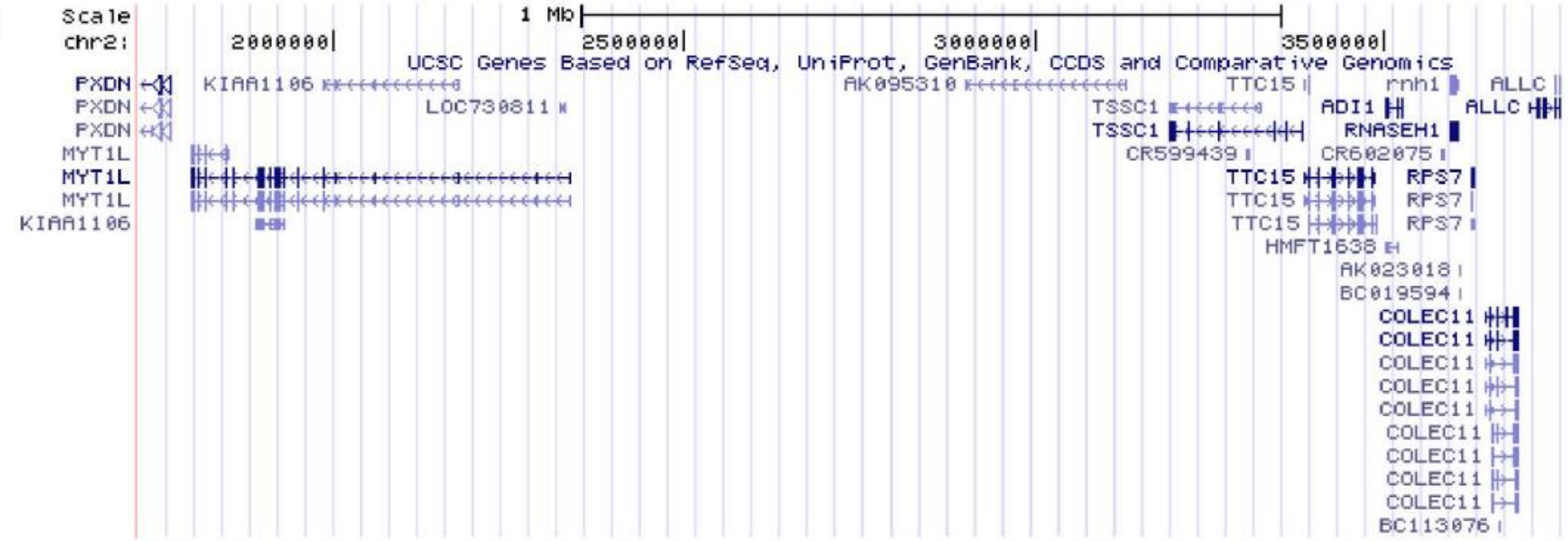


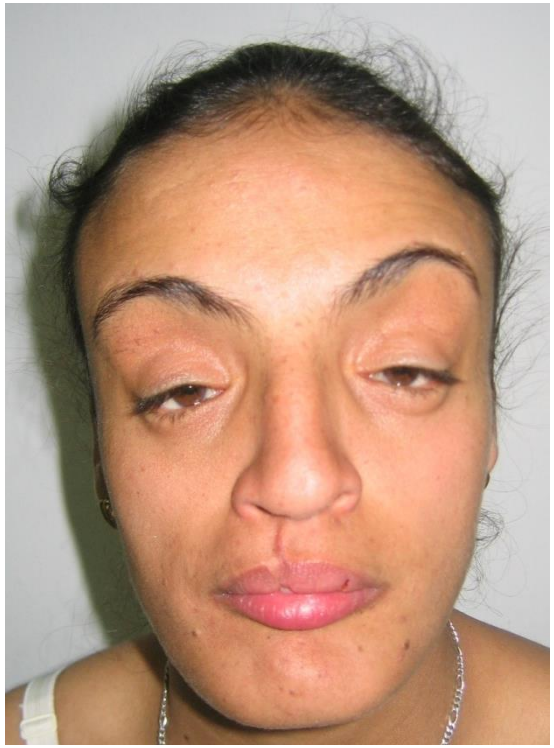


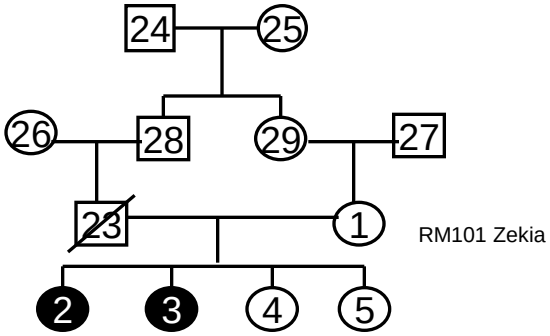

Parametric Analysis for Recessive
LOD = 3.556
4.0
0.0
-4.0
-8.0
50.0
100.0
150.0
200.0
250.0
Chromosome 2 Position (cM)

Chr2p: fam 2 and 5: 4MB: 17 genes

chr2:1-4,152,993

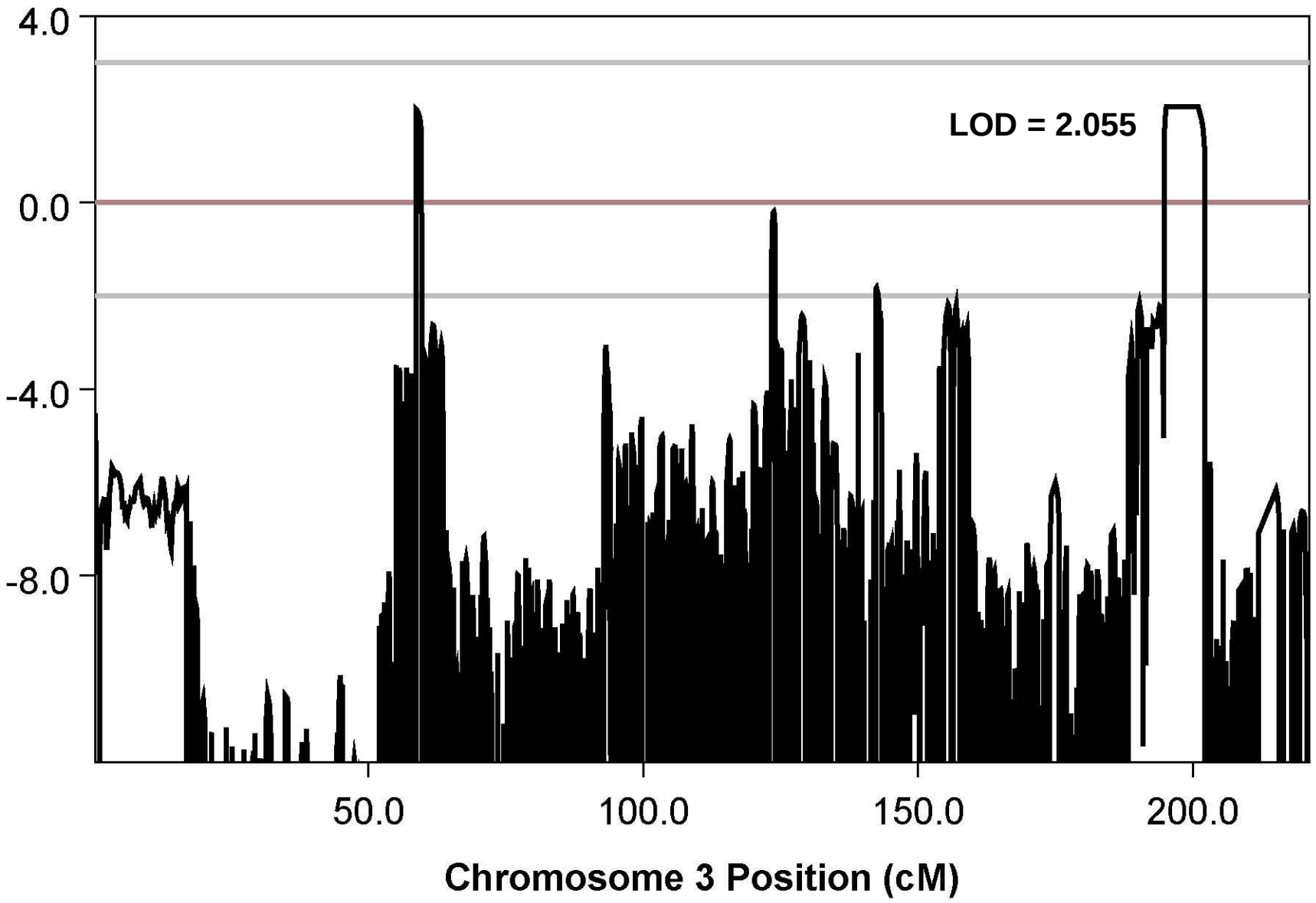






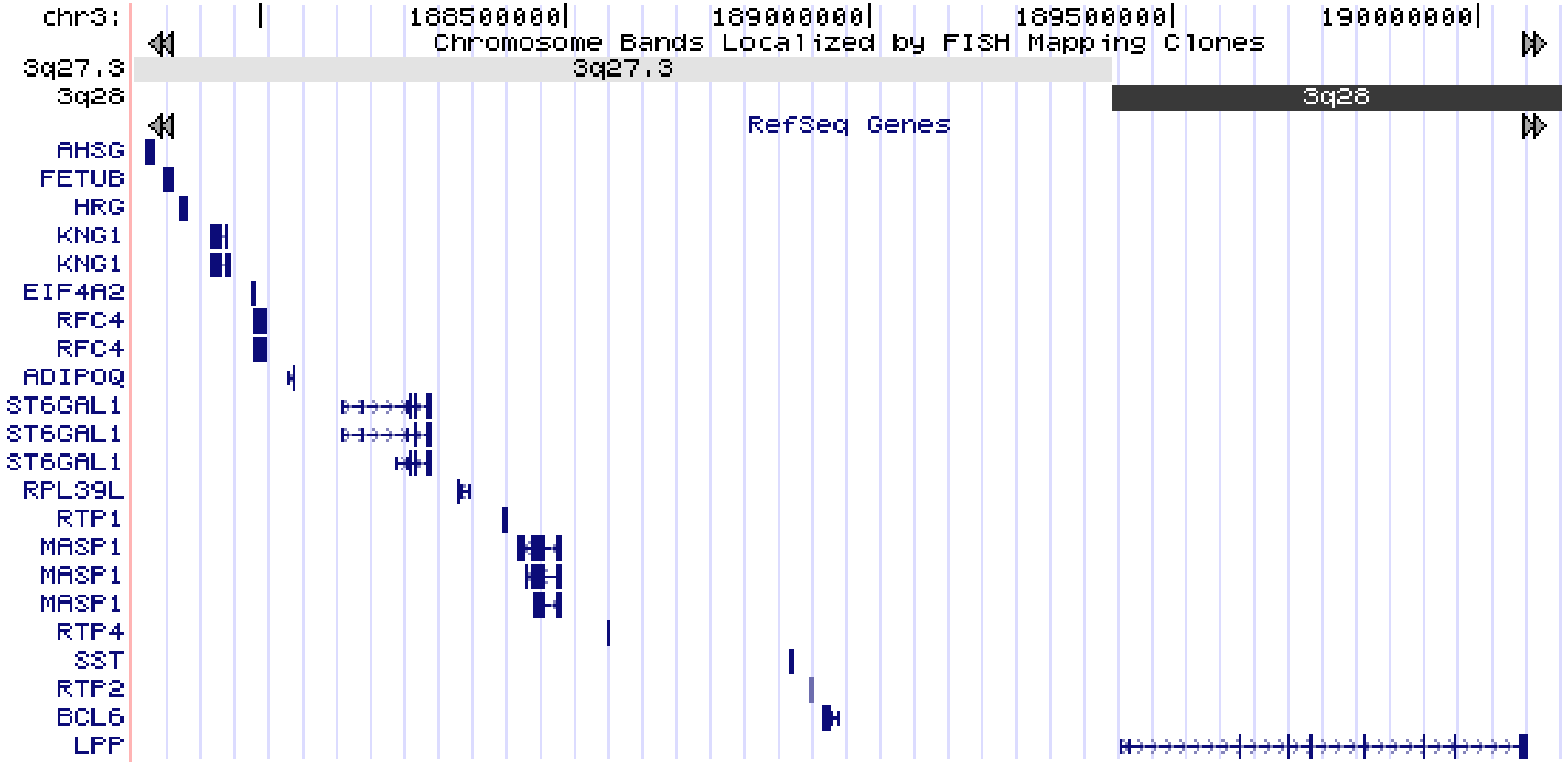
Ped.1 *Tunisia*

Parametric Analysis for Recessive

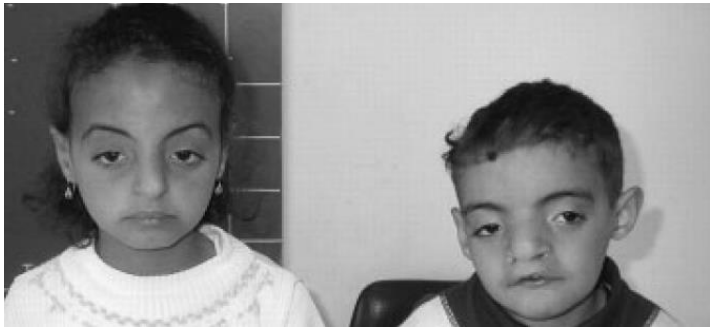


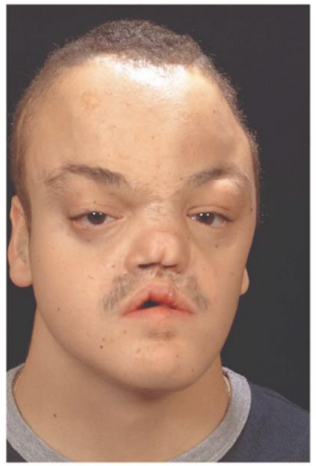
Chr3q: fam 1: 3MB: 16 genes

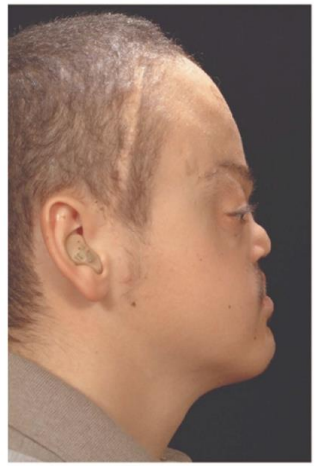
chr3:187,792,745-190,137,470

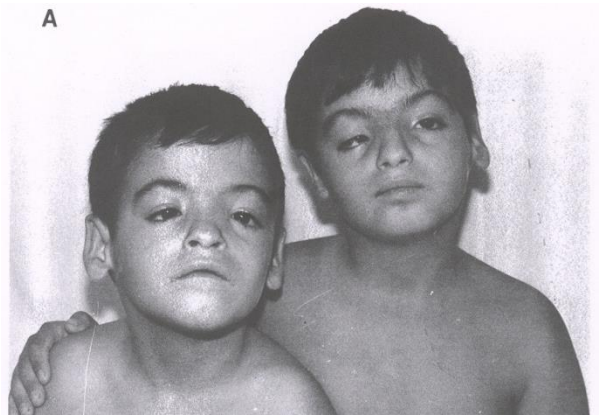


Al Kaissi A, Klaushofer K, Safi H, Chehida FB, Ghachem MB, Chaabounni M, Hennekam RC. Asymmetrical skull, ptosis, hypertelorism, high nasal bridge, clefting, umbilical anomalies, and skeletal anomalies in sibs: is Carnevale syndrome a separate entity? Am J Med Genet A. 2007 Feb 15;143(4):349-54.



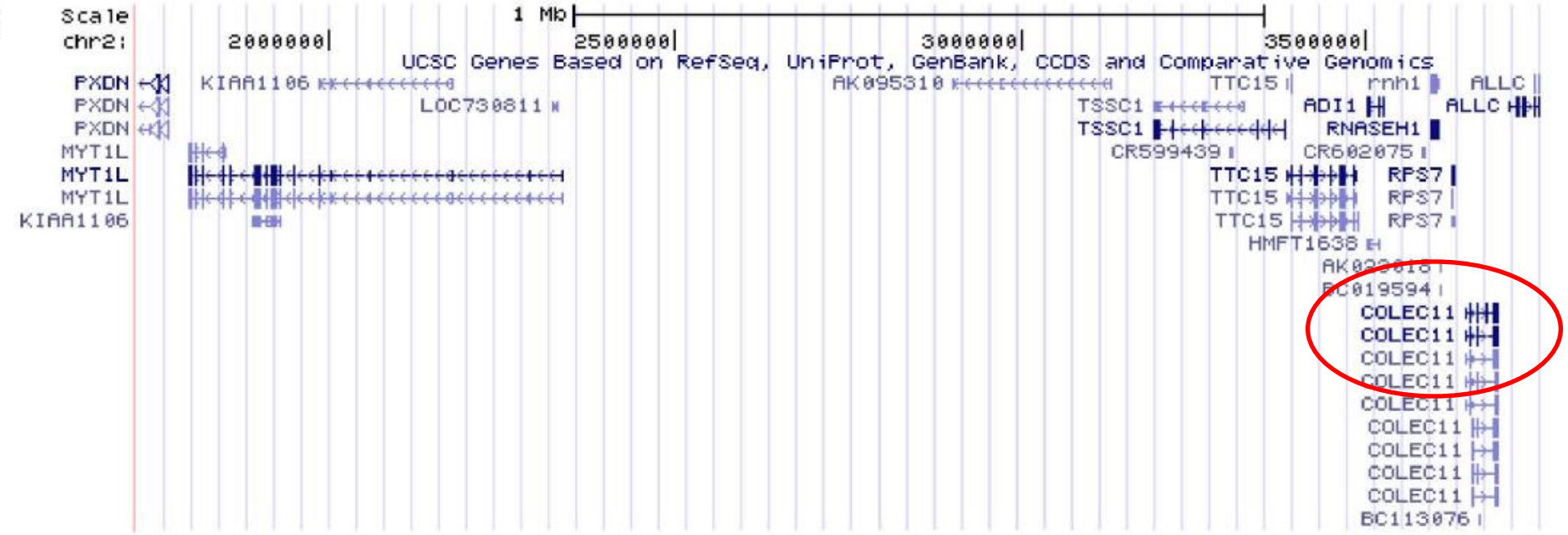






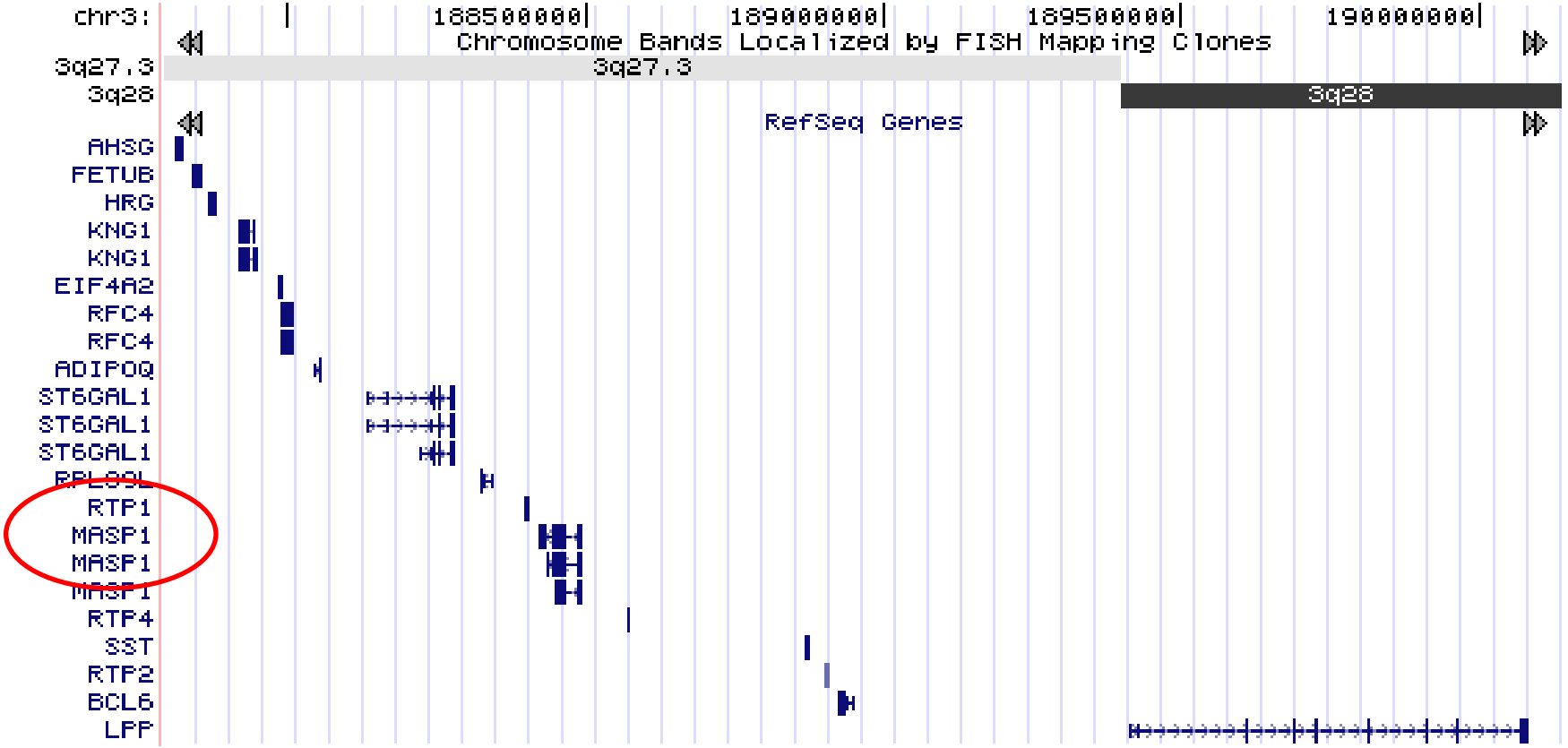
Chr2p: fam 2 and 5: 4MB: 17 genes

chr2:1-4,152,993

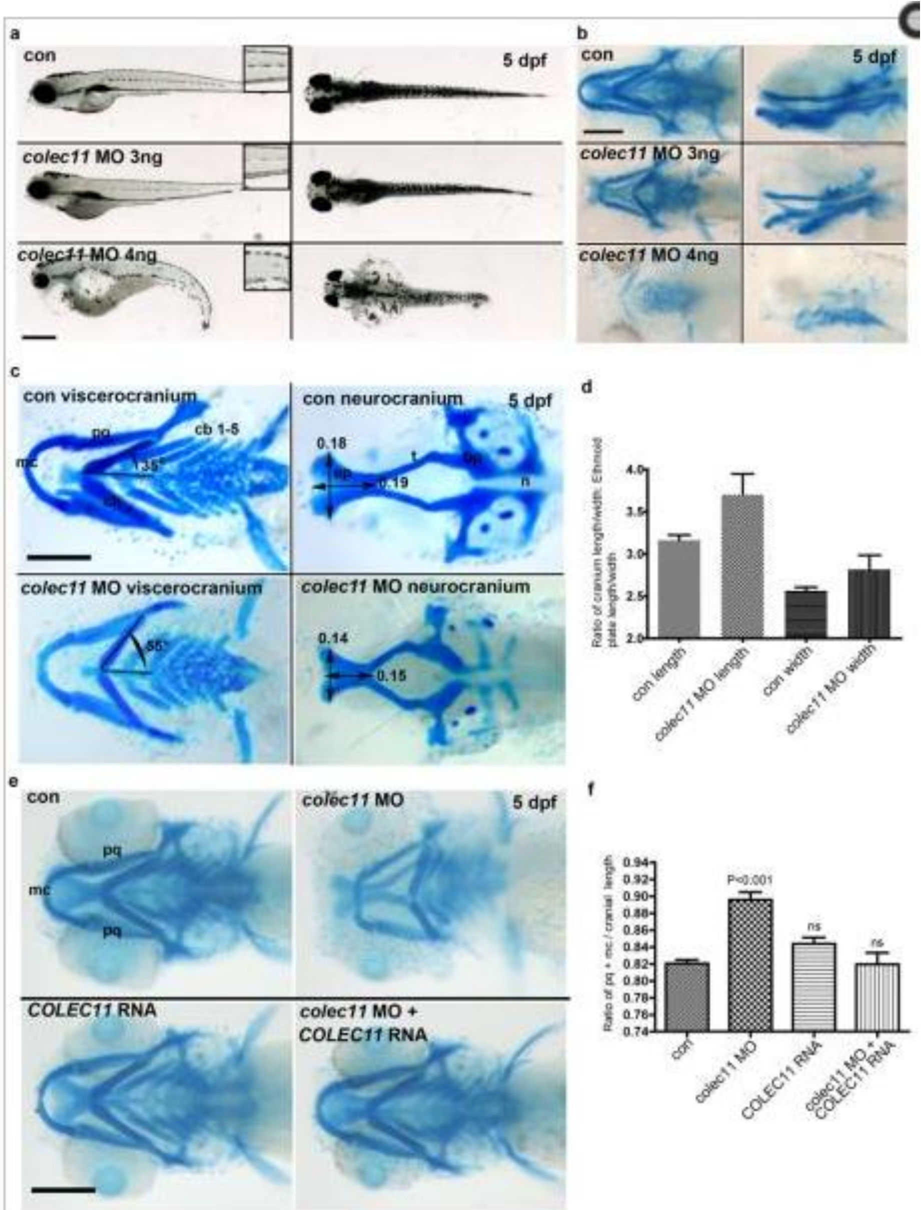


Chr3q: fam 1: 3MB: 16 genes

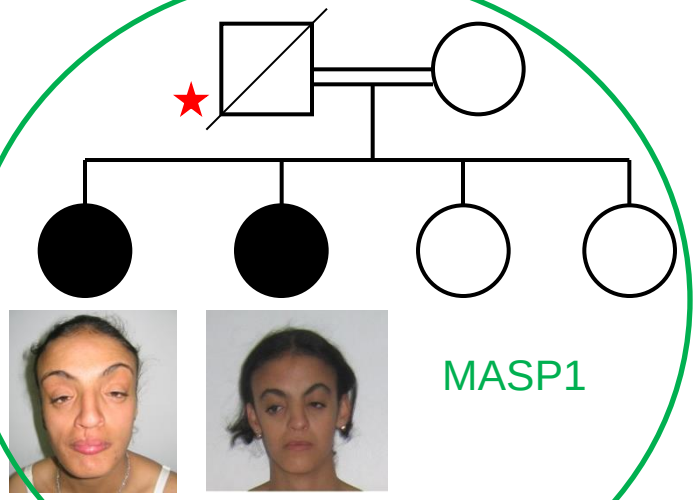
chr3:187,792,745-190,137,470



Family	Subject	Diagnosis	Origin	Mutated gene	Nucleotide change	Protein change	Control chromosomes
MC1	1.1	Carnevale	Tunisia	*COLEC11*	c.496T>C	p.Ser169Pro	60 Tunisian; 284 North European
	1.2	Carnevale	Tunisia	*COLEC11*	c.496T>C	p.Ser169Pro	60 Tunisian; 284 North European
MC2	2.1	Malpuech	Bangladesh	*COLEC11*	c.45delC	p.Phe16Ser*fs*X85	94 Bangladeshi; 284 North European
	2.2	Malpuech	Bangladesh	*COLEC11*	c.45delC	p.Phe16Ser*fs*X85	94 Bangladeshi; 284 North European
MC4	4.1	Malpuech or Michels	Afghanistan	*COLEC11*	c.610G>A	p.Gly204Ser	72 Bangladeshi; 284 North European
	4.2	Malpuech or Michels	Afghanistan	*COLEC11*	c.610G>A	p.Gly204Ser	72 Bangladeshi; 284 North European
MC8	8.1	Carnevale	Saudi Arabia	*COLEC11*	c.648_650delCTC	p.Ser217del	192 Saudi
MC9	9.1	Malpuech	Pakistan	*COLEC11*	c.610G>A	p.Gly204Ser	72 Bangladeshi; 284 North European
MC10	10	Mingarelli	Italy	*COLEC11*	c.300delT	p.Gly101Val*fs*X113	334 North European
MC11	11	Carnevale	Italy	*COLEC11*	Exon 1–3 deletion	Nonfunctional protein?	286 North European
MC3	3.1	Carnevale	Greece	*MASP1*	c.1489 C>T	p.His497Tyr	572 North European
MC5	5.1	Malpuech	Italy	*MASP1*	c.1888T>C	p.Cys630Arg	506 North European
	5.2	Malpuech	Italy	*MASP1*	c.1888T>C	p.Cys630Arg	506 North European
MC6	6.1	3MC	Brazil	*MASP1*	c.1997G>A	p.Gly666Glu	506 North European
	6.2	3MC	Brazil	*MASP1*	c.1997G>A	p.Gly666Glu	506 North European
MC7	7.1	Michels	Brazil	*MASP1*	c.1997G>A	p.Gly666Glu	506 North European

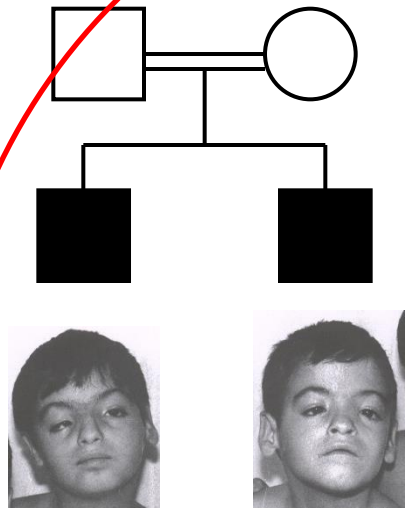

a
con
5 dpf
colec11 MO 3ng
colec11 MO 4ng
b
con
5 dpf
colec11 MO 3ng
colec11 MO 4ng
c
con viscerocranium
pq
cb 1-5
mc
35°
con neurocranium
5 dpf
0.18
0.19
t
n
colec11 MO viscerocranium
55°
colec11 MO neurocranium
0.14
0.15
d
Ratio of cranium length/width: Ethmoid plate length/width
4.0
3.5
3.0
2.5
2.0
con length
colec11 MO length
con width
colec11 MO width
e
con
pq
mc
pq
colec11 MO
5 dpf
COLEC11 RNA
colec11 MO + COLEC11 RNA
f
Ratio of pq + mc / cranial length
0.94
0.92
0.90
0.88
0.86
0.84
0.82
0.80
0.78
0.76
0.74
P<0.001
ns
ns
con
colec11 MO
COLEC11 RNA
colec11 MO + COLEC11 RNA

Families Available

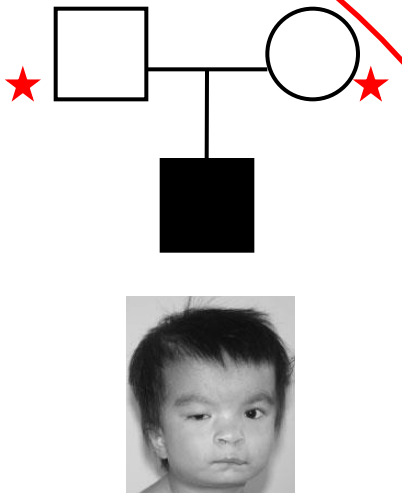


MASP1

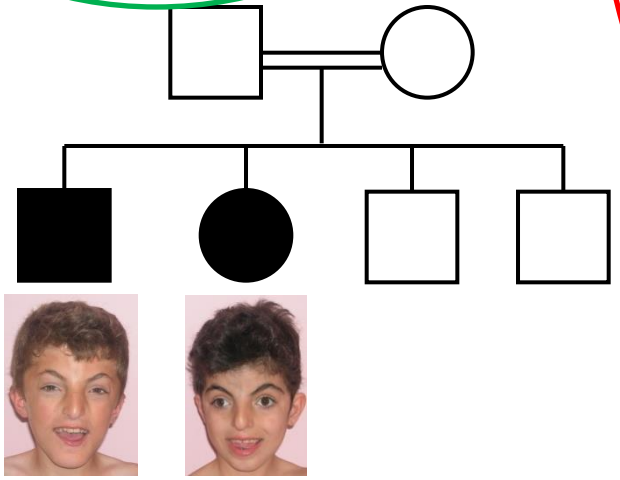
Ped.1 Tunisia



Ped.2 Italy: original Carnevale

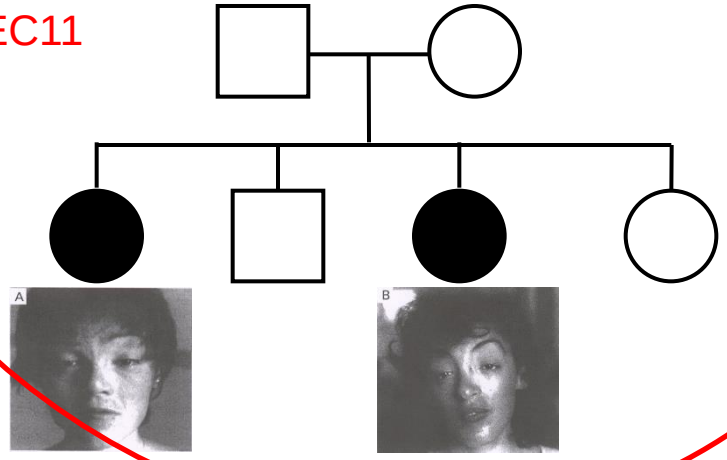


Ped.3 China: A Verloes



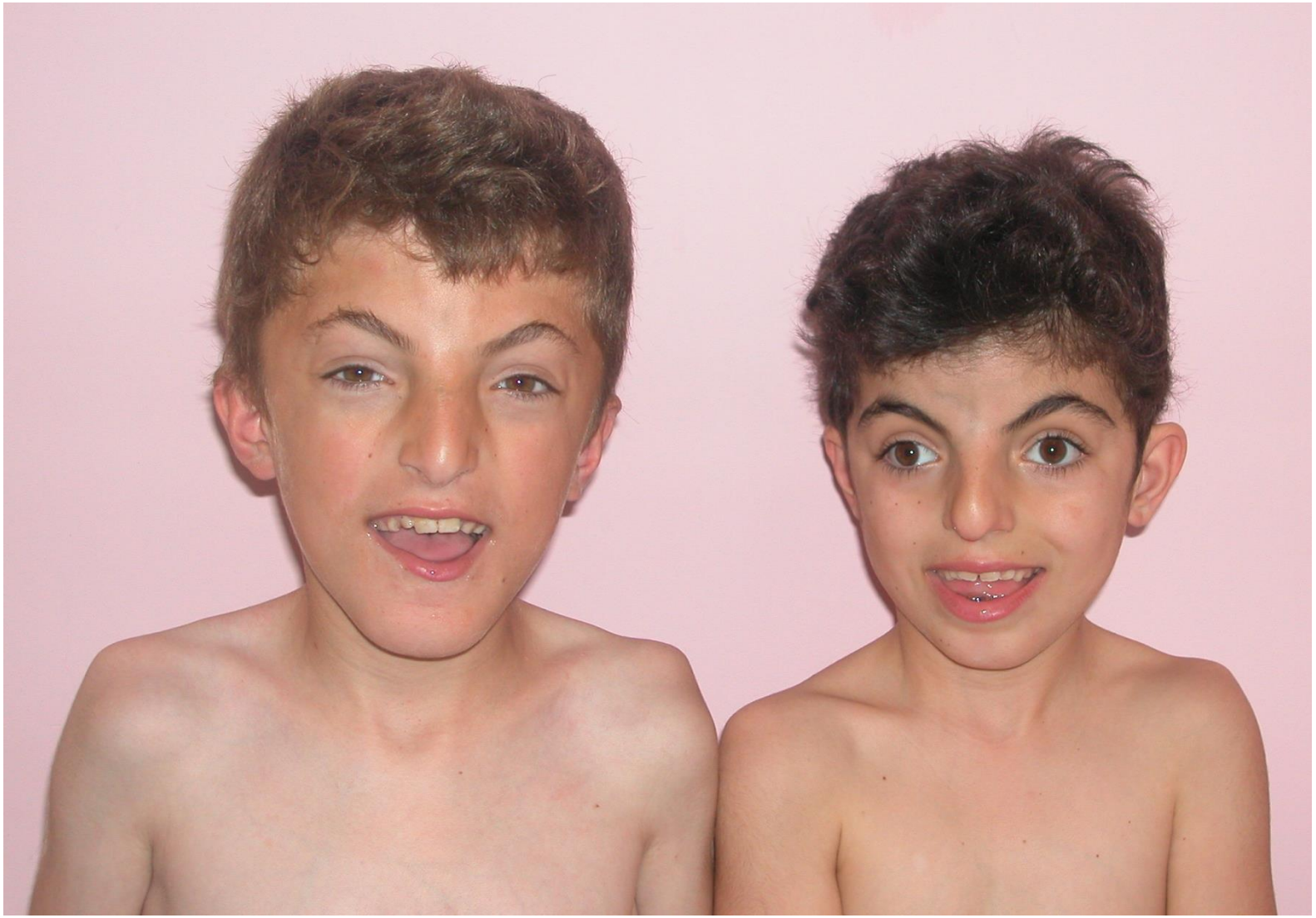
Ped.4 Turkey

COLEC11



Ped.5 Italy: original Mignarelli

★ DNA not available



Mutations in the lectin complement pathway genes *COLEC11* and *MASP1* cause 3MC syndrome

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