AGT Mutations and Population Genetics of AGT Polymorphisms

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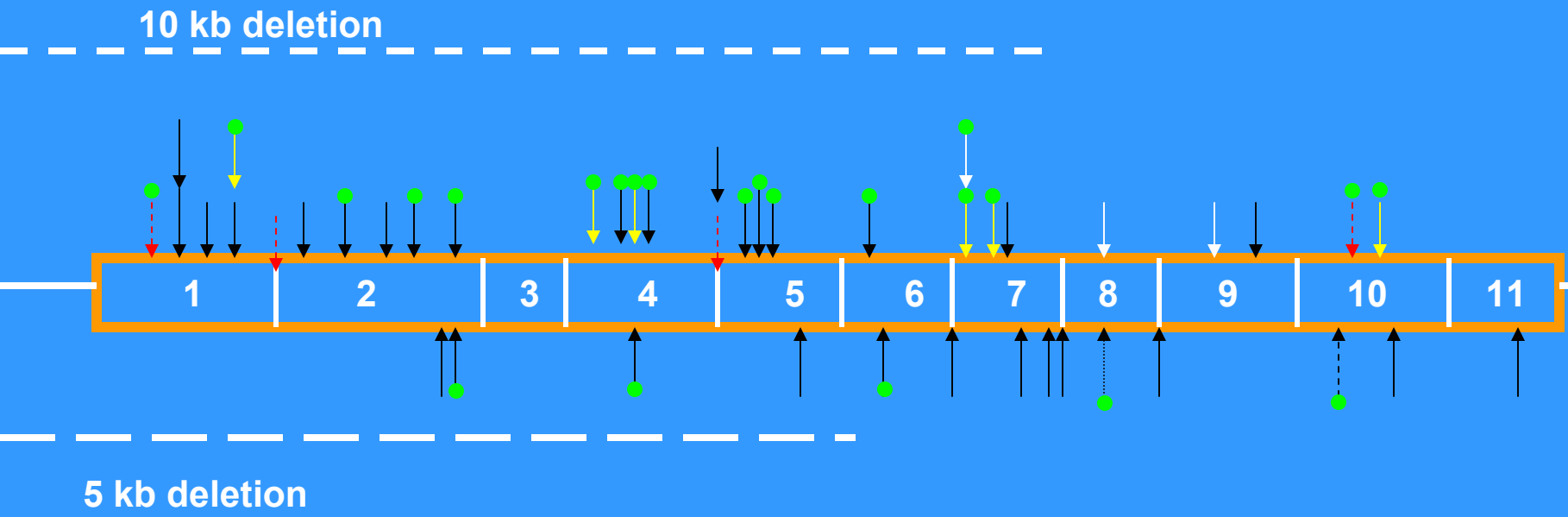
MAP OF MUTATIONS IDENTIFIED:



Minor allele markers

Major allele mutations

Minor allele mutations

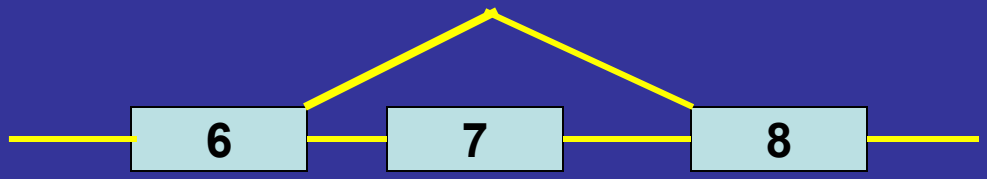
Major/minor uncertain

Missense mutation

Mutation in Hong Kong Chinese PH1

Deletion exon 6/intron 6 junction

A g NNNAG/gtaagt	consensus splice sequence
GCCAA/gtgagtgaccca	normal AGT exon6/intron6
GCCGA/gtgaccca	Hong Kong Chinese PH1



Exon skipping

lys227glu

Common Major Allele Mutation

156insC

9	10	11	12	13
thr	pro	pro	lys	ala
ACC	CCC	CCC	AAG	GCC
		↓		
ACC	CCC	CCC	CAA	GGC
thr	pro	pro	gln	gly

Frameshift
Exon 1

ETHNIC BACKGROUNDS OF PH1 CASES WITH 156INSC

First discovered:	**Italian***	**13%**
	Croatian**	**3 alleles in 2 patients**
My findings:	**American Black**	**1 heterozygote**
	South African Indian	**1 homozygote**
	Caucasian	**6 heterozygotes**
		1 homozygote

*Pirulli et al Hum Genet 104:523, 1999

**Milosevic et al Pediatr Nephrol 17: 896, 2002

ALLELE FREQUENCIES OF PH1 MUTATIONS

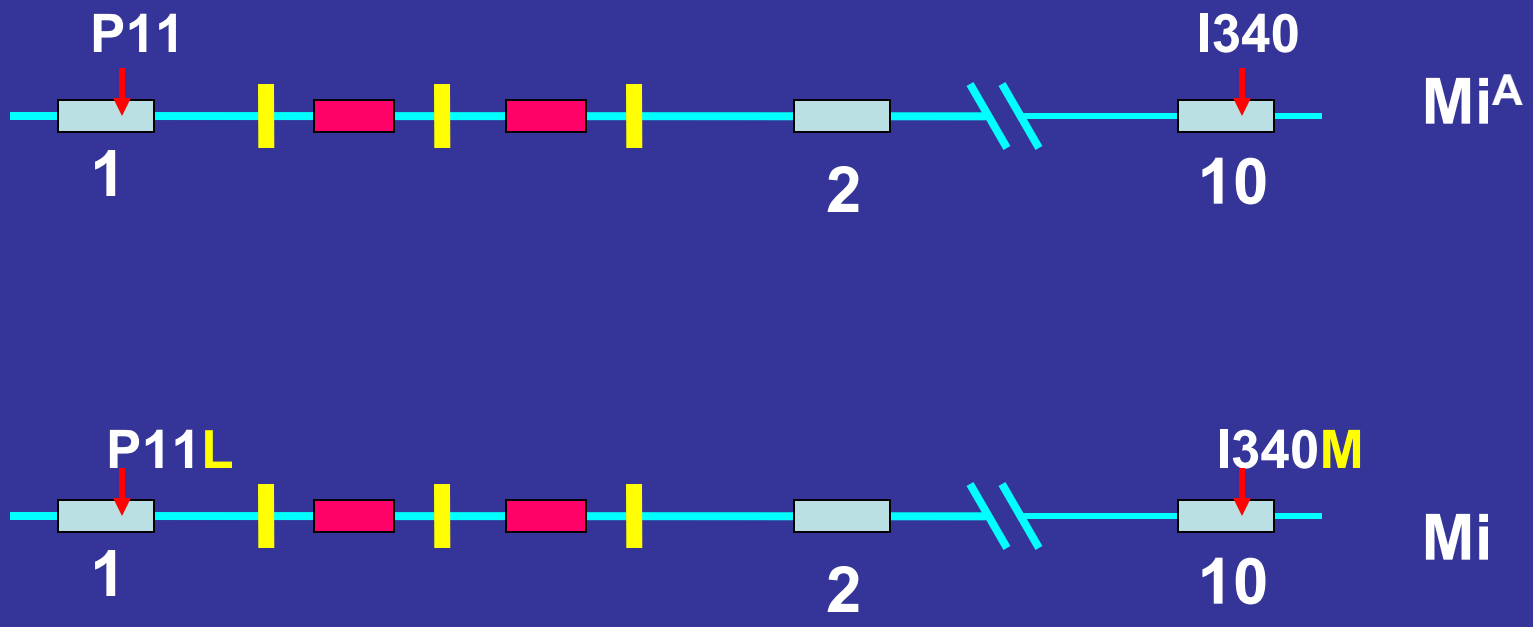
	156insC	Gly170Arg
PH1 alleles	12.5%	35%
PH1 Major alleles	28%	0
PH1 Minor alleles	0	70%
PH1 patients	18.9%	56.8%


North Atlantic Ocean
South Atlantic Ocean
Indian Ocean
Indian Ocean
Mediterranean Sea
Black Sea
Red Sea
Arabian Sea
Gulf of Guinea
Mozambique Channel
Tropic of Cancer
Tropic of Capricorn
Equator
RUSSIA
KAZAKSTAN
BELARUS
UKRAINE
POLAND
GERMANY
FRANCE
SPAIN
PORTUGAL
ITALY
GREECE
TURKEY
CYPRUS
SYRIA
IRAQ
IRAN
JORDAN
ISRAEL
LEBANON
KUWAIT
SAUDI ARABIA
QATAR
U.A.E.
OMAN
YEMEN
EGYPT
LIBYA
TUNISIA
ALGERIA
MOROCCO
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
ETHIOPIA
SOMALIA
DJIBOUTI
KENYA
UGANDA
TANZANIA
RWANDA
BURUNDI
DEM. REP. OF THE CONGO
CENTRAL AFRICAN REPUBLIC
CAMEROON
NIGERIA
BENIN
TOGO
GHANA
CÔTE D'IVOIRE
LIBERIA
SIERRA LEONE
GUINEA
GUINEA-BISSAU
THE GAMBIA
SENEGAL
CAPE VERDE
BURKINA FASO
REP. OF THE CONGO
GABON
EQUATORIAL GUINEA
SAO TOME AND PRINCIPE
ANGOLA
NAMIBIA
BOTSWANA
ZIMBABWE
ZAMBIA
MALAWI
MOZAMBIQUE
SOUTH AFRICA
LESOTHO
SWAZILAND
MADAGASCAR
SEYCHELLES
COMOROS
Algiers
Tunis
Tripoli
Benghazi
Cairo
Alexandria
Khartoum
Addis Ababa
Nairobi
Kampala
Dar es Salaam
Mombasa
Luanda
Kinshasa
Brazzaville
Yaoundé
Bangui
Juba
Lusaka
Harare
Maputo
Windhoek
Walvis Bay
Pretoria
Johannesburg
Durban
Port Elizabeth
Antananarivo
Mogadishu
Scale 1:51,400,000
Azimuthal Equal-Area Projection
0 800 Kilometers
0 800 Miles
Boundary representation is not necessarily authoritative.

BLACK AFRICAN MUTATIONS

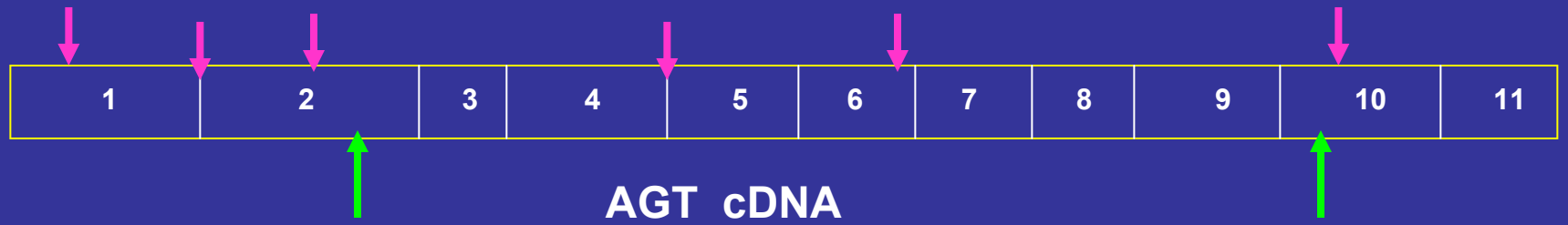
Ala112Asp	deleterious mutation
GCC → GAC	exon 2
Val326Ile	polymorphism (3% Blacks)
GTA → ATA	exon 10

Intron 1 74 bp insertion Mi^A vs Mi



Haplotype of African Variant

	11	dup	A88A	VNTR	S218S	340
Ma	P	-	GCC	38/17/12	TCG	I
Mi	L	+	GCT	38	TCA	M
Mi^A	P	+	GCC	38	TCA	I



ALLELE FREQUENCIES:

	Mi	Mi^A
Caucasians	~20%	
South Africans Blacks	3%	12%
Japanese*	2%	

*Danpure et al. Hum Gen 94:55 (1994)

IMPLICATIONS-1

1. Should not rely on the presence of an intron 1 duplication as the sole indicator of a minor allele if the ethnic background of the patient is Black or unknown.

2. Low frequency of Mi in South Africa suggests that mis-targeting is unlikely to be the most common phenotype in Black Africans with PH1.

IMPLICATIONS-2

3. The Mi^A haplotype may be found in Blacks throughout southern Africa and worldwide in descendents of emigrants from these areas.


North Atlantic Ocean
South Atlantic Ocean
Indian Ocean
Indian Ocean
Mediterranean Sea
Black Sea
Red Sea
Arabian Sea
Gulf of Guinea
Mozambique Channel
Tropic of Cancer
Tropic of Capricorn
Equator
RUSSIA
KAZAKSTAN
BELARUS
UKRAINE
POLAND
GERMANY
FRANCE
SPAIN
PORTUGAL
ITALY
GREECE
TURKEY
CYPRUS
SYRIA
IRAQ
IRAN
JORDAN
ISRAEL
LEB.
KUWAIT
SAUDI ARABIA
QATAR
U.A.E.
OMAN
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DJIBOUTI
SENEGAL
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GUINEA-BISSAU
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SIERRA LEONE
LIBERIA
CÔTE D'IVOIRE
GHANA
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IMPLICATIONS -3

4. Evolution of the minor allele?

   Is the Mi^A a predecessor of Mi?

   Has the duplication event occurred more than once?

SUMMARY

1. Aside from a few common mutations, the mutations causing PH1 are heterogeneous.

2. The most common Ma mutation, 156insC, has been found in a variety of ethnic groups including American Blacks and South African Indians.

3. A deletion in the exon 6/intron 6 junction may be associated with Hong Kong Chinese PH1 patients.

SUMMARY -2

4. A missense mutation, A112D, and a normal polymorphism, V326I found in 2 patients from South Africa and Botswana may be specific to this ethnic group.

5. An African variant haplotype, designated Mi^{A} was linked to A112D and V326I and was found at 12% in the normal Black population of South Africa.

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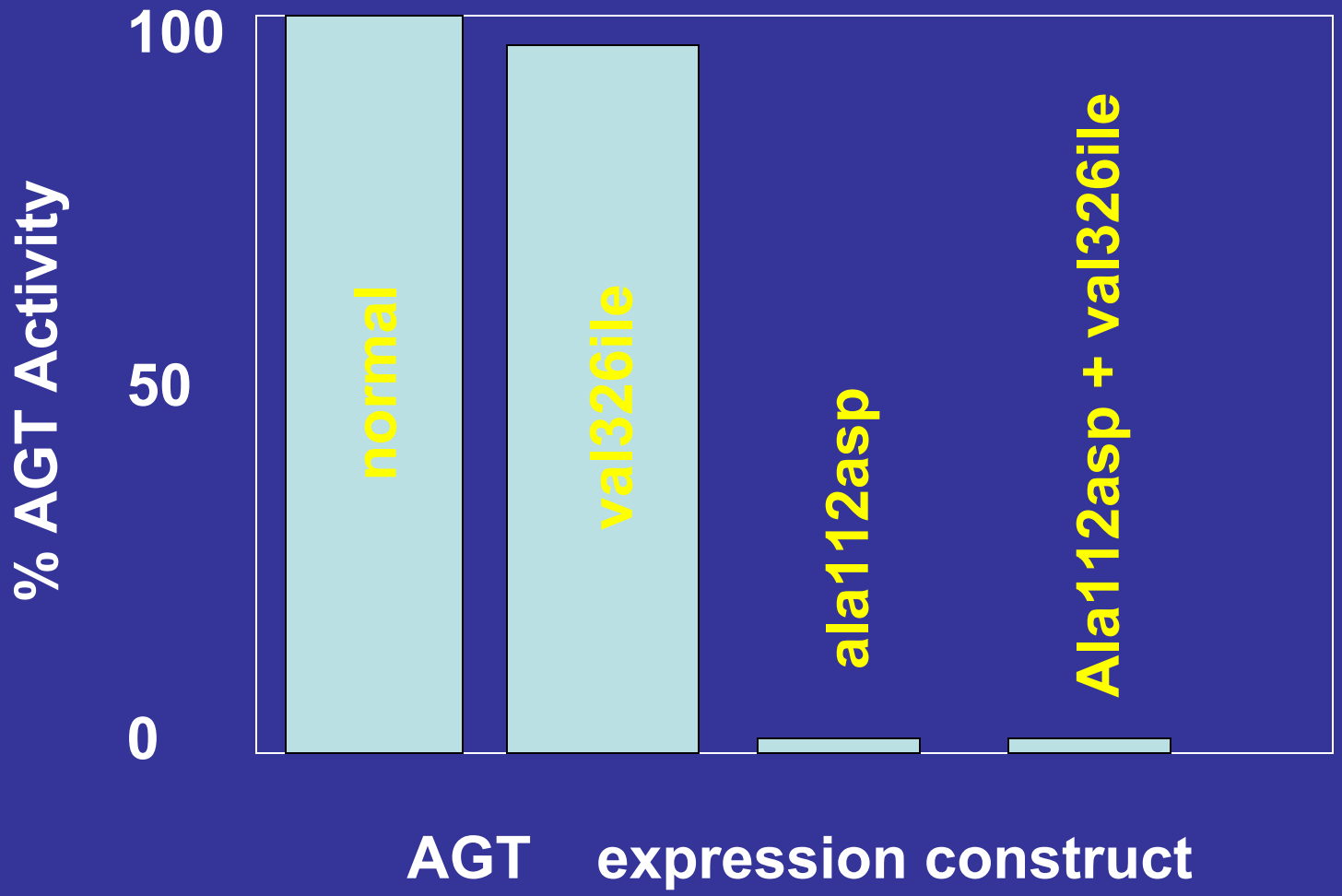
Frequencies of Mutant Alleles (37 PH1 patients)

	Ma	Mi	G170R	F152I	I244T	156insC
# alleles	32	37	26	5	2	9
# patients	25	27	21	5	1	7
# homozygotes	8	10	5	0	1	2
% patients	67.6	73.0	56.8	13.5	2.7	18.9
Allele frequency	43.2	50	35.1	6.8	2.7	12.1
(published values)	50-60	40-50	30	4	9	13

EFFECTS OF MUTATIONS ON AGT ACTIVITY



A MUTATION THAT RESULTS IN NO TARGETING

FRAMESHIFT MUTATION IN EXON 11

GTG GAC CGC GTG ACG GAG GCC…
V D R V T E A

GTG GAC CGT GAC GGA GGC…
V D R D G G

normal
...VDRVTEALRAALQHCPKKKLstop

frameshift
…VDRDGGPEGGPAALPQEEAVTCPLAHSWHWHTPVPCPPstop