Ağ Hesaplamasına Dayalı Biyolojik Veriler Işığında Karmaşık Kökenli Hastalıklarının Nedenbilimi

Uğur Sezerman

Acıbadem Üniversitesi

ACIBADEM
ÜNİVERSİTESİ

Goals:

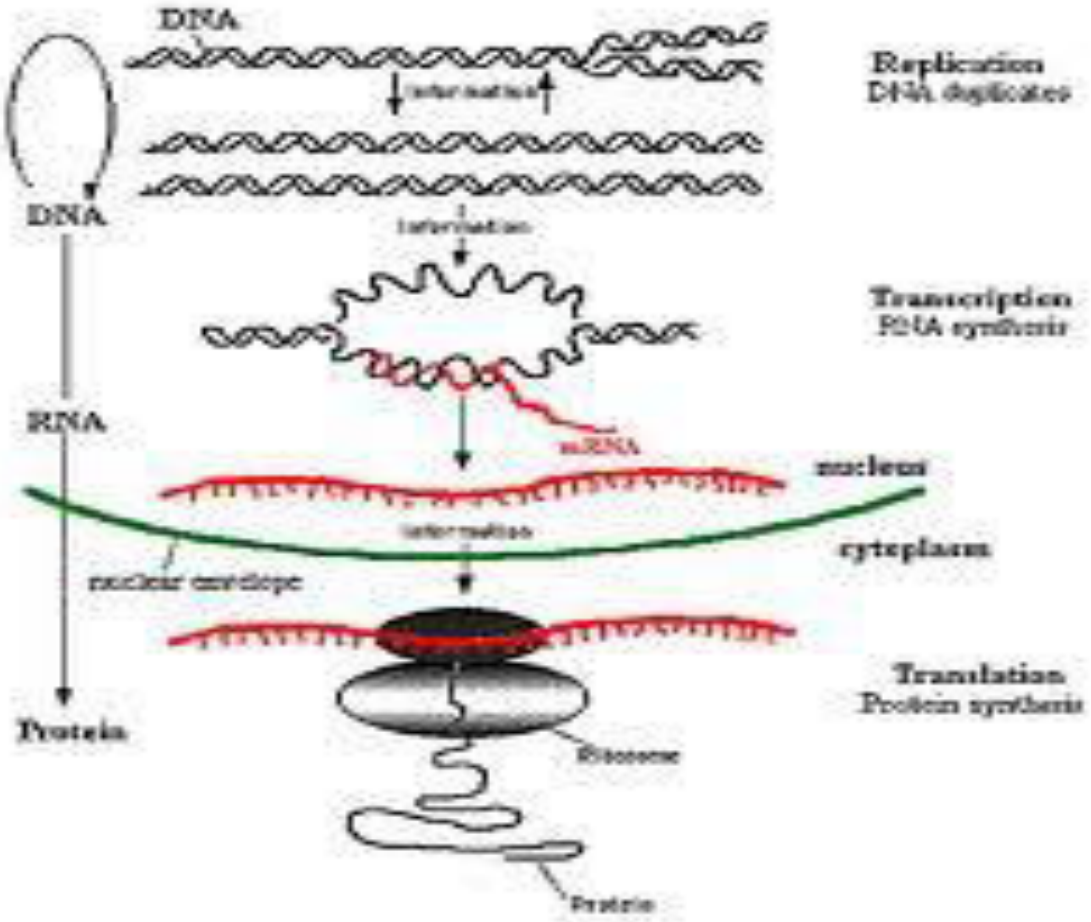
- identify all the approximate 30,000 genes in human DNA,
- determine the sequences of the 3 billion chemical base pairs that make up human DNA,
- store this information in databases,
- improve tools for data analysis,
- transfer related technologies to the private sector, and
- address the ethical, legal, and social issues (ELSI) that may arise from the project.

Milestones:

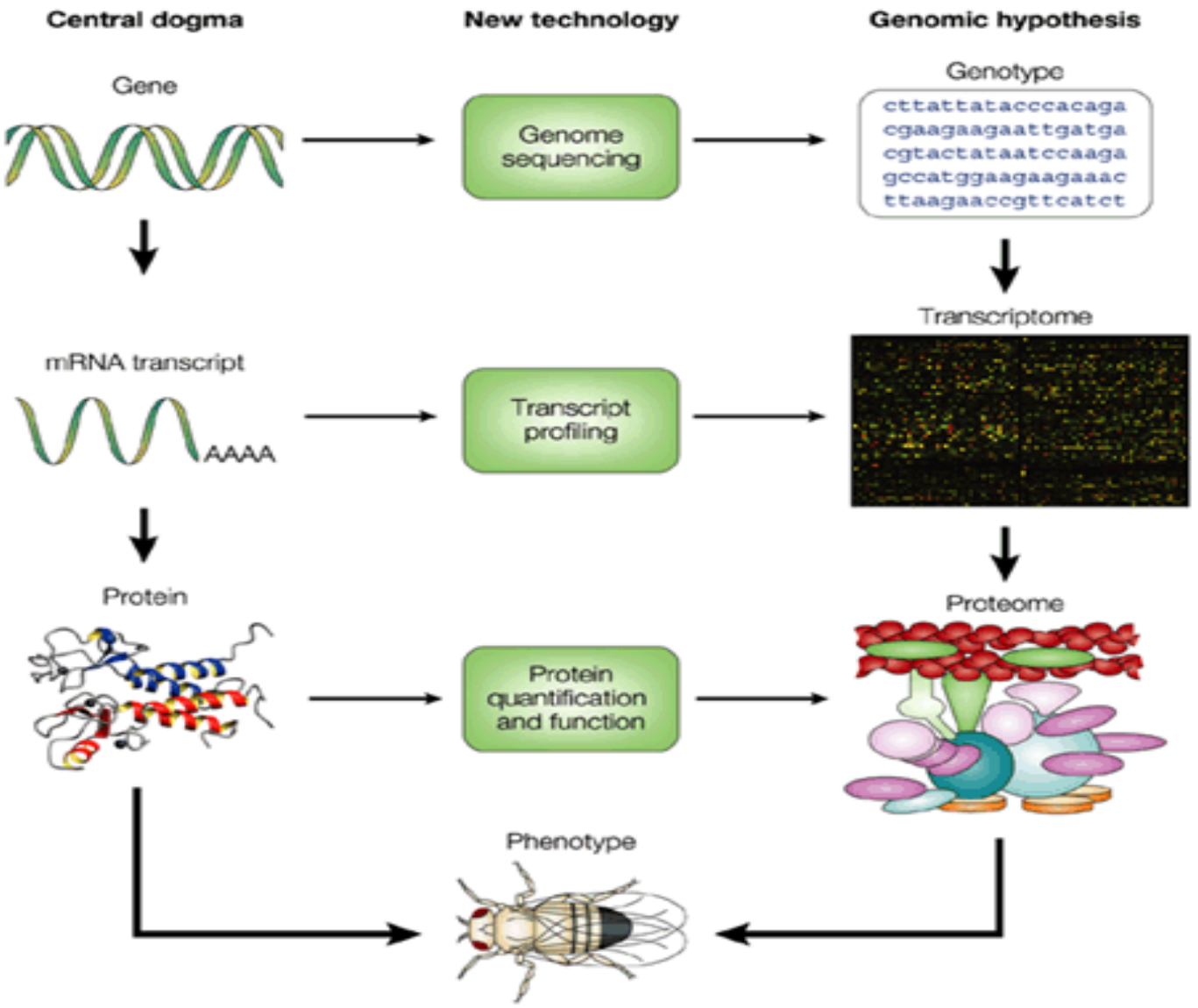
- 1990: Project initiated as joint effort of U.S. Department of Energy and the National Institutes of Health
- June 2000: Completion of a working draft of the entire human genome (covers >90% of the genome to a depth of 3-4x redundant sequence)
- February 2001: Analyses of the working draft are published
- April 2003: HGP sequencing is completed and Project is declared finished two years ahead of schedule

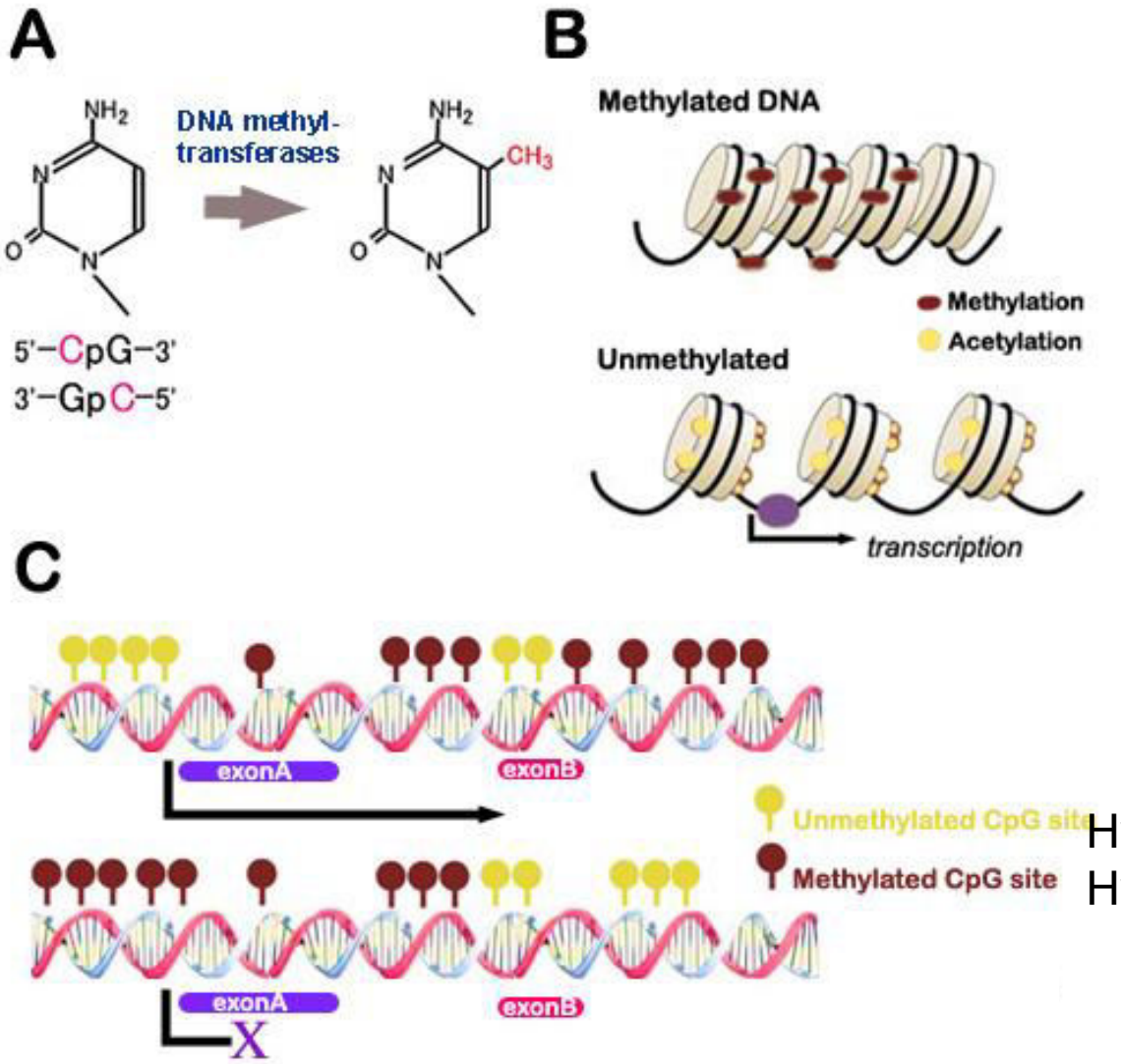
http://doegenomes.org
http://www.sanger.ac.uk/HGP/overview.shtml

U.S. Department of Energy Genome Programs, Genomics and Its Impact on Science and Society, 2003



The Central Dogma of Molecular Biology

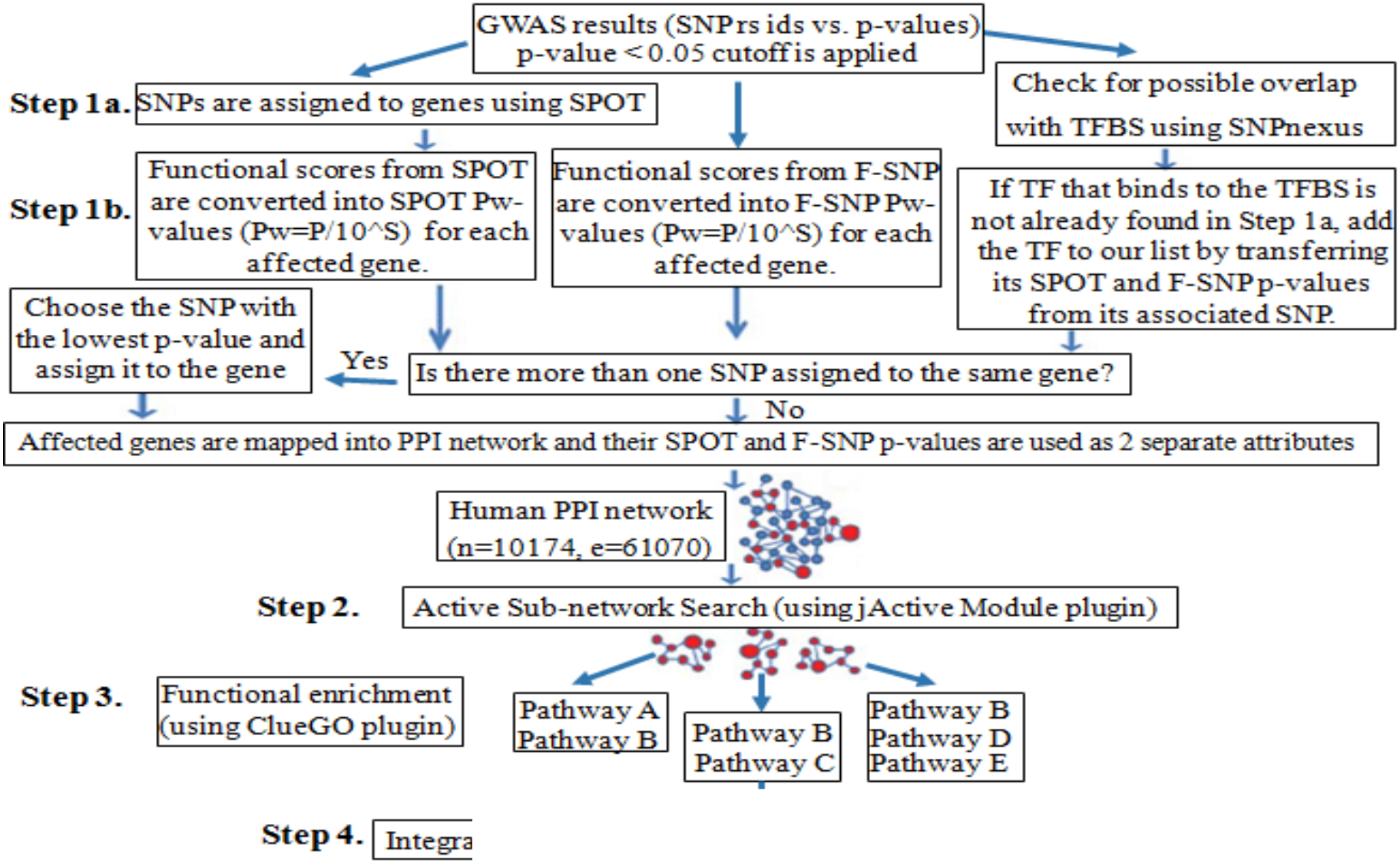

Central dogma
New technology
Genomic hypothesis
Gene
Genome sequencing
Genotype
cttattatacccacaga
cgaagaagaattgatga
cgtactataatccaaga
gccatggaagaagaaac
ttaagaaccgttcatct
mRNA transcript
AAAA
Transcript profiling
Transcriptome
Protein
Protein quantification and function
Proteome
Phenotype
Nature Reviews | Genetics



Hypomethylation
Hypermethylation

http://www.cellscience.com/reviews7/Taylor1.jpg

Our Methodology (PANOGA)



Partial Epilepsy Dataset

# of Cases	# of Controls	# of genotyped SNPs	Platform
3,445	6,935	528,745 SNPs	Illumina, Human610-Quadv1 genotyping chips

Table 5. Summary of Partial Epilepsy (PE)dataset (Kasperaviciute, et al., 2010).

- 1429 patients with epilepsies of unknown cause (classified as "cryptogenic"), 919 cases with mesial temporal lobe epilepsy with hippocampal sclerosis, 241 with cortical malformations and 222 patients with various tumors, other smaller subgroups such as trauma, stroke, perinatal insults, infections, etc.
- Cochran–Mantel–Haenszel test results were used as the genotypic p-values of the identified SNPs.
- Using $P<0.05$ cutoff:
  - 28,450 SNPs were included.

KEGG Term	p values	SNPs in GWAS	SNP Targeted Genes	Previous Studies Showing Support	Wang et al. Study	OMIM	GWAS on PE	CNV Study on Epilepsy	Epi GAD	Rogic et al. Study
Complement and coagulation cascades	2,16E-25	34	12	(Aronica, et al., 2008; Okamoto, et al., 2010)	-	Y	-	-	-	Y
Cell cycle	1,03E-24	24	14	(Aronica, et al., 2008; Jimenez-Mateos, et al., 2008; Limviphuvadh, et al., 2010)	-	Y	-	-	-	Y
Focal adhesion	7,10E-23	97	20	(Brockschmidt, et al., 2012)	Y	Y	Y	-	-	Y
ECM-receptor interaction	1,62E-22	62	14	(Aronica, et al., 2008)	Y	Y	-	-	-	Y
Jak-STAT signaling pathway	1,16E-21	24	16	(Jimenez-Mateos, et al., 2008; Okamoto, et al., 2010)	Y	Y	-	-	-	Y
MAPK signaling pathway	2,32E-19	73	23	(Jimenez-Mateos, et al., 2008; Okamoto, et al., 2010; Zhou, et al., 2011)	Y	Y	Y	-	Y	Y
Proteasome	1,15E-18	11	4	(Lauren, et al., 2010)	-	-	-	-	-	-
Ribosome	1,57E-18	2	2	(Lauren, et al., 2010)	-	-	-	-	-	Y
Calcium signaling pathway	5,73E-18	154	22	(Jimenez-Mateos, et al., 2008; Limviphuvadh, et al., 2010; Okamoto, et al., 2010; Zhou, et al., 2011)	Y	Y	Y	Y	Y	Y
Regulation of actin cytoskeleton	9,23E-18	88	19		Y	Y	-	Y	-	Y
Adherens junction	1,01E-17	79	13		-	-	Y	-	-	Y
Pathways in cancer	3,94E-17	112	22		Y	Y	Y	-	-	Y
Gap junction	6,32E-17	147	18	(Lauren, et al., 2010)	Y	Y	Y	-	-	Y
Apoptosis	3,72E-16	37	13	(Jimenez-Mateos, et al., 2008)	Y	Y	-	-	-	Y
Long-term depression	2,90E-15	151	15	(Lauren, et al., 2010)	Y	Y	Y	Y	Y	Y
Axon guidance	4,01E-15	59	12	(Jimenez-Mateos, et al., 2008; Limviphuvadh, et al., 2010)	-	-	-	-	-	Y
Fc gamma R-mediated phagocytosis	2,22E-14	66	12		Y	Y	Y	Y	-	Y
Tight junction	2,82E-14	82	13		Y	Y	Y	-	-	Y
ErbB signaling pathway	4,04E-14	86	12		Y	Y	Y	-	-	Y
Wnt signaling pathway	6,28E-14	44	13	(Aronica, et al., 2008; Okamoto, et al., 2010)	Y	Y	Y	-	-	Y

Table 6. Comparison of the top 20 SNP-targeted pathways with the pathways of the known genes, as associated to partial epilepsy.

Intracranial Aneurysm Dataset

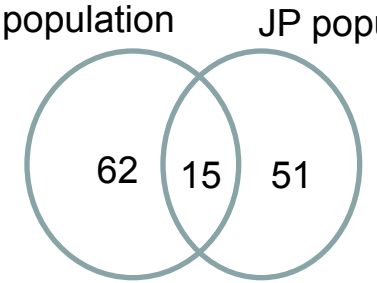
Population	# of Cases	# of Controls	# of genotyped SNPs	Platform
European	2,780	12,515	832,000	Illumina
Japanese	1,069	904	312,712	Illumina,

Table 7. Summary of Intracranial Aneurysm (IA)dataset.

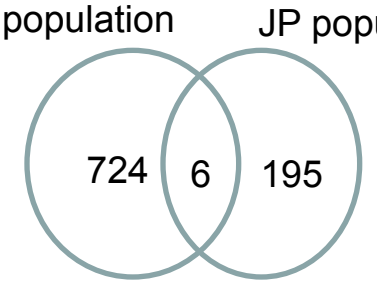
- In both datasets, each SNP's genotypic p-value of association is calculated via Cochran-Armitage trend test.
- Using $P<0.05$ cutoff:
  - 44,351 SNPs were included for EU population,
  - 14,034 SNPs were included for JP population.

	P-values		Rank		# of Associated SNPs in GWAS		# of Common SNPs in GWAS	# of SNP Targeted Genes (STGs)		# of Com-mon STGs	% Common Genes in Both Populations		Common SNPs in GWAS
KEGG Term	EU	JP	EU	JP	EU	JP		EU	JP		EU	JP	
MAPK signaling pathway *	3.53E-27	2.70E-18	1	8	133	43	1	14	18	2	14.29	11.11	rs791062
						18	1	11	10	2	18.18	20	rs744910
					6	20	3	15	9	5	33.33	55.56	rs2053423. rs1440375. rs744910
					0	15	0	6	4	0	0	0	
					7	45	1	21	14	5	23.81	35.71	rs4678167
					2	1	0	6	1	0	0	0	
					5	34	1	13	11	2	15.38	18.18	rs1561798
					5	13	0	8	4	1	12.5	25	
					2	36	1	18	14	1	5.556	7.143	rs4678167
					3	14	0	7	7	1	14.29	14.29	

# of SNP Targeted Genes in Top 10 Pathways



# of SNPs from GWAS in Top 10 Pathways



r both populations in IA. 7 out of the top 10 pathways are

related diseases in KEGG Disease Pathways Database.

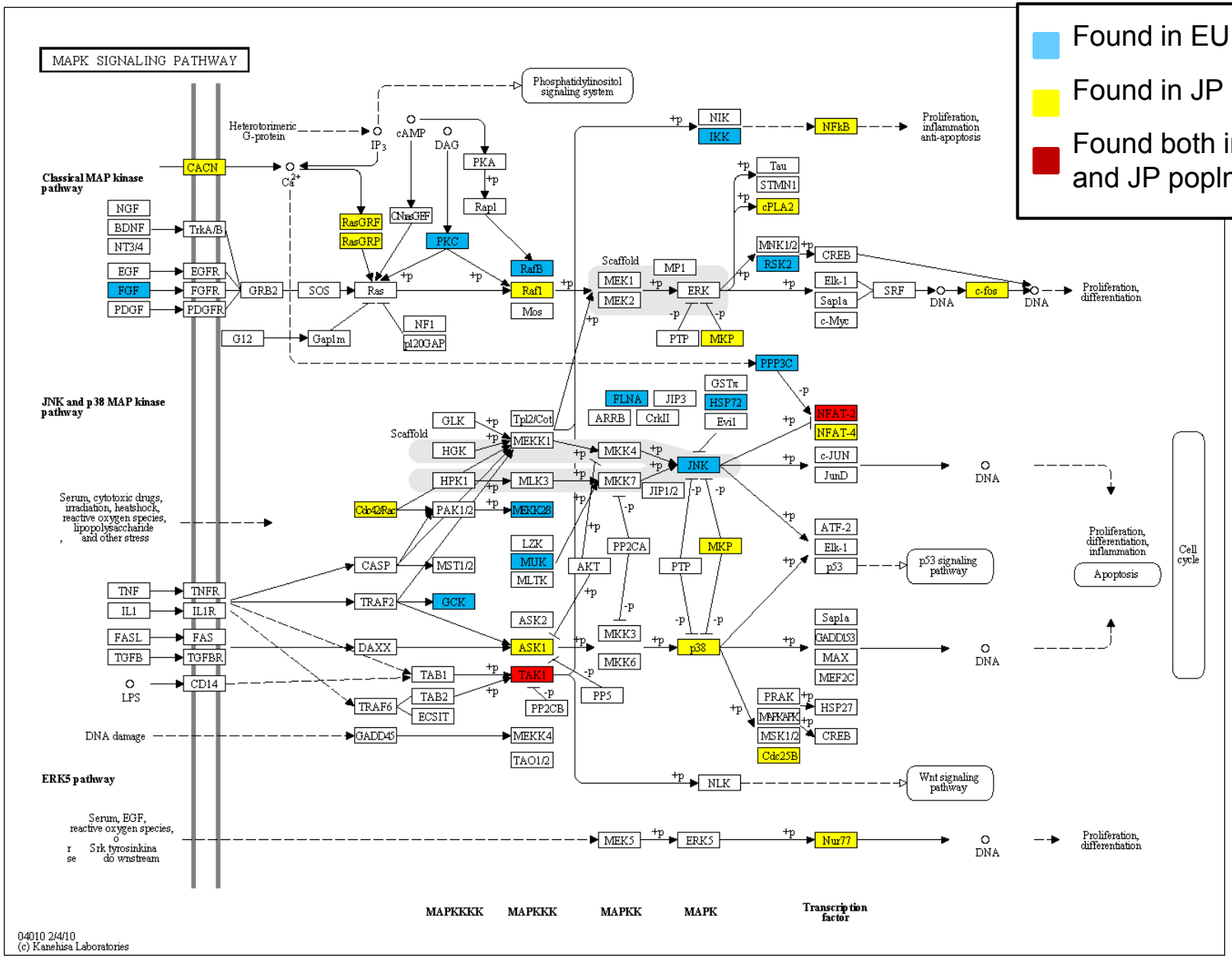


Figure 17. KEGG pathway map for MAPK signaling pathway. The set of genes shown in blue includes genes that are found for EU dataset; yellow includes genes that are found for JP dataset; red includes genes that are found both by EU and JP GWAS of IA.

Behcet's disease dataset

Population	# of Cases	# of Controls	# of genotyped SNPs	Platform
Turkish	1,215	1,278	311,459	Illumina, Infinium assay
Japanese	612	740	500,568	Affymetrix Gene Chip Human Mapping 500K

Table 10. Summary of Behcet's disease dataset.

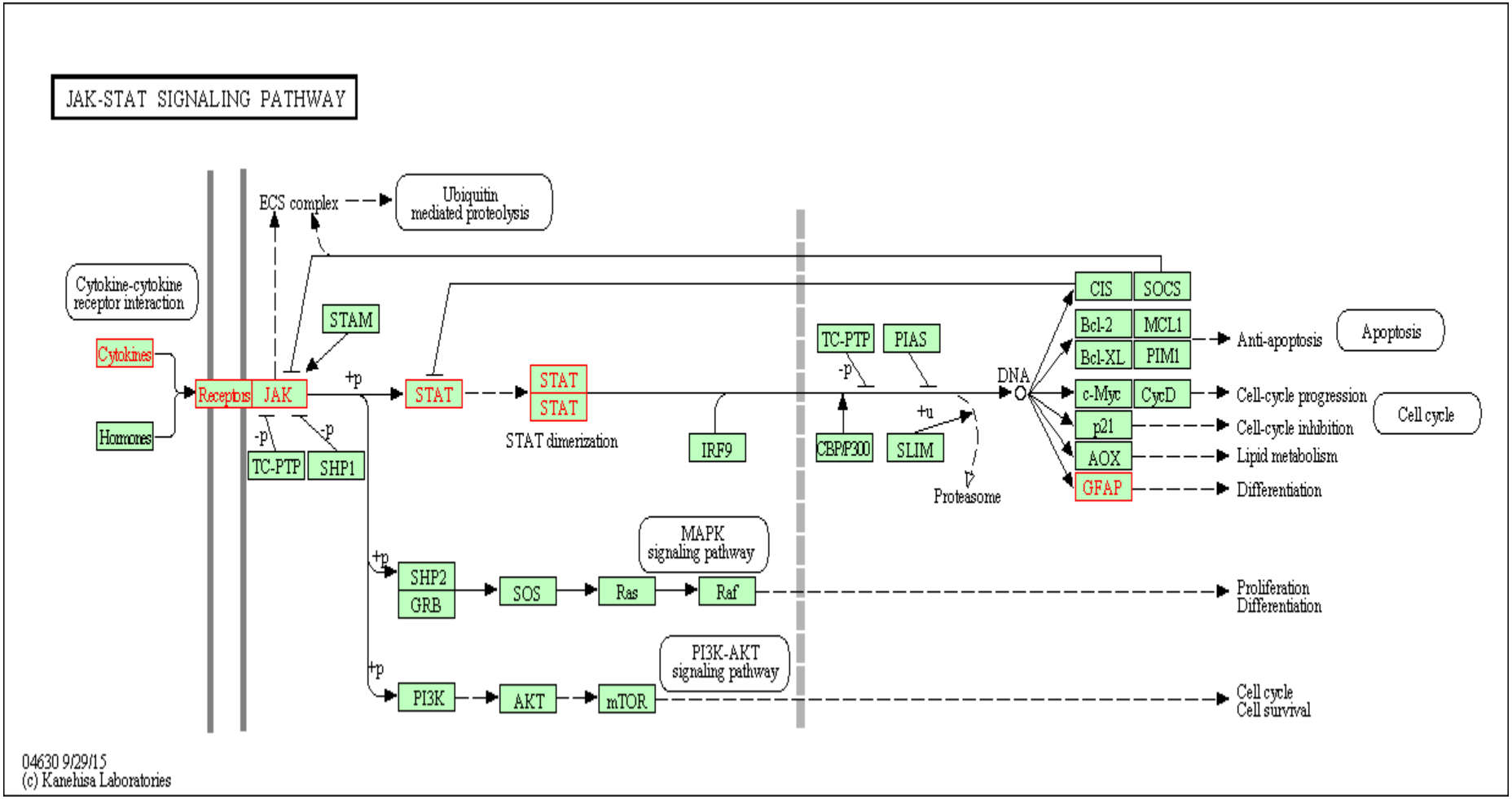
- In both datasets, each SNP's genotypic p-value of association is calculated via calculated via allelic chi-squared test.
- Using $P<0.05$ cutoff:
  - 18,479 SNPs were included for TR population,
  - 20,594 SNPs were included for JP population.

Common pathways in Turkish and Japanese Populations

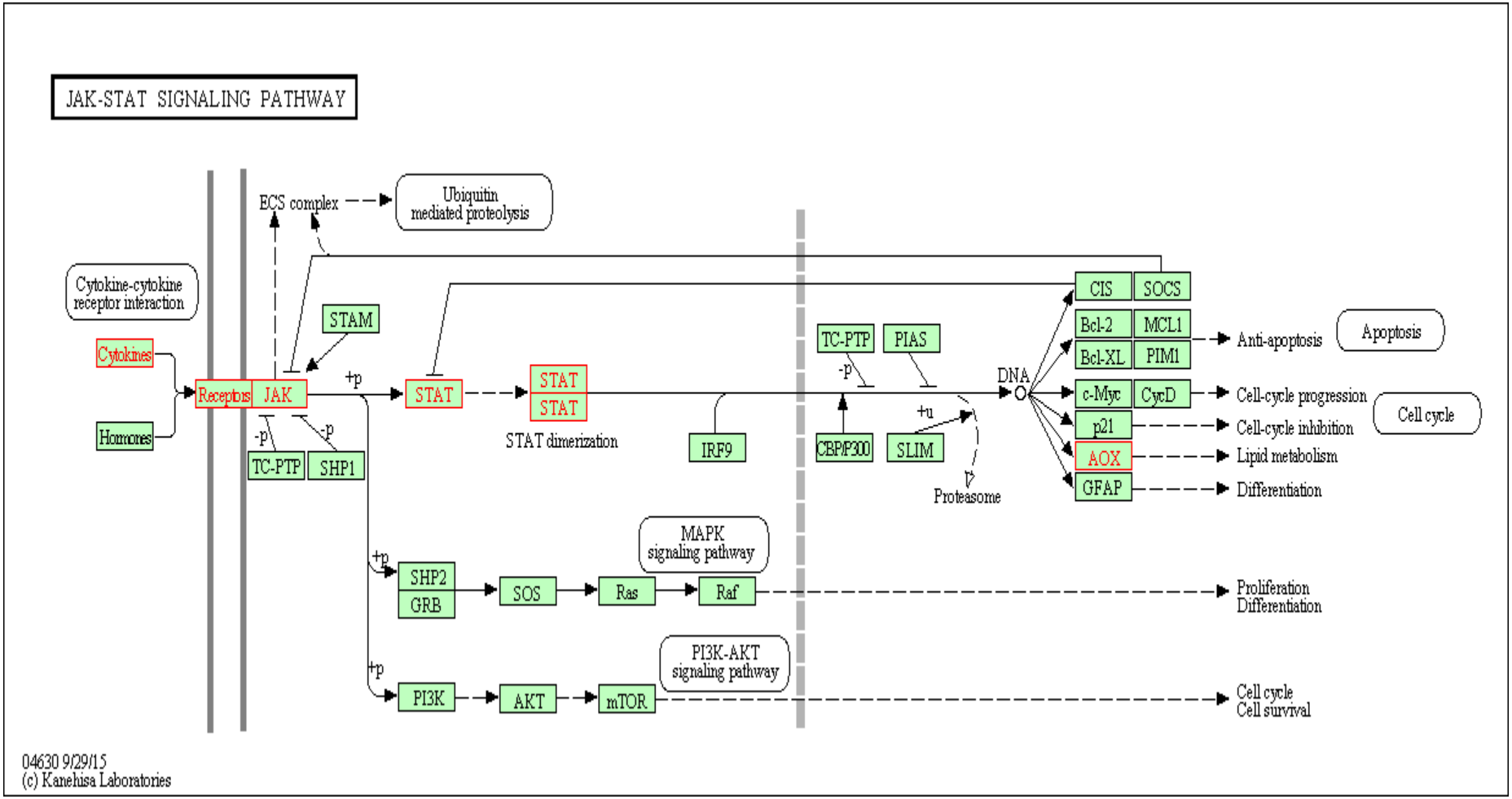
Antigen processing and presentation	Jak-STAT signaling pathway
Adipocytokine signaling pathway	MAPK signaling pathway
Aldosterone-regulated sodium reabsorption	Maturity onset diabetes of the young
Amoebiasis	NOD-like receptor signaling pathway
AMPK signaling pathway	Notch signaling pathway
Axon guidance	PPAR signaling pathway
cAMP signaling pathway	Prolactin signaling pathway
cGMP-PKG signaling pathway	Rap1 signaling pathway
Circadian rhythm	Ras signaling pathway
ErbB signaling pathway	Tight junction
Fc gamma R-mediated phagocytosis	Tuberculosis
Herpes simplex infection	Wnt signaling pathway
Inflammatory mediator regulation of TRP channels	

* Common pathways (25) in first 40 pathways of each population

Highest scoring Jak-STAT path in Turkish population

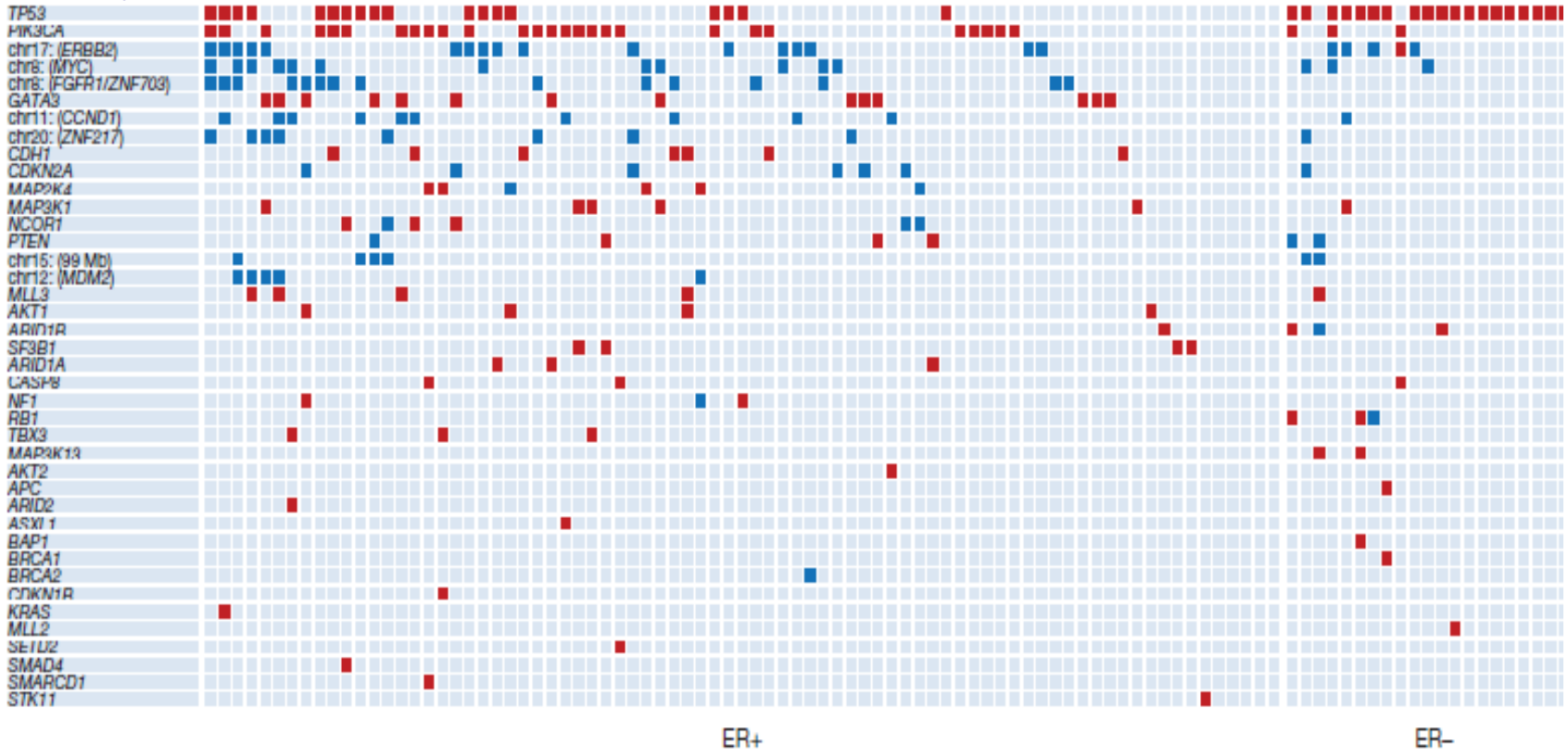


Highest scoring Jak-STAT path in Japanese population



Frequent cancers include high number of very rare genomic segments

- Somatic mutation
- Copy Number Variation



(whole genome sequencing breast cancers)

Stephens, Nature, 2012

Identification of Cancer drivers

- Identification of individualized driver mechanisms that lead to tumour specific cancer progression can improve patient's outcome

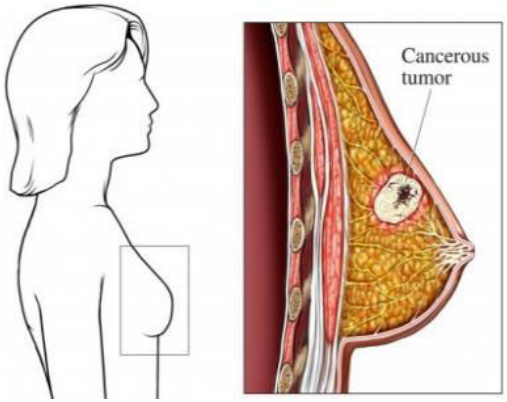
- Goal: Identification of targetable driver mechanism

Precision Medicine

Concept: Identify the targets to be treated in each patient

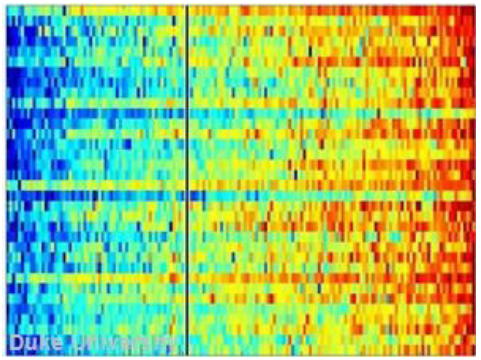
Clinical evidence

Therapy matched to genomic alteration



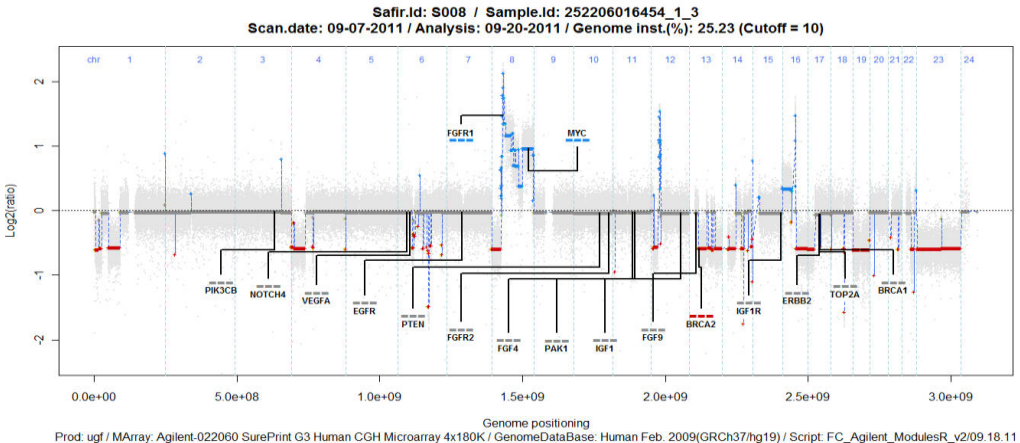
What is the optimal Biotechnology ?

Molecular analysis



What is the optimal Algorithm ?

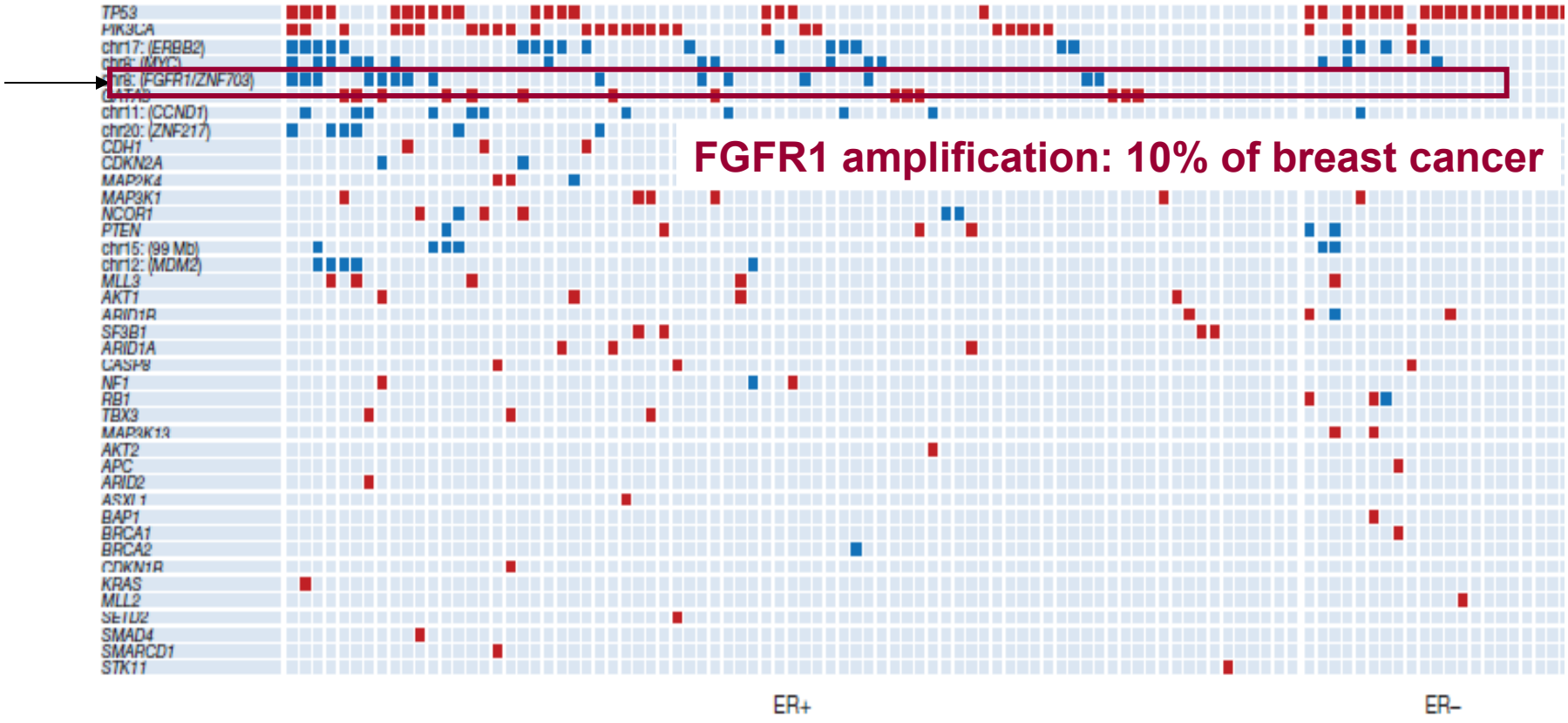
Target identification



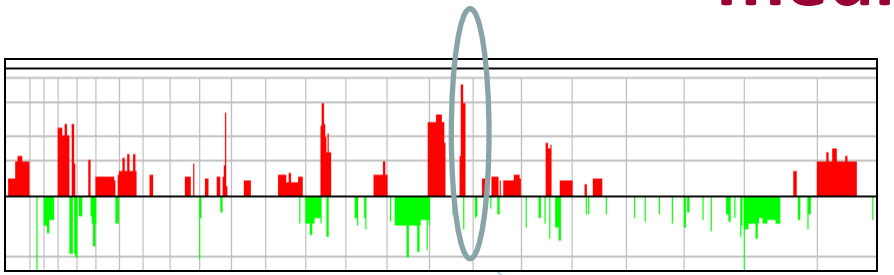
Andre, ESMO, 2012

Stratified medicine

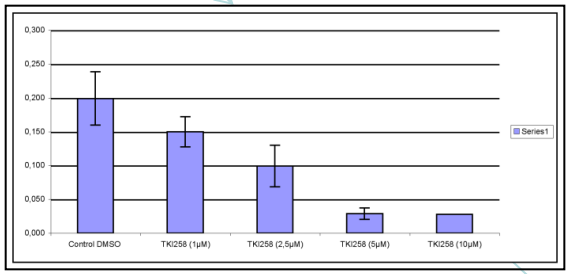
- Drug development or implementation in a strate defined by a molecular alteration



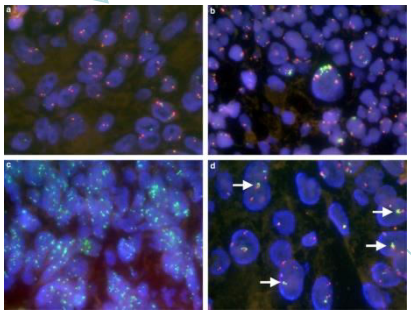
Translational research to feed stratified medicine



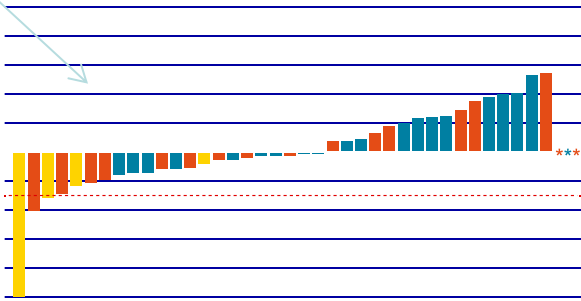
FGFR1: amplification in 10% BC



FGFR1 inhibitors present
higher sensitivity
on FGFR1-amplified CC

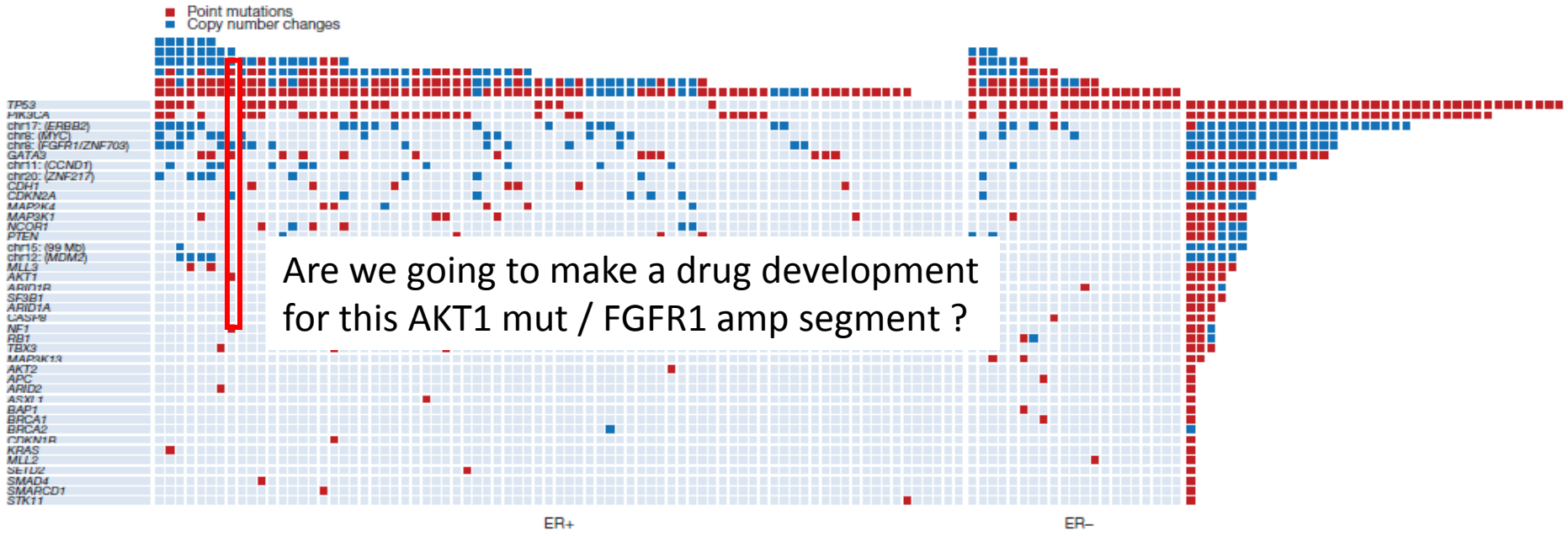


Set-up genomic test
(FISH)



Run phase II trial
Testing the FGFR1
Inh in patients with
FGFR1 amp BC

Evolution:
GENOMIC DISEASES ARE BECOMING TO RARE OR COMPLEX TO ALLOW DRUG DEVELOPMENT IN GENOMIC SEGMENTS

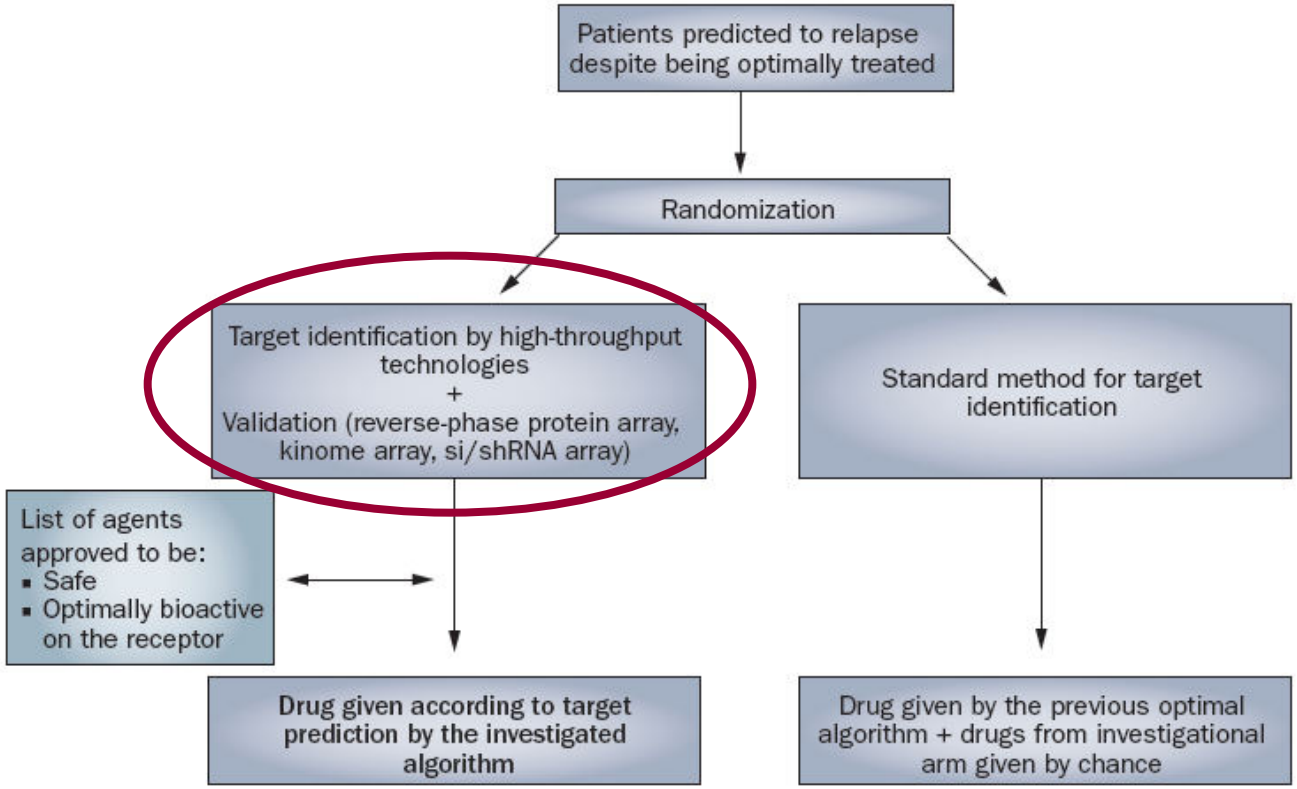


Are we going to make a drug development for this AKT1 mut / FGFR1 amp segment ?

How to move forward ?

Stephens, Nature, 2012

Implications of Personalized Medicine



How to move there ???

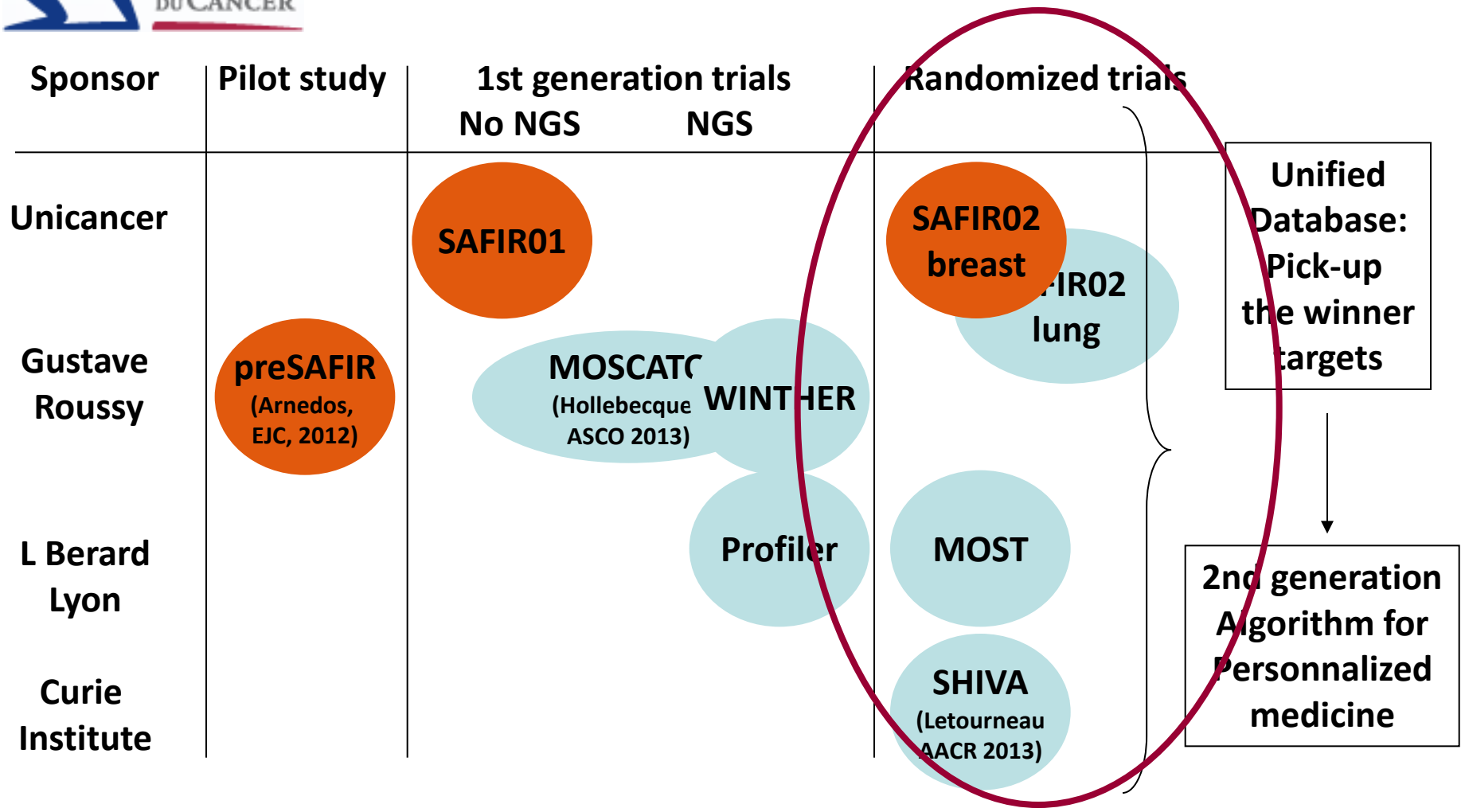
OPINION

Implications of personalized medicine —perspective from a cancer center

Thomas Tursz, Fabrice Andre, Vladimir Lazar, Ludovic Lacroix and Jean-Charles Soria

Tursz, T. *et al. Nat. Rev. Clin. Oncol.* **8**, 177–183 (2011)

Ongoing molecular screening or personalized medicine programs in France



Overall : >2 000 planned patients (all tumor types), >800 already included

Breast Cancer: > 1 000 planned, >70 already treated

Goal: To generate optimal algorithm for individualized therapy

SAFIR01

- 423 patients were included, and biopsy samples were obtained from 407 (metastatic breast cancer was not found in four). CGH array and Sanger sequencing were feasible in 283 (67%) and 297 (70%) patients, respectively.
- A targetable genomic alteration was identified in 195 (46%) patients, most frequently in PIK3CA (74 [25%] of 297 identified genomic alterations), CCND1 (53 [19%]), and FGFR1 (36 [13%]). 117 (39%) of 297 patients with rare genomic alterations (<5% of the general population), including AKT1 mutations, and EGFR, MDM2, FGFR2, AKT2, IGF1R, and MET high-level amplifications.
- Therapy could be personalised in 55 (13%) of 423 patients. Of the 43 patients who were assessable and received targeted therapy, four (9%) had an objective response, and nine others (21%) had stable disease for more than 16 weeks.
- Serious (grade 3 or higher) adverse events related to biopsy were reported in four (1%) of enrolled patients, including pneumothorax (grade 3, one patient), pain (grade 3, one patient), haematoma (grade 3, one patient), and haemorrhagic shock (grade 3, one patient).

A Protocol to Determine Somatic Modifications

- Exome Sequencing of tumour sample and control sample(Blood)
- Identification of somatic alterations in the tumour

Driver mutations

Copy Number Variations (CNV)

SNPs

Chr	Pos	Ref -> Alt Genome Protein Effect	Gene	dbSNP	CGC* Tumor Type	DrugBank
2	209113112	C -> T R -> H Missense	IDH1	rs121913500	Glioblastoma	-
17	7577545	T -> C M -> V Missense	TP53	rs483352695 rs397516437	Glioma	Acetylsalicylic acid

* Cancer Gene Census

SNPs

Chr	Pos	Ref -> Alt Genome Protein Effect	Gene	dbSNP	CGC* Tumor Type	DrugBank
2	209113112	C -> T R -> H Missense	IDH1	rs121913500	Glioblastoma	-
17	7577545	T -> C M -> V Missense	TP53	rs483352695 rs397516437	Glioma	Acetylsalicylic acid

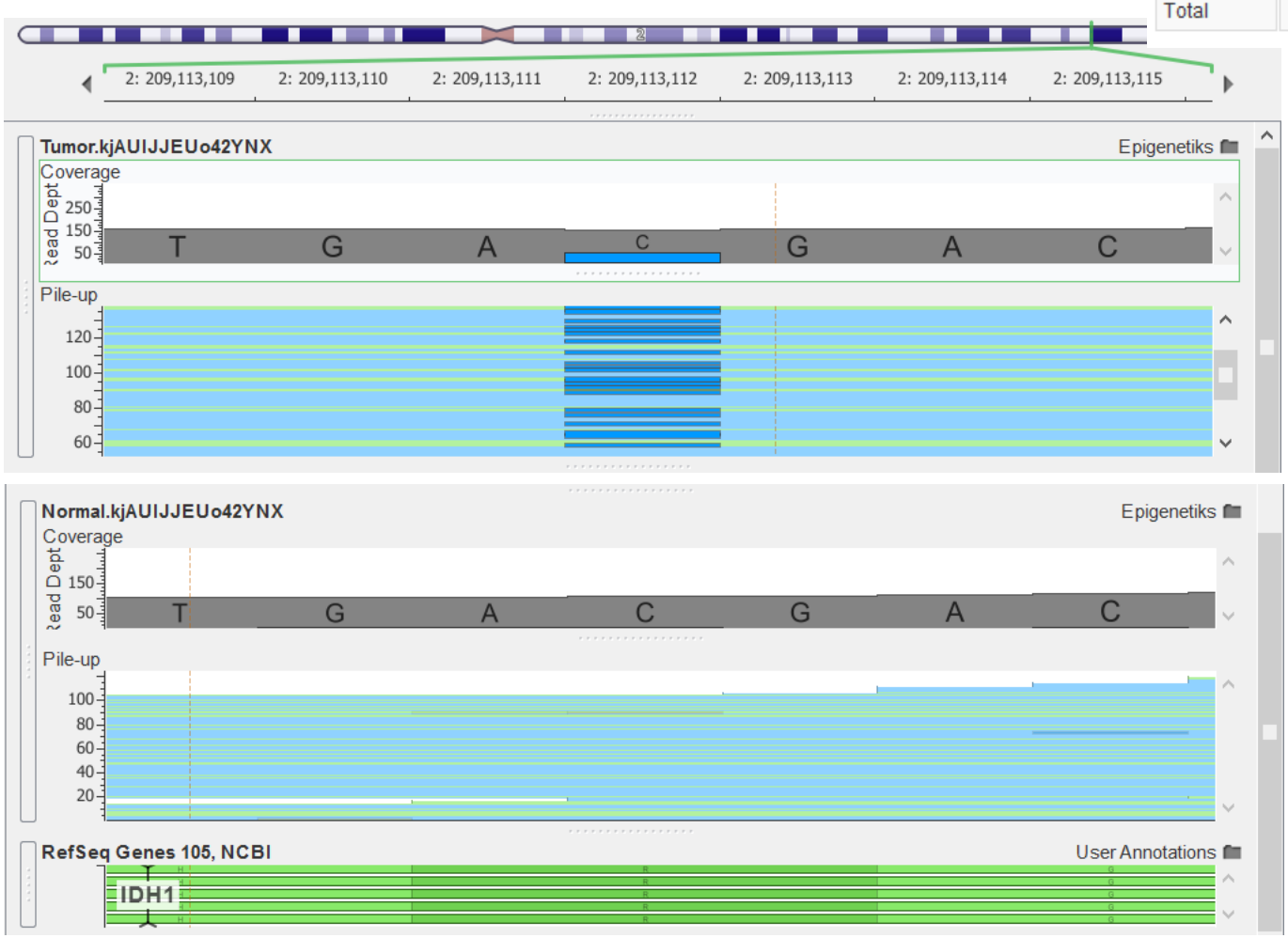
* Cancer Gene Census

SNPs

Chr2: 209,113,112

Matches / Mismatches / Deletions

Type	Base	Count	% of Total	Mean Quality
(match)	C	99	66.4	30.8
(mismatch)	T	50	33.6	32.3
Total		149	100	31.3



SNPs

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2	209113112	C -> T R -> H Missense	IDH1	rs121913500	Glioblastoma	-
17	7577545	T -> C M -> V Missense	TP53	rs483352695 rs397516437	Glioma	Acetylsalicylic acid

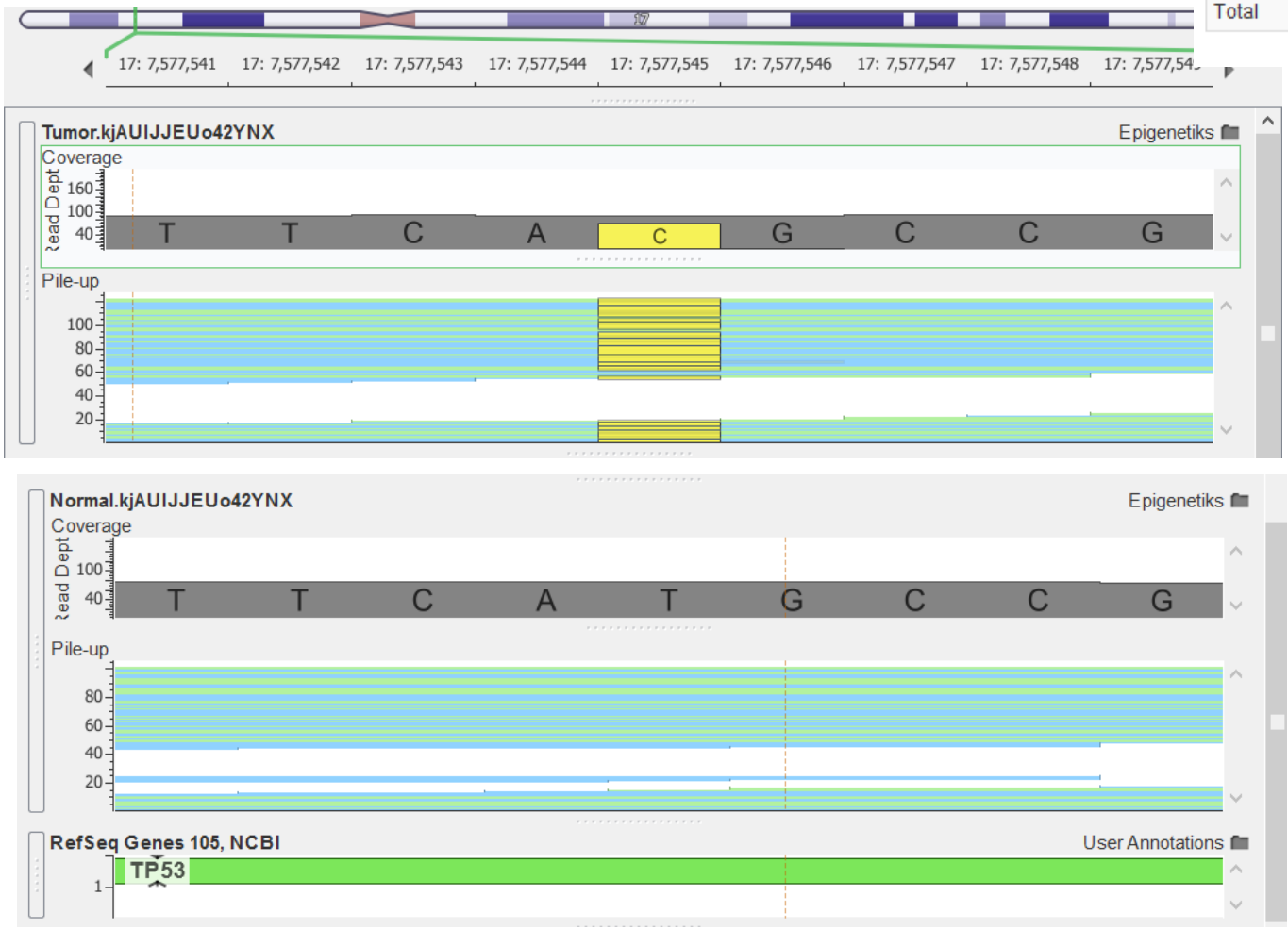
* Cancer Gene Census

SNPs

Chr17: 7,577,545

Matches / Mismatches / Deletions

Type	Base	Count	% of Total	Mean Quality
(match)	T	21	24.1	29.7
(mismatch)	C	66	75.9	29.0
Total		87	100	29.1



INDELs

Chr	Pos	Ref	Alt	Normal GT	Tumor GT	CGC* Tumor Type	DrugBank
5	67575323	ATT	A	0/1	0/1	Glioblastoma	Isoprenaline
17	7579643	CCCCCAGCCCTCCAGGT	C	0/0	0/1	Glioma	Acetylsalicylicacid

* Cancer Gene Census

INDELs

Chr	Pos	Ref	Alt	Normal GT	Tumor GT	CGC* Tumor Type	DrugBank
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* Cancer Gene Census

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17	7579643	CCCCCAGCCCTCCAGGT	C	0/0	0/1	Glioma	Acetylsalicylic acid

* Cancer Gene Census

INDELs


17
17: 7,579,637
17: 7,579,642
17: 7,579,647
17: 7,579,652
17: 7,579,657
17: 7,579,662
17: 7,579,667
17: 7,579,672
Tumor.kjAUIJJEUo42YNX
Epigenetiks
Coverage
Read Dept
150
50
A G C C C C C C A G C C C C C C A G C C C T C C A G G T C C C C A G C C C T C C A G C
Pile-up
100
80
60
40
20
Normal.kjAUIJJEUo42YNX
Epigenetiks
Coverage
Read Dept
100
60
20
A G C C C C C C A G C C C C C C A G C C C T C C A G G T C C C C A G C C C T C C A G C
Pile-up
70
50
30
10
RefSeq Genes 105, NCBI
User Annotations
TP53
1

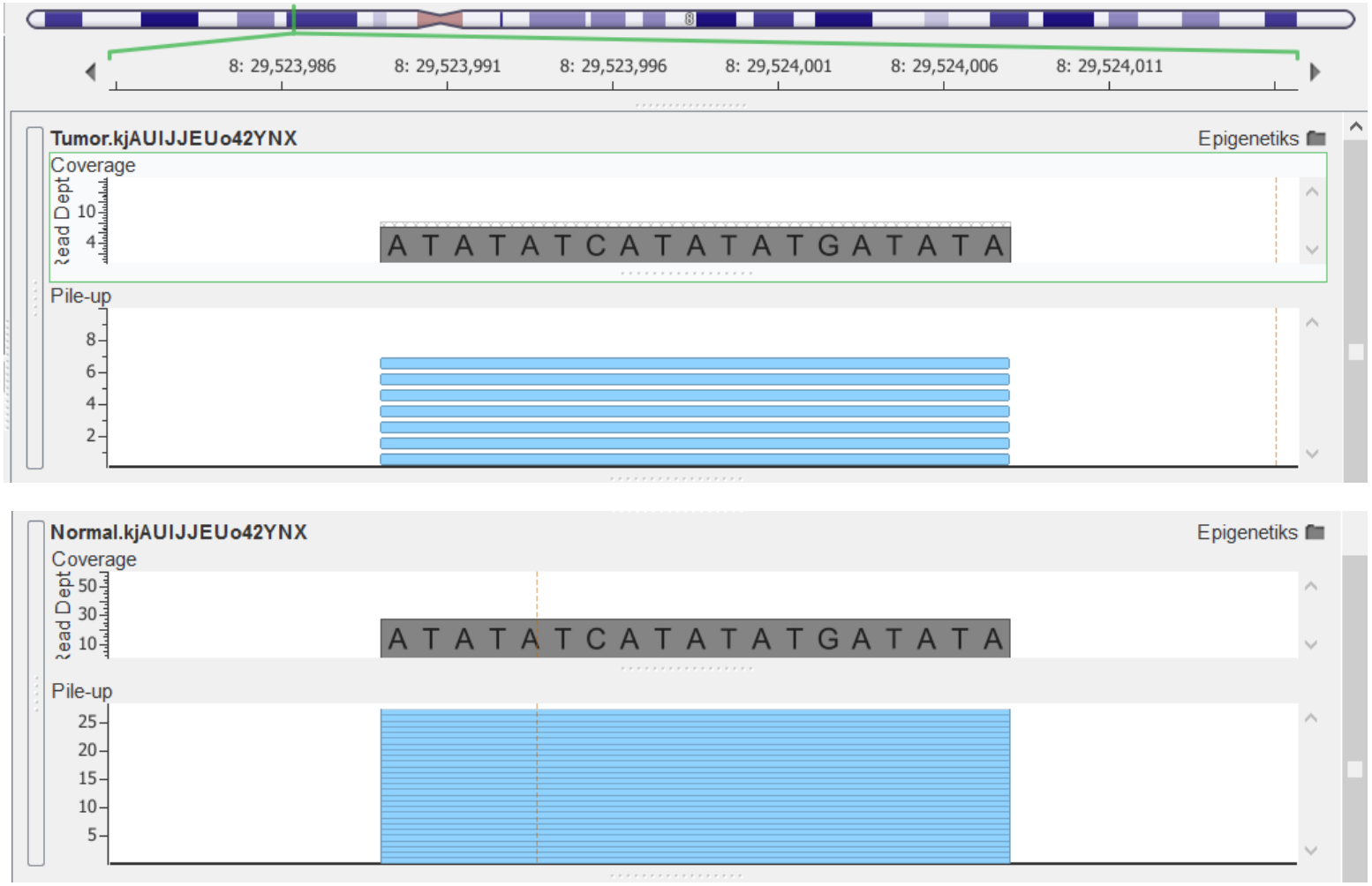
Copy Number Variation

Chr	Start	End	Normal Depth	Tumor Depth	Log Ratio
8	29523990	29524007	20.6	4.3	-2.348

CNV Annotation

CNV type	Disease	Platform	Pubmed
Deletion	Medulloblastoma	SNP arrays	21979893
Loss	Glioblastoma multiforme	CGH	19960244
Loss	Glioblastoma multiforme	conventional CGH	21080181
Loss	Glioblastoma multiforme	aCGH	21080181
Loss	Medulloblastoma	CGH	16968546

Copy Number Variation



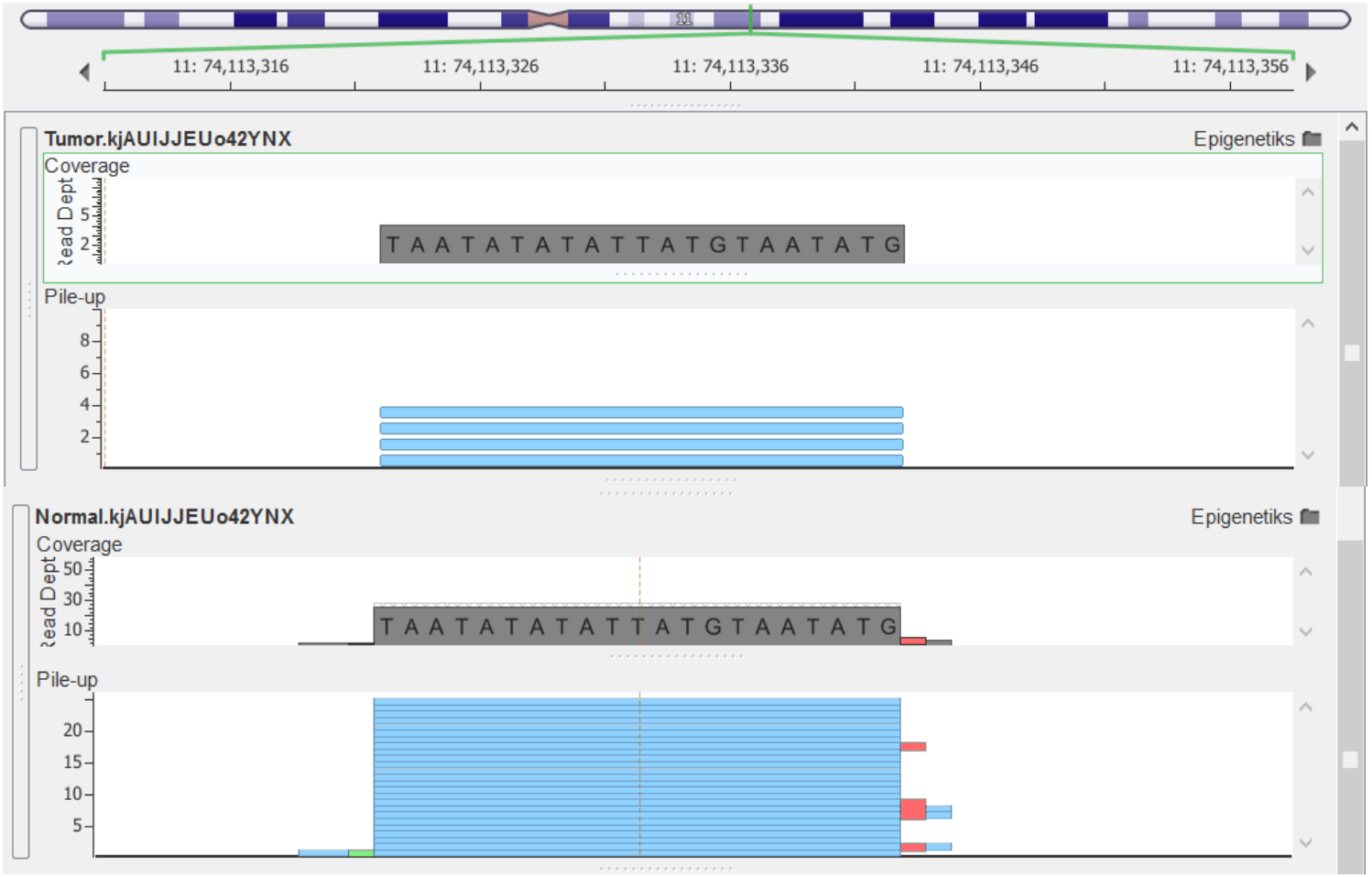
Copy Number Variation

Chr	Start	End	Normal Depth	Tumor Depth	Log Ratio
11	74113323	74113342	24.0	4.0	-2.559

CNV Annotation

CNV type	Disease	Platform	Pubmed
Deletion	Medulloblastoma	SNP arrays	21979893
Loss	Glioblastoma multiforme	CGH	19960244
Loss	Glioblastoma multiforme	conventional CGH	21080181
Loss	Glioblastoma multiforme	aCGH	21080181

Copy Number Variation



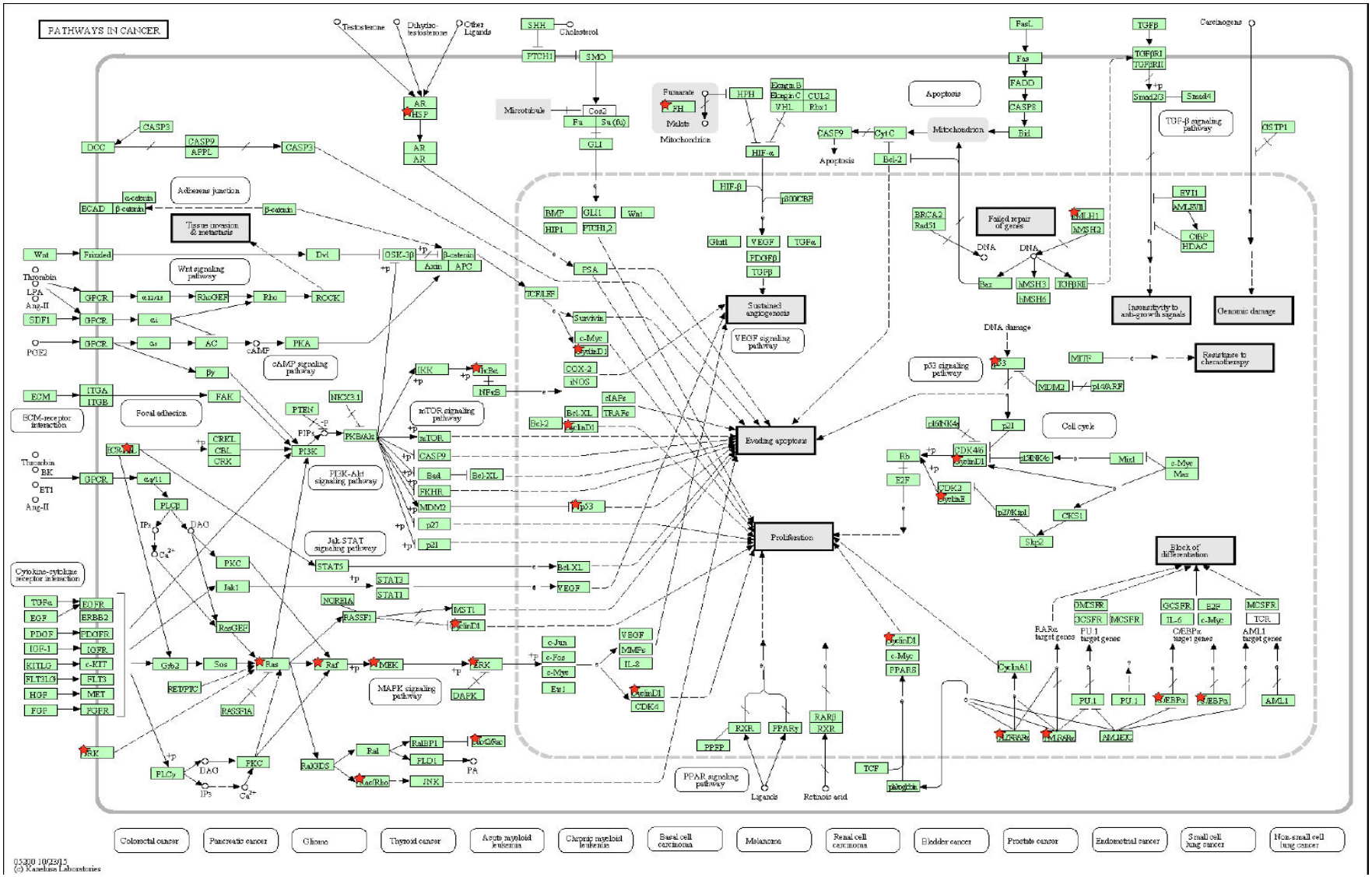
Scoring Algorithm

- Scoring system to identify major pathways leading to tumor progress
- Scoring System for targetable alterations in the tumor
- Scoring system for available drugs targeting most of the driver alterations

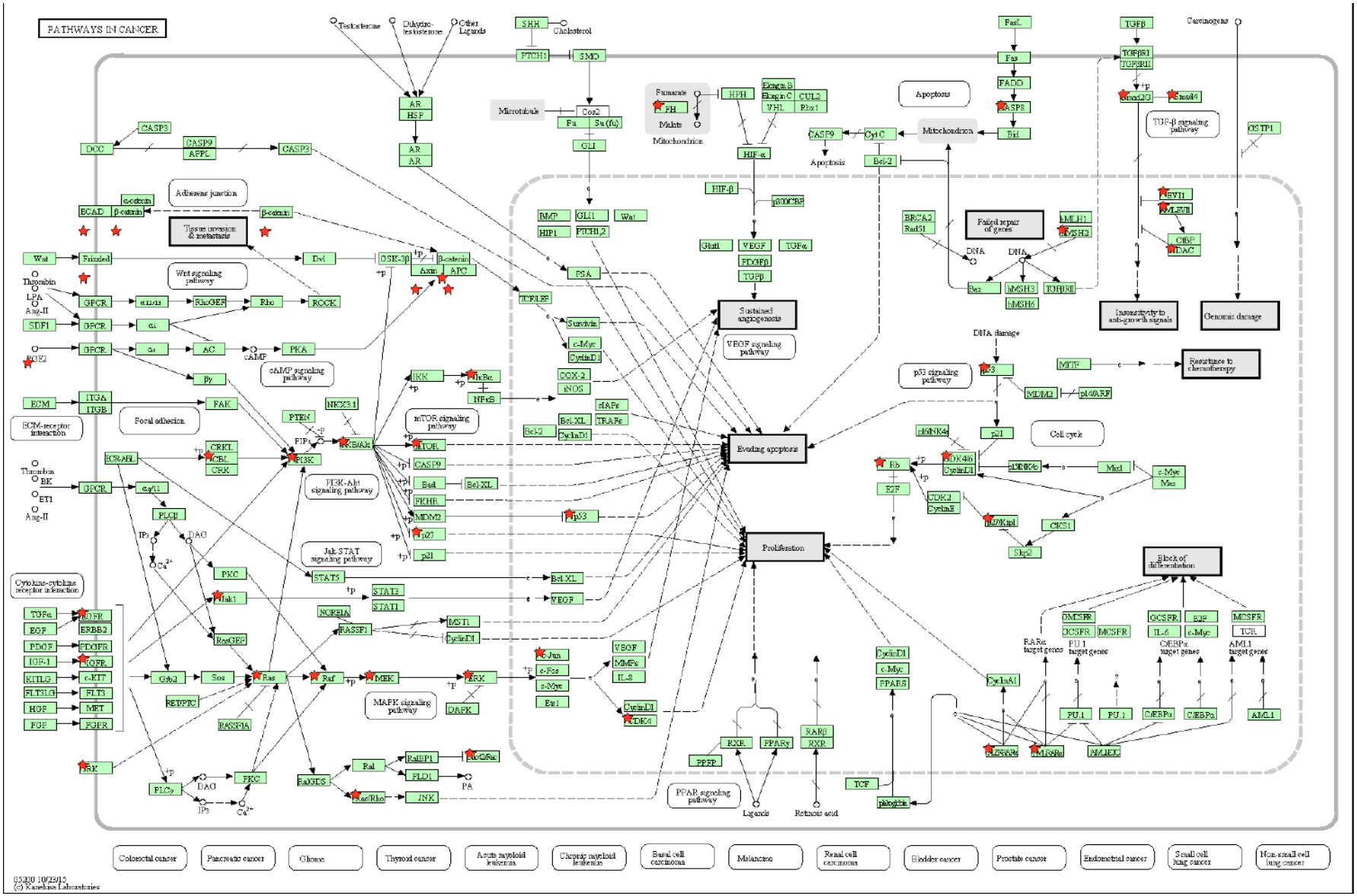
EXAMPLES of Exome Sequencing Data

- Patient 1 has CyclinD1 pathway over activated
- Patient 2 has Mtor pathway and CDK4 pathway activate
- Patient 3 has over amplification of Growth Factor receptors along with c-myc amplification
- Each has different driver mechanisms and requires different theraupeutical scheme

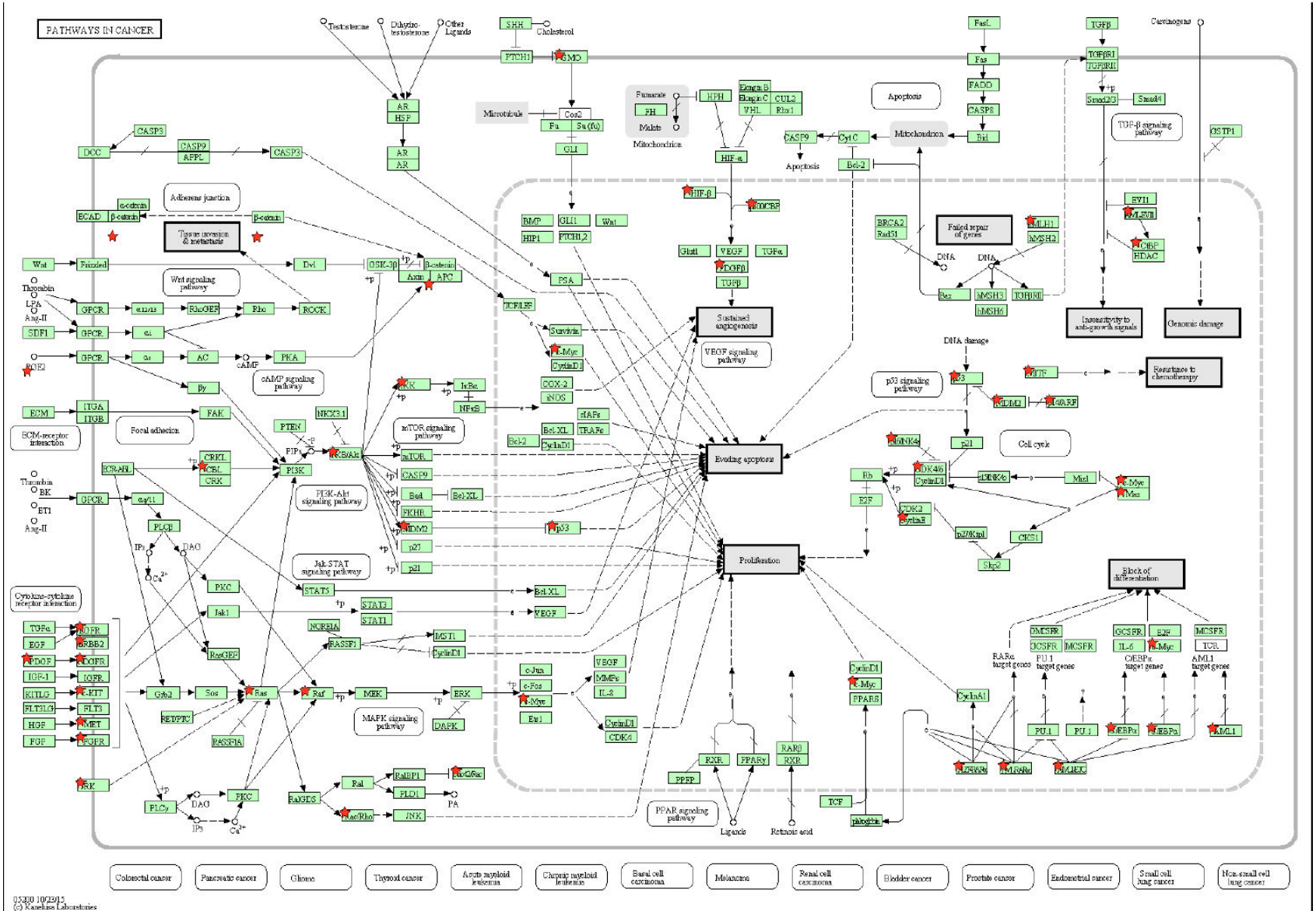
Patient 1


PATHWAYS IN CANCER
Colorectal cancer
Pancreatic cancer
Glioma
Thyroid cancer
Acute myeloid leukemia
Chronic myeloid leukemia
Basal cell carcinoma
Melanoma
Renal cell carcinoma
Bladder cancer
Prostate cancer
Endometrial cancer
Small cell lung cancer
Non-small cell lung cancer

Patient 2


PATHWAYS IN CANCER
Colorectal cancer
Pancreatic cancer
Glioma
Thyroid cancer
Acute myeloid leukemia
Chronic myeloid leukemia
Basal cell carcinoma
Melanoma
Renal cell carcinoma
Bladder cancer
Prostate cancer
Endometrial cancer
Small cell lung cancer
Non-small cell lung cancer

Patient 3


PATHWAYS IN CANCER
Proliferation
Evading apoptosis
Sustained angiogenesis
Invasion & metastasis
Insensitivity to anti-growth signals
Genomic damage
Resistance to chemotherapy
Cell cycle
Block of differentiation
Colorectal cancer
Pancreatic cancer
Glioma
Thyroid cancer
Acute myeloid leukemia
Chronic myeloid leukemia
Basal cell carcinoma
Melanoma
Renal cell carcinoma
Bladder cancer
Prostate cancer
Endometrial cancer
Small cell lung cancer
Non-small cell lung cancer

Genotyping for prevention Timoma (Sternum)Patient 4

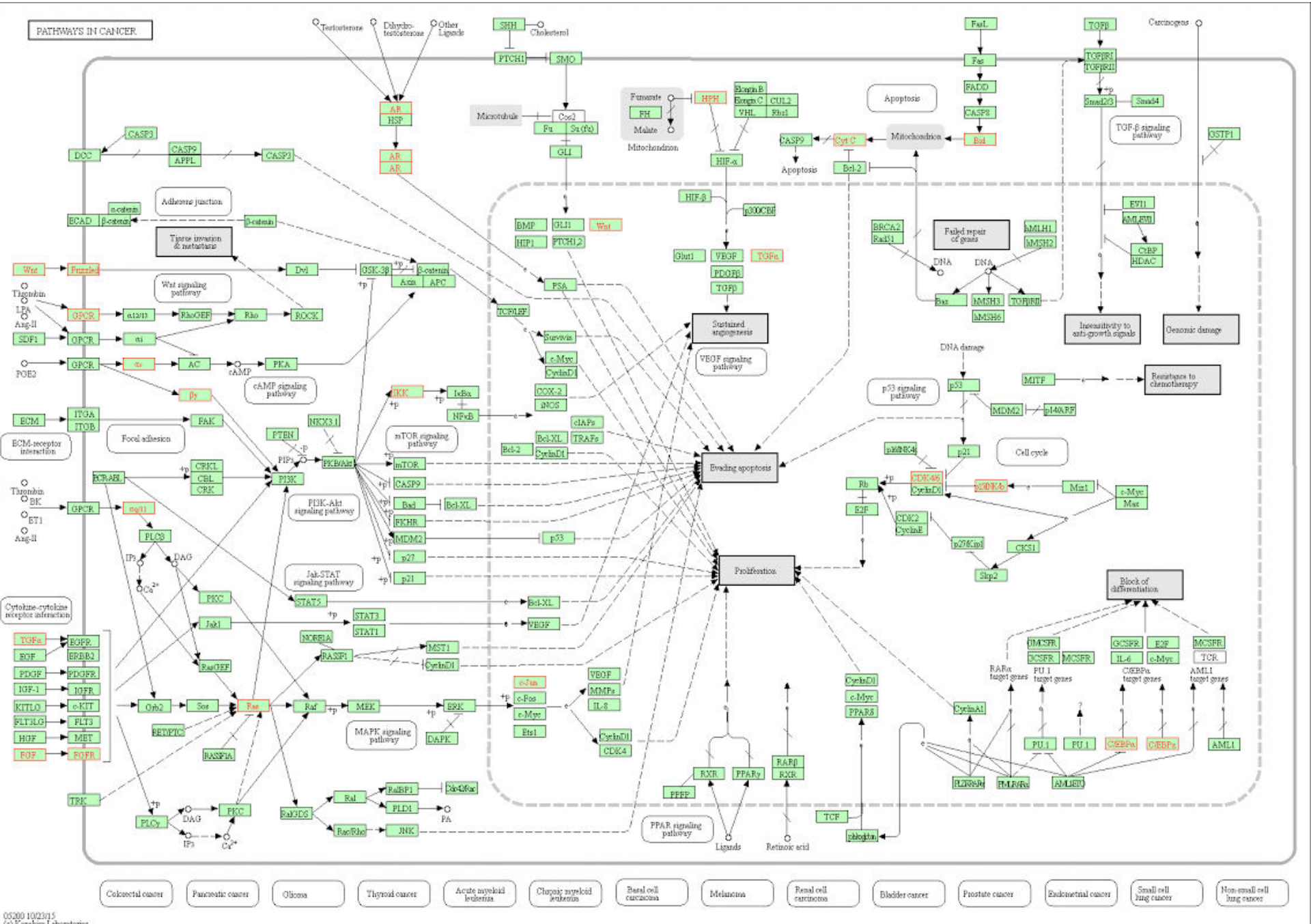
- AMPD1 chr1 115236056_115236057

GA 192 snp rs17602729 Caa/Taa

Q/* protein_coding stop_gain stop_gained HIGH pathogenic

Muscle_AMP_deaminase_deficiency|

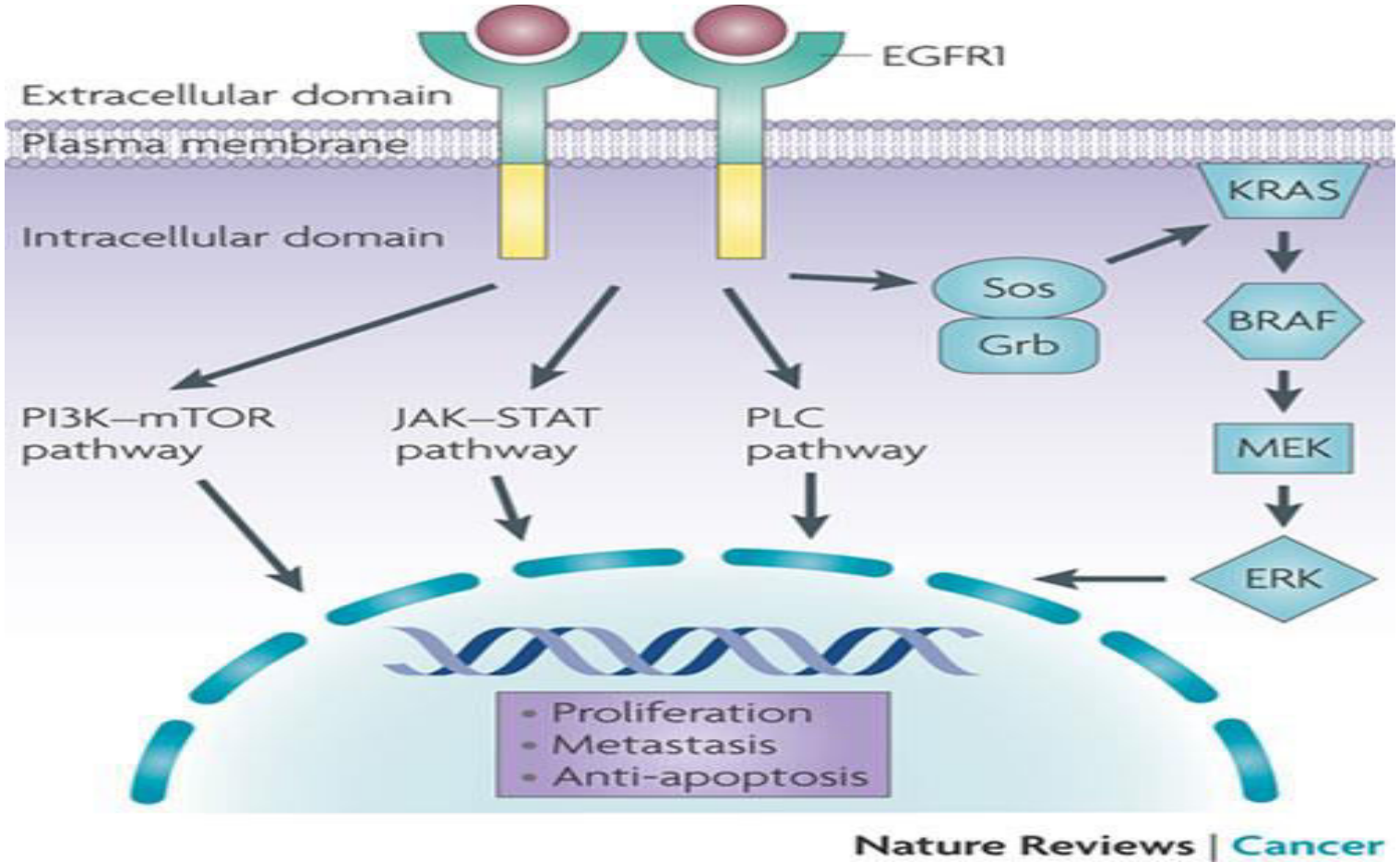
Myestenia Gravis



05200 10/23/15

Target	Cancer	Variation type	Marker	Drug	Test
EGFR	Lung cancer	Mutation	Predict benefit to EGFR TKIs	Erlotinib	DNA
				Gefitinib	
ALK	Lung cancer	Rearrangement	Predict response to ALK inhibitors	Crizotinib	FISH
ROS	Lung cancer	Rearrangement	Predict response to TKIs	Crizotinib	FISH
RET	Lung cancer	Rearrangement	Predict response to TKIs	Vandetanib	FISH
BRAF	Melanoma	Mutation	Predict response to BRAF inhibitors	Vemurafenib	DNA
				Dabrafenib	
KRAS	Colorectal cancer	Mutation	Predict lack of response to anti-EGFR antibodies	Panitumumab	DNA
				Cetuximab	
HER2	Breast cancer	Amplification	Predict response to anti-HER2 antibodies	Trastuzumab	FISH, IHC
	Gastric cancer	Overexpression		Lapatinib	
				Pertuzumab	
KIT	GIST	Mutation	Predict response to c-Kit inhibitors	Imatinib	IHC
Estrogen receptor	Breast cancer	Overexpression	Predict response	Examestane	IHC
				Fulvestrant	
				Letrozole	
				Tamoxifen	
Progesterone receptor	Breast cancer	Overexpression	Predict response	Examestane	IHC
				Letrozole	

Personalized Treatment
Imatinib



- THANKS to
- Burcu Bakır Gungor
- Ozan Ozısık

Türk 100.000 Genom projesi

- Türkiye insan genomunun yapısının anlaşılması
- Türk genom veri analizi ile yeni bilimsel buluşular ve tıbbi uygulamaların gerçekleştirilmesi
- Türkiye'de genomik tıbbın uygulamalarını hızlandırılması
- Sağlık hizmetlerinde etkin uygulamalar geliştirilmesi
- Genomik veriye dayalı Endüstriyi ve yatırımları başlatılması
- Uluslararası bölgede (Balkanlar ve Türki devletleri) örnek ve referans merkez olmak

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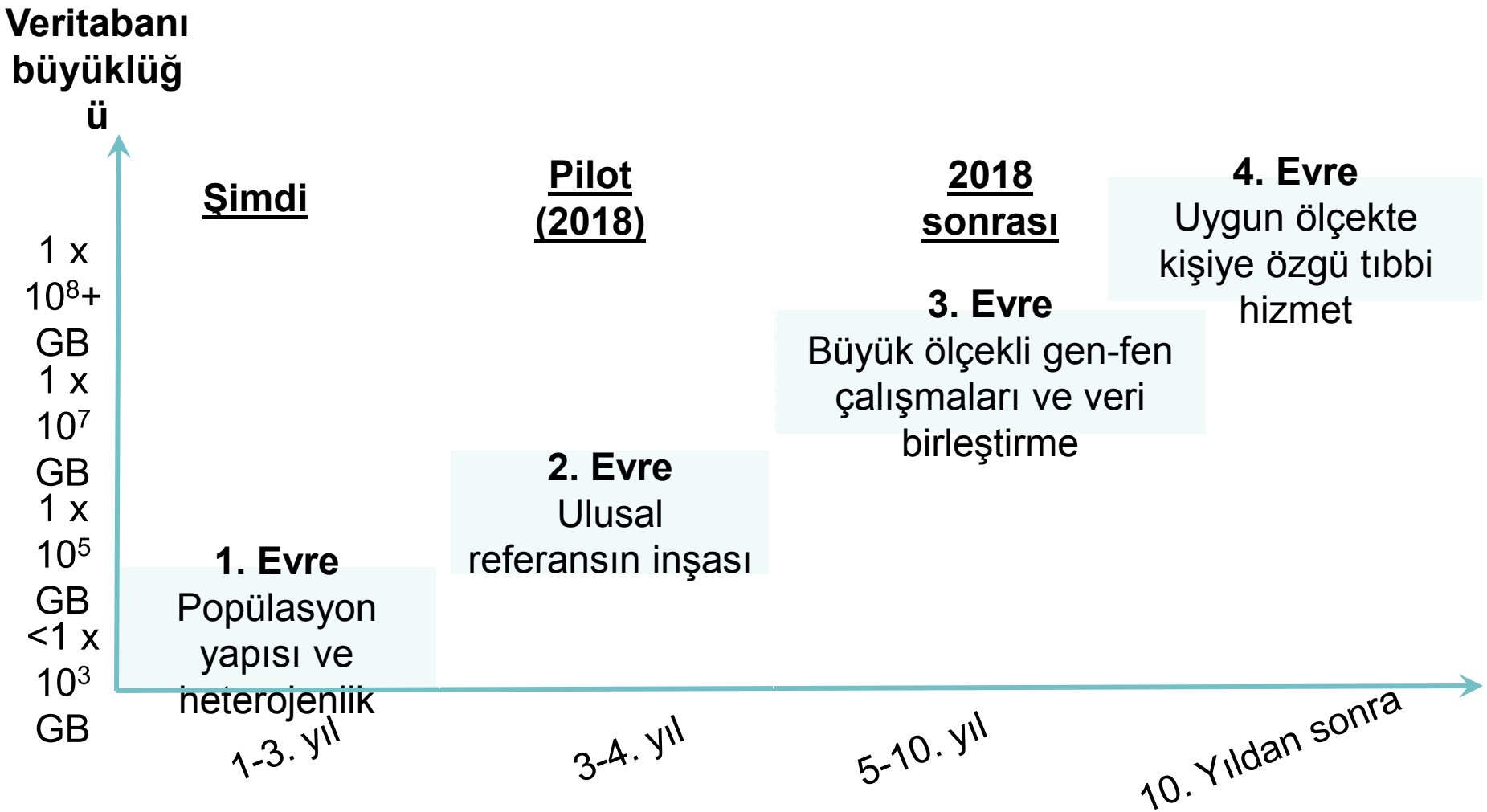
28. Prof. Dr. Sinan TÜRKYILMAZ, Hacettepe Ü.
29. Doç. Dr. Şükrü TÜZMEN, Doğu Akdeniz Ü.

Süreç Bilgilendirilmesi ve Değerlendirilmesi

1. • ETİK ve HUKUK
2. • ÖRNEKLEME
3. • BİYOBANKALAR
4. • DİZİLEME MERKEZİ
5. • BİYOENFORMATİK

PİLOT DENEMENİN ÖTESİ: TÜRK GENOM PROGRAMININ GELECEĞİ



Süreç Bilgilendirilmesi ve Değerlendirilmesi

Doktor tanıyı koyar onam alır.

Onaylanmış merkezlerde örnek alınır

Xxxxp01 (Tek hasta kodu -QR)

Türkiye genom portalı

Onaylanmış Örnekler Biyobanka

Tüm genom dizileme (TGD-WGS)

Dizi verisi portala Yüklenir

Portal ve Veri Amb

Biyoenformatik analizler

Genom varyasyon verilerinin meta-analiz Araştırma projeleri

Fenotip/Genotip korelasyon araştırma Projeleri

Portaldan Raporlarlama

XXXXP01 kodu hastanın raporu

Süreç Bilgilendirilmesi ve Değerlendirilmesi

Türkiye Genom Projesi Başlangıç Aşaması için Hizmet Alımı

TGP başlangıç aşamasıda 100 000 genom için ölçeklenebilir Türkiye Genom projesi dizileme platformu ve veri paylaşım portalının 100 sağlıklı bireyden elde edilecek referans genom grafiği kapsamında işlevsel halde gerçekleştirilmesi

"Eksik teşhis konmuş sağlıklılar"

40 yaş üzerinde, bilinci yerinde, mental retarde olmayan, kendisinde ve 1. Derece akrabalarında (anne-baba-kardeş ve çocukları) kalıtsal hastalığı olmayan bireyler

TGP kapsamında çalışılması planlanan hastalık gruplarının belirlenmesi

ÖNCELİK : Nadir hastalıklar

- Nadir hastalıkların ~%80'i tek gen hastalığı,
- Az sayıda genom dizisi ile (1000-2000) ile yeni hastalık genleri keşfedilebilir,
-
- Hastalık yükü belirgindir (finansal maliyet, mortalite, morbidite)
  SMA gen tedavisi ~3-4M TL/hasta
  "En çok engellik veren ve en çok öldüren hastalıkladır"
- Toplumun %10'un da nadir hastalıklar gözlemleniyor (Türkiye'de ~7 milyon)
- Ulusal sosyolojik yapı (akraba evlilikleri) diğer genom projelerine göre Türkiye Genom Projesi açısından fark yaratacaktır

TGP kapsamında çalışılması planlanan hastalık gruplarının belirlenmesi

ÖNCELİK : Nadir hastalıklar

- Ulusal Kohortlara katılacak örnekleri belirlemek amacıyla değişik hastalıklar için genom projesine dahil edilme protokolleri “Human Phenotype Ontology” vb. rehberliğinde belirlenebilir
- Genom projesi dahil edilme algoritması ile uygun veya yetersiz tanı alan örneklerin belirlenerek biyobankalarda kataloglanabilir
- Fenotip varyasyon tanımlarının hekimlere portal üzerinden sunulabilir ve örnekler bu kapsamda projeye dahil edilebilir

Genom Çalışmalarının Fonlanması

Çağrılı projeler

-Çok ortaklı konsorsiyum projeleri

-Merkezler destekleri (Merkez kurulması destek veya alt yapı projeleri ile)

-Hastalık temalı disiplinler arası projeler

-Özelleşmiş biyoenformatik veri analizi projeleri

-Hesaplamalı Biyoloji/algoritma geliştirme projeleri

-Genom analiz teknolojileri ve tanı/tedavi/takip araçları geliştirme projeleri

-Çığır açıcı projeler

Proje destek süresi

-Proje çağrısının kapsamına göre 1-5 yıllık

-Proje başarı oranına göre süresi artıralabilen aşamalı projeler

Kohort çalışmalarında klinik tahlil ve testlerin fonlanması

-Kohort çalışmalarında hastalara ait tamamlayıcı klinik verilerin (klinik testler) fonlanması

-Klinik verilerin tamamlanması için projelendirmede mevzuat düzenlemesi gerekebilir.