НАСЛЕДСТВЕННОСТЬ И СПОРТ

Курс лекций
в.н.с. Глотов А.С., в.н.с. Глотов О.С.,
Пакин В.С.

СПбГУ, ФГБУ «НИИАГ им.Д.О.Отта» СЗО РАМН
2013

План 1-й лекции:

1. Таланты и наследственность. Генетика и признаки человека.
2. Методы генетики и генетический паспорт.
3. История и современность в спортивной генетике.
4. Геномная дактилоскопия.
5. Генный допинг. Мифы и реальность.

Составляющие физической работоспособности

Генетическая предрасположенность (сила, выносливость, быстрота реакции)

70-75%

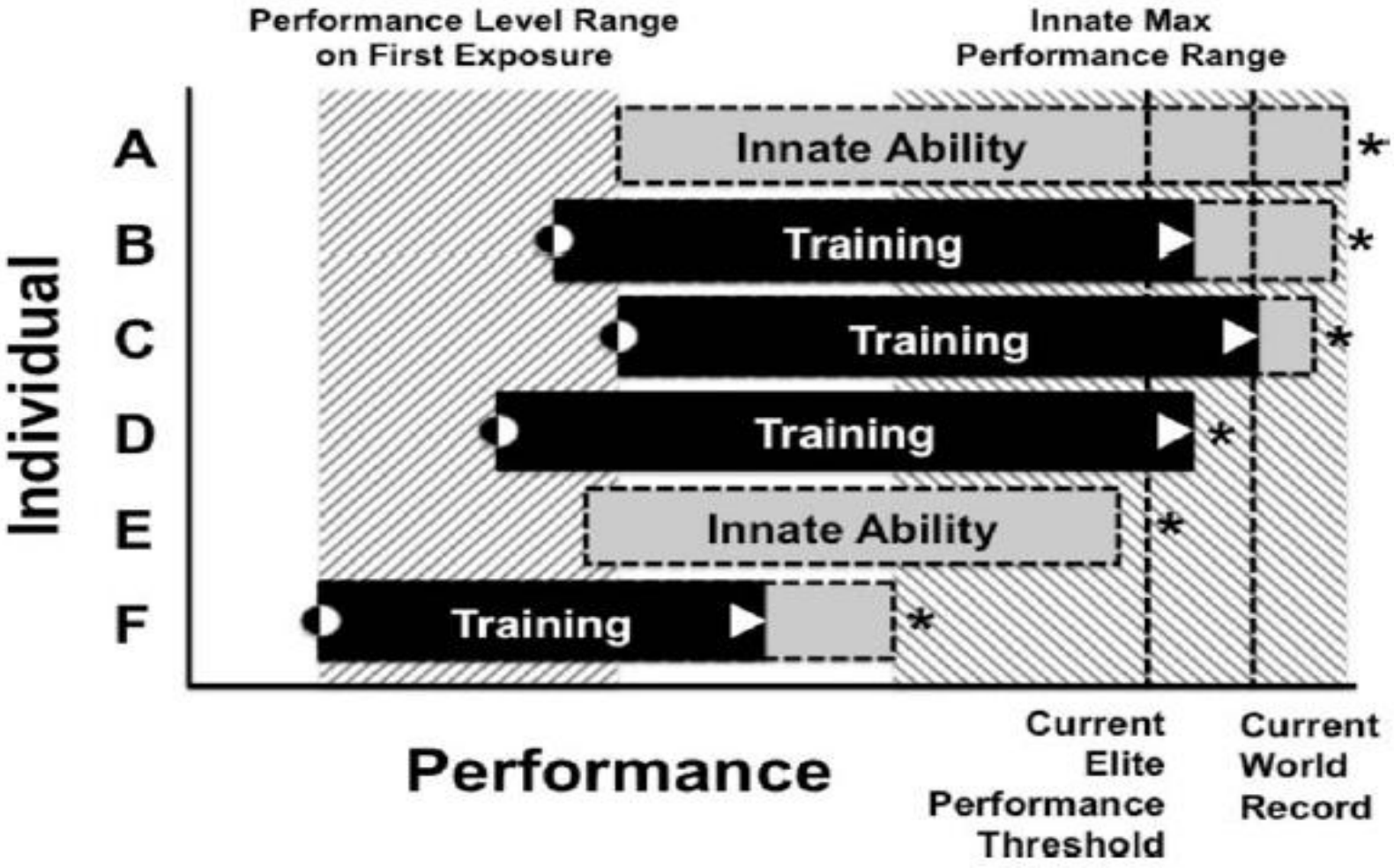
ФИЗИЧЕСКАЯ РАБОТОСПОСОБНОСТЬ

Психологические факторы (морально-волевые качества)

Условия внешней среды 25-30%

Таймазов, Соглогуб, 2000

Теоретическая модель физической работоспособности (Tucker & Collins, BJSM, 2012)



ГЕНЕТИКА И СПОРТ

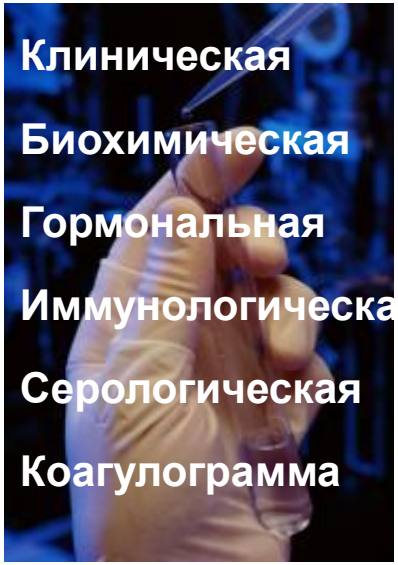
Общая
наследственность

gotennis.ru/forum/index.php?showtopic=5

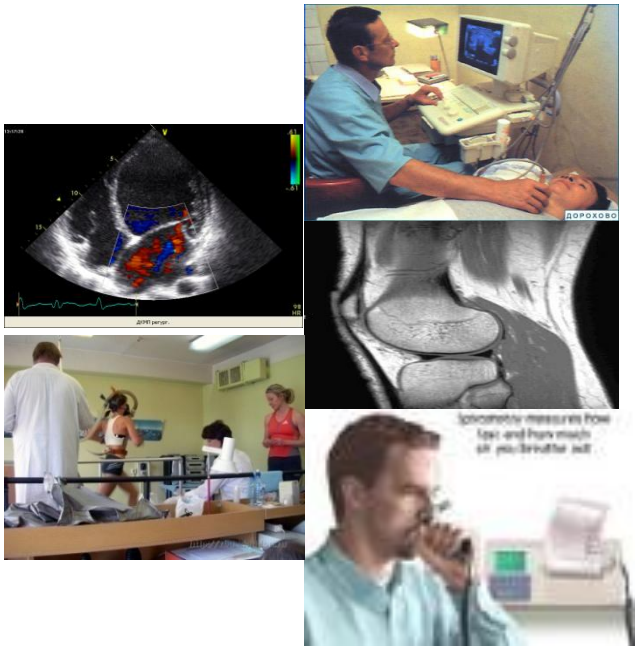
http://newshopper.sulekha.com/marat-safin-dinara-safina_photo_612886.htm

Комплексное обследование и генетическое тестирование теннисистов детского возраста

Лабораторная диагностика 90 - 300 параметров



Инструментальная диагностика 6-14 видов



Генетическое тестирование 30 – 120 генов

Совокупный клинический, спортивно-медицинский и генетический анализ

«Теннис XXI века»

Медицинская комиссия ФТР

Отдаленные результаты и естественный отбор в детском теннисе (n=120)

Генетика и фенотип

Генетика обуславливает многие количественные и качественные признаки человека

Наследуемость признаков составляет:

Рост – 80-85%

Масса тела – 70-80%

Цвет глаз, кожи, волос – 95-99%

Форма ушей – 98%

Сахарный диабет – 60%

Артериальное давление – 40-45%

Уровень липидов – 60-80%

Выносливость – 65%

Быстрота – 80%

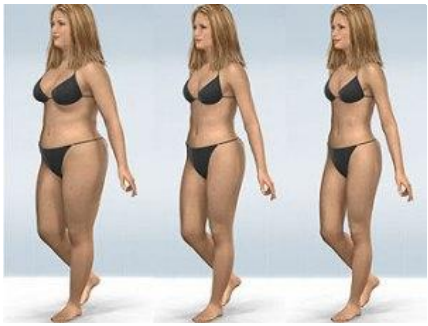
Интеллект – 70%

Оценка наследуемости признаков на основании близнецовых и семейных исследований

Parameter	Reference	Heritability
Muscle enzymes	Bouchard *et al*. (1986)	~ 50%
% fibre type	Simoneau & Bouchard (1995)	~ 50%
Maximal oxygen uptake	Bouchard *et al*. (1998)	~ 50%
Δ maximal oxygen uptake	Bouchard *et al*. (1999)	~ 50%
Leg strength	Tiainen *et al*. (2004)	~ 30%
Leg strength	Zhai *et al*. (2005)	~ 60%
Mesomorphy	Peeters *et al*. (2007)	~ 80%
Athlete status	de Moor *et al*. (2007)	~ 70%
LV mass	Busjahn *et al*. (2009)	~ 80%

Генетические маркеры веса человека

Вес (масса) тела - один из важнейших показателей физического состояния человека. Полногеномные исследования позволили выявить целый более 150 локусов на различных хромосомах ответственных за ожирение. Например:

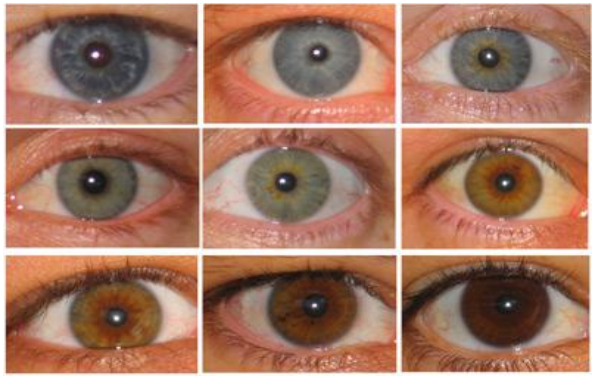


Ген	Функция продукта гена	SNP
MGAT1	Участвует в метаболизме углеводов, необходим для преобразования маннозы.	rs12517906
FTO	Участвует в регуляции глобального обмена веществ, расхода энергии и энергии гомеостаза. Также участвует в регуляции размеров тела и накопления жировых отложений.	rs8050136
		rs6499640
TMEM18	Участвует в клеточной миграции, усиливает миграционную способность нервных стволовых клеток и нейронных клеток-предшественников.	rs7561317
MC4R	Вовлечен в спектр физиологических функций, в т.ч. энергетический гомеостаз, обмен веществ, пигментация, воспаление.	rs12970134
…		

(по Thorleifsson et al., 2009)

Генетические маркеры цвета глаз

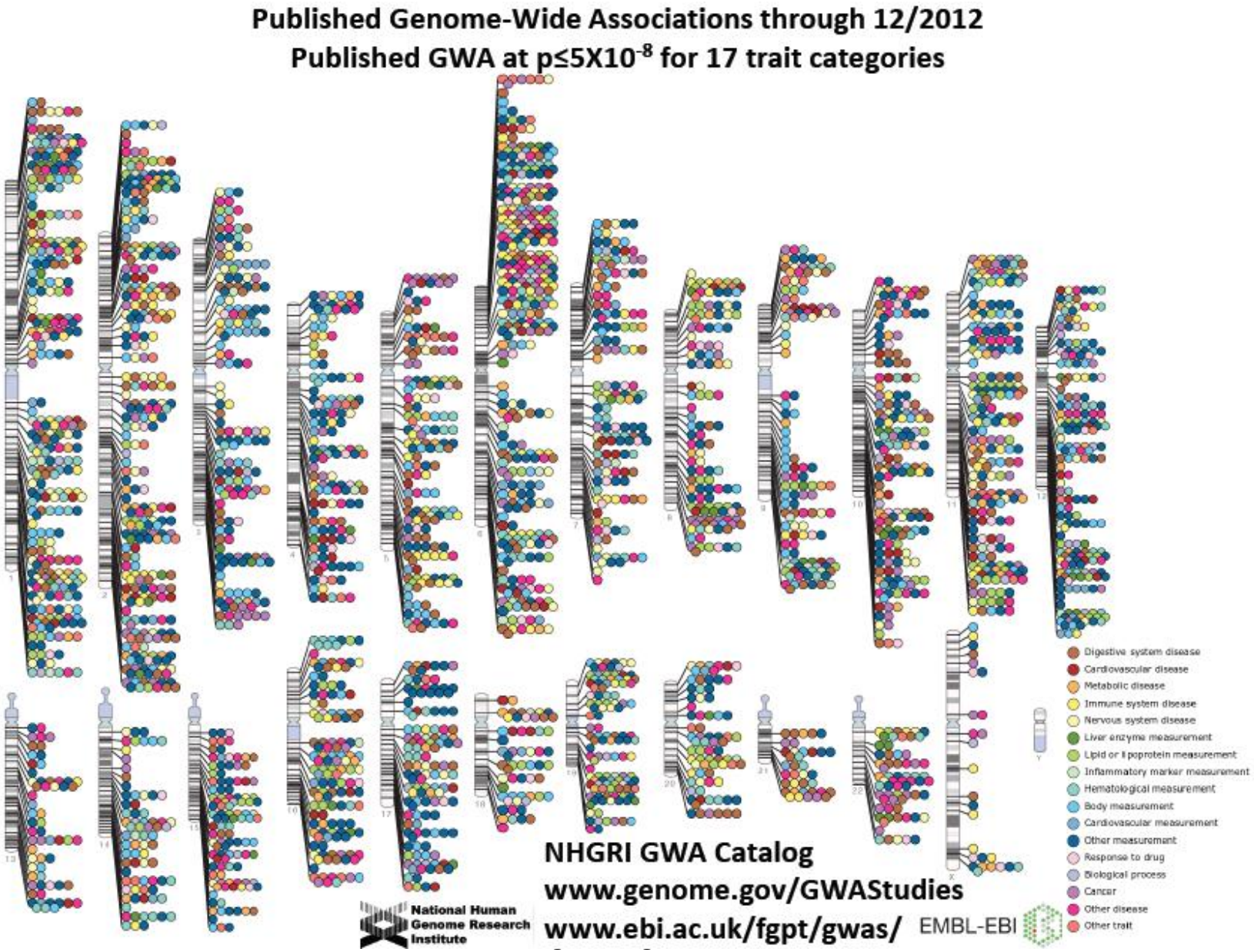
Ученые из медицинского центра Роттердамского университета (Erasmus University Medical Center Rotterdam) проанализировали 37 SNP из 8 генов у 6000 коренных жителей Роттердама (Liu et al., 2009). 67.6% из них имели голубые глаза, 22.8% - карие, 9.6% - промежуточный цвет глаз. В итоге были отобраны лишь 6 наиболее значимых замен в 6 генах. Все эти гены кодируют белки, отвечающие за производство составляющих радужной оболочки глаза, кожи и пигментов волос (эумеланин и феомеланин).



Ген	SNP
HERC2	rs12913832
OCA2	rs1800407
SLC24A4	rs12896399
SLC45A2	rs16891982
TYR	rs1393350
IRF4	rs12203592

Тестирование этих генов позволяет предсказать карий цвет глаз с вероятностью 93%, голубой — 91%, промежуточный цвет - 73%.

Опубликованные данные GWAS исследований



Геном человека

•3,2 миллиарда нуклеотидов

•Организованы около в 22-23 тысяч генов, которые составляют 3% общей длины ДНК

•99,9% ДНК одинаковы у людей

•90% ДНК человека идентична

Выявлено более 10 млн SNP

ПРЕДМЕТ ИССЛЕДОВАНИЯ -

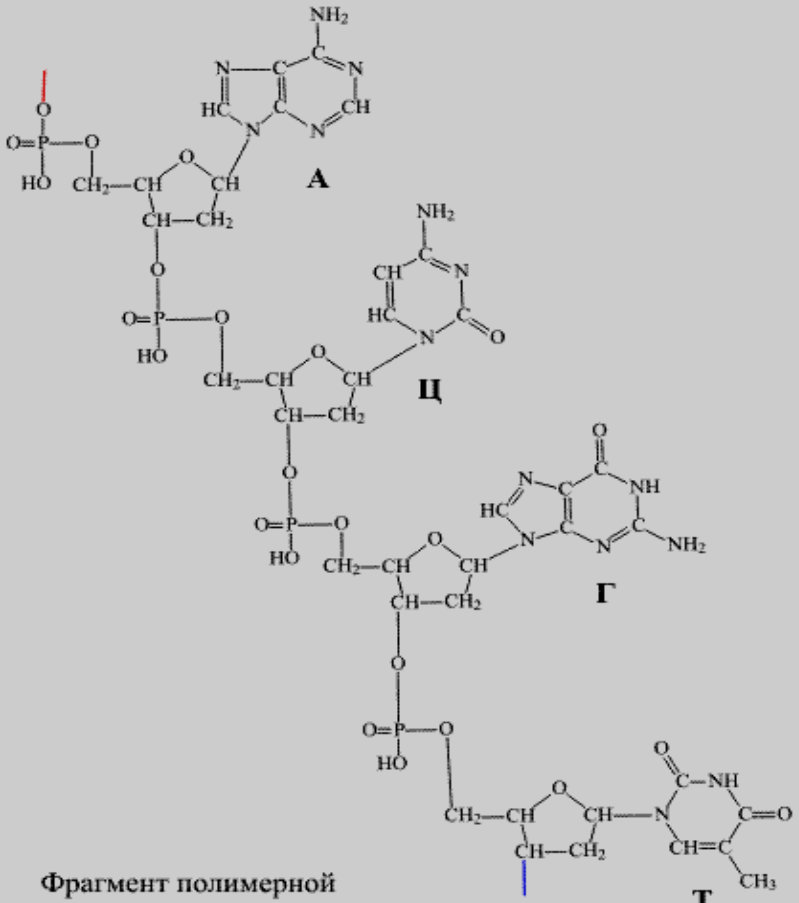
различия в первичной структуре ДНК

cggggcgggg cgcacagagc ca ***g*** aggggct tgcgagcggc ggctgaggga ccgcggggag

cggggcgggg cgcacagagc ca ***c*** aggggct tgcgagcggc ggctgaggga ccgcggggag

Мутация
(полиморфизм)

МОЛЕКУЛА ДНК



Фрагмент полимерной молекулы ДНК

Методы молекулярной диагностики

- Блот-гибридизация
- ПЦР
- ЛЦР
- ASO (метод аллель-специфических олигонуклеотидов
- Real-time ПЦР (ПЦР в реальном времени)

И многое другое

Полимеразная цепная реакция (ПЦР)

Предложена в 1983 г. K.Mullis (Нобелевская премия 1989 г.)

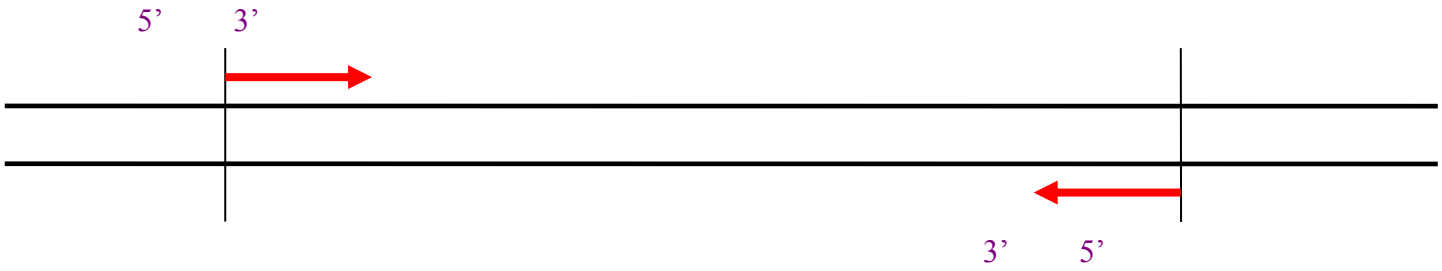
Позволяет получить in vitro большое число идентичных копий специфических нуклеотидных последовательностей

Полимеразная цепная реакция (ПЦР)

Необходимы:

- ДНК-мишень (80 – 1000 пн)
- Специфические олигонуклеотидные праймеры
- ДНК-полимераза Taq или Tth (из Thermus aquaticus или T.Thermopilus)
- Дезоксирибонуклеоидтрифосфаты

ПЦР – выбор праймеров

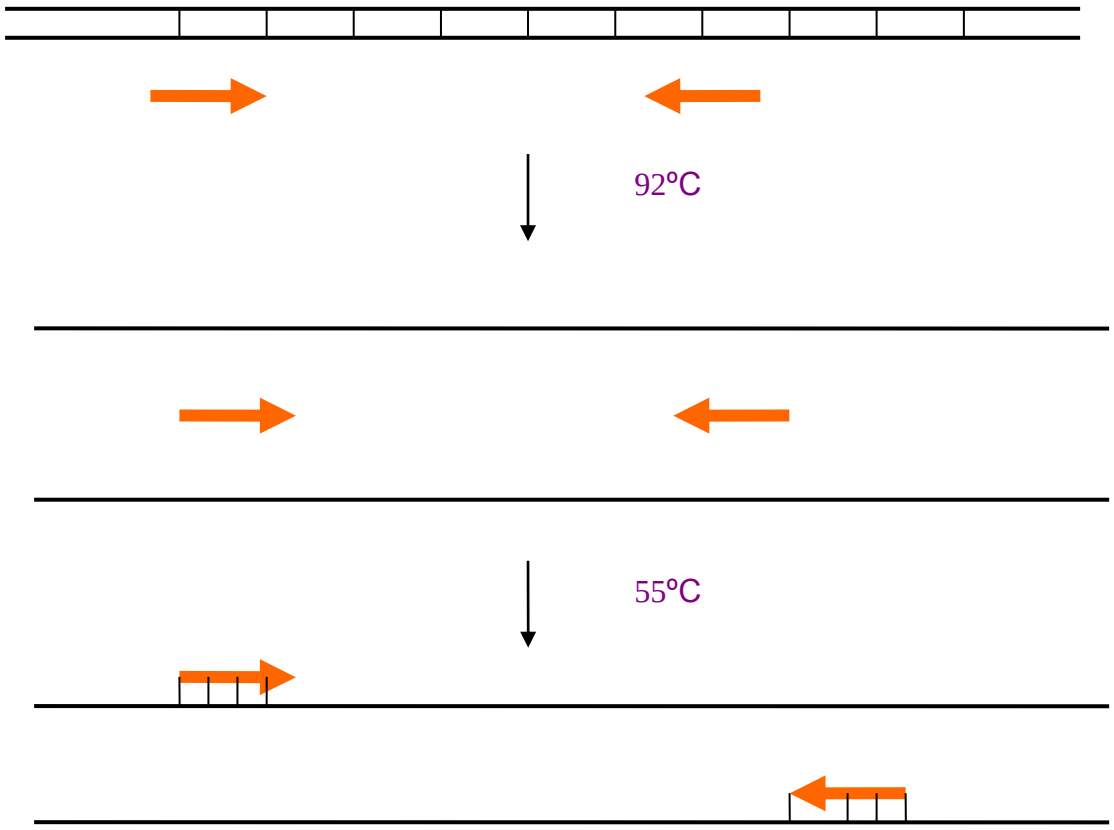


ПЦР – выбор праймеров

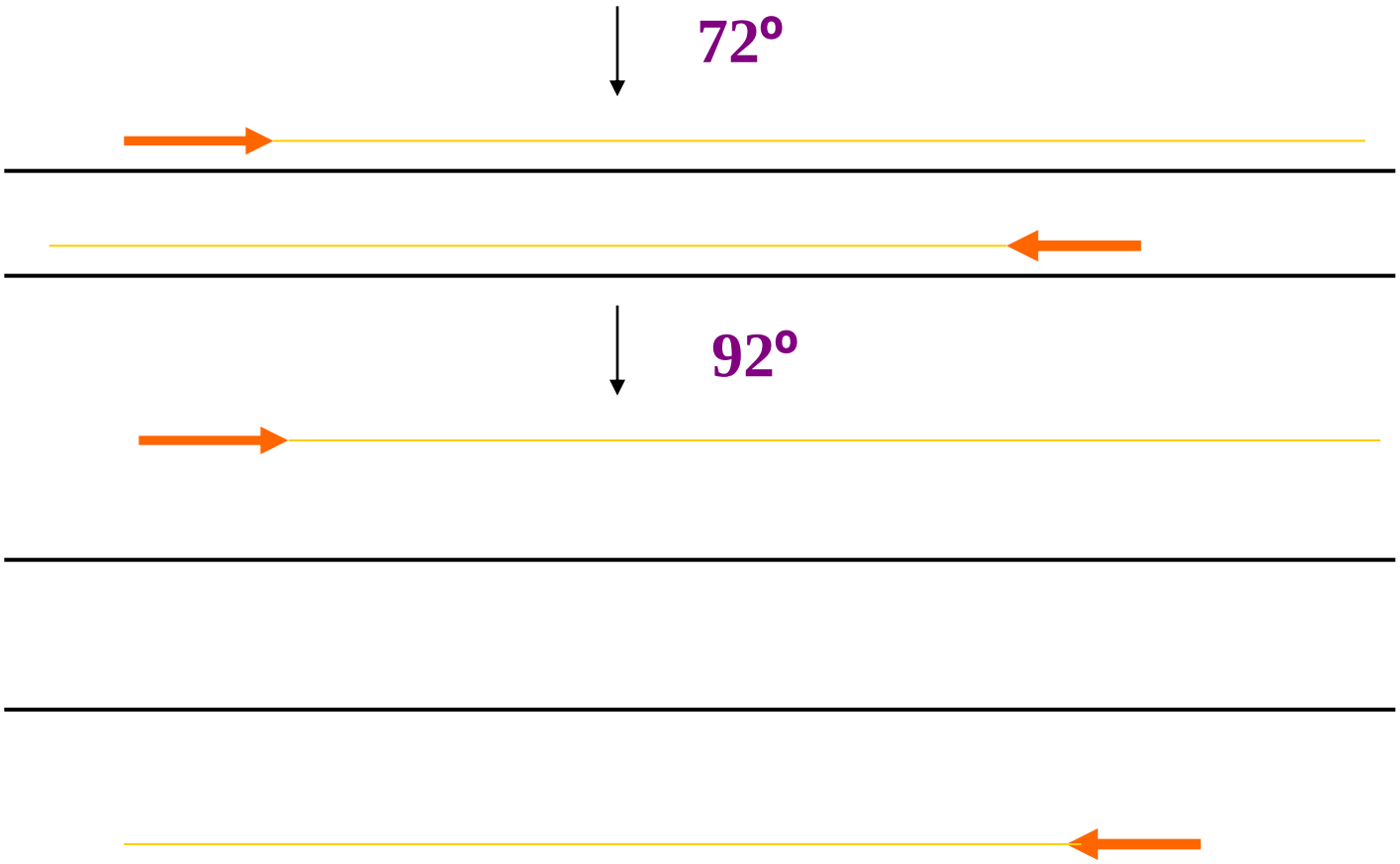
5’*cggggcgggg* **cgcacagagc cagaggggct tgcgagcggc ggctgaggga ccgcggggag ggggcgccga gcggctccag cgcagagact ctcactgcac gccggagggc gcccttcctc gctcgcgccc gcgcgaccgc gcgccccagt cccgccccgc cccgctaacc gccccagaca cagcgctcgc cgagggtcgc ttggaccctg** *atcttacccg tgggcaccct* 3’

- Прямой праймер: 5’ **cgcacagagccagaggggct -**3’
- Обратный праймер: 5’ **cagggtccaagcgaccctcg** -3’

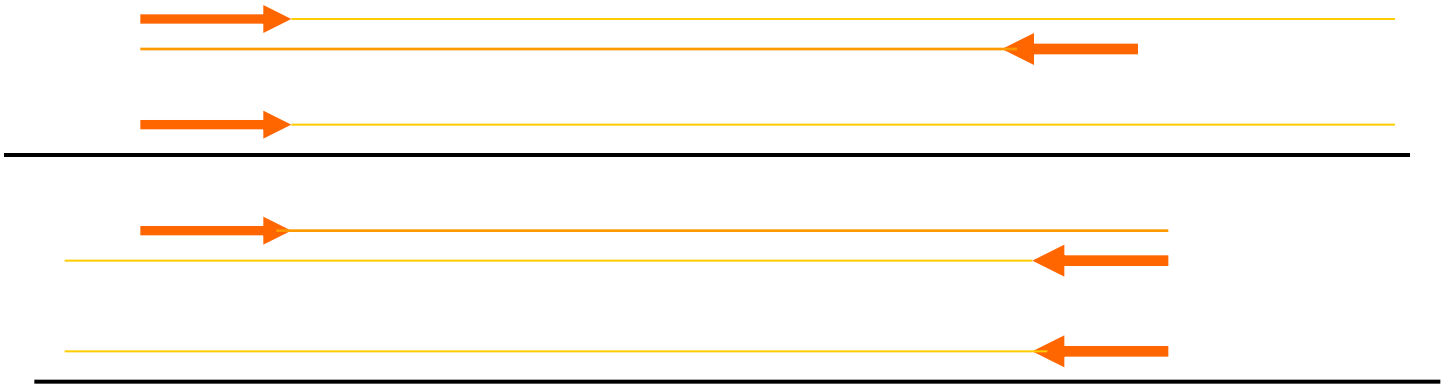
ПЦР – начало



ПЦР - 2

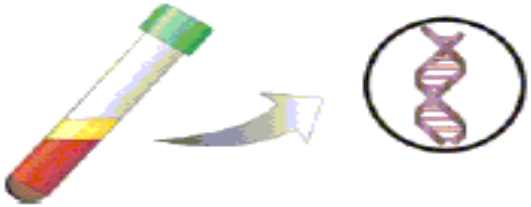


ПЦР - 3



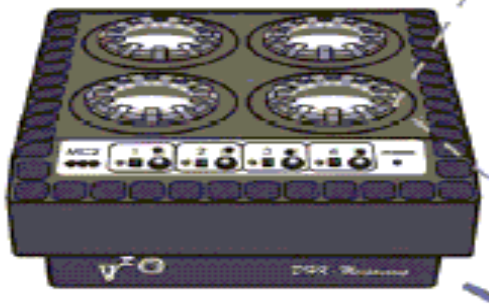
Результат

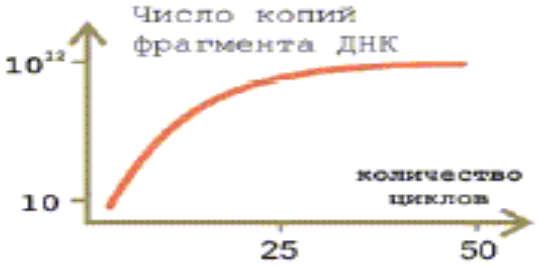
1. Пробоподготовка



Выделение ДНК биологического материала (крови, слюны)

2. Амплификация

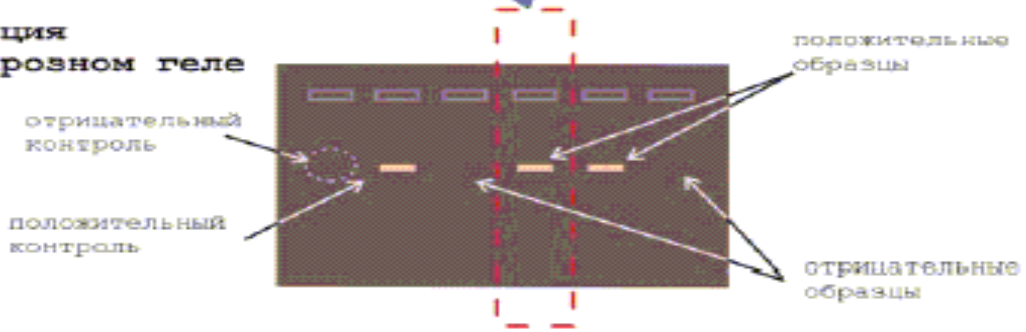




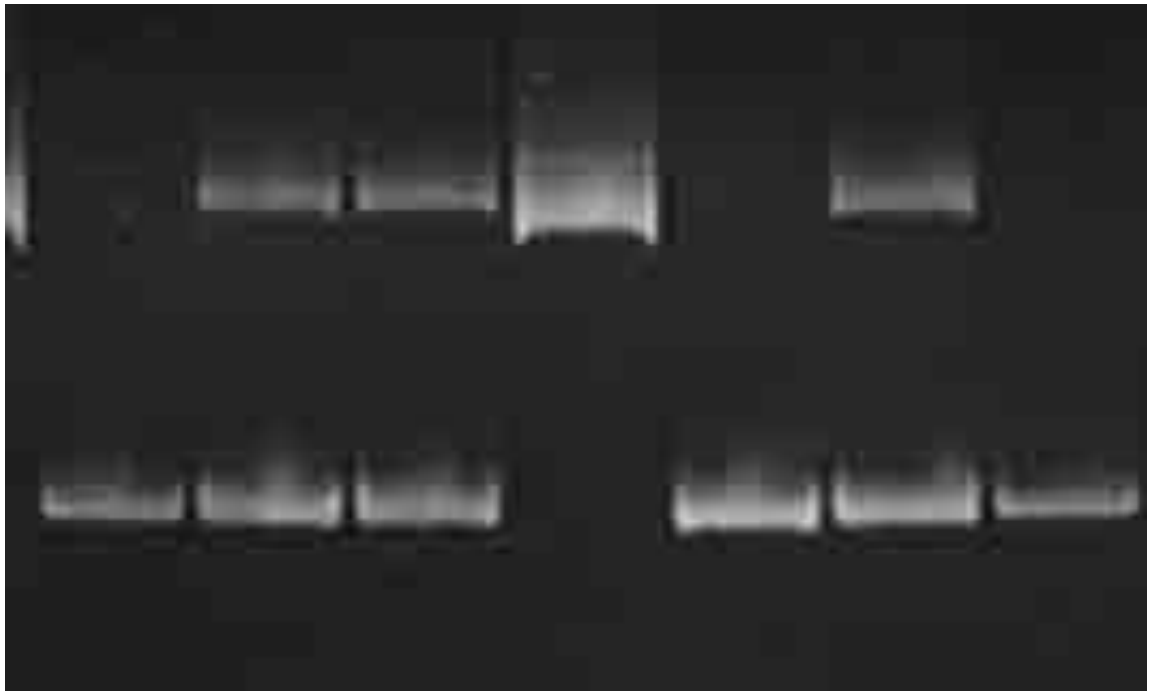
Амплификация нужного участка ДНК с помощью специфичных праймеров

4. Рестриктный анализ

3. Детекция в агарозном геле



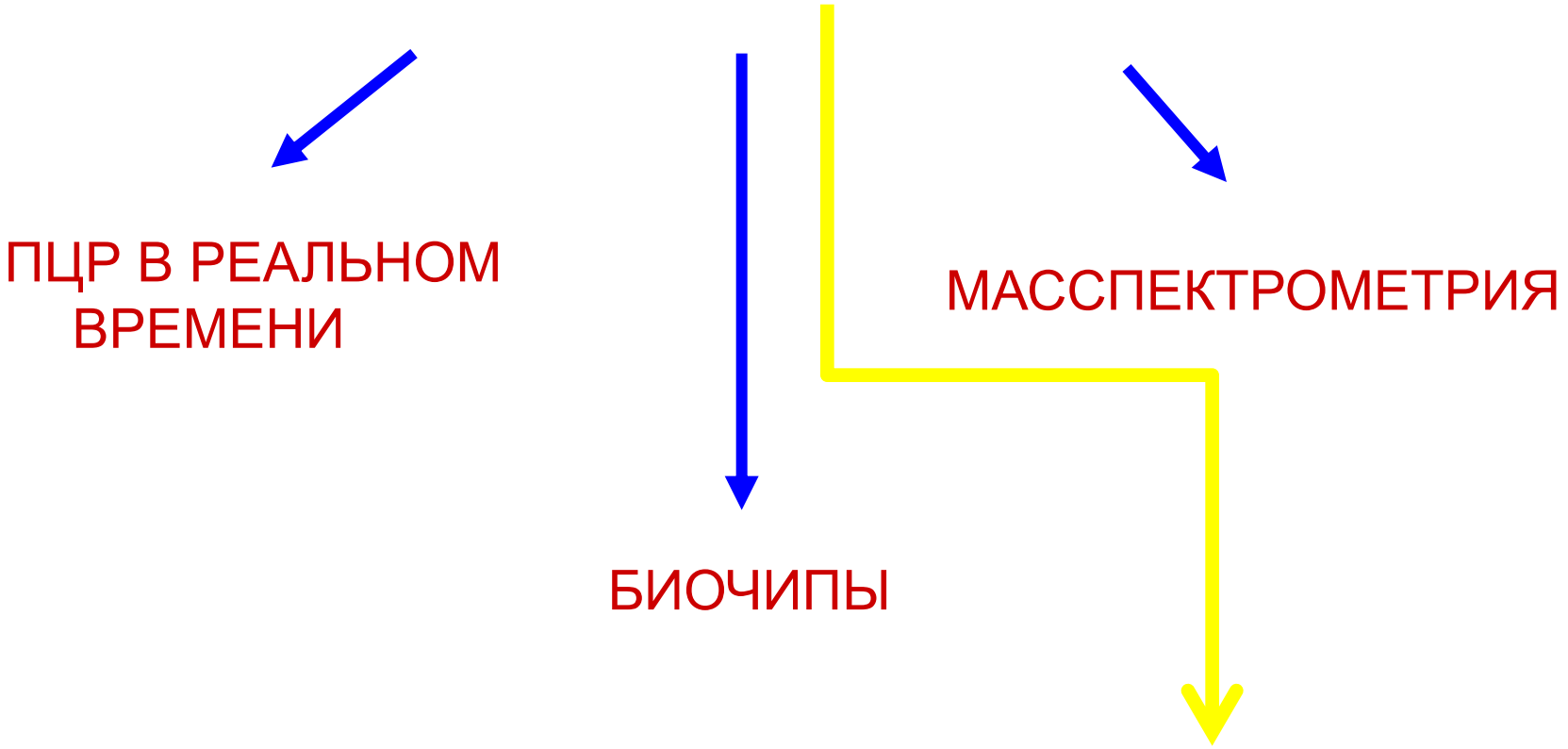
Инсерция Alu-элемента



Инсерция

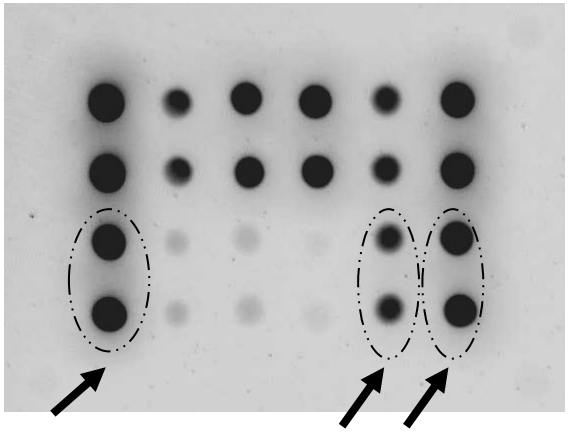
Делеция

СОВРЕМЕННЫЕ МЕТОДЫ АНАЛИЗА SNP

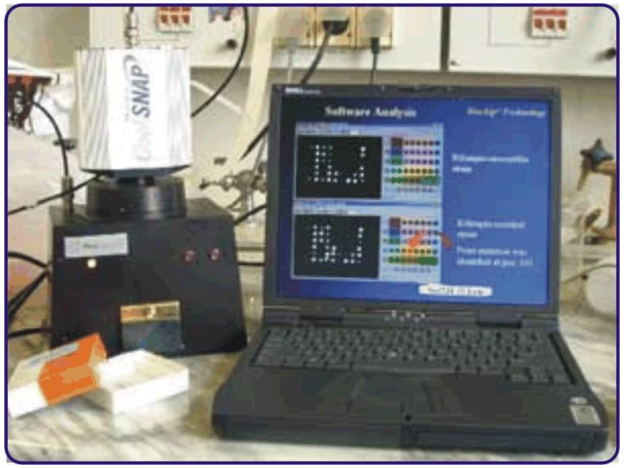


ТЕХНОЛОГИЯ БИОЧИПОВ

биочип

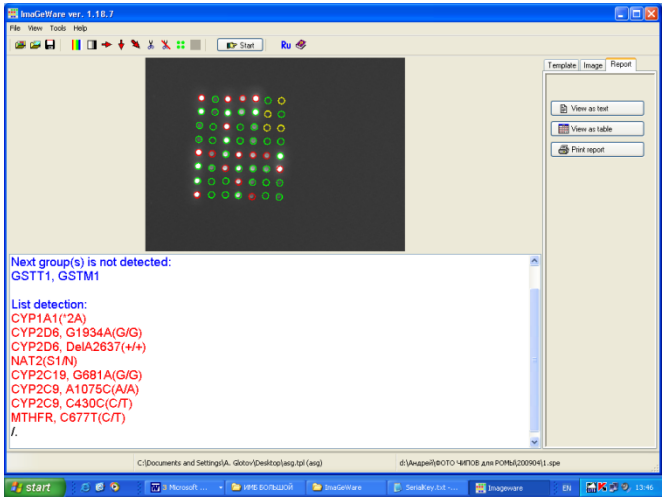


робот



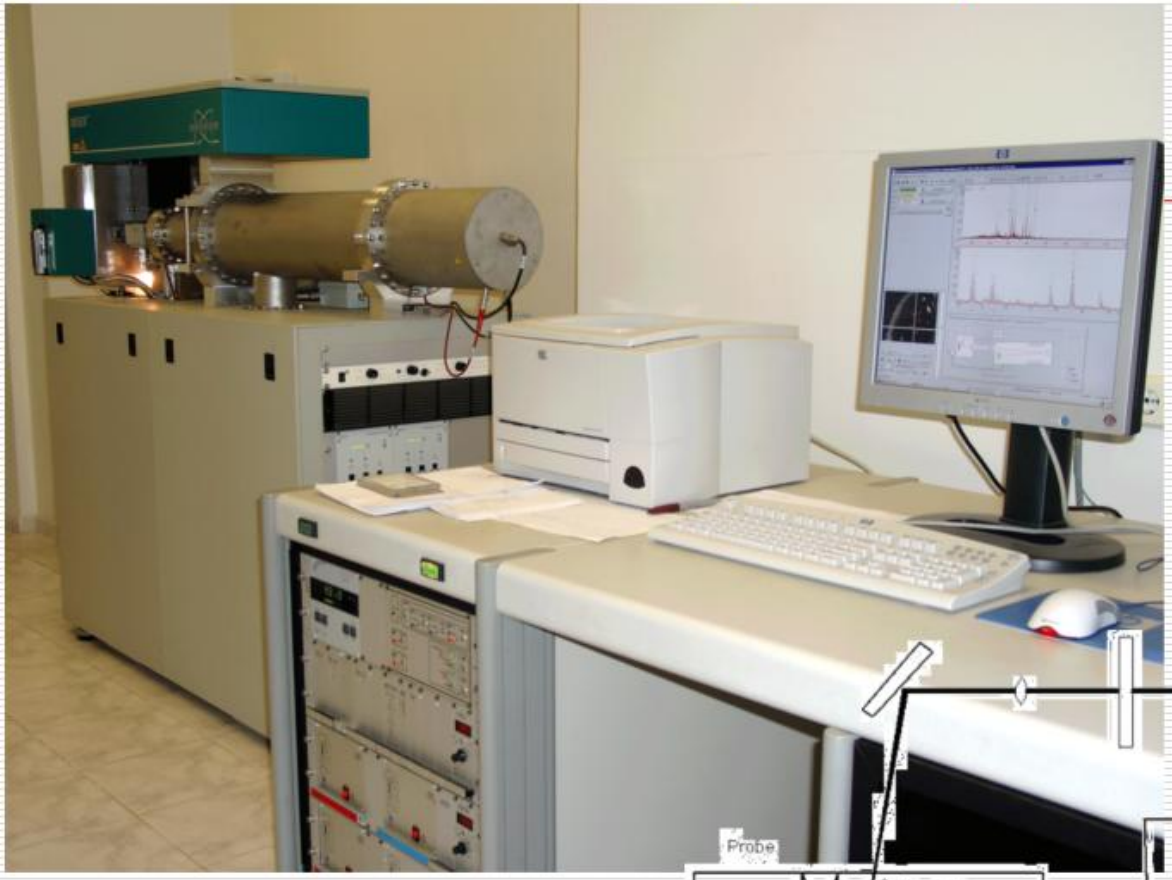
Портативный анализатор

б) Генотип:
FV (G/A)
FGB (G/G)
FII (G/G)
GPIIIa (T/T)
PAI-1 (5G/4G)
MTHFR (C/T)

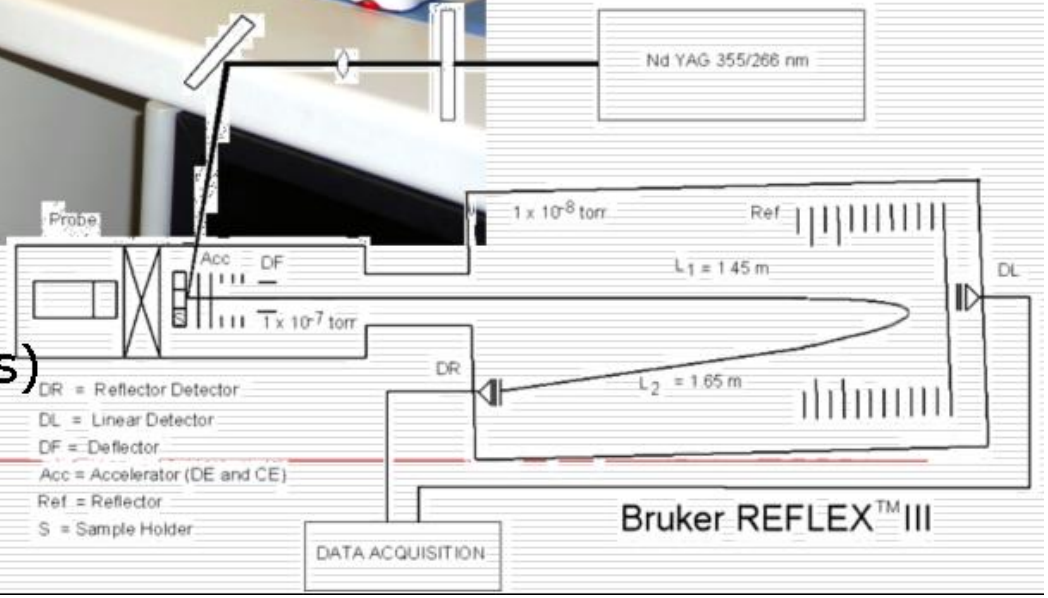


Автоматический анализ генетических изменений (до 100 образцов в день)

Масс-спектрометрический этап



Reflex IV (Bruker Daltonics)



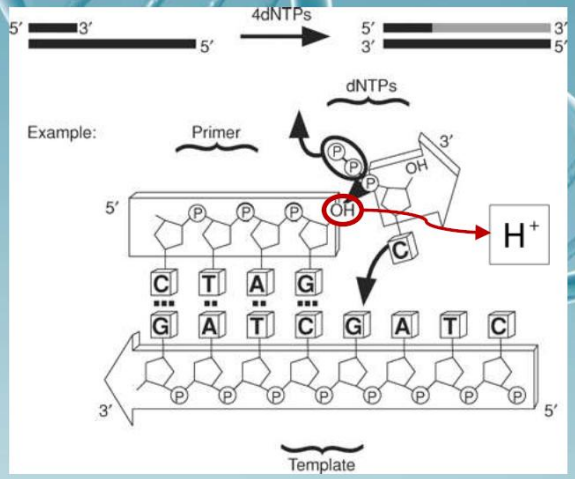
Развитие технологий секвенирования

ВЫСОКОВОСПРОИЗВОДИТЕЛЬНЫЕ ГЕНОМНЫЕ СЕКВЕНАТОРЫ ДЛЯ «ОБЫЧНОЙ» ПЦР-ЛАБОРАТОРИИ

Ion Torren – геномный секвенатор, в основе которого лежит эффект полупроводниковой платформы

GS Junior – геномный секвенатор, на основе технологии пирофосфатного секвенирования

Simple Natural Chemistry



Eliminate source of sequencing errors:

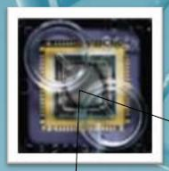
- Modified bases
- Fluorescent bases
- Laser detection
- Enzymatic amplification cascades

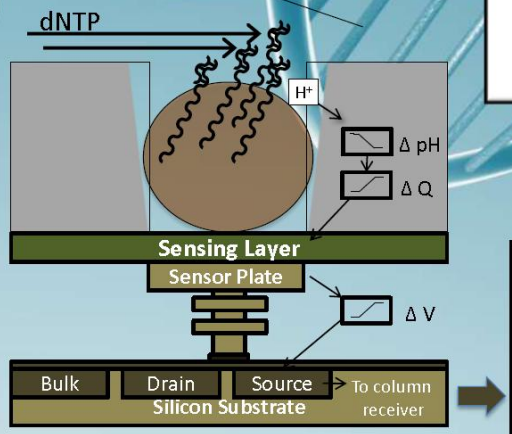
Eliminate source of read length limitations:

- Unnatural bases
- Faulty synthesis
- Slow cycle time

Технология на основе эффекты полупроводнико-вых пластин (секвенирование)

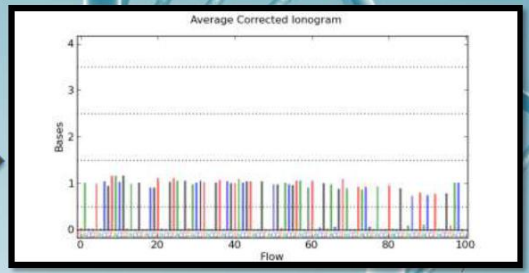
Fast Direct Detection





DNA → Ions → Sequence

- Nucleotides flow sequentially over Ion semiconductor chip
- One sensor per well per sequencing reaction
- Direct detection of natural DNA extension
- Millions of sequencing reactions per chip
- Fast cycle time, real time detection



Геномика **-** *наука, изучающая гены и их продукты как динамично развивающуюся систему, их взаимодействия и влияние на метаболические пути и физиологические реакции организма*

Предиктивная медицина

Фармакогеномика
Нутригеномика
Токсикогеномика
Кардиогеномика
Психогеномика
Дерматогеномика
Спортивная геномика
Геномика старения

ГЕНЕТИЧЕСКИЙ ПАСПОРТ -

- индивидуальная база ДНК-данных, отражающая уникальные генетические особенности каждого человека, его предрасположенность к тем или иным наследственным мультифакториальным и другим заболеваниям и состояниям

ГЕНЕТИЧЕСКИЙ ПАСПОРТ

Генетический паспорт - индивидуальная база ДНК-данных, отражающая уникальные генетические особенности каждого человека, его предрасположенность к тем или иным наследственным, мультифакториальным и другим заболеваниям (В.С.Баранов, 2000).

Тестирование генов «предрасположенности» - ***путь к ранней профилактике частых заболеваний*** и ***коррекции образа жизни***

Паспортизация актуальна:

супругам, беременным женщинам, спортсменам, людям экстремальных профессий

УПРАВЛЯЙ СВОИМ ГЕНОМОМ САМ!!

Human gene for physical performance

A specific genetic factor that strongly influences human physical performance has not so far been reported, but here we show that a polymorphism in the gene encoding angiotensin-converting enzyme does just that. An 'insertion' allele of the gene is associated with elite endurance performance among high-altitude mountaineers. Also, after physical training, repetitive weight-lifting is improved eleven-fold in individuals homozygous for the 'insertion' allele compared with those homozygous for the 'deletion' allele.

The endocrine renin–angiotensin system is important in controlling the circulatory system. Angiotensin-converting enzyme (ACE, or kininase II) degrades vasodilator kinins, and converts angiotensin I (ATI) to the vasoconstrictor angiotensin II (ATII). In addition, local renin–angiotensin systems may influence tissue growth[1]. A polymorphism of the human *ACE* gene has been described in which the deletion (*D*) rather than insertion (*I*) allele is associated with higher activity by tissue ACE[2].

There is evidence for a skeletal muscle renin–angiotensin system[3], suggesting that muscle growth, and thus physical performance, might be positively associated with the *D* allele. However, our initial studies suggested that the *I* allele was associated with improved endurance performance. We investigated this association in two parallel experiments.

High-altitude mountaineers perform extreme-endurance exercise. Thirty-three elite unrelated male British mountaineers, with a history of ascending beyond 7,000 metres without using supplementary oxygen, were identified by the British Mountaineering Council. DNA was extracted from a mouthwash sample of the 25 male respondents, and *ACE* genotype was determined using a three-primer polymerase chain reaction amplification[4].

Genotype distribution was compared with that of 1,906 British males free from clinical cardiovascular disease[5]. Mean age was 40.6 ± 6.5 years in the 25 subjects, and 55.6 ± 3.2 years for the controls. Both groups were in Hardy–Weinberg equilibrium. Both genotype distribution and allele frequency differed significantly between climbers and controls (Fig. 1a; P was 0.02 and 0.003 respectively (χ^2 test)), with a relative excess of *II* genotype and deficiency of *DD* genotype found in the climbers.

Among the 15 climbers who had ascended beyond 8,000 m without oxygen, none was homozygous for *D* (6 *II* and 9 *ID*: *I* allele frequency = 0.65). Further, ranked by number of ascents above 8,000 m without oxygen, the top performer was homozygous for *I* (5 ascents, compared with a mean of 2.4 ± 0.3 ascents, or 1.44 ± 0.3), as were the top two in this group for number of additional 7,000-m ascents (> 100 and 18, compared with a mean of 10.3 ± 6.5 ascents).

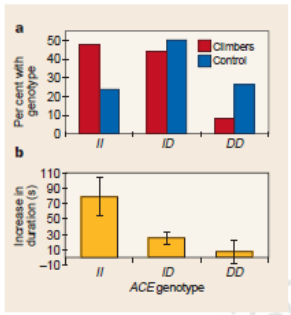


Figure 1 Association of *ACE* alleles with performance. **a,** Distribution of *ACE I/D* genotypes in 25 elite British mountaineers and 1906 healthy British men. **b,** Mean (± s.e.m.) of individual improvement in duration of repetitive elbow flexion after 10 weeks of physical training among British army recruits. An initial cycle frequency of 0.3 Hz was strictly regulated by an electronic metronome and was increased by 0.05 Hz every minute. Performance was independent of skill or variation in technique. For each individual, the absolute difference between pre- and post-training data was obtained, and the mean of these differences calculated. Pre-training and post-training data were compared using two-tailed paired *t*-tests. Means were compared by generalized linear modelling with Statistical Analysis Software[6]. Data were adjusted by including baseline values as a covariate in the statistical model.

In a second study, *ACE* genotype was determined in 123 Caucasian males recruited to the UK army consecutively. Seventy-eight completed an identical 10-week general physical training programme (age, 19.0 ± 0.2 years; height, 176.6 ± 0.7 cm; body mass index, 22.2 ± 0.2 kg m^2). Their *ACE* genotype (20 (25.6%) *II*, 46 (59.0%) *ID*, 12 (15.4%) *DD*) matched that of those who failed training, as did their physical characteristics (neck, chest and waist circumference, elbow diameter and armspan), and all characteristics were independent of genotype.

The maximum duration (in seconds) for which they could perform repetitive elbow flexion while holding a 15-kg barbell was assessed both before and after the training period. Pre-training performance was independent of genotype (mean, 119.8 ± 6.2 s). Duration of exercise improved significantly for those (66 individuals) of *II* and *ID* genotype (79.4 ± 25.2 and 24.7 ± 8.8 s: P was 0.005 and 0.007 respectively) but not for the 12 of *DD* genotype (7.1 ± 14.9 s: P = 0.642) (Fig 1b). Improvement was thus eleven-fold greater (P = 0.001) for those of *II* than for those of *DD* genotype.

Genotype-dependent improvements were unlikely to be due to changes in individual muscle fibre size and strength (which need more than three months of specific strength-training to occur) or altered co-ordination, neural firing pattern or recruitment of fast motor units (given the lack of specific training for the test task)[6–8]. Increased performance is therefore most likely to be due to an improvement in the endurance characteristics of the tested muscles.

The association of the *I* allele with improved endurance might derive from variable increases in substrate delivery due to increases in cardiac output and muscle capillary density; from changes in the nature of substrate used, due to a differential shift to stored fatty acids as fuel[9], or in the efficiency of substrate utilization relating to altered muscle fibre type; from altered mitochondrial density, or from raised muscle myoglobin content[10,11]. Elevated catecholamine, cortisol and growth hormone concentrations may all increase the availability of oxidative fuel[12].

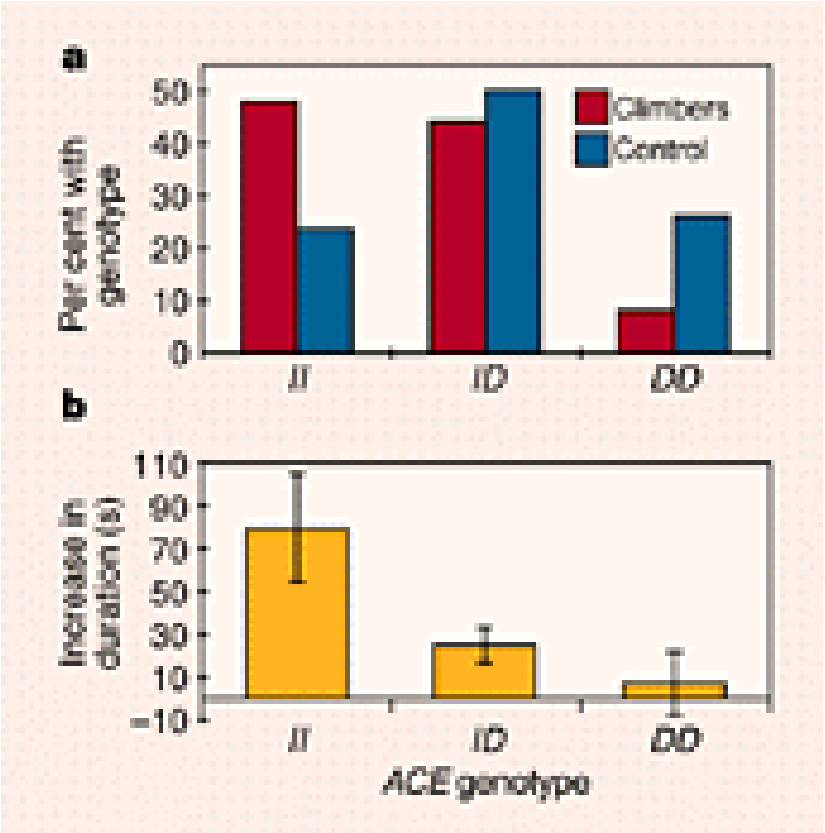
Further work will be needed to determine whether this correlation holds beyond the limited group studied here and to explore the mechanisms underlying these observations.

H. E. Montgomery, R. Marshall, H. Hemingway, S. Myerson
University College London Centre for Cardiovascular Research, Rayne Institute, University Street, London WC1E 6JJ, UK
P. Clarkson, C. Dollery, M. Hayward
University College London Hospital, London WC1E 6DB, UK
D. E. Holliman
Centre for Human Sciences, DERA Farnborough GU14 0LX, UK
M. Jubb, M. World
Royal Defence Medical College, HMS Dolphin, Gosport, Hampshire PO12 2AB, UK
E. L. Thomas, A. E. Brynes, N. Saeed, M. Barnard, J. D. Bell
Imperial College School of Medicine MRI Unit, London W12 0HS, UK
K. Prasad
St George's Hospital, Department of Cardiovascular Sciences, London SW17 0RE, UK
M. Rayson
Optimal Performance, Farnham GU9 7EB, UK
P. J. Talmud, S. E. Humphries
University College London Centre for Cardiovascular Genetics, Rayne Institute, University Street, London WC1E 6JJ, UK

Первая публикация по спортивной генетике -

Montgomery H.E., Marshall R., Hemingway H., Myerson S., Clarkson P., Dollery C., Hayward M., Holliman D.E., Jubb M., World M., Thomas E.L., Brynes A.E., Saeed N., Barnard M., Bell J.D., Prasad K., Rayson M., Talmud P.J., Humphries S.E. **Human gene for physical performance** // **Nature**. – 1998. – V.393. – P.221-222.

В 2011 обзор



Montgomery H.E., Marshall R., Hemingway H., Myerson S., Clarkson P., Dollery C., Hayward M., Holliman D.E., Jubb M., World M., Thomas E.L., Brynes A.E., Saeed N., Barnard M., Bell J.D., Prasad K., Rayson M., Talmud P.J., Humphries S.E. **Human gene for physical performance** // **Nature**. – 1998. – V.393. – P.221-222.

Nazarov I.B., Woods D.R., Montgomery H.E., Shneider O.V., Kazakov V.I., Tomilin N.V., Rogozkin V.A. The angiotensin converting enzyme I/D polymorphism in Russian athletes // Eur. J. Hum. Genet. 2001. V. 9. P. 797-801.

ACE – 12 лет спустя (Хью Монтгомери)

Table II. Studies in athletes associating the *ACE* insertion/deletion (I/D) genotype with sporting performance

Study	Cohort	No. of subjects and ethnicity	Performance[a]	Outcome measure[b]	Association with performance	I/D associations
Amir et al.[42]	Runners	121 Israeli	Elite	Performance	Yes	D and endurance
Cam et al.[45]	Sprinters	88 Caucasian	Non-elite	Performance	Yes	D and short distance
Cerit et al.[46]	Army	186 Caucasian	Army	Performance	Yes	D and short duration
Colakoglu et al.[47]	Athletes	99 Caucasian	Non-elite	Performance	Yes	D and strength
Juffer et al.[48]	Footballers	52 mixed	Elite	Prevalence	Yes	D more prevalent
Lucia et al.[49]	Cyclists	50 Caucasian	Elite	Performance	Yes	D/D and endurance
Munisea et al.[50]	Mixed	141 mixed	Elite	Prevalence	Yes	D/D and endurance rowers
Winnicki et al.[51]	Mixed	233 mixed	Sedentary	Performance	Yes	D/D and sedentary lifestyle
Nazarov et al.[9]	Mixed	217 Caucasian	Elite	Sport performance	Yes	D/D and short distance
Costa et al.[52]	Swimmers	72 Caucasian	Elite	Prevalence and performance	Yes	D/D and short distance
Woods et al.[34]	Swimmers	102 Caucasian	Elite	Prevalence and performance	Yes	D/D and short distance
Giaccaglia et al.[53]	Elderly	213 mixed	Sedentary	Training	Yes	D/D and strength
Zhao et al.[54]	Army	67 Chinese	Army	Performance	Yes	D/D and $\dot{V}O_{2max}$
Tsianos et al.[55]	Climbers	284 mixed	Elite	Performance	Yes	I and high ascent
Gayagay et al.[31]	Rowers	64 Caucasian	Elite	Prevalence	Yes	I and endurance
Myerson et al.[29]	Runners	91 Caucasian	Elite	Sport performance	Yes	I and endurance
Montgomery et al.[1]	Army	78 Caucasian	Army	Performance	Yes	I and endurance
Collins et al.[33]	Triathletes	166 Caucasian	Elite	Performance	Yes	I and endurance
Hruskovicova et al.[56]	Runners	445 Caucasian	Elite	Performance	Yes	I and endurance
Cieszczyk et al.[57]	Rowers	55 Caucasian	Elite	Prevalence	Yes	I and endurance
Min et al.[58]	Track and field	277 Japanese	Non-elite	Prevalence	Yes	I and endurance
Rankinen et al.[36]	Mixed	192 Caucasian	Elite	Prevalence and performance	Mixed	I and endurance

Continued next page

Puthucheary et al., 2011

ACE – 12 лет спустя (Хью Монтгомери)

Table II. Contd

Study	Cohort	No. of subjects and ethnicity	Performance[a]	Outcome measure[b]	Association with performance	I/D associations
Tsianos et al.[30]	Swimmers	35 Caucasian	Elite	Performance	Yes	I and endurance, D and short distance
Cam et al.[59]	Runners	55 Caucasian	Non-elite	Performance	Yes	I and endurance, D and short distance
Moran et al.[60]	Mixed	1027 Caucasian	Adolescents	Performance	Yes	I and endurance, D and strength
Thompson et al.[61]	Climbers	139 Caucasian	Elite	Prevalence and performance	Yes	I and high ascent
Hurlbut et al.[62]	Sedentary	40 Caucasian	Sedentary	Training	Yes	I and insulin requirements
Dekany et al.[63]	Mixed	50 Caucasian	Elite	Performance	Yes	I and metabolic efficiency
Williams et al.[64]	Army	58 Caucasian	Army	Training	Yes	I and metabolic efficiency
Kim et al.[44]	Power athletes	155 Korean	Elite	Sport performance	Yes	I and power
Kritchevsky et al.[65]	Elderly	3075 Caucasian	Sedentary	Activity	Yes	I/I and mobility limitation
Goh et al.[66]	Rugby players	17 Singaporean	Non-elite	Performance	Yes	I/I and $\dot{V}O_{2max}$
Alvarez et al.[32]	Mixed	60 Caucasian	Elite	Prevalence	Yes	I and elite status
Turgut G et al.[67]	Mixed	160 Turkish	Athletes and sedentary	Prevalence	Yes	I and athletes
Scott et al.[68]	Sprinters	230 African-Americans	Elite	Sport performance	No	
Sonna et al.[39]	Army	148 mixed	Army	Training	No	
Frederiksen et al.[69]	Elderly	684 Caucasian	Sedentary	Activity	No	
Scott et al.[70]	Runners	271 Africans	Elite	Performance	No	
Day et al.[71]	Sedentary	62 Caucasian	Sedentary	Performance	No	
Oh[72]	Mixed	139 Korean	Elite	Performance	No	
Papadimitriou et al.[73]	Track and field	101 Greek	Elite	Prevalence	No	
Thomis et al.[74]	Twins	54 Caucasian	Sedentary	Training	No	
McCauley et al.[75]	Active	79 Caucasian	Active	Performance	No	
Frederiksen et al.[69]	Elderly	203 Caucasian	Sedentary	Performance	No	

a Elite performance status refers to athletes involved in competition at an international level.

b Training as an outcome measure refers to an alteration in a pre-determined set of training exercises.

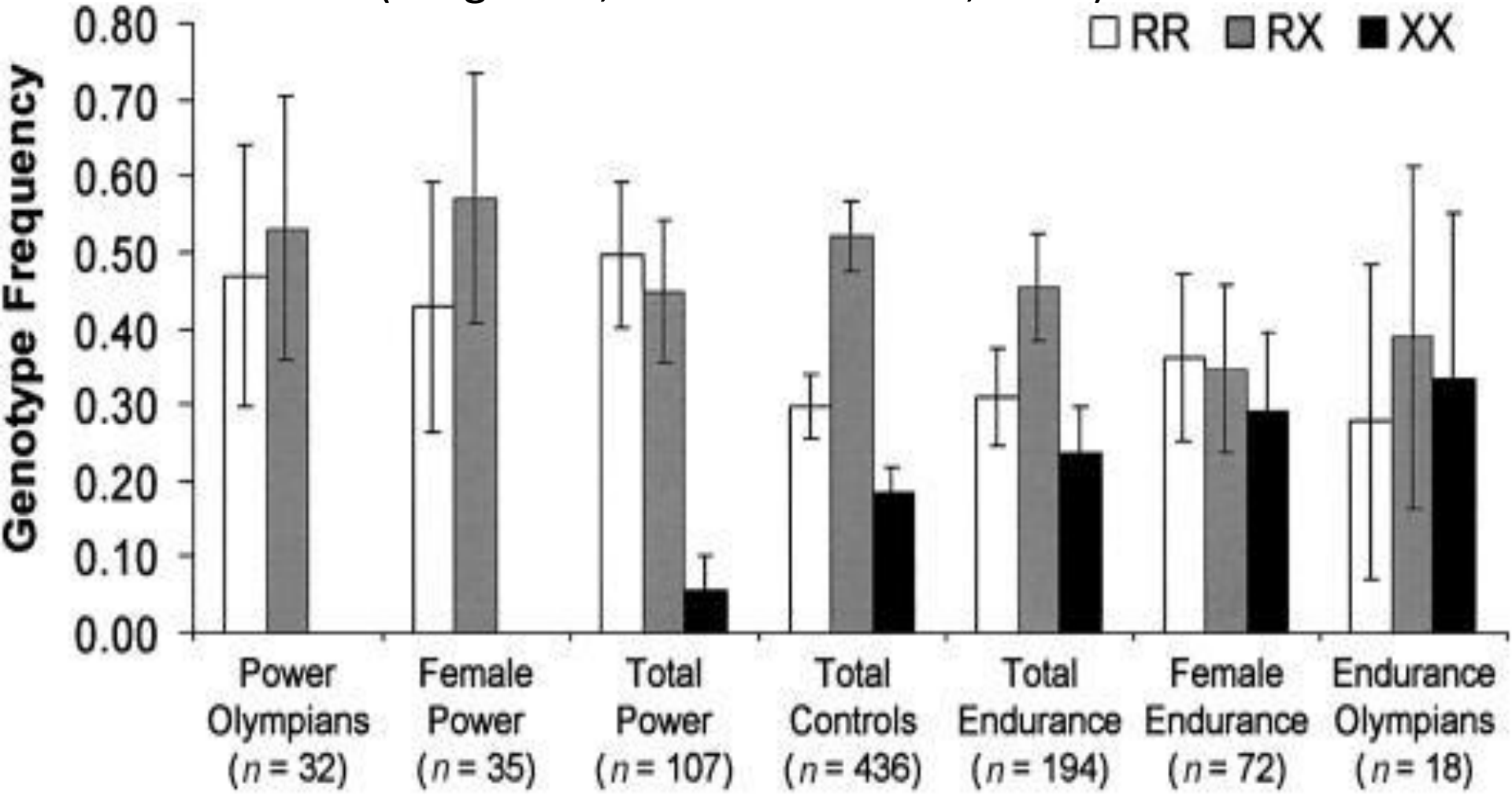
D = deletion; **I** = insertion; $\dot{V}O_{2max}$ = maximal oxygen consumption.

Sports Med 2011; 41 (6)

Puthucheary et al., 2011

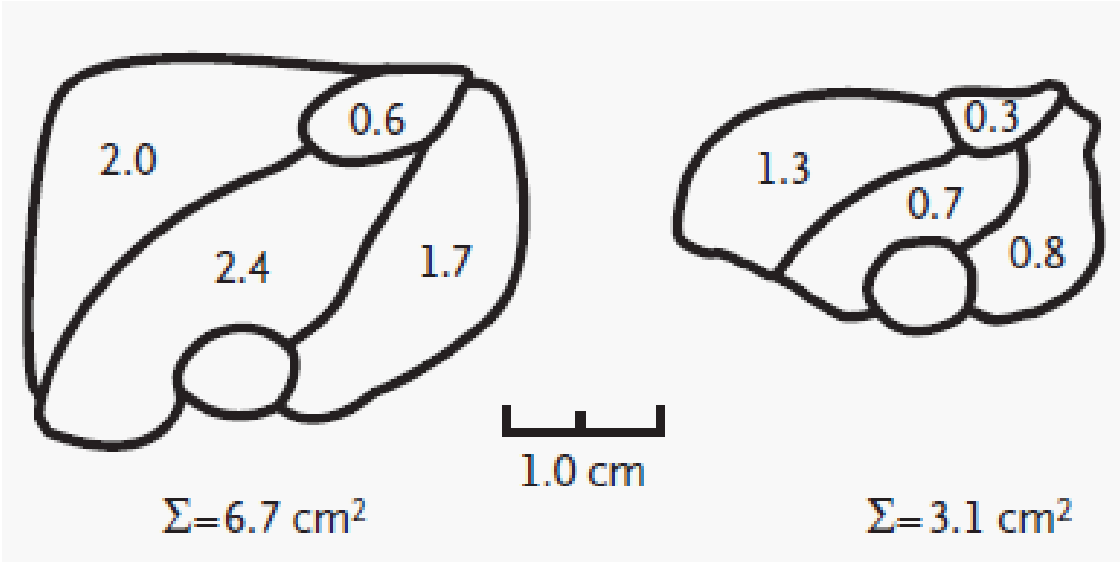
Распределение генотипов по гену *ACTN3* у элитных атлетов

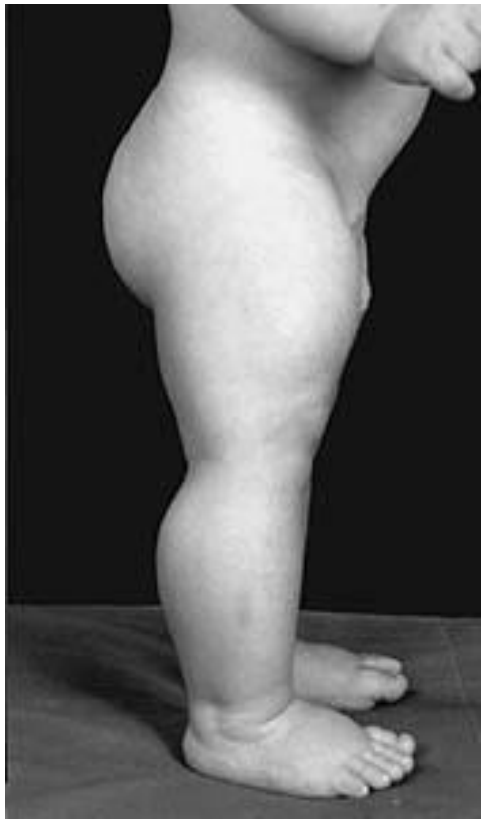
(Yang et al., Am J Hum Genet, 2003)

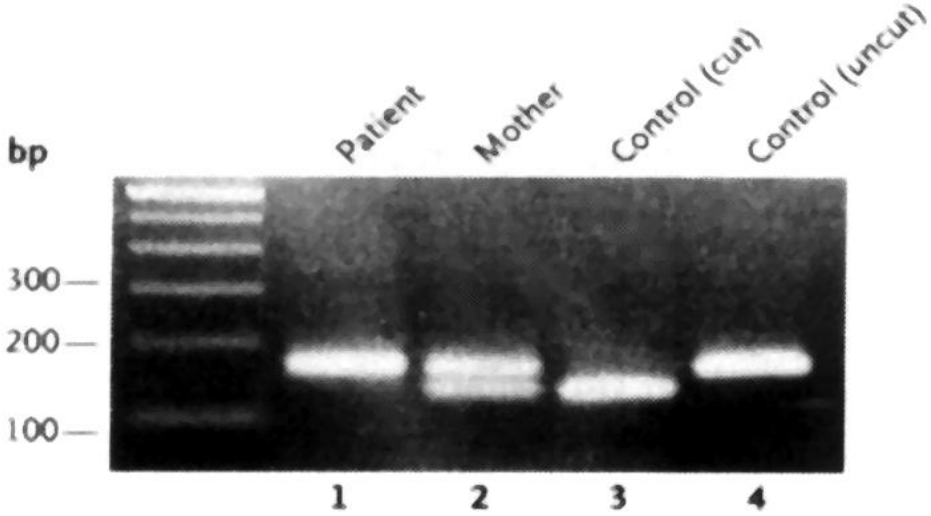


MSTN - миостатин

Variation in the myostatin gene linked to extreme muscle mass (Schuelke et al. 2004)



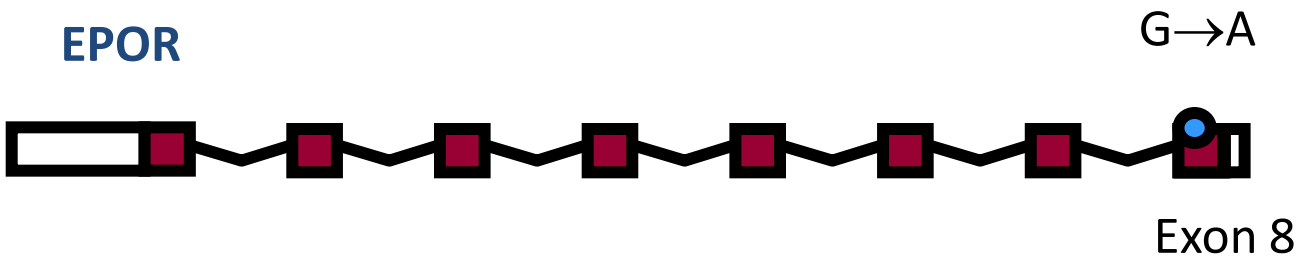




Manchester Metropolitan University

EPOR –рецептор эритропоэтина

Eero Antero Mäntyranta had a very high haematocrit due to a mutation in the erythropoietin receptor gene (de la Chapelle *et al*. 1993)



Manchester Metropolitan University

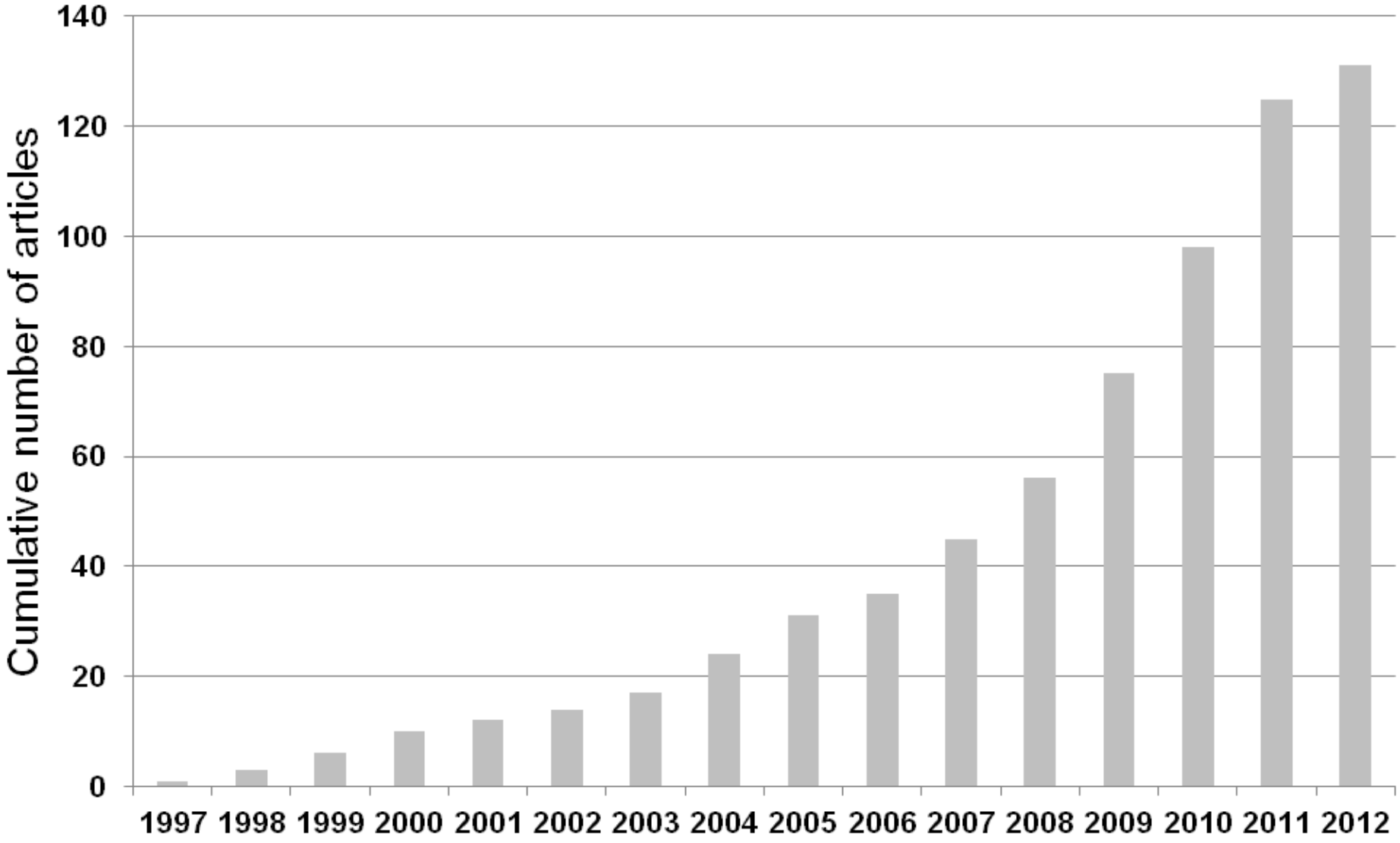
Современное состояние

Основные группы генов для спорта:

- Гены «артериального давления»
- Гены «углеводного и липидного (жирового)» обмена
- Гены риска «тромбозов» и «внезапной смерти»
- Гены «костей и суставов»
- Гены «мышц»
- Гены «питания и лекарств»
- Гены «роста»
- Гены «мотивации»
- Гены «адаптации к гипоксии» и другие.

Литература в геномике спорта

Ahmetov, I.I. & Fedotovskaya, O.N.
(in press, Cell Mol Ex Physiol)



THE HUMAN VARIOME PROJECT

sharing data · reducing disease

Latest News

Ensuring the Free and Open Sharing of Clinically Relevant Genome Variants - A Statement by the Human Variome Project Consortium

Genetic tests for diagnostic, predictive and screening purposes are a routine part of clinical care in most modern health care systems, and as we discover more about the genetic determinants of our health, we can expect genetic testing to become more prevalent. At the same time, new technological advancements, lower costs and increased training and education will see genetic testing spread rapidly into routine clinical practice in countries with, to date, less advanced health care systems.

Read more...

A Global Alliance to Enable Responsible Sharing of Genomic and Clinical Data

Over 70 leading health care, research, and disease advocacy organizations, including the Human Variome Project announced today that they have taken the first steps to form an international alliance dedicated to enabling secure sharing of genomic and clinical data to improve research into the genetic basis of human disease.

Read more...

Join the Consortium

Individuals wishing to apply to join the Human Variome Project consortium can register here.

Sign up to the *HVP Transcript*

Sign up to the HVP Transcript to stay up to date with the progress and achievements of the Human Variome Project.

Upcoming Events

International Society for Gastrointestinal Hereditary Tumours - 5th Biennial Meeting

28-31 August, 2013
(HVP Workshop 28 August)
Cairns Convention Centre
Cairns
Australia

HVP5: The 5th Biennial Meeting of the Human Variome Project Consortium

19-23 May, 2014
UNESCO Headquarters
Paris, France

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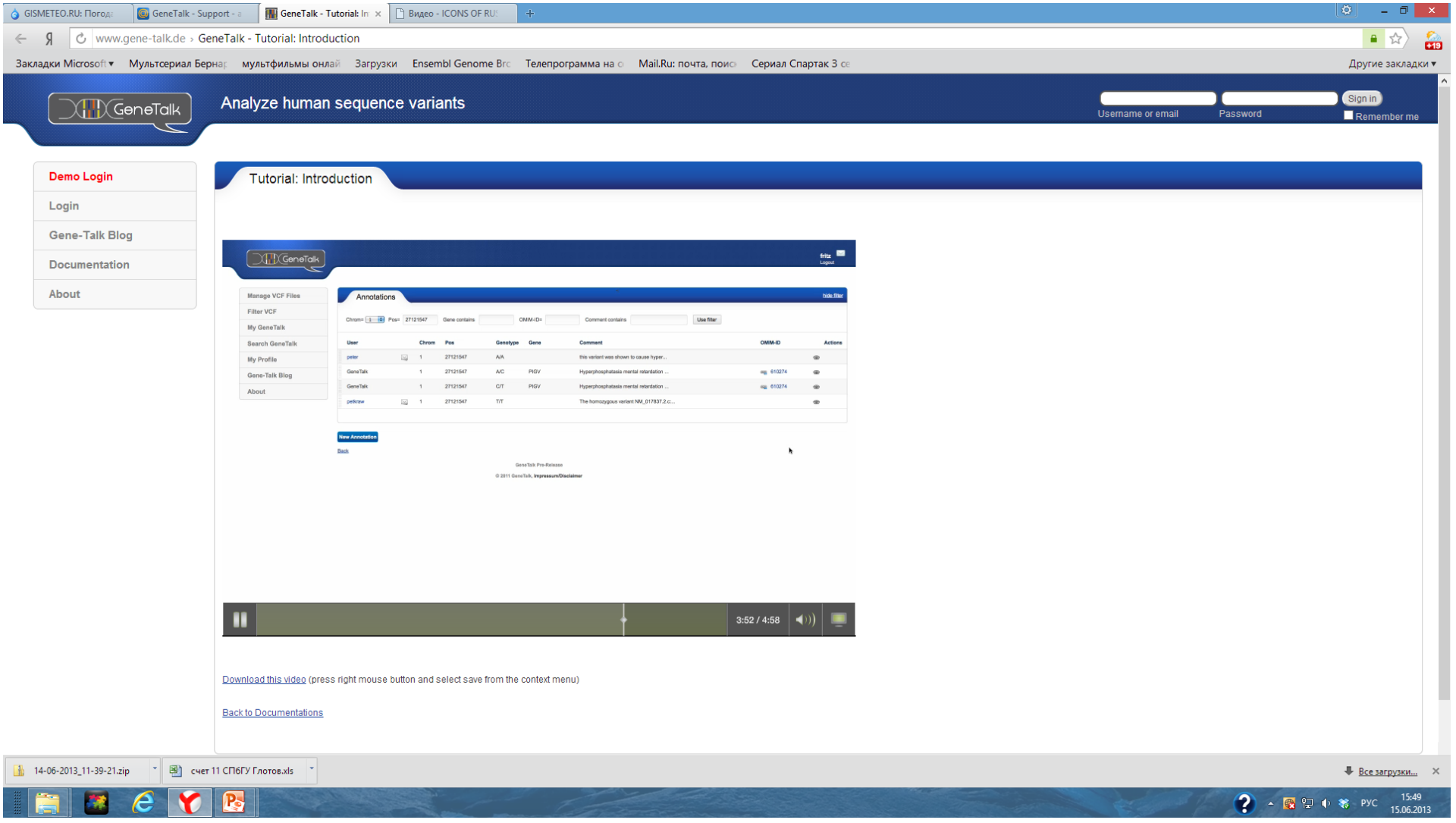


СУДЕБНО-МЕДИЦИНСКАЯ ЭКСПЕРТИЗА

- Идентификация личности
- Установление кровного родства

Метод ДНК-фингерпринт

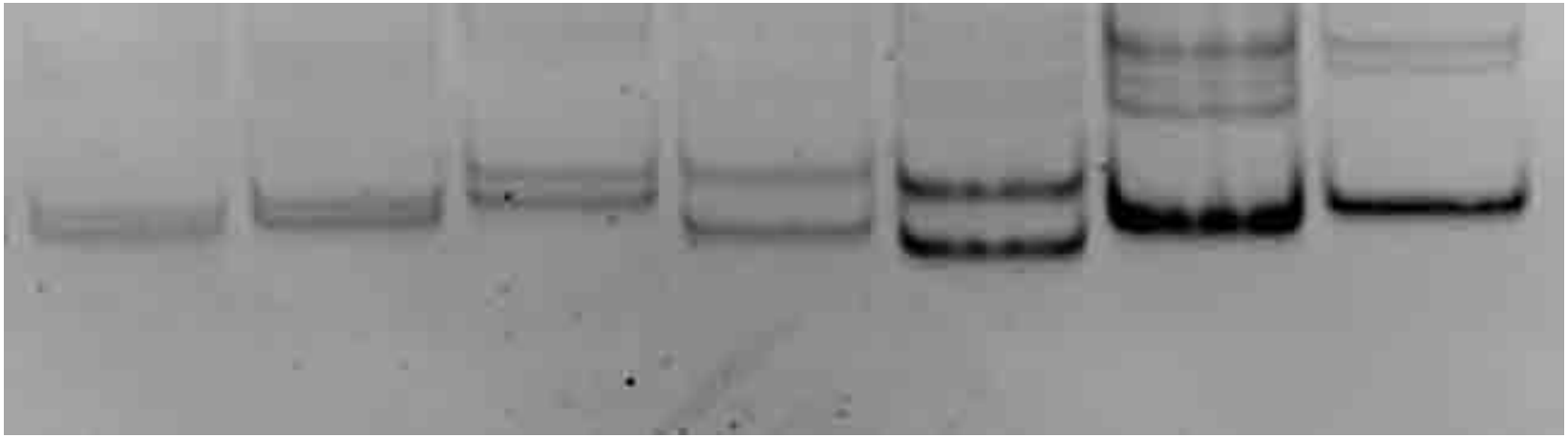
ДНК-дактилоскопия, метод «отпечатков пальцев ДНК»

Предложен в 1987 году

Недостатки

- Трудоемкий и капризный
- Требуется большое количество ДНК
- Сложная система контроля

Принцип идентификации личности: анализ локусов, содержащих STR (короткие тандемные повторы)



Количество локусов (STR), необходимое для идентификации личности

- Минимум – 4-5 локусов
- Стандарт CODIS (США) – 7 локусов
- Стандарт CODIS в случае особой важности – 14 локусов
- Всего известно около 30 000 локусов, содержащих STR

Два этапа ДНК-диагностики в судебно-медицинской экспертизе

- Выявление совпадений

Если совпадения выявлены, то необходим:

- Расчет вероятности того, что совпадение не случайно

Необходимая точность

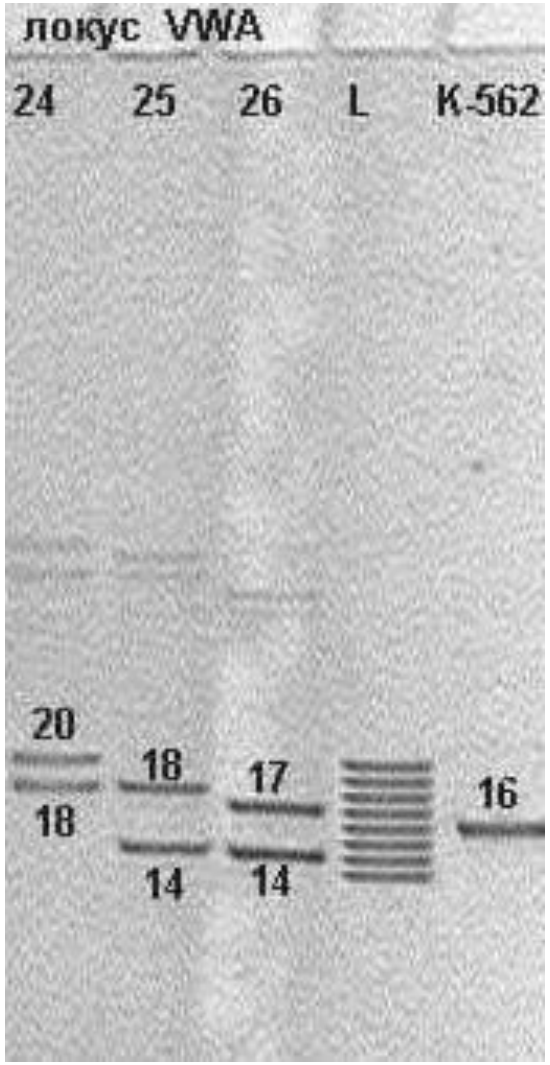
99,98%- точность идентификации

0,02% или

1 из 5 000 – вероятность случайного совпадения

ОПРЕДЕЛЕНИЕ КРОВНОГО РОДСТВА

- В 95% случаев – вопросы спорного отцовства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Правила опровержения

- Для опровержения отцовства в геноме ребенка и предполагаемого отца должно быть выявлено несовпадение по крайней мере по двум локусам

Генный допинг

BBC NEWSWATCH

Rigorous sport

Roger Mosey
3 April 2006

Sport is a massive international business, and it makes globalisation real every time you see a Manchester United shirt in the Far East or Africa. **The total world market generated by sport is estimated to reach $111 billion by 2009.**

Forbes.com

The World's Top-Earning Athletes

Kurt Badenhausen

October 26, 2007

July 2006-June 2007

1. Tiger Woods
Earnings: $100 million
Sport: Golf
Nationality: American

5. Michael Schumacher
Earnings: $36 million
Sport: Auto racing
Nationality: Germany

9. (tie) Ronaldinho
Earnings: $31 million
Sport: Soccer
Nationality: Brazilian

11. Valentino Rossi
Earnings: $30 million
Sport: Motorcyling
Nationality: Italian

JOS COLLIGNON

Effects on organ systems/tissues

- Heart
  - Bigger – greater stroke volume
  - Increased maximal cardiac output
- Blood vessels (in the heart & those skeletal muscles that have been trained):
  - More capillaries
  - Improved dilatory capacity

Effects on organ systems/tissues

- Blood
  - Increased total amount of red blood cells
  - Even larger expansion of plasma volume
    - → => reduced blood count in a blood sample
- Adipose tissue
  - Reduced amount
- Connective tissue/bone/cartilage
  - Increased amount/strengthened

Effects on organ systems/tissues

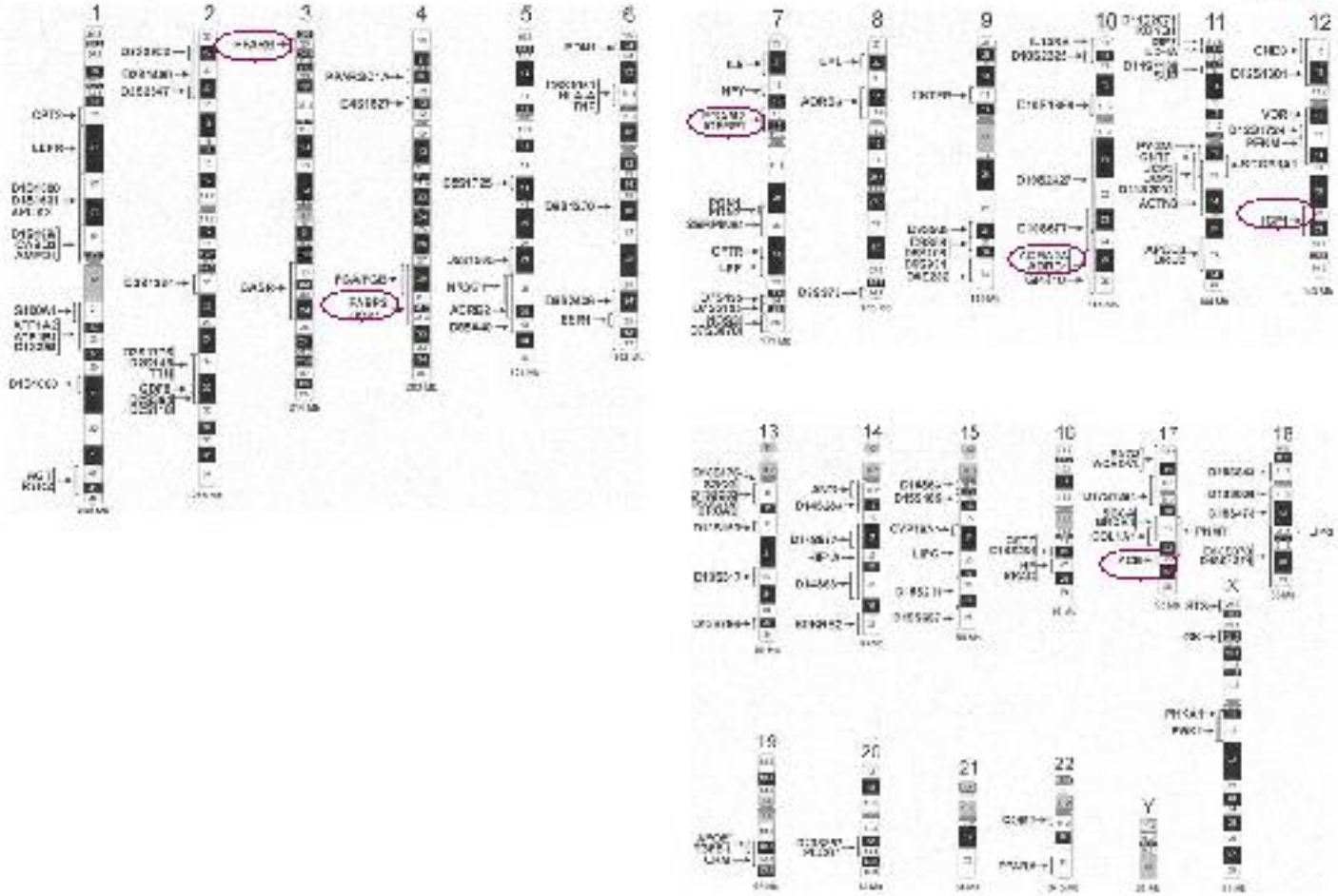
- Endocrine system
  - Insulin sensitivity
  - Catecholamine & Growth hormone responses to exercise
- Skin
- Immune system
- Lungs
- Nervous system/brain

Effects on skeletal muscle

- ↑ # & volume of mitochondria
- ↑ capillary amount

- ↑ glycogen storage
- ↑ insulin sensitivity/ glucose transport capacity
- ↓ proportion of type IIb/x-fibres

What factors regulate human muscle performance – genes ??



- No agreement yet on 'key genes' using population genetics
- Difficult to validate – separate population studies required

Bouchard, C et al 2005

> 500 genes 'activated' by exercise in humans

Karolinska Institutet

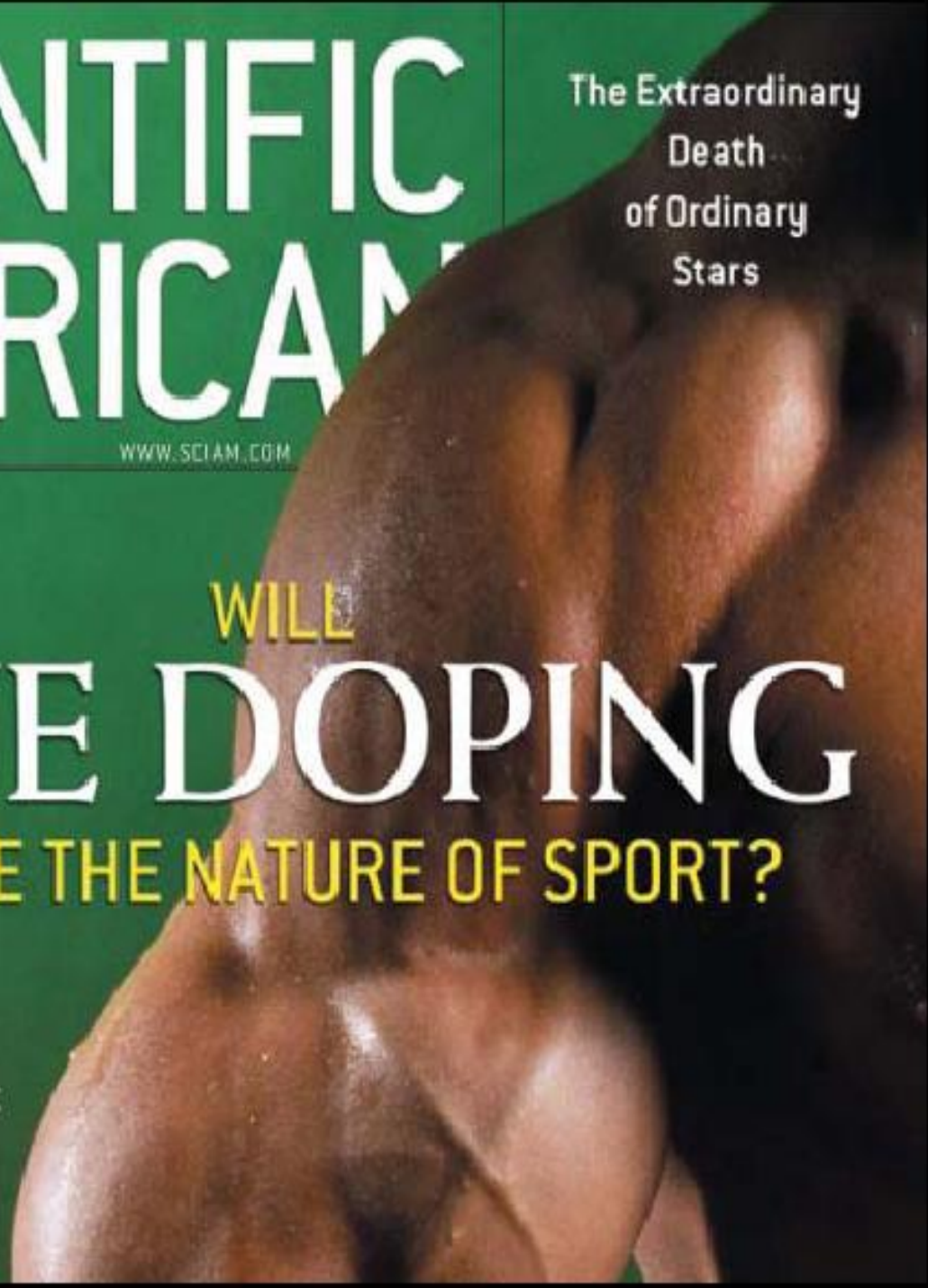
A2M	CaMKIINalpha	DDR2	GJA1	LAMP1	OAS1	S100A13	TRDN	60050_at
ACLY	CAP1	DHRS8	GLS	LAP1B	OLFML2A	S100A4	TREM4	62263_at
ACTA2	CAPN3	DKFZP434B044	GLUL	LASP1	OLFML2B	SCN4B	TRIB1	62480_at
ACTB	CAV1	DKFZp434B1231	GNA12	LDHB	OSRF	SCOTIN	TUBA3	62539_at
ACTC	CAV2	DKFZp434L142	GNAI2	LGALS1	OTUD1	SDPR	TUBB	62594_at
ACTG1	CCDC3	DKFZp564I1922	GNB1	LGALS3	PABPC1	SEMA3C	TXNDC5	63296_at
ACTN1	CCND1	DKFZP564O0823	GNG11	LHFP	PALM2	SERPING1	TYROBP	64084_at
ACTN2	CD164L1	DKFZP566K1924	GPAM	LILRB1	PC326	SERPINH1	UBE2G1	65114_at
ACTN3	CD34	DKFZp761C169	GPNMB	LIM	PCDH18	SESN1	UBE2S	65904_at
ACTN4	CD81	DLC1	GPR124	LNK	PCOLCE2	SESN3	UCP2	67792_r_at
ADAMTS5	CDH5	DMD	GPR34	LOC162073	PDGFRB	SFRP2	UCP3	71786_at
ADAR	CDW92	DNCL1	GPX3	LOC283241	PDK4	SH3BGRL	URB	72674_at
ADD3	CFL1	DPYSL2	GRPS8	LOC339924	PDLIM3	SH3BGRL3	USP13	72728_at
AGTRL1	CGI-121	DSTN	GSN	LOC387763	PEA15	SIPA1L2	UTRN	73441_at
AMPD1	CHST1	ECM2	GUCY1A3	LOC388962	PECAM1	SLC20A2	VAT1	74566_at
ANGPTL2	CIDE-3	ECRG4	HBAP1	LOC51668	PFN2	SLC38A1	VDP	75430_r_at
ANKRD1	CKLFSF6	EDIL3	HBB	LOXL1	PHKG1	SLC41A1	VIM	75969_f_at
ANTXR1	CLDN5	EEF1A1	hIAN2	LOXL2	PHLDB2	SMOC2	VWF	76236_r_at
ANXA1	CLIC1	EFHD2	HIPK3	LPL	PLAC9	SNRPN	WSB1	77207_at
ANXA2	CLIC4	EHD2	HLA-B	LUM	PLN	SOX4	YWHAQ	78727_at
ANXA2P3	CLU	EIF4A1	HLA-C	MADH1	PLS3	SOX7	ZAK	79933_at
ANXA5	CMIP	ELOVL5	HLA-DPB1	MAFB	PLSCR4	SPARC	ZC3HAV1	83026_i_at
AOC3	CMYA5	ELTD1	HLA-DRA	MAGED2	PLTP	SPARCL1	ZFP36	85922_r_at
APOE	CNK2	EMCN	HLA-DRB1	MALAT-1	PLVAP	SPIN	ZFP36L2	90557_at
APP	CNN3	EMP3	HLA-F	MARCKS	PODN	SPON2	ZNF145	
ARHGAP1	CNNM3	ENG	HN1	MEOX2	PORIMIN	SPP1	1164_at	
ARHGAP8	COL15A1	ENPP2	HSPC121	MESDC1	PP1057	SPTBN1	1173_g_at	
ARHGDIB	COL4A2	EPS8	HSPC242	MGC1136	PP2135	SSPN	1664_at	
ARPC5	COL3A1	ERG	HSPG2	MGC15606	PPIA	SULT1A1	1882_g_at	
ARRDC3	COL4A1	ETS1	IER5	MGC4083	PPIB	TAGLN	296_at	
ART3	COL4A2	F11R	IFI27	MGC45780	PRCP	TARSH	311_s_at	
ATP2B2	COL5A2	FABP4	IFITM1	MGC45871	PRKAG2	TAZ	35474_s_at	
B2M	COL6A1	FABP5	IFITM3	MGC52010	PRND	TCF7L2	40657_r_at	
BASP1	COL6A2	FADS3	IGF1	MIDORI	PRSS11	TGFBI	41732_at	
BGN	COL6A3	FASN	IGF2	MLF1	PTMA	TGFBR2	44066_s_at	
BMPR2	CORO1C	FBN1	IGFBP2	MRC2	PTPLB	THBS4	44583_at	
BNIP3L	COTL1	FBXL7	IGFBP4	MSN	PTRF	THRSP	44868_s_at	
BOC	COX6A1	FBXO3	IGFBP5	MT1X	PTTG1IP	TIMP1	45660_at	
BRP44L	CPE	FCGR3A	IGFBP7	MYADM	QKI	TIMP2	46653_at	
BTEB1	CRIP1	FER1L3	IGLJ3	MYH11	RAB8B	TIP-1	46898_at	
BTG1	CRIP2	FKBP2	IL17D	MYH9	RAFTLIN	TM4SF1	47482_at	
C10orf104	CSPG2	FKBP5	IQGAP1	MYL6	RAI14	TM4SF3	48069_at	
C10orf58	CTBP2	FLJ10849	ITGB1	MYL9	RAP1B	TMEM16E	48074_at	
C14orf139	CTGF	FLJ14146	ITGB1BP3	MYLK	RBM3	TMSB10	48853_at	
C19orf10	CTNNA1	FLJ20618	ITGB5	MYLK2	RBMS3	TMSB4X	49967_at	
C1QA	CTSO	FLJ23153	ITM2A	MYO1B	RBP1	TNA	50007_at	
C1QG	CXCL12	FLNA	JAM2	NEB	RBP4	TNC	50411_at	
C1QR1	CXCL14	FN1	JPH1	NEXN	RCN1	TncRNA	51939_at	
C1S	CYBRD1	FNDC1	K-ALPHA-1	NGFRAP1	RHOC	TNFAIP3	54668_at	
C20orf3	CYGB	FOS	KCNJ8	NID	RNASE1	Tnfrsf6	54980_at	
C6orf198	D2S448	FOXO3A	KCTD10	NID2	ROD1	TOB2	55328_r_at	
C9orf19	DAB2	FOXP1	KCTD12	NOTCH3	RPL3	TP53INP1	55837_at	
C9orf58	DACH1	FSCN1	KIAA1109	NPC2	RRAD	TPM1	56323_at	
CACNA2D1	DACT1	FXYD6	LAMA4	NR2F2	RSN	TPM2	56543_i_at	
CALD1	DC2	FYN	LAMB1	NRAP	S100A10	TPM3	56600_at	
CALM2	DC-TM4F2	GANAB	LAMC1	NRP1	S100A11	TPM4	59809_f_at	

Timmons *et al* *FASEB J* 2005

SCIENTIFIC AMERICAN

JULY 2004 WWW.SCIAM.COM

The Extraordinary Death of Ordinary Stars



WILL

GENE DOPING

CHANGE THE NATURE OF SPORT?

Mad Cow Disease: Faster Tests, Future Therapies

Possible methods and approaches for doping to enhance athletic performance

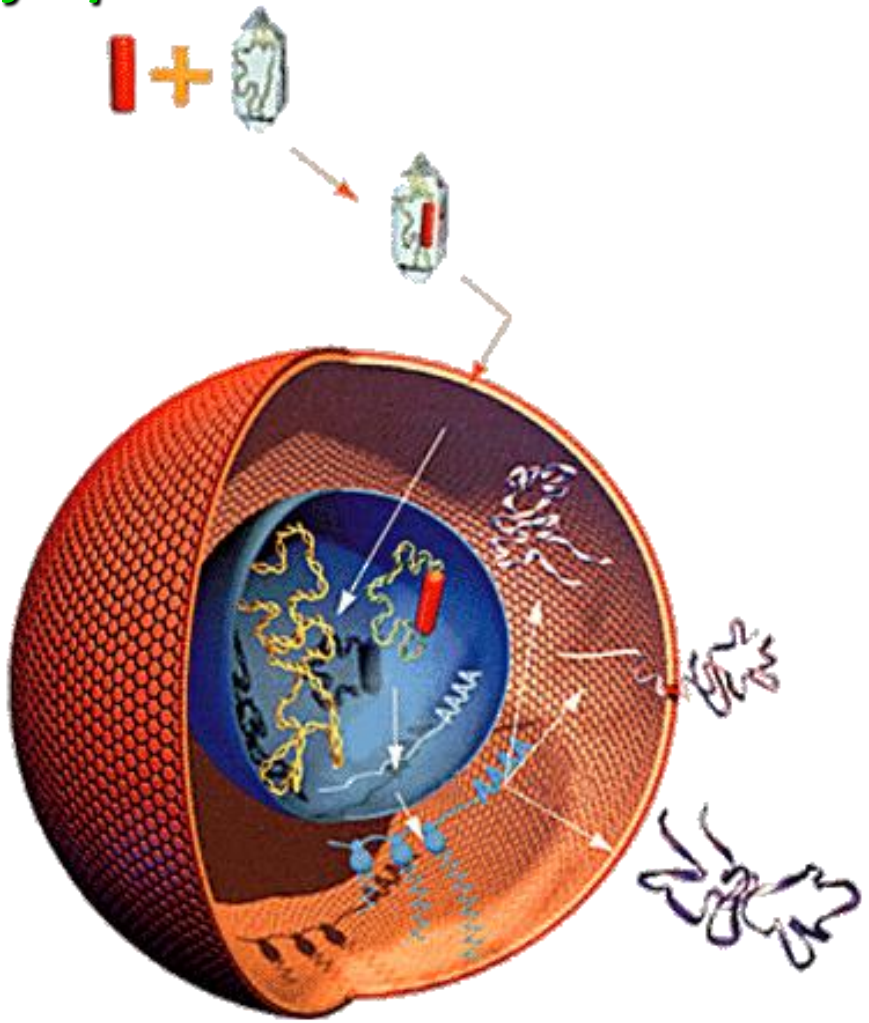
-Gene Therapy

-Targeting of Signaling Pathways and Gene Regulatory Elements

-Introduction of small interfering RNA

Gene therapy -

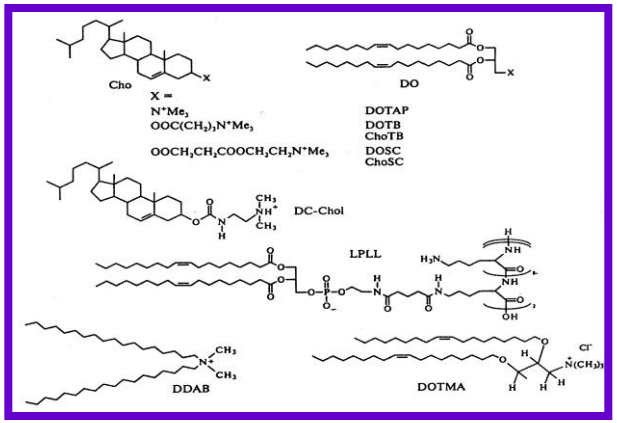
the transfer of genetic material into a cell, tissue, or whole organ, with the goal of curing a disease or at least improving the clinical status of a patient.



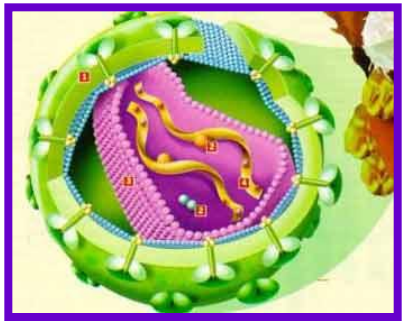
Gene Therapy:

Gene transferring methods

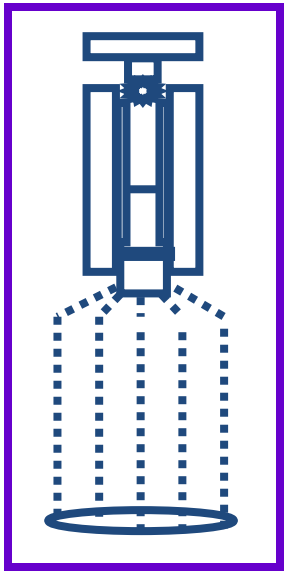
Nonviral vectors



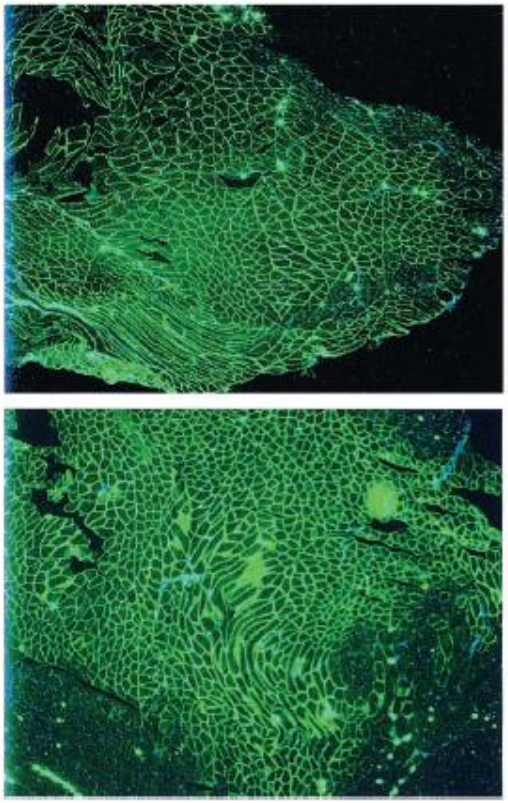
Viral



Physical

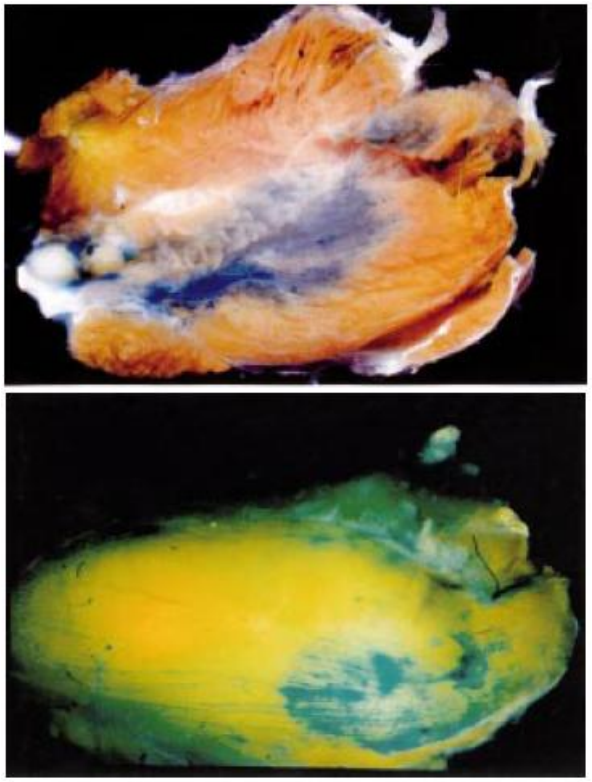


Efficient expression of adeno-associated virus vector carrying human minidystrophin genes in mdx mouse model



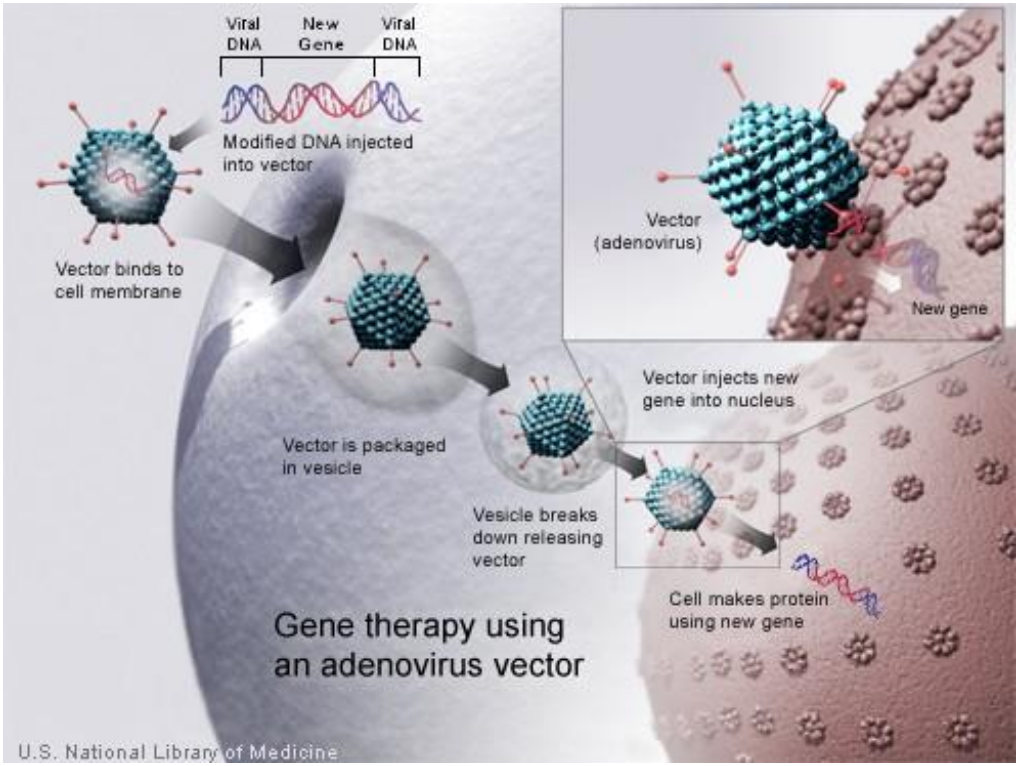
Expression efficacy < 88% cells

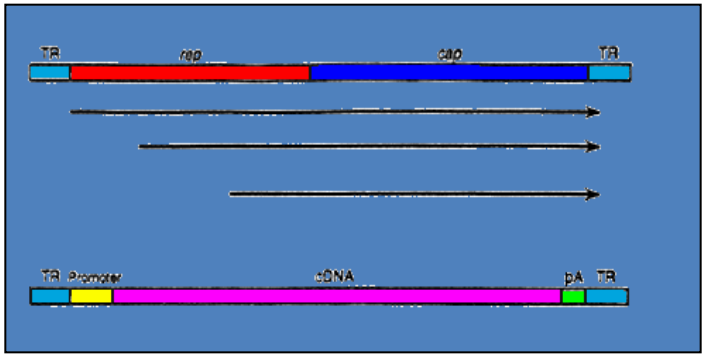
Efficient expression of *lacZ and* human minidystrophin genes delivered by polymer microspheres to mdx mouse muscles



Expression efficacy < 18% cells

Gene therapy and vector construction

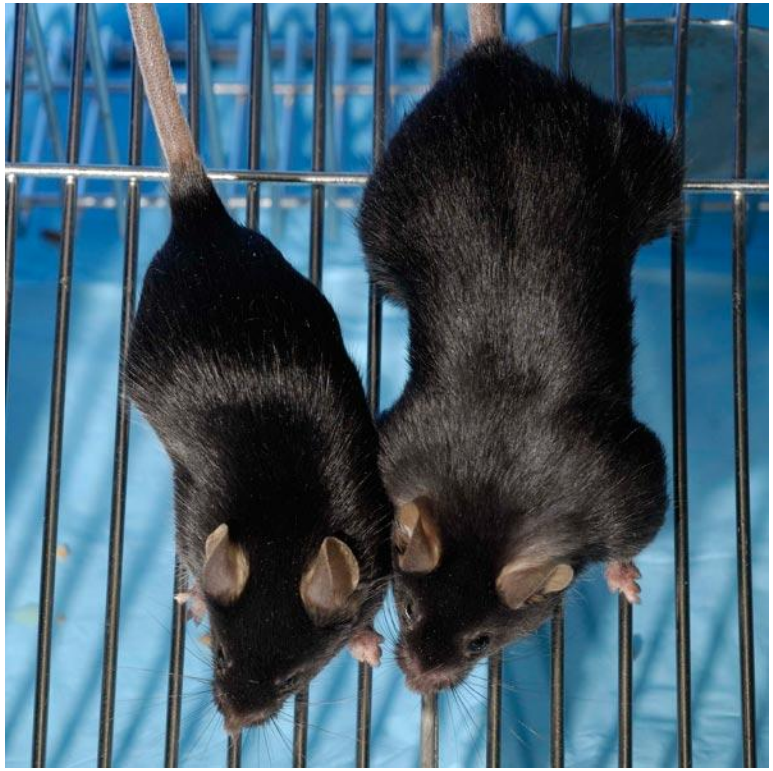




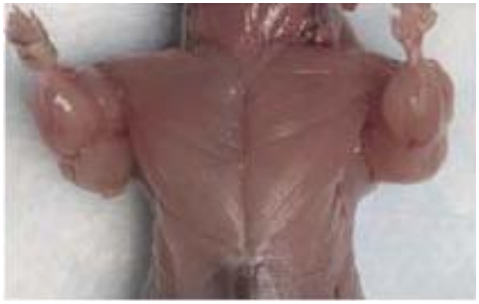
http://ghr.nlm.nih.gov/handbook/illustrations/therapyvector
http://www.microbiologybytes.com/virology/peel/peel3.html


100 M MENS FINAL
1 GENE THERAPIST H. HAISMA 9.85
2 GENE THERAPIST T. FRIEDMANN 9.87
3 GENE THERAPIST O. RABIN 9.90
41

Drug targeting of signaling pathways, genome regulatory elements etc.



Wild type



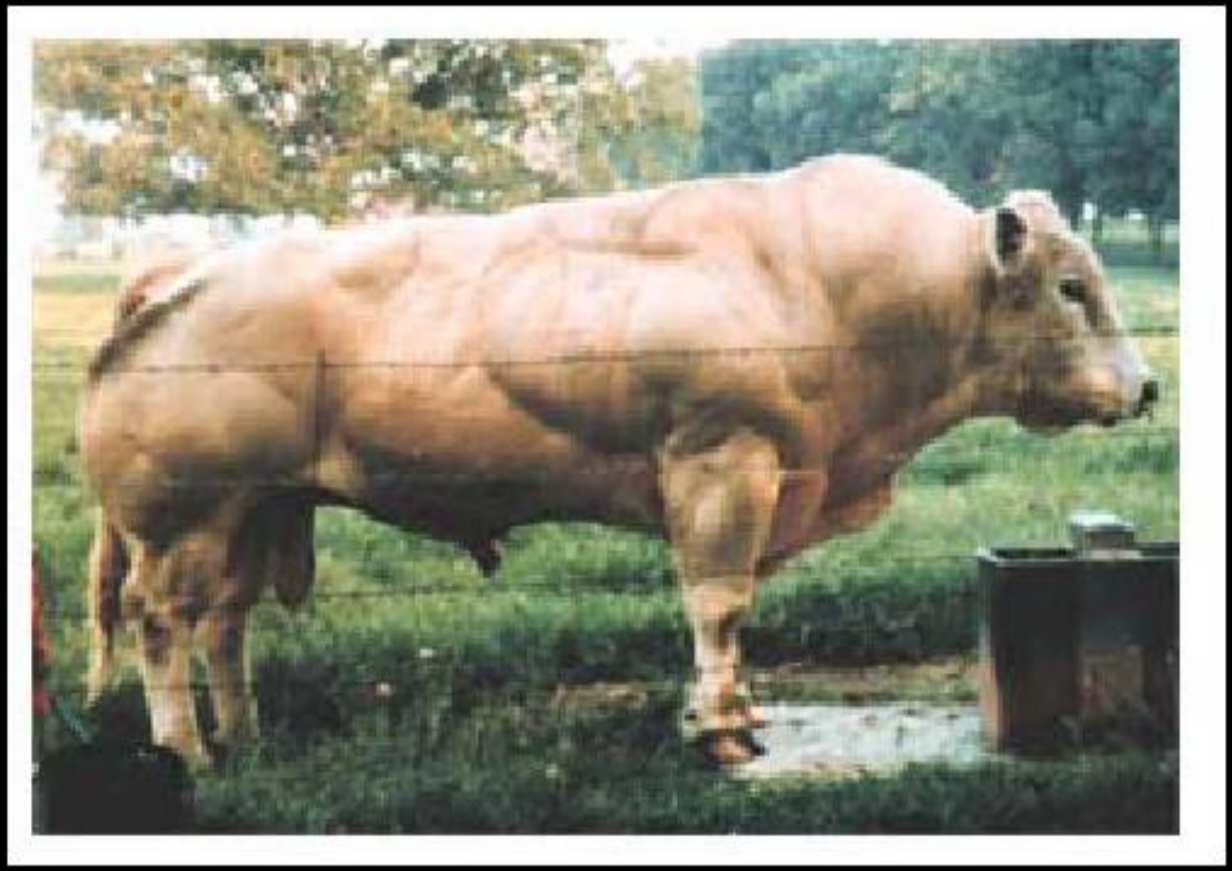
Myostatin knockdown

MYOSTIM
Myostatin Binder
Enhance muscle tissue growth

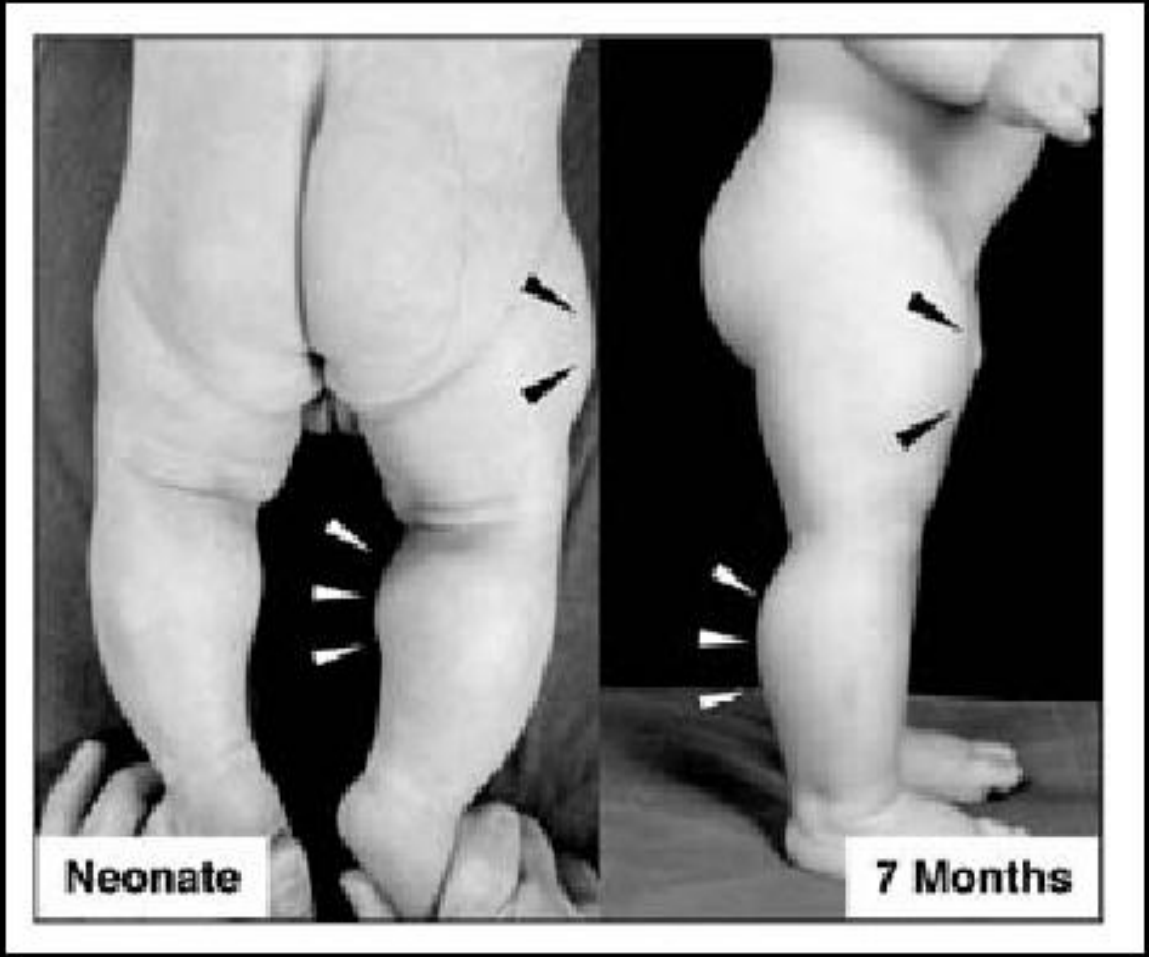
Today, we are standing at the forefront of the greatest discovery for athletes in the last fifty years. Recently researchers have discovered the primary gene for the control of muscle. They call it myostatin. This compound binds strongly to myostatin, thereby deactivating it.

This discovery made it possible for Champion Nutrition to begin work on the first product ever specifically designed to bind myostatin in humans.
MyoStim™ – the first generation of the new age

Myostatin Null Cow

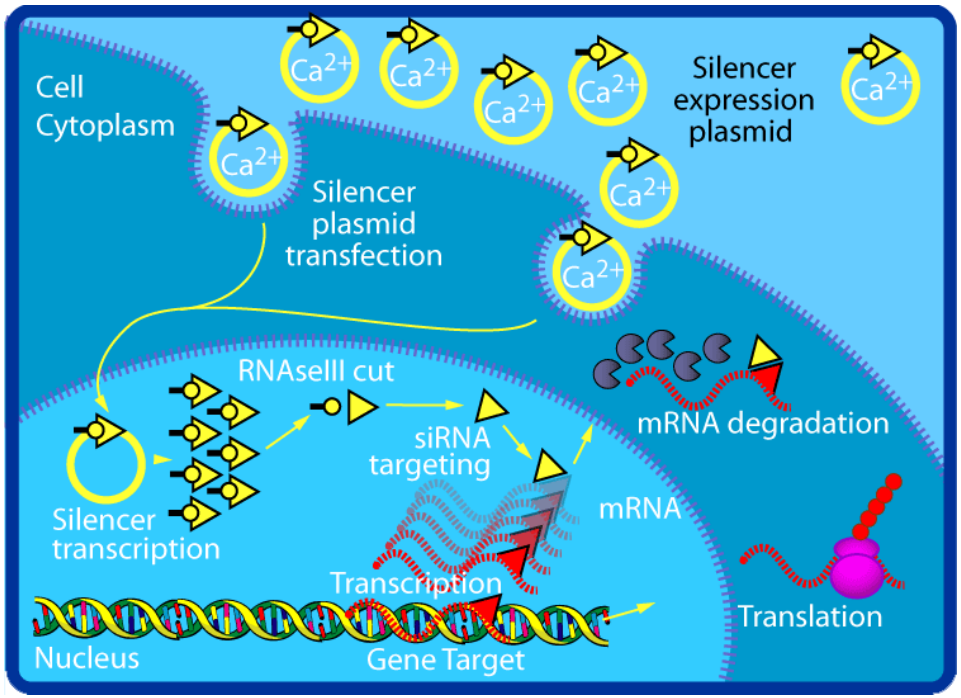


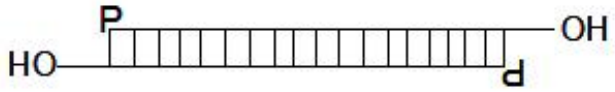
Myostatin Null Human



Small interfering RNA

- ***20-25 nucleotides***
- ***double-stranded RNA molecules***
- ***inhibition of gene expression***





Schematic representation of a siRNA molecule: a ~19-21basepair RNA core duplex that is followed by a 2 nucleotide 3' overhang on each strand. OH: 3' hydroxyl; P: 5' phosphate.

http://en.wikipedia.org/wiki/Small_interfering_RNA

Genes of Interest:

- ***Myostatin (MSTN)***
- ***Erythropoietin (EPO)***
- ***Insulin-like growth factor I (IGF1)***
- ***Peroxisome proliferator-activator receptors (PPARs)***
- ***Other genes (which associated with enhancement of athletic performance)***

What are the motifs that can be used as objects for genetic doping detection?

- ***A) sequence of vector elements***
- ***B) sequence of cDNA (foreign DNA)***
- ***C) expression profiling***
- ***D) antibody for foreign proteins or constructions***
- ***E) complex approaches***

Problems of detection

- ***Low concentration of target DNA/RNA sequences in the sample***
- ***Difficulty of regulatory elements analysis (promoters, enhancers, silencers, terminators, exon-intron boundaries)***
- ***Possible use of new target genes and new methods of transfer***
- ***Detection of end-product is impossible***
- ***Low stability of the material***

Requirements for antidoping gene analysis:

- ***Simplicity of sample collection***
- ***Non-invasive (desirable)***
- ***Sufficient sample quality***
- ***Opportunity to divide the sample for 2 identical tests***

Which biological material can be used for the molecular genetic analysis?

- ***Blood***
- ***Urine***
- ***Saliva***
- ***Biopsy***

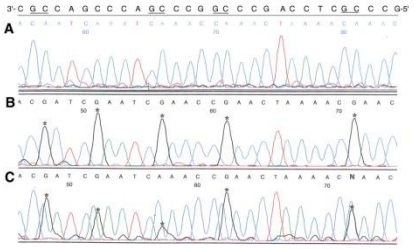
The Best Method – direct analysis of DNA sequence

- ***Possibility to detect primary sequences***
- ***Opportunity to analyze regulatory elements (promoters, enhancers, silencers, terminators, exon-intron boundaries)***
- ***Simplification of the analysis (decreasing number of steps)***
- ***DNA is more stable than RNA***
- ***Direct method of gene doping detection***

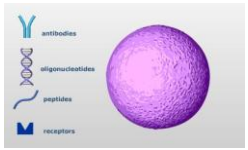
MODEN TECHNIQUES OF DNA ANALYSIS

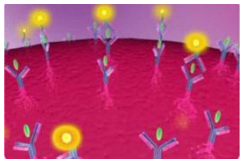
PCR +

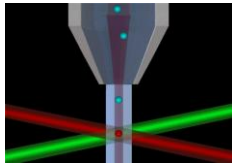
Sequencing



FCBS (xMAP)

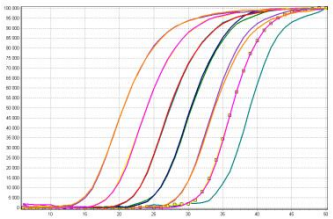




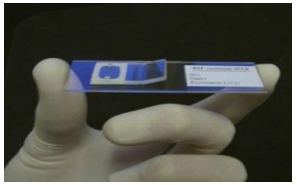


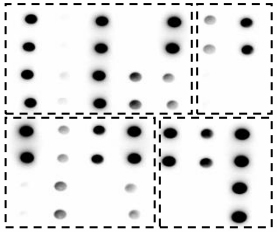
MALDI-TOF mass spectrometry

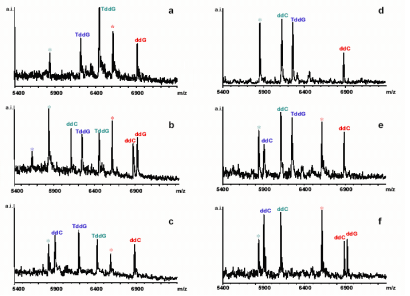
Real-Time PCR



Microarray







Proteomics

Sample Preparation

(I)

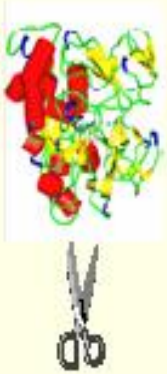
2-D Electrophoresis

(II)

Spot Detection & Image Analysis

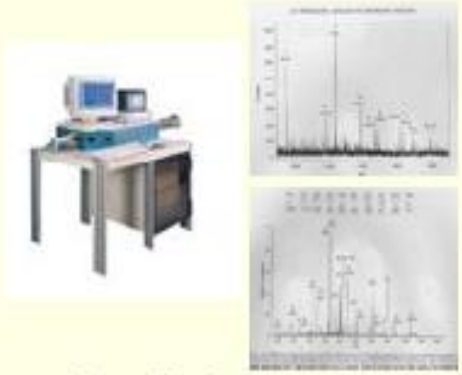
(III)

Enzymatic Digestion



(IV)

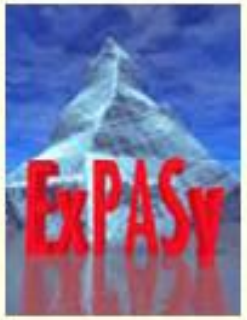
Peptide-Mass Fingerprinting



Peptide Sequencing via MS

(V)

Protein Identification



Database Search

(VI)

Post Translational Modifications

Table 1. Some common and important post-translational modifications

PTM type	ΔMass[a] (Da)	Stability[b]	Function and notes
Phosphorylation			Reversible, activation/inactivation of enzyme activity, modulation of molecular interactions, signaling
pTyr	+80	+++	
pSer, pThr	+80	+/++	
Acetylation	+42	+++	Protein stability, protection of N terminus. Regulation of protein–DNA interactions (histones)
Methylation	+14	+++	Regulation of gene expression
Acylation, fatty acid modification			Cellular localization and targeting signals, membrane tethering, mediator of protein–protein interactions
Farnesyl	+204	+++	
Myristoyl	+210	+++	
Palmitoyl	+238	+/++	
etc.			
Glycosylation			
N-linked	>800	+/++	Excreted proteins, cell–cell recognition/signaling
O-linked	203, >800	+/++	O-GlcNAc, reversible, regulatory functions
GPI anchor	>1,000	++	Glycosylphosphatidylinositol (GPI) anchor. Membrane tethering of enzymes and receptors, mainly to outer leaflet of plasma membrane
Hydroxyproline	+16	+++	Protein stability and protein–ligand interactions
Sulfation (sTyr)	+80	+	Modulator of protein–protein and receptor–ligand interactions
Disulfide bond formation	−2	++	Intra- and intermolecular crosslink, protein stability
Deamidation	+1	+++	Possible regulator of protein–ligand and protein–protein interactions, also a common chemical artifact
Pyroglutamic acid	−17	+++	Protein stability, blocked N terminus
Ubiquitination	>1,000	+/++	Destruction signal. After tryptic digestion, ubiquitination site is modified with the Gly-Gly dipeptide
Nitration of tyrosine	+45	+/++	Oxidative damage during inflammation

[a]A more comprehensive list of PTM Δmass values can be found at: http://www.abrf.org/index.cfm/dm.home
[b]Stability: + labile in tandem mass spectrometry, ++ moderately stable; +++ stable.

Mann and Jensen, Nature Biotech. 21, 255 (2003)