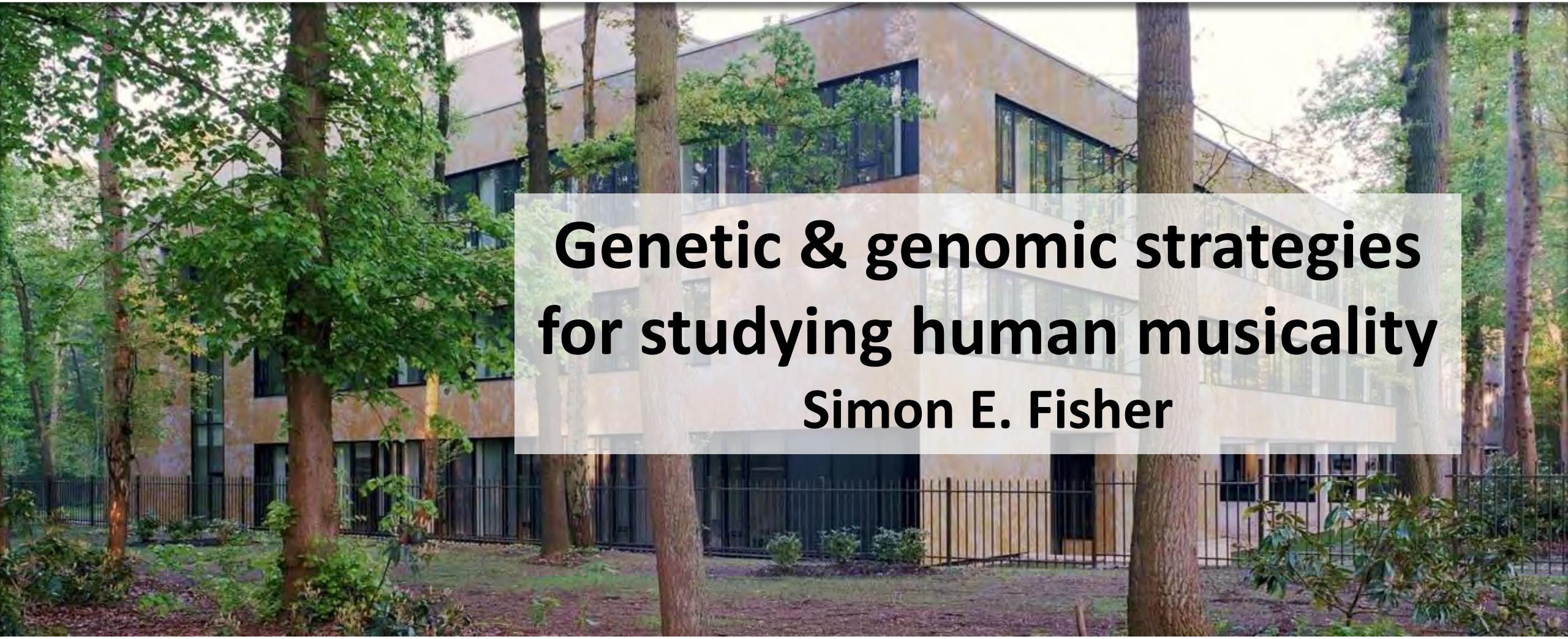
MAX PLANCK INSTITUTE FOR PSYCHOLINGUISTICS

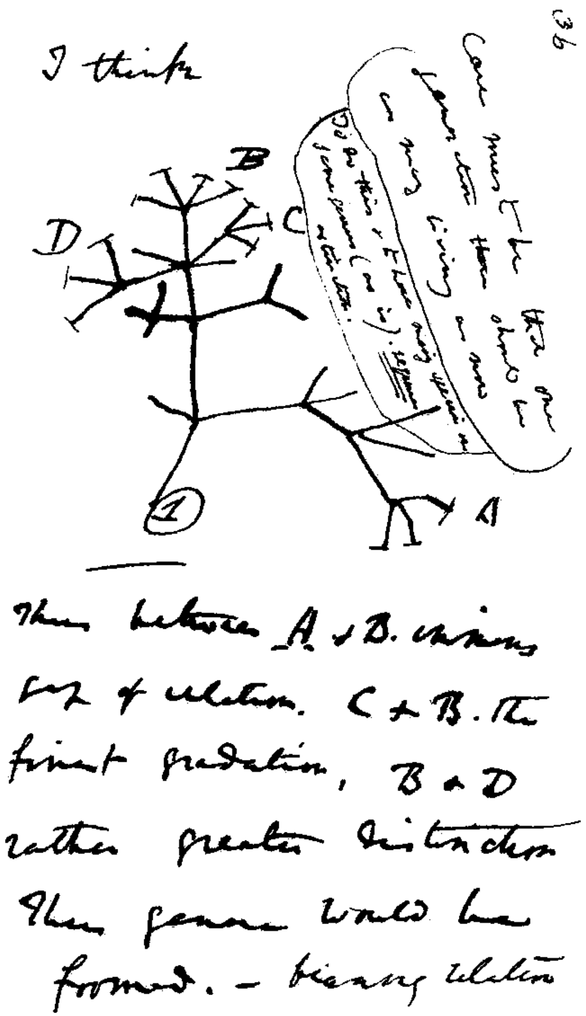
DONDERS INSTITUTE

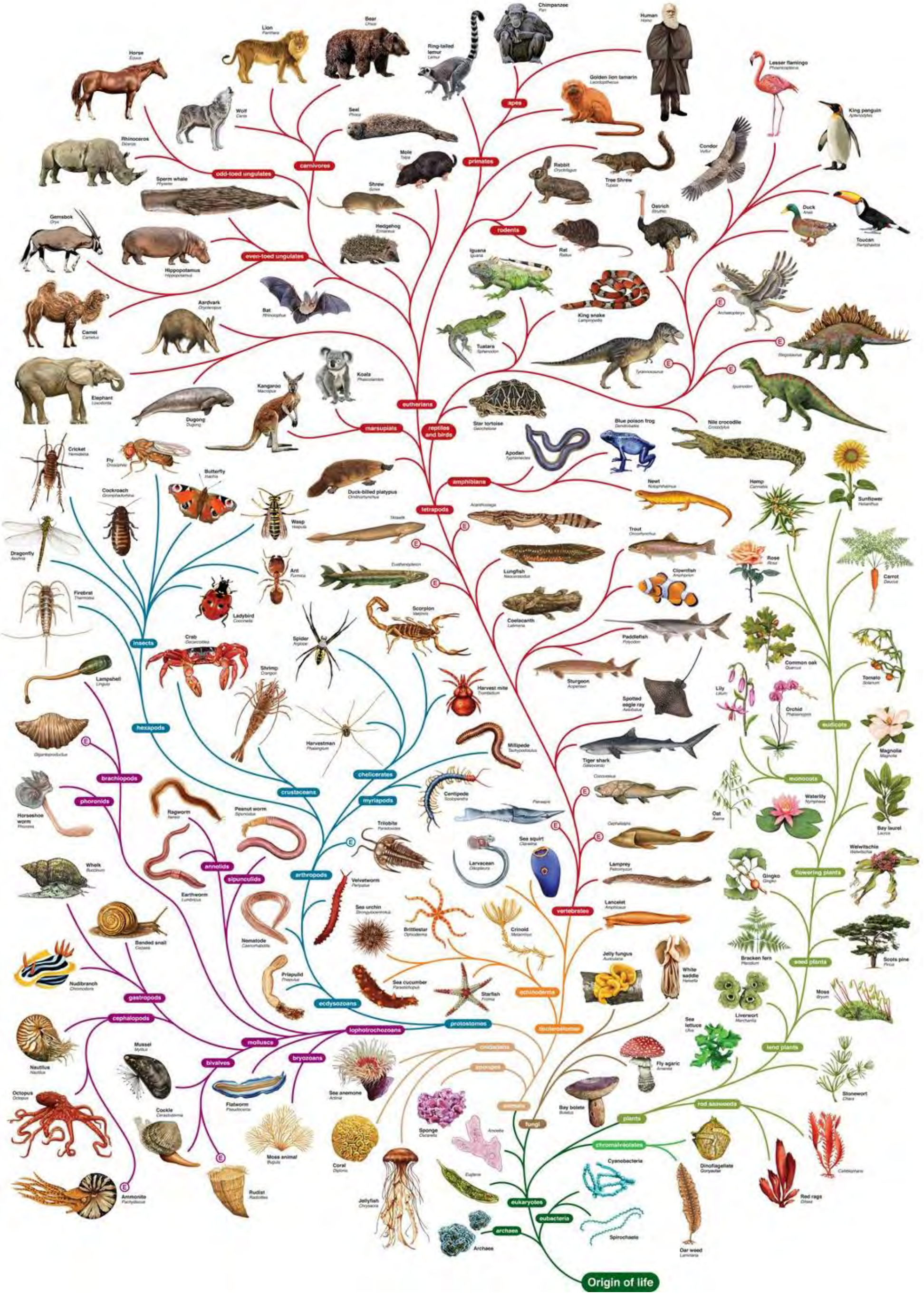


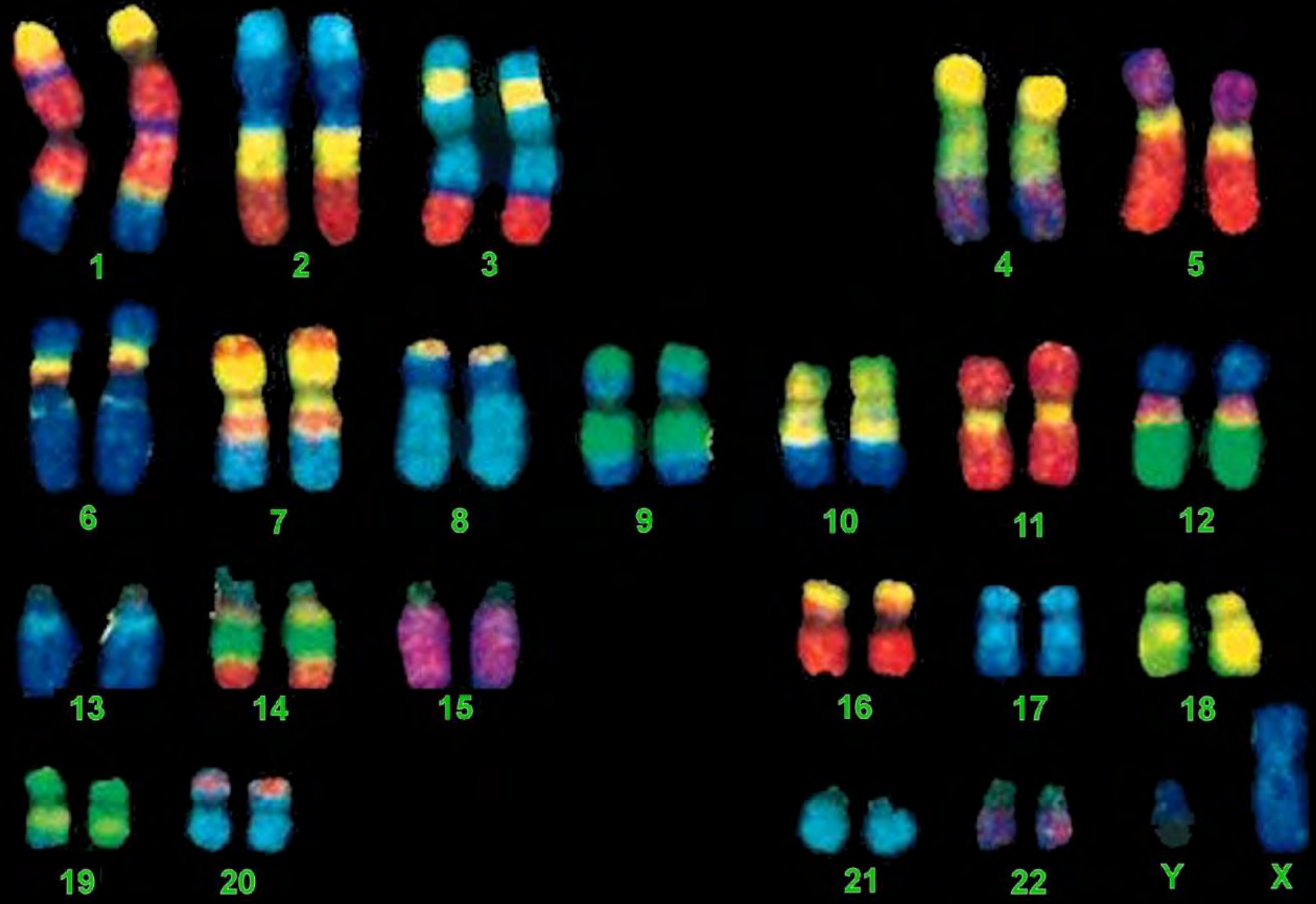
Genetic & genomic strategies for studying human musicality

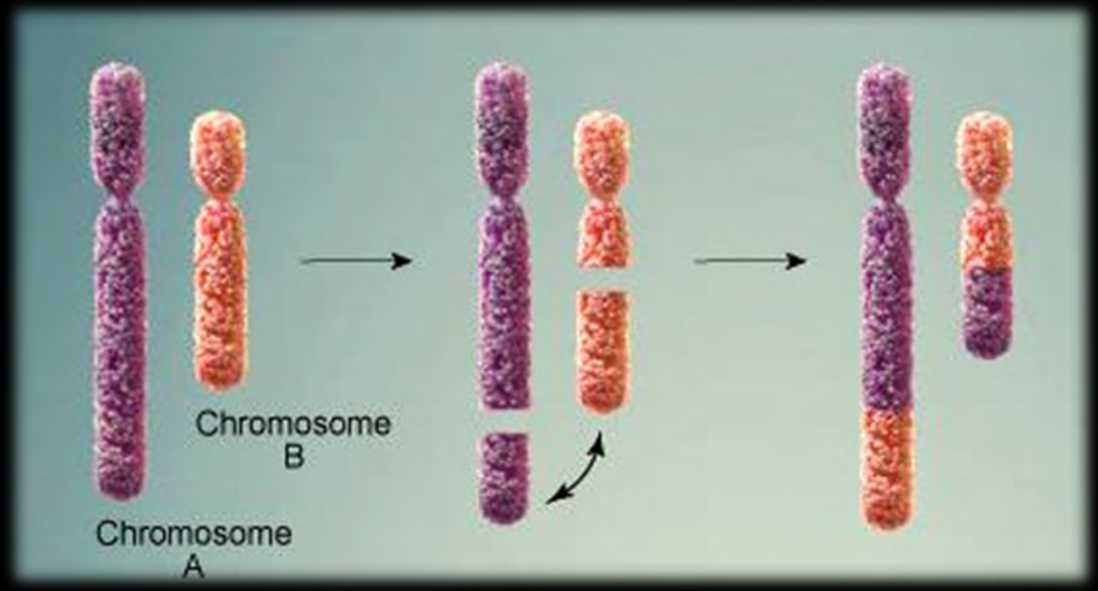
Simon E. Fisher

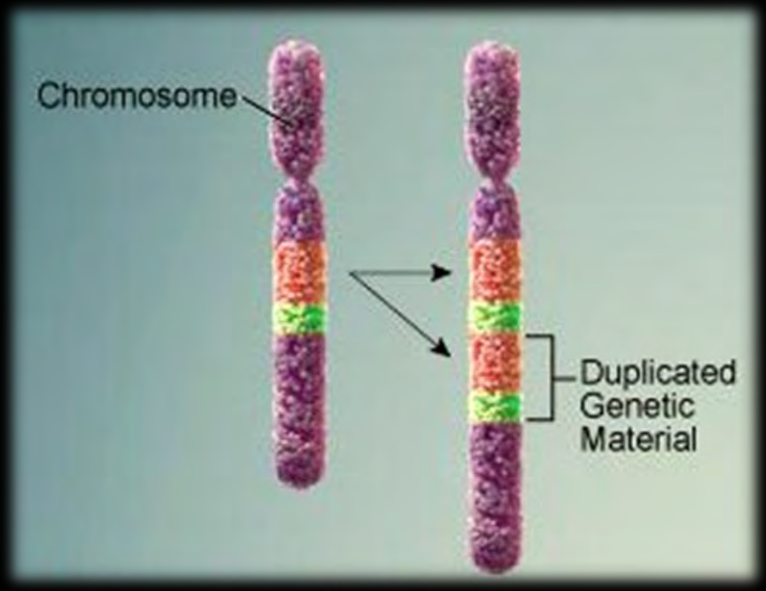
@ProfSimonFisher

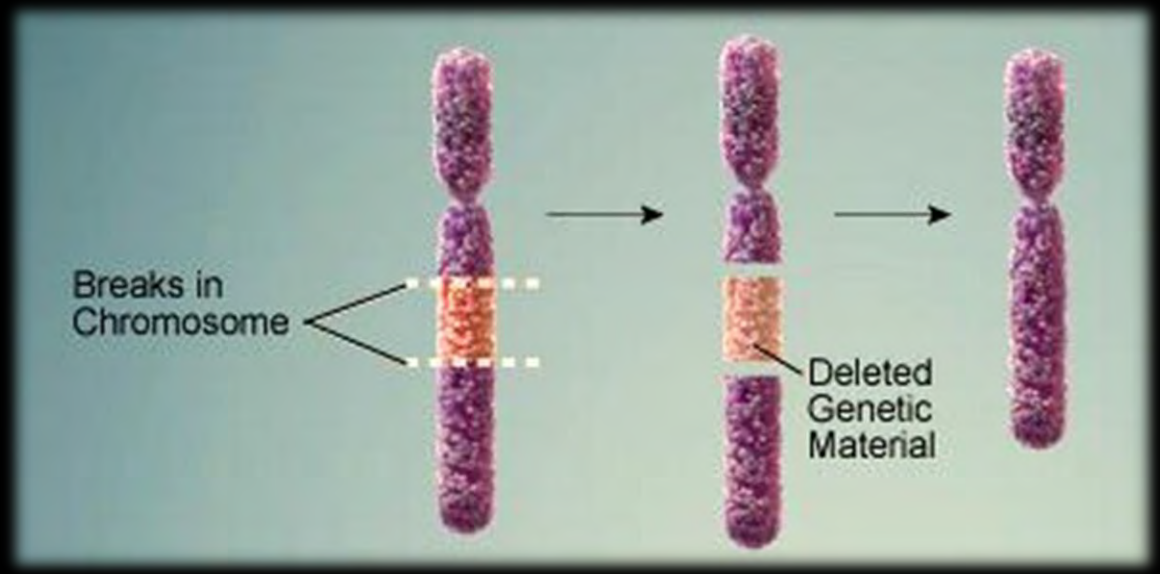

I think
A
B
C
D
1
Thus between A & B. immens gap of relation. C & B. the finest gradation, B & D rather greater distinction Thus genera would be formed. —

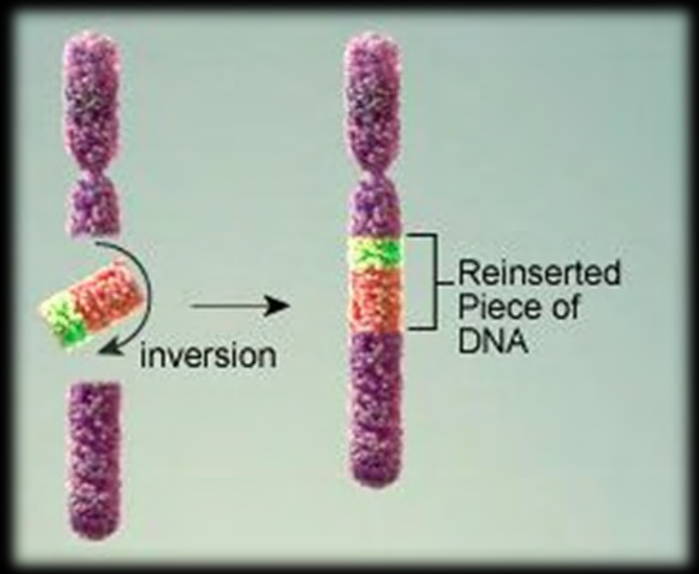

Origin of life

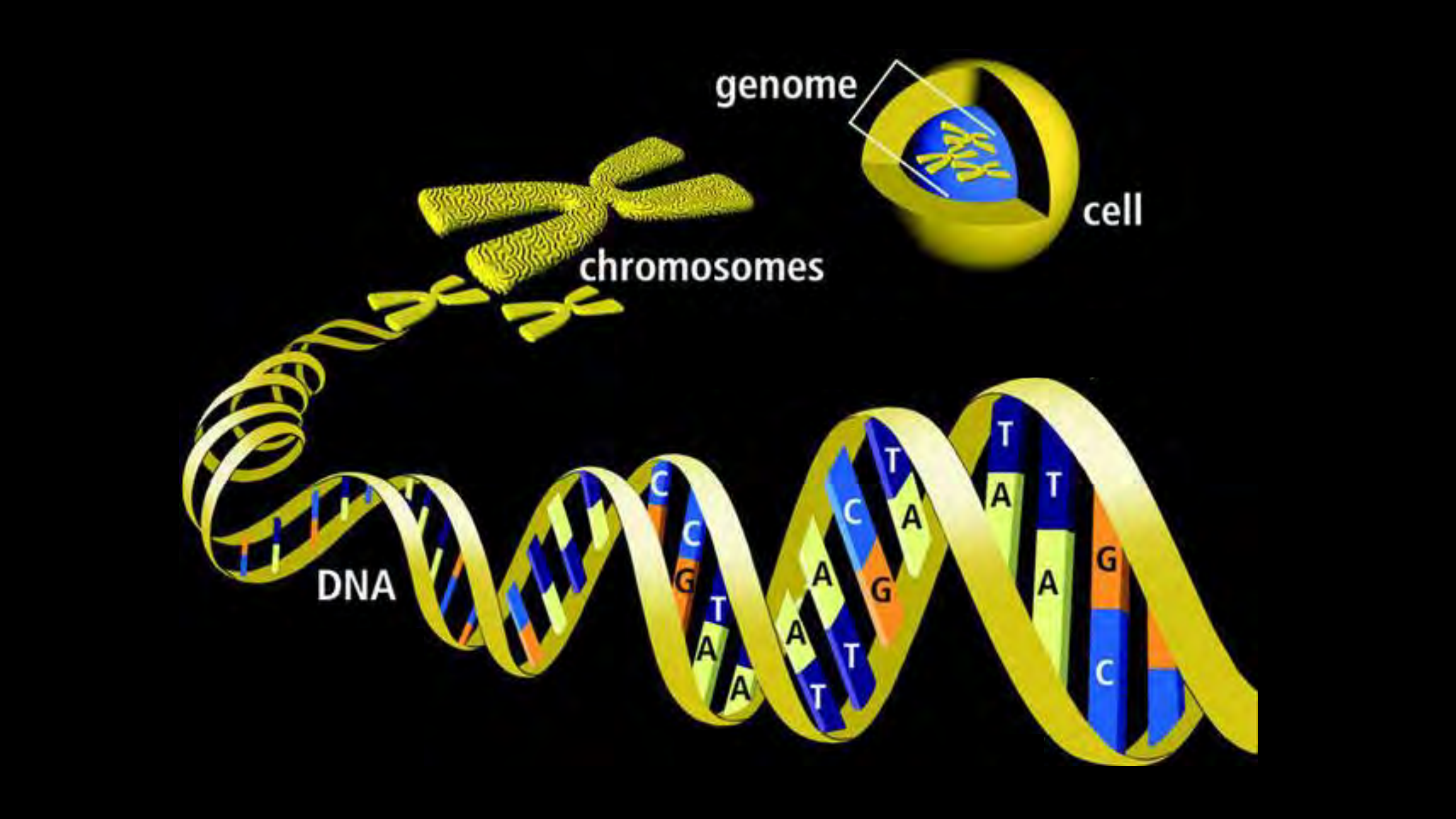

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Y
X


Chromosome
B
Chromosome
A


Chromosome
Duplicated
Genetic
Material

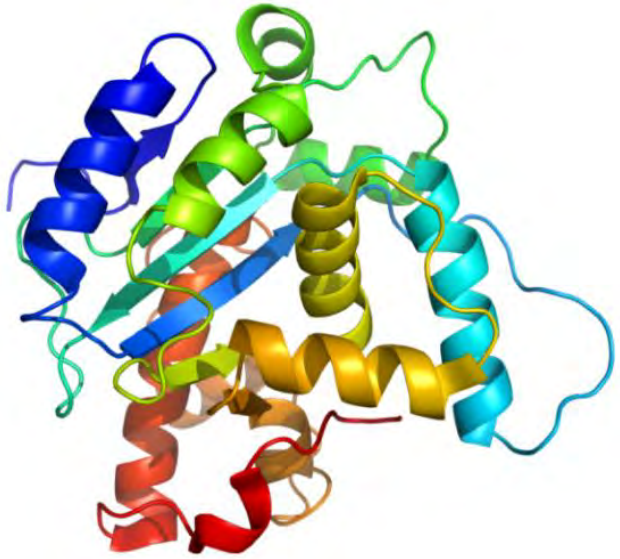

Breaks in
Chromosome
Deleted
Genetic
Material


inversion
Reinserted
Piece of
DNA


genome
cell
chromosomes
DNA
C
C
G
T
A
A
C
T
A
G
A
T
T
T
A
T
A
G
C

AUGAUGCAGGAAUCUGCGACAGAGACAAUAAGCAACAGU

MetMetGlnGluSerAlaThrGluThrIleSerAsnSer



DNA

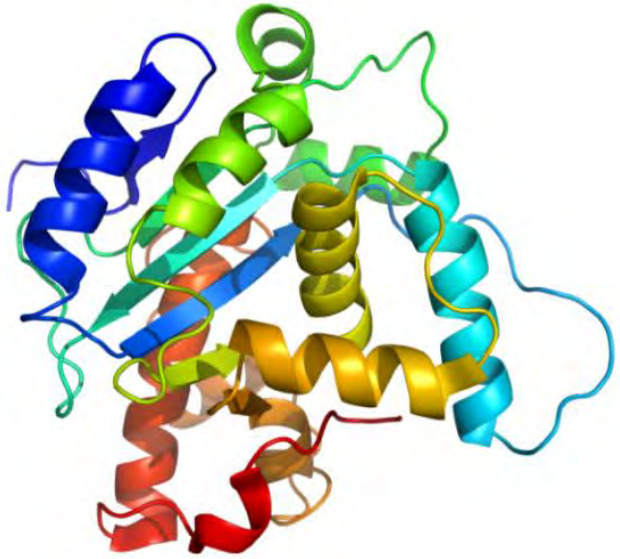
AUGAUGCAGGAAUCUGCGACAGAGACAAUAAGCAACAGU

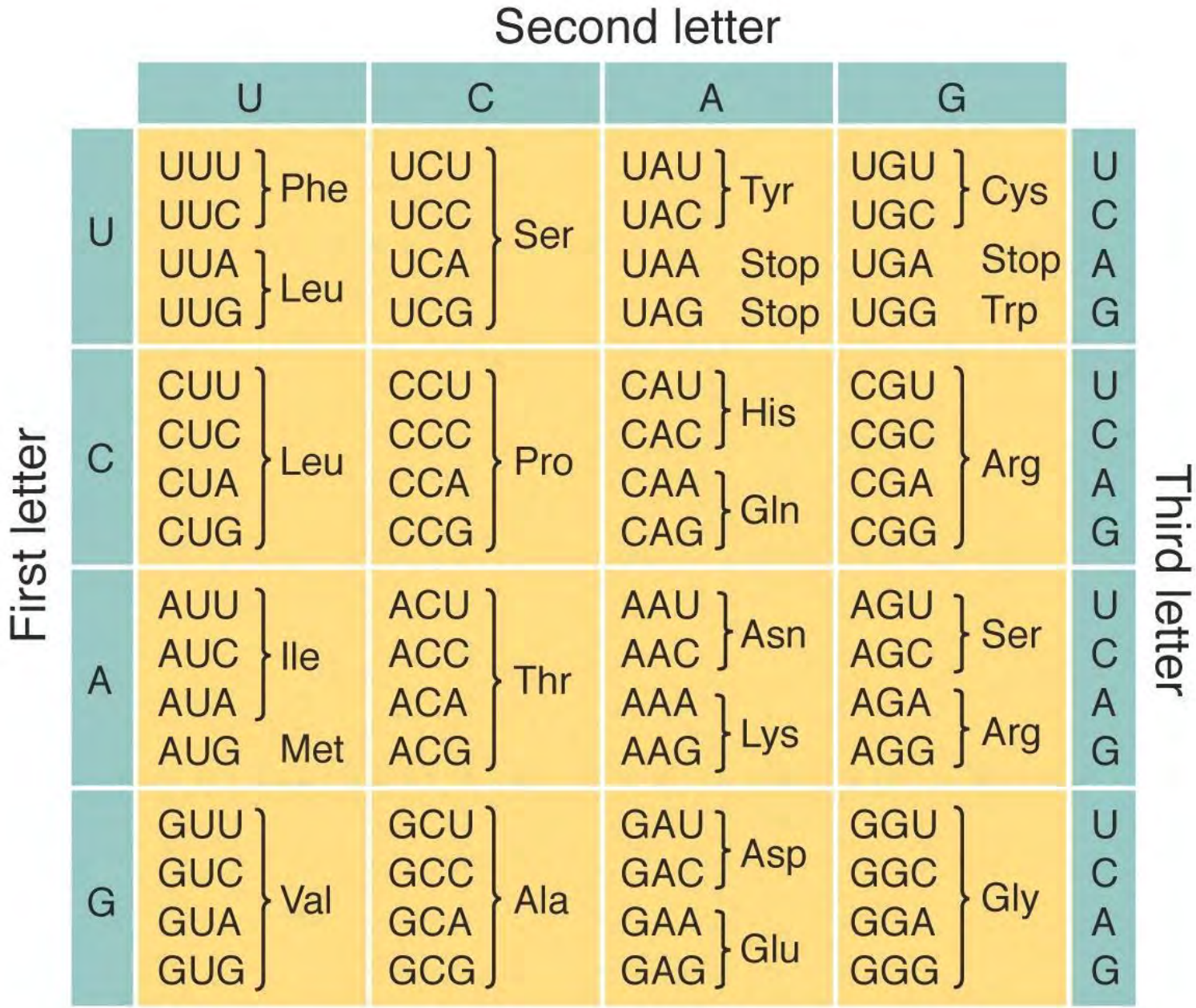
messenger RNA

...MetMetGlnGluSerAlaThrGluThrIleSerAsnSer...

polypeptide (string of amino acids)

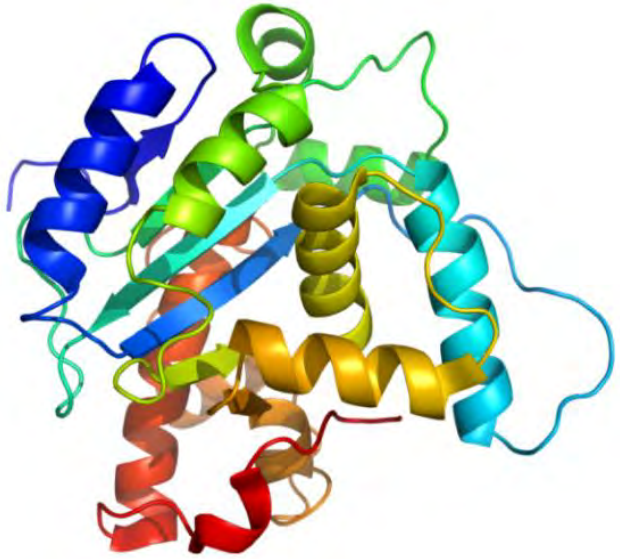
protein



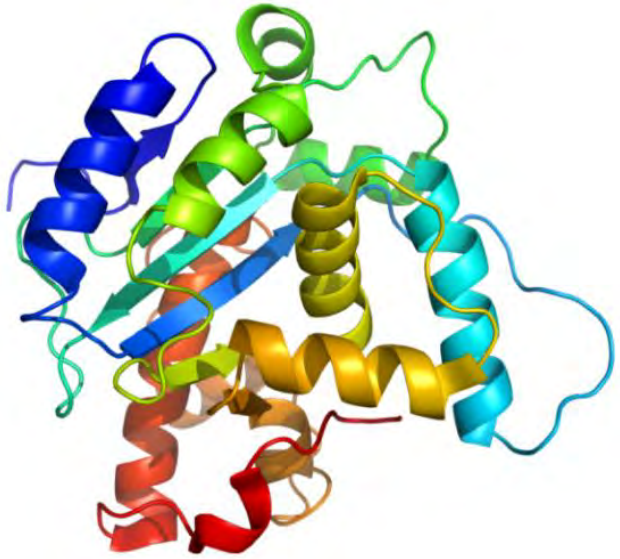

Second letter
U
C
A
G
First letter
Third letter
U
UUU Phe
UUC
UUA Leu
UUG
UCU Ser
UCC
UCA
UCG
UAU Tyr
UAC
UAA Stop
UAG Stop
UGU Cys
UGC
UGA Stop
UGG Trp
C
CUU Leu
CUC
CUA
CUG
CCU Pro
CCC
CCA
CCG
CAU His
CAC
CAA Gln
CAG
CGU Arg
CGC
CGA
CGG
A
AUU Ile
AUC
AUA
AUG Met
ACU Thr
ACC
ACA
ACG
AAU Asn
AAC
AAA Lys
AAG
AGU Ser
AGC
AGA Arg
AGG
G
GUU Val
GUC
GUA
GUG
GCU Ala
GCC
GCA
GCG
GAU Asp
GAC
GAA Glu
GAG
GGU Gly
GGC
GGA
GGG

AUGAUGCAGGAAUCUGCGACAGAGACAAUAAGCAACAGU

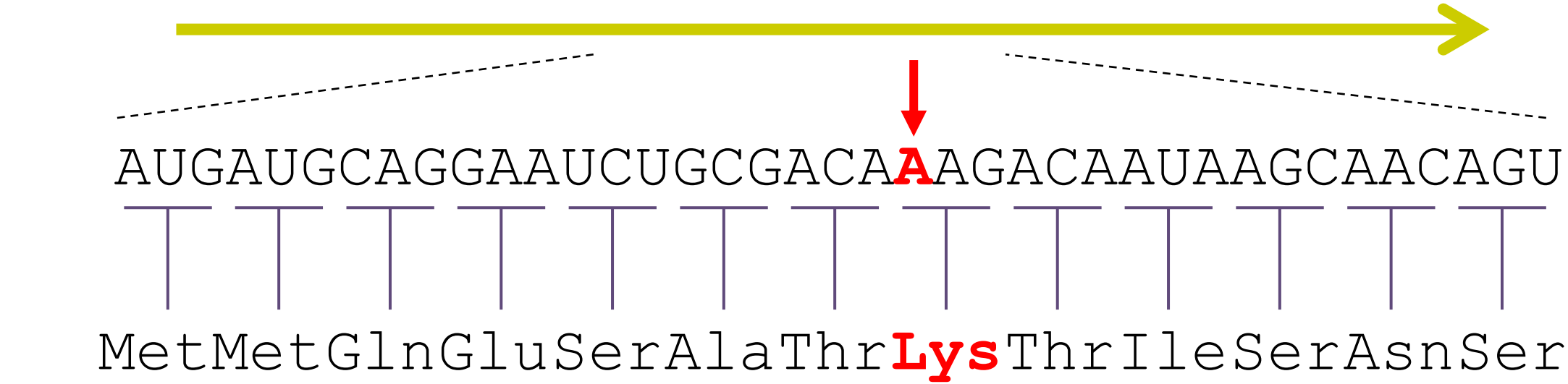
MetMetGlnGluSerAlaThrGluThrIleSerAsnSer

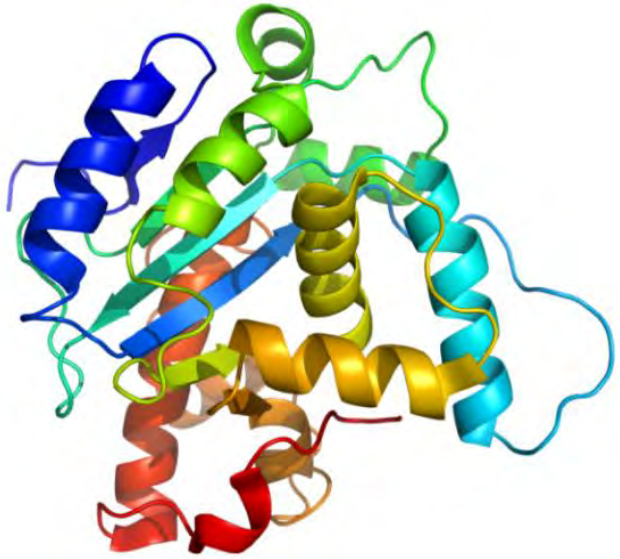



AUGAUGCAGGAAUCUGCGACAGAAACAAUAAGCAACAGU
MetMetGlnGluSerAlaThrGluThrIleSerAsnSer

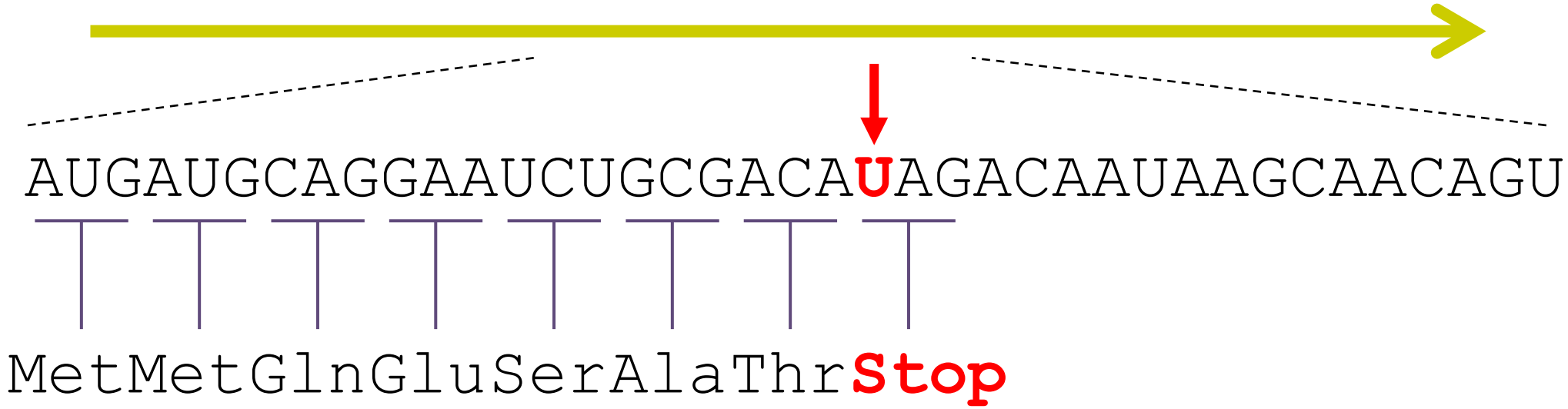


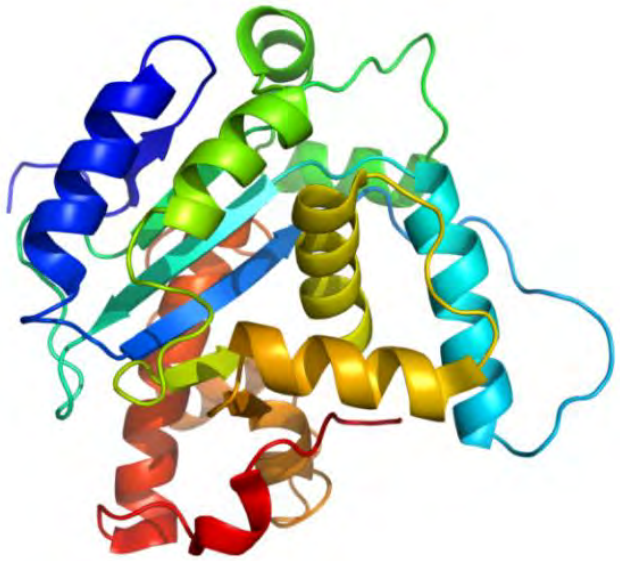
synonymous



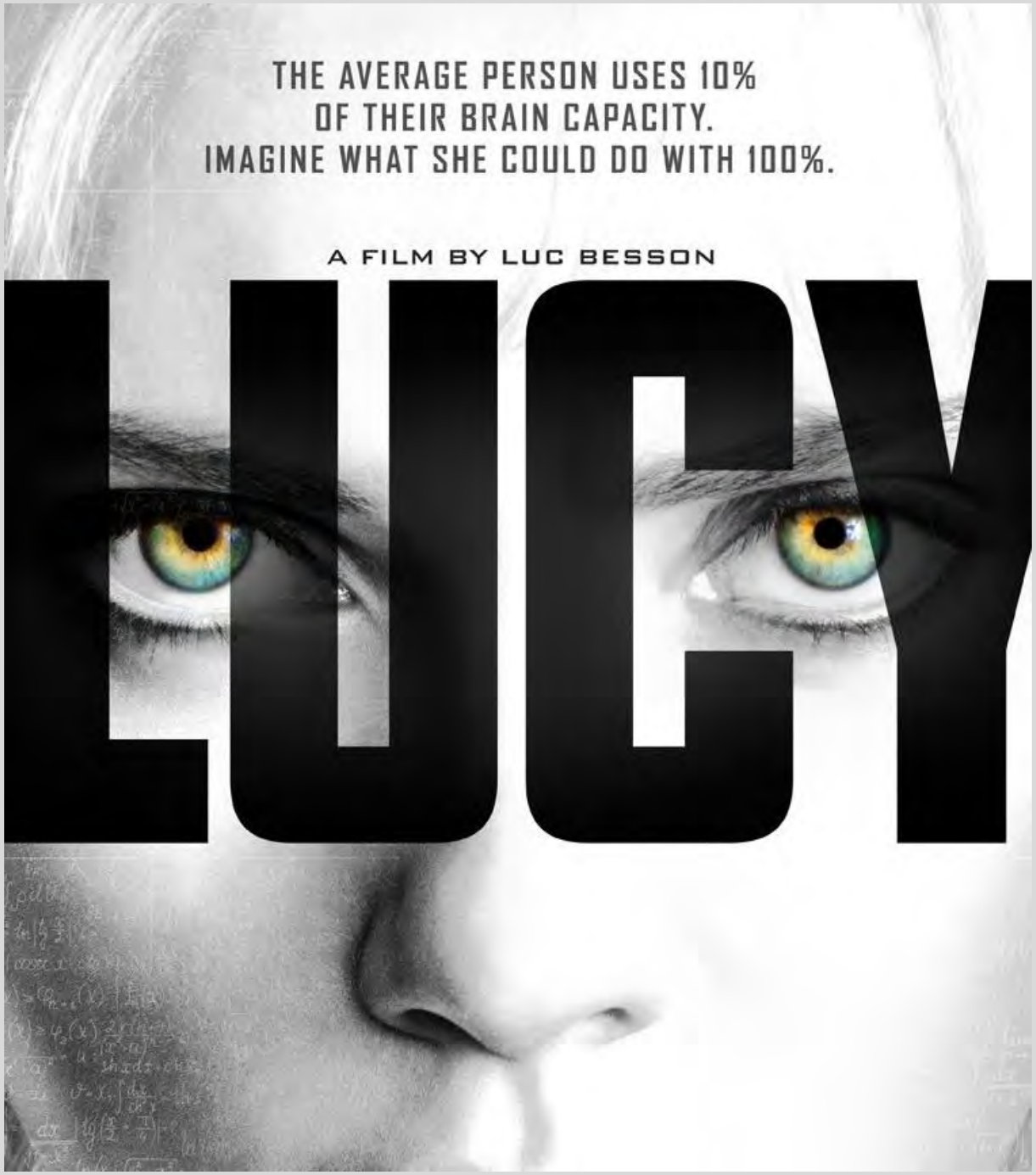


non-synonymous (missense)



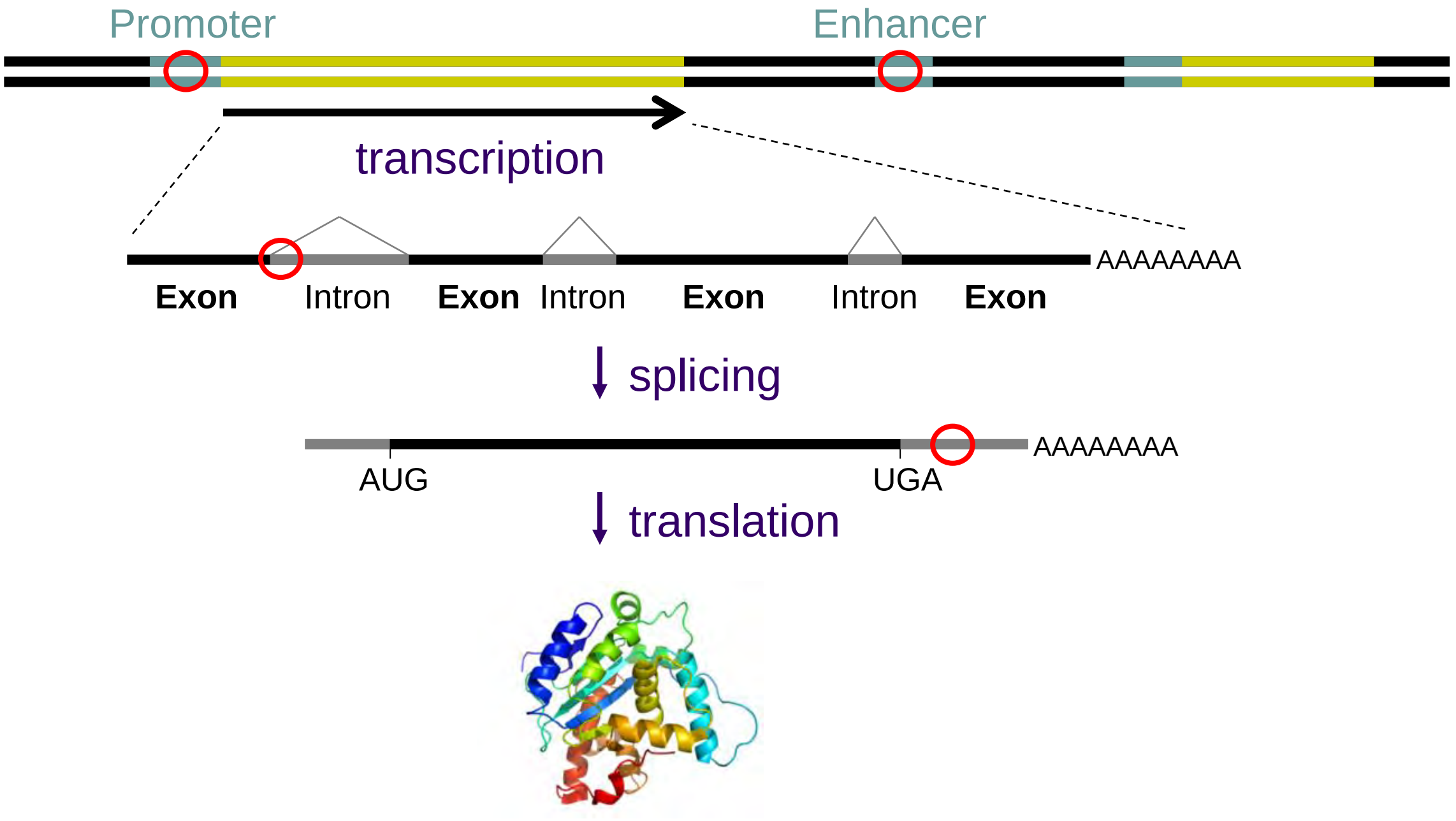


stop-gain (nonsense)



THE AVERAGE PERSON USES <1.5% OF
THEIR GENOME TO ENCODE PROTEINS.
IMAGINE WHAT SHE CAN DO WITH 100%.

LUCY 2: EXOME UNLEASHED


Promoter
Enhancer
transcription
AAAAAAAA
Exon
Intron
Exon
Intron
Exon
Intron
Exon
splicing
AAAAAAAA
AUG
UGA
translation

- Chromosomal rearrangements:
  - Translocations, deletions, duplications, inversions
  - Submicroscopic “copy number variants” (CNVs)
- Single nucleotide variants:
  - Variants changing sequences of encoded proteins
  - Regulatory variations affecting transcription, splicing, translation, stability/breakdown of transcripts
- Range of frequencies: highly rare to very common
- Range of effects: severe to completely benign

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  - Translocations, deletions, duplications, inversions
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- Range of frequencies: highly rare to very common
- Range of effects: severe to completely benign

Is the trait influenced by genetic variation?


15 February 2001
nature
www.nature.com
the human genome
Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic ice
Career prospects
Sequence creates new opportunities


SPRING/SUMMER 2014
The Portland Hospital Parenting Magazine
nurture
EXERCISING DURING PREGNANCY
JOOLS OLIVER'S Favourite Baby Items
AVA'S REAL LIFE STORY
COCHLEAR IMPLANT SURGERY
Practical Parenting with MARINA FOGLE
SMALL TALK
HOW TO HELP YOUR CHILD GET CHATTING
Mealtime Meltdowns

Genetics

Are we products of nature or nurture? Science answers age-old question

Twin studies collated over the past 50 years reveal human traits and disease are almost equally determined by genetic and environmental factors

▲ Researchers collated 2,748 studies involving more than 14.5 million pairs of twins and found the average variation for human traits and disease is 49% due to genetic factors and 51% due to environmental factors. Photograph: Alamy

Monica Tan

@m_onicatan

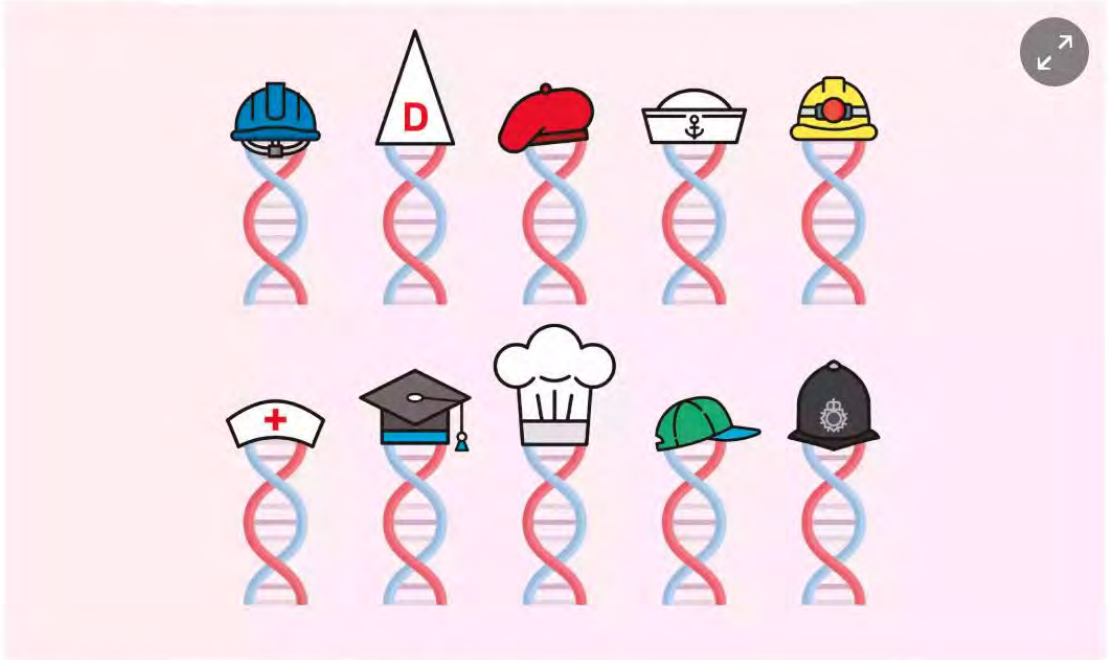
Tue 19 May 2015 08.38 BST

19 May 2015

The Observer Science

So is it nature not nurture after all?

In a new book likely to rekindle fierce controversy, psychologist Robert Plomin argues that genes largely shape our personalities and that the latest science is too compelling to ignore



▲ What really makes us who we are? Illustration: Bryan Mayes

Andrew Anthony

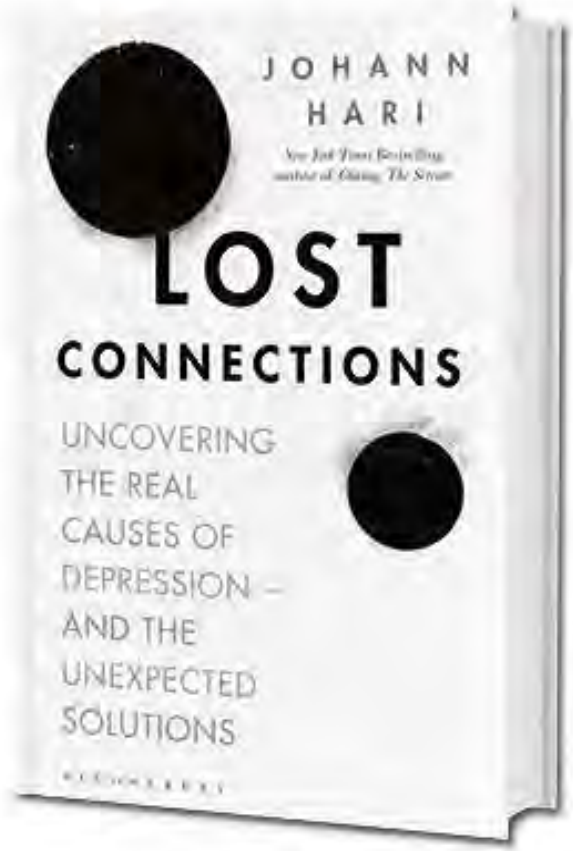
Sat 29 Sep 2018 15.00 BST

29 September 2018

Heritability

Your genes explain 35% of your depression. They are a real part of the story – but they're not most of it.

#DepressionIsNotWhatYouThinkItIs



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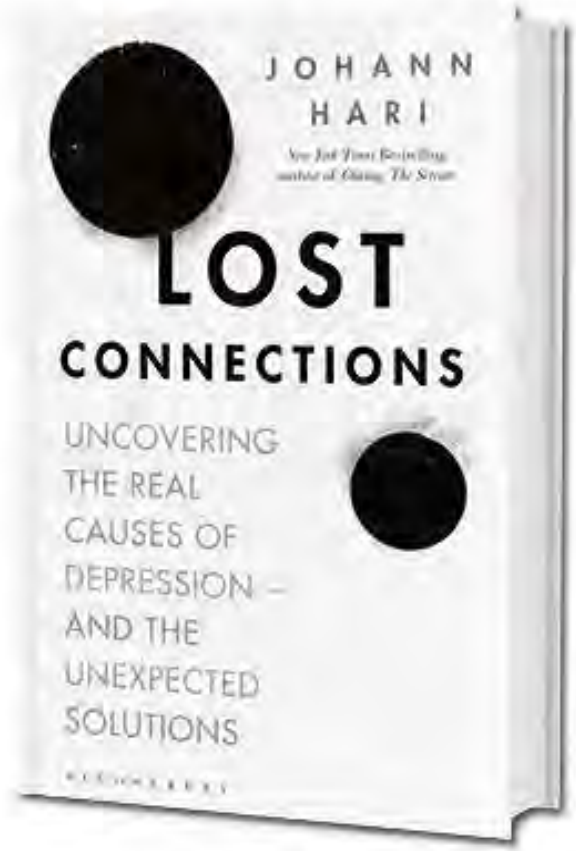
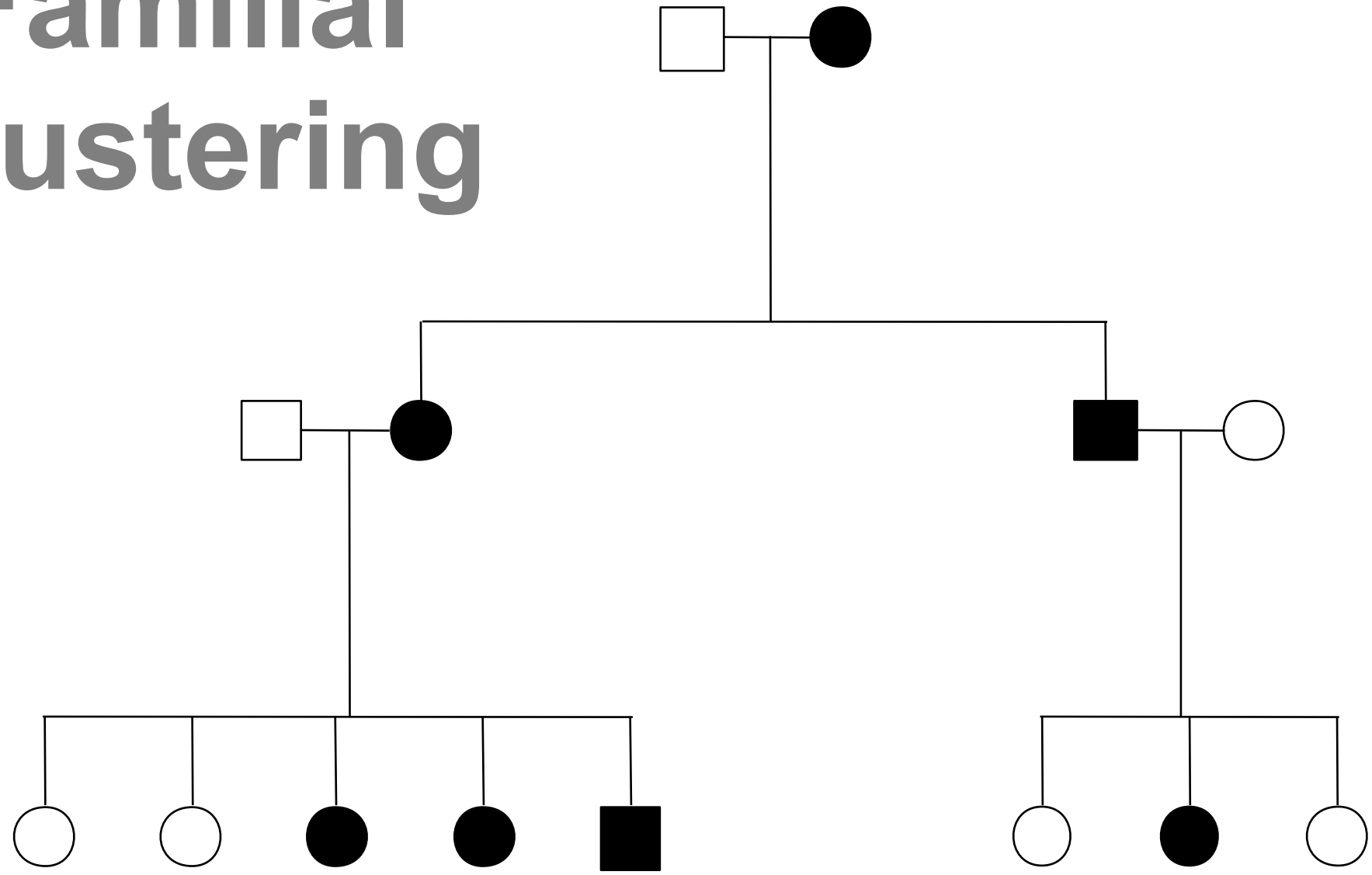


#HeritabilityIsNotWhatYouThinkItIs

- It is a statistical description of a particular group of individuals; proportion of phenotypic variability accounted for by genetic variations
- It is not a property of a single person
- It does not map directly to biology
- Heritability of the same measured trait can vary in different (sets of) environments & depending on developmental timepoint of group


NATIONAL

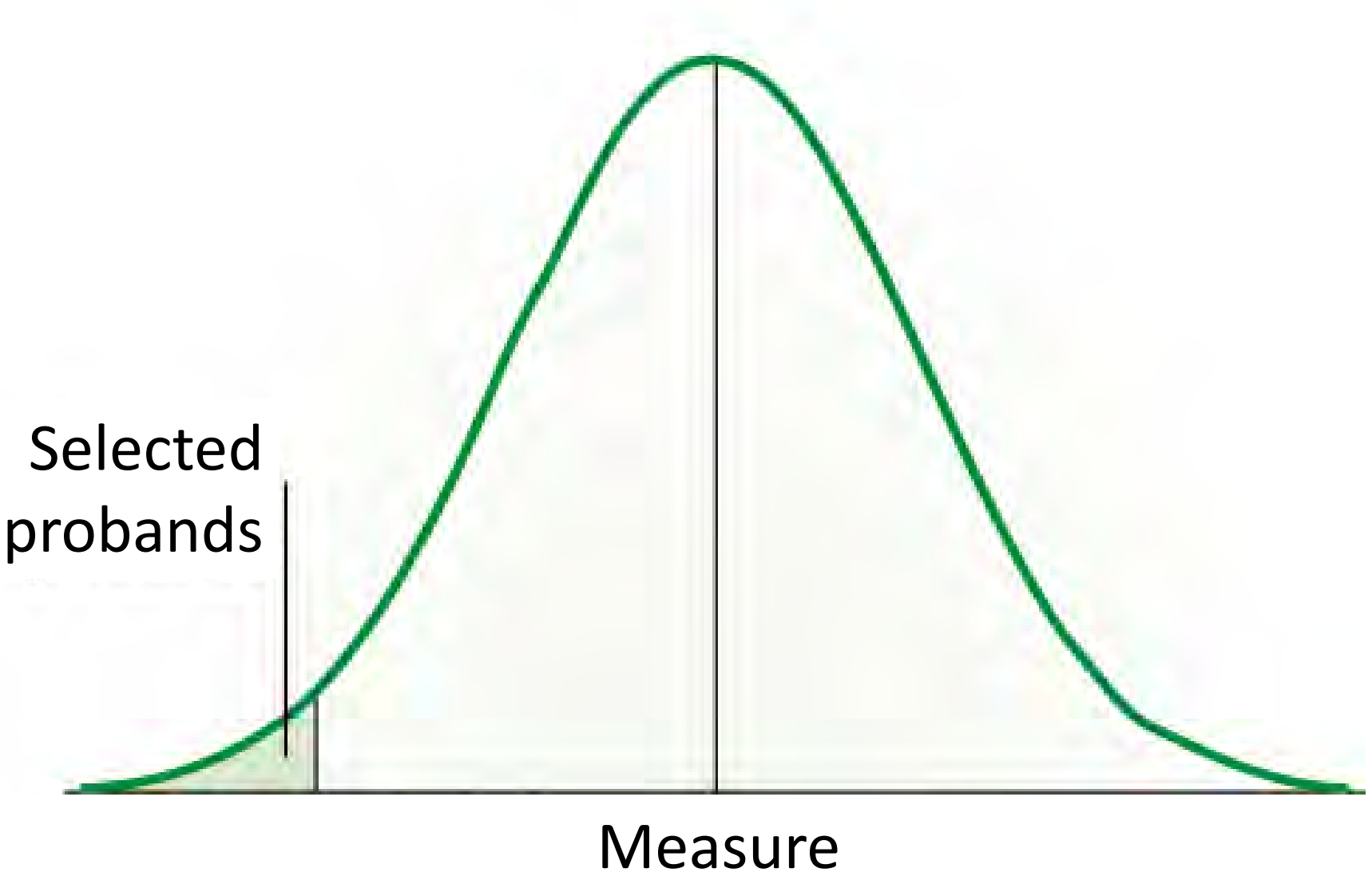
Familial Clustering



Molecular windows

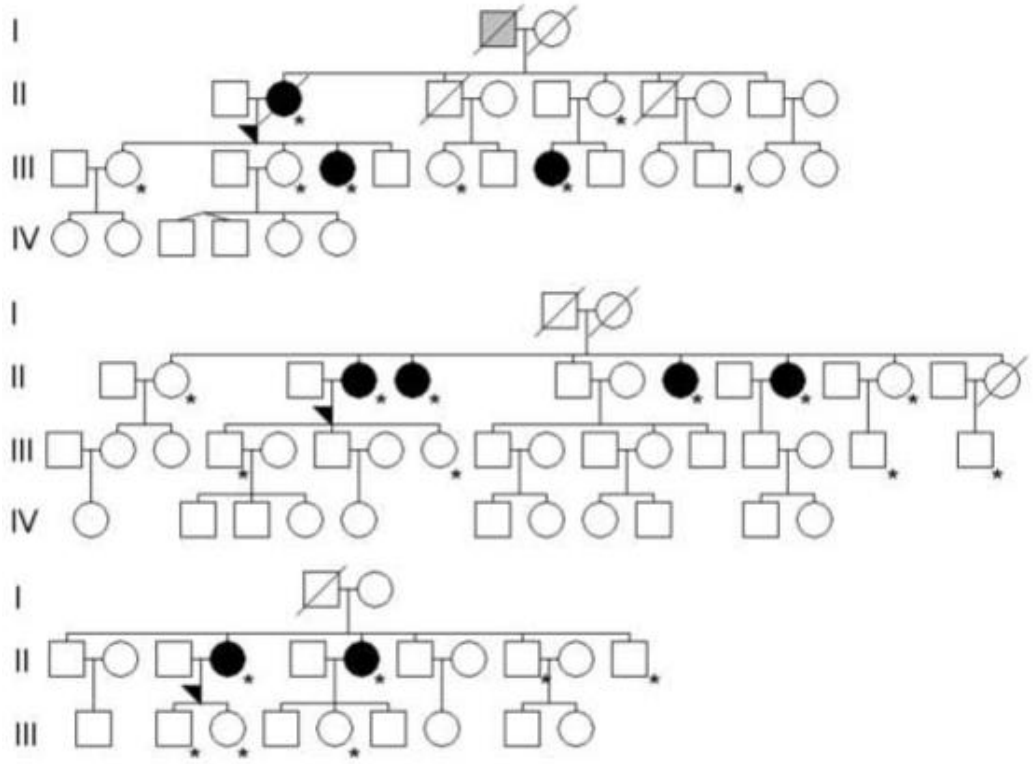
Musicality

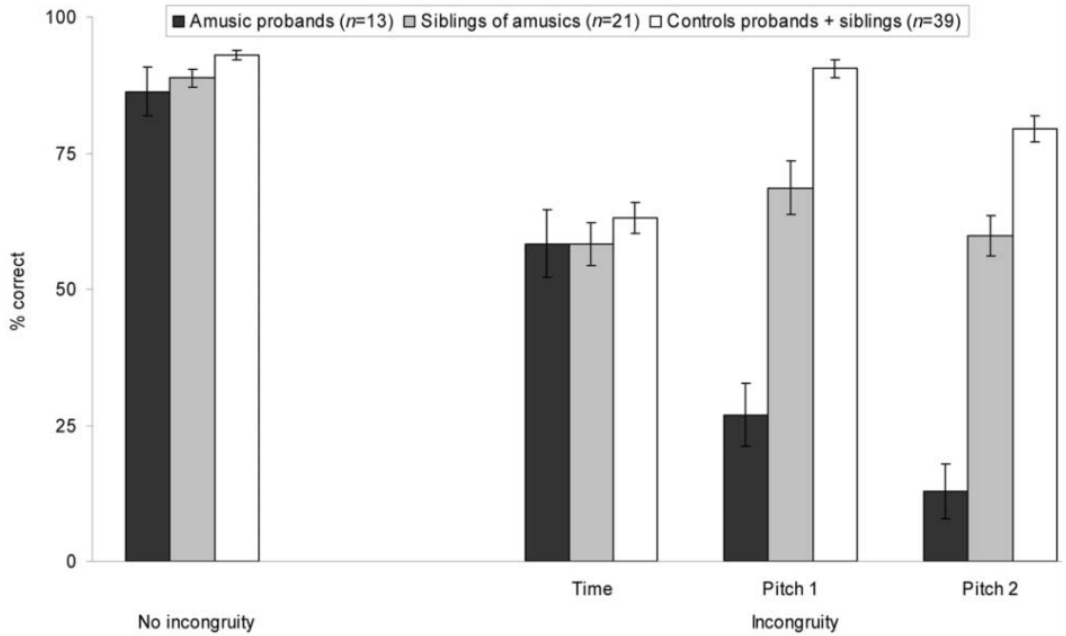
Musicality at the extremes

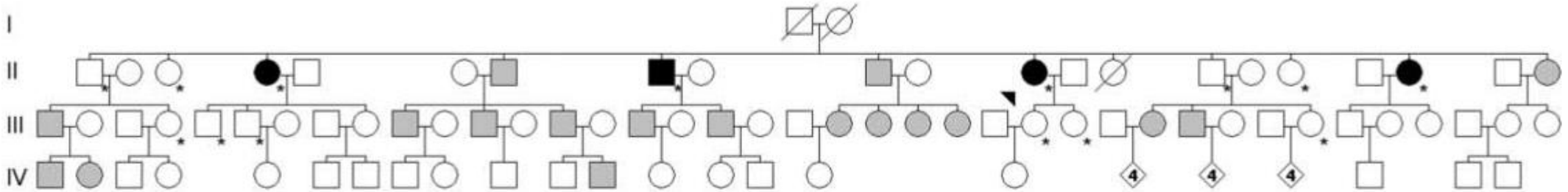


The Genetics of Congenital Amusia (Tone Deafness): A Family-Aggregation Study

Isabelle Peretz, Stéphanie Cummings, and Marie-Pierre Dubé







Am. J. Hum. Genet. 2007;81:582–588.

The Genetics of Congenital Amusia (Tone Deafness): A Family-Aggregation Study

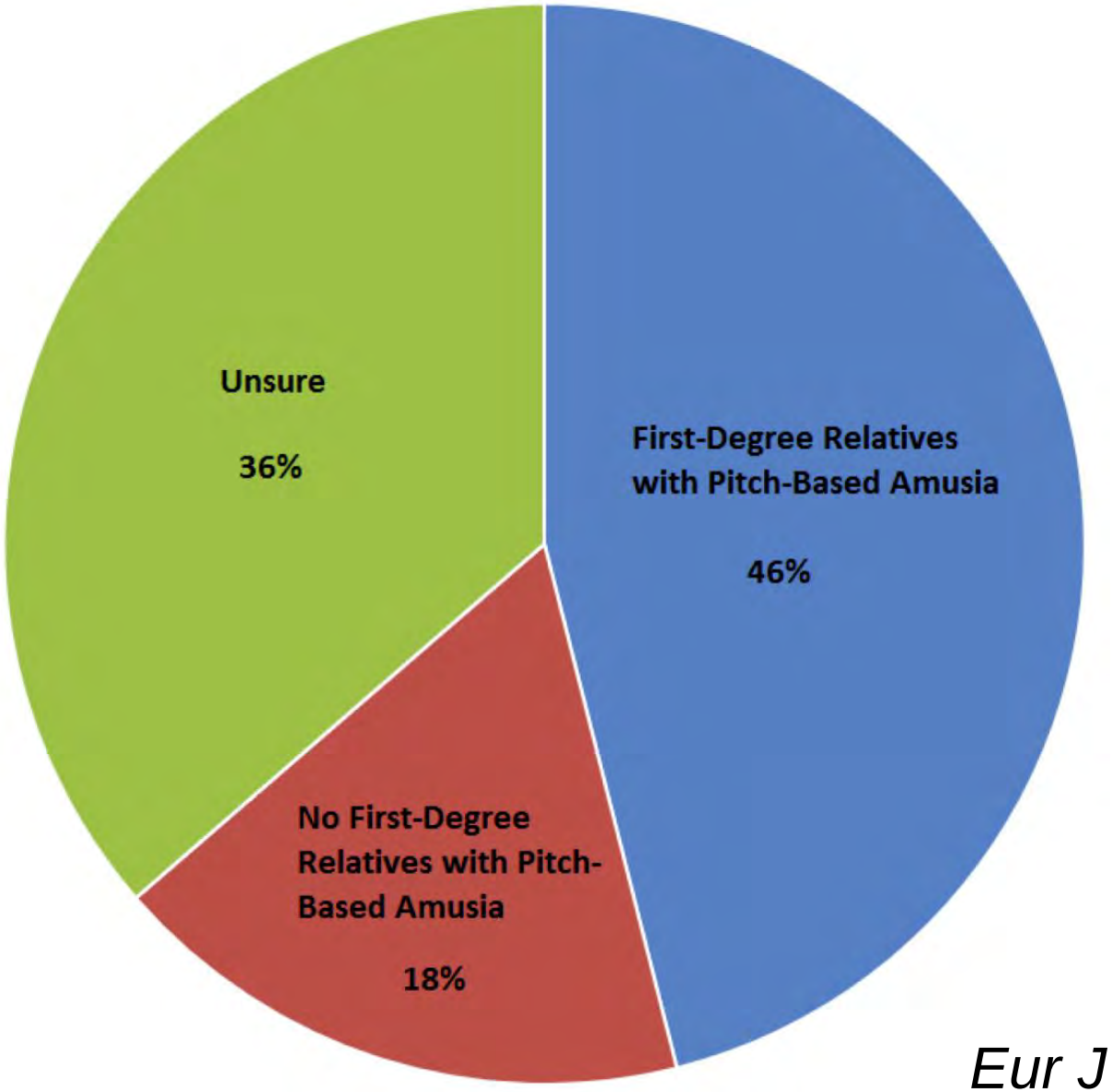
Isabelle Peretz, Stéphanie Cummings, and Marie-Pierre Dubé

- 9 families (n = 71) with an amusic proband, 39% of first-degree relatives were also affected
- In 10 control families (n = 75), the prevalence was only 3%

=> Sibling recurrence risk of ~10.8

Am. J. Hum. Genet. 2007;81:582–588.

214 pitch-based amusia cases from 16,625 adults screened online



Peretz & Vuvan (2017)
Eur J Hum Genet 25: 625-30

214 pitch-based amusia cases from 16,625 adults screened online

457 cases of "time-based" amusia

Disorder	*Controls*	*Pitch-based amusics*	*Time-based amusics*
Dyslexia	6.9%	7.7% ($P=0.70$)	12.5%[a] ($P<0.001$)
Speech disorder	8.4%	12.0% ($P=0.10$)	13.4%[a] ($P=0.001$)
Dyscalculia	15.0%	10.2% ($P=0.09$)	22.9%[a] ($P<0.001$)
Attentional disorder	19.2%	16.7% ($P=0.43$)	24.0%[a] ($P=0.02$)
Memory problem	15.2%	12.9% ($P=0.43$)	19.1%[a] ($P=0.04$)
Spatial orientation difficulty	9.1%	15.0%[a] ($P=0.01$)	16.2%[a] ($P<0.001$)

Peretz & Vuvan (2017)
Eur J Hum Genet 25: 625-30

frontiers in PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 05 February 2014
doi: 10.3389/fpsyg.2014.00018

Dysrhythmia: a specific congenital rhythm perception deficit

Jacques Launay*[1], *Manon Grube*[2] *and Lauren Stewart*[3]

[1] *Department of Experimental Psychology, University of Oxford, Oxford, UK*
[2] *Auditory Group, Institute of Neuroscience, The Medical School, Newcastle University, Newcastle-upon-Tyne, UK*
[3] *Goldsmiths College, University of London, London, UK*

Edited by:
Chris Muller, Ghent University, Belgium

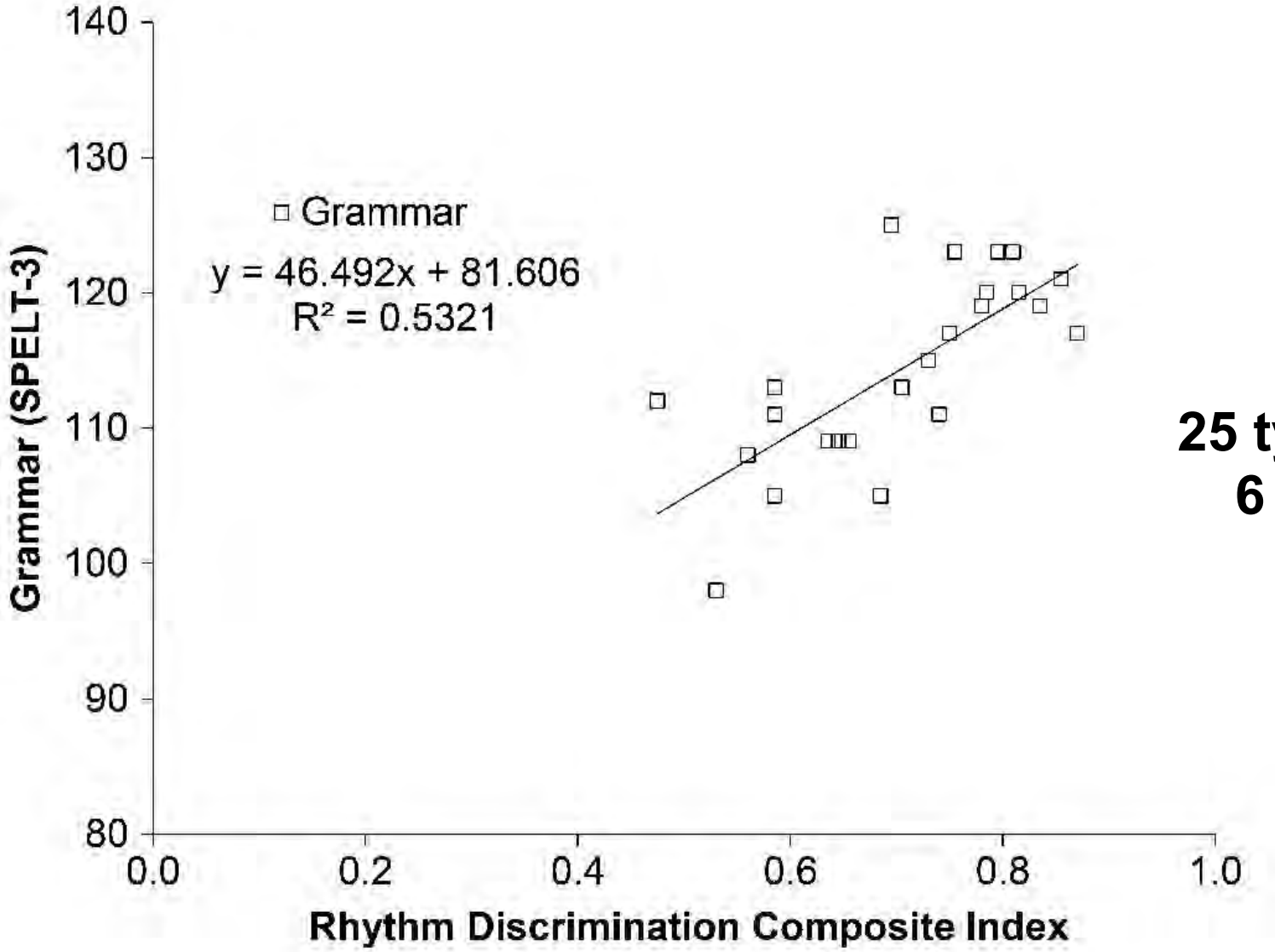
Reviewed by:
Patricia E. G. Bestelmeyer, Bangor University, UK
Robert J. Ellis, Beth Israel Deaconess Medical Center, USA

***Correspondence:**
Lauren Stewart, Goldsmiths College, University of London, New Cross, London SE14 6NW, UK
e-mail: l.stewart@gold.ac.uk

N = 89,000

Why do some people have problems "feeling the beat"? Here we investigate participants with congenital impairments in musical rhythm perception and production. A web-based version of the Montreal Battery of Evaluation of Amusia was used to screen for difficulties with rhythmic processing in a large sample and we identified three "dysrhythmic" individuals who scored below cut-off for the rhythm subtest, but not the pitch-based subtests. Follow-up testing in the laboratory was conducted to characterize the nature of both rhythm perception and production deficits in these dysrhythmic individuals. We found that they differed from control participants when required to synchronize their tapping to an external stimulus with a metrical pulse, but not when required to tap spontaneously (with no external stimulus) or to tap in time to an isochronous stimulus. Dysrhythmics exhibited a general tendency to tap at half the expected tempo when asked to synchronize to the beat of strongly metrical rhythms. These results suggest that the individuals studied here did not have motor production problems, but suffer from a selective rhythm perception deficit that influences the ability to entrain to metrical rhythms.

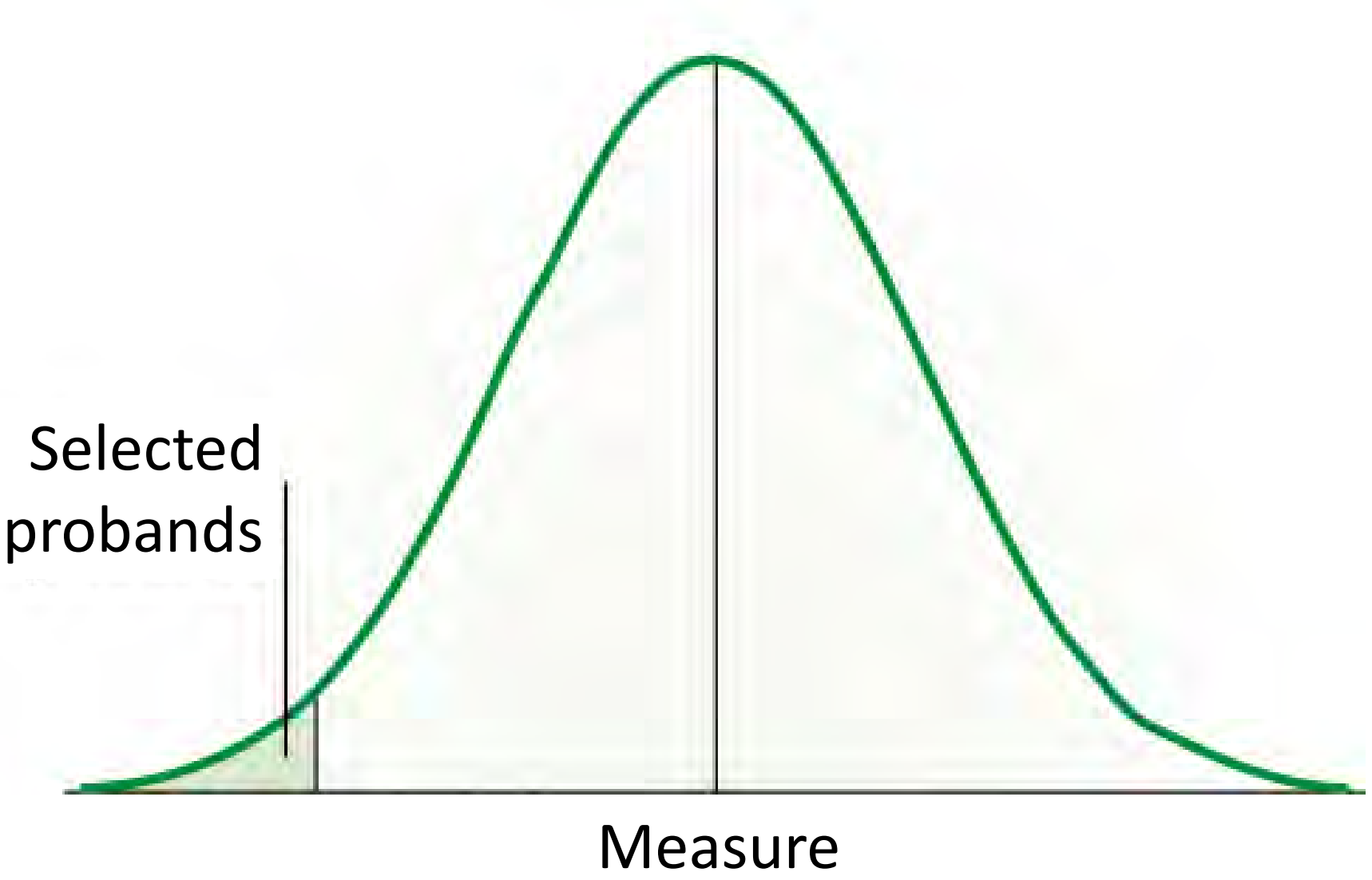
Musical rhythm discrimination explains individual differences in grammar skills in children



25 typically developing 6 year old children

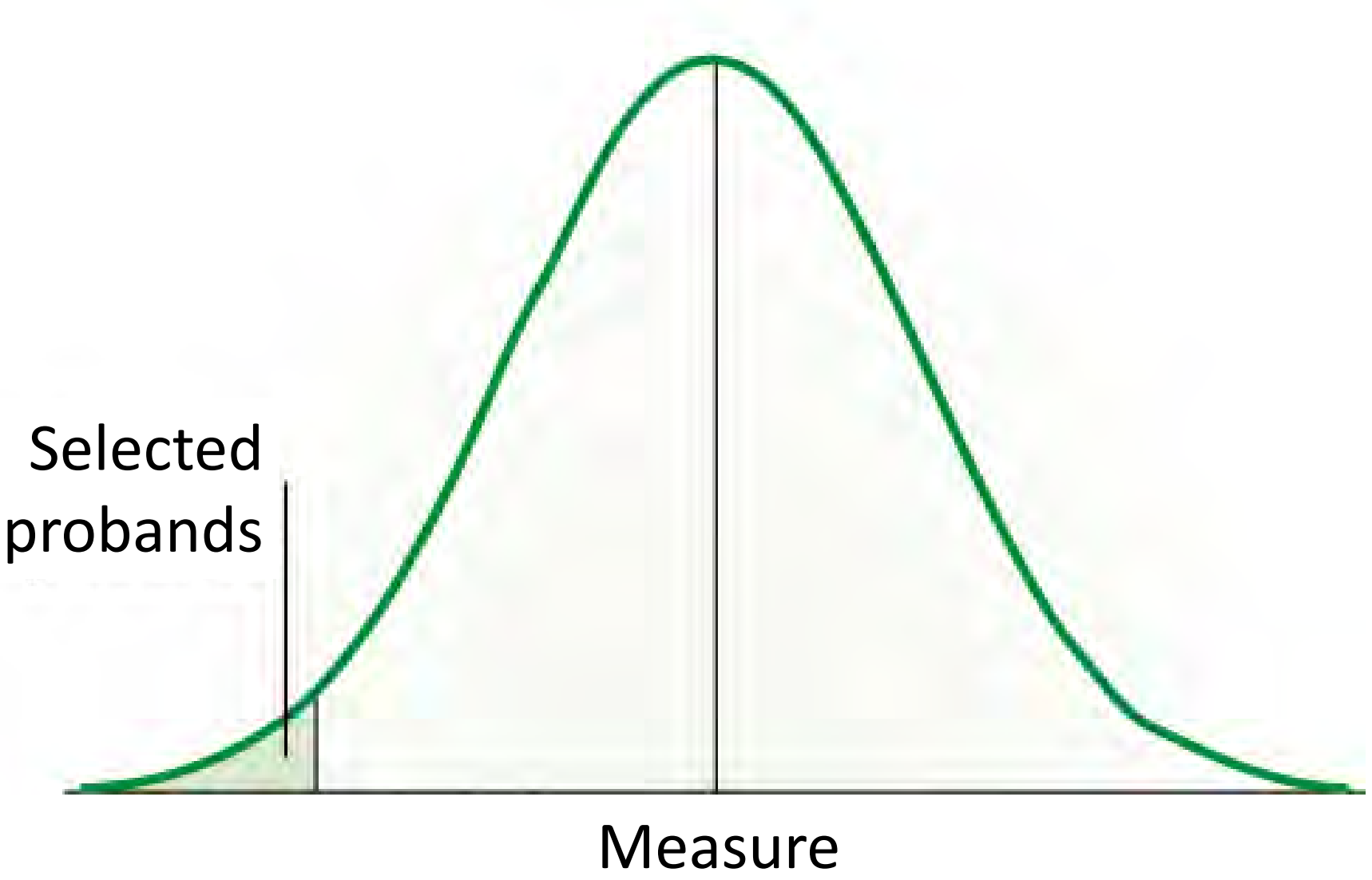
Gordon et al. (2015)
Dev Sci 18: 635-44

Musicality at the extremes

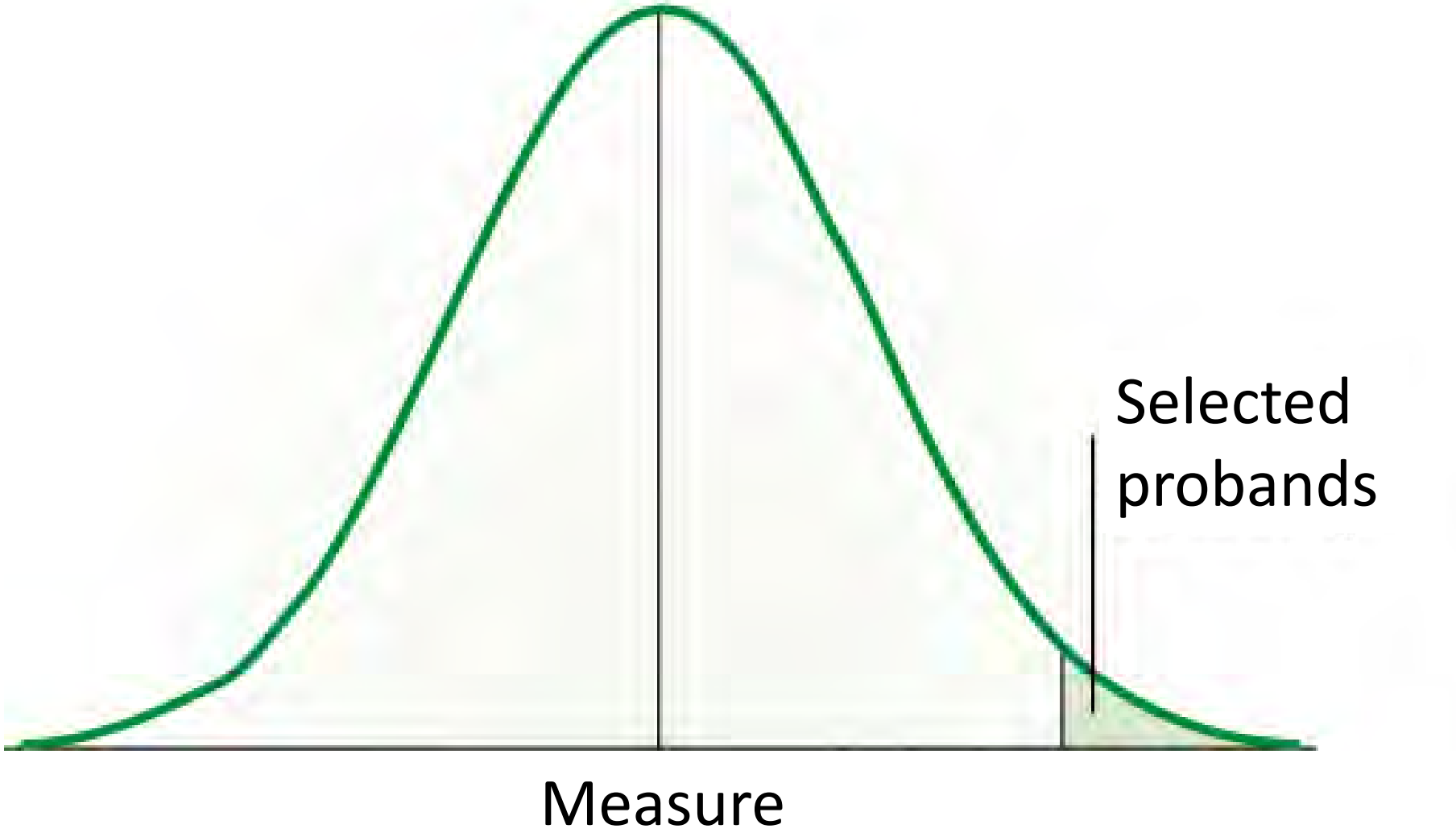


Molecular windows

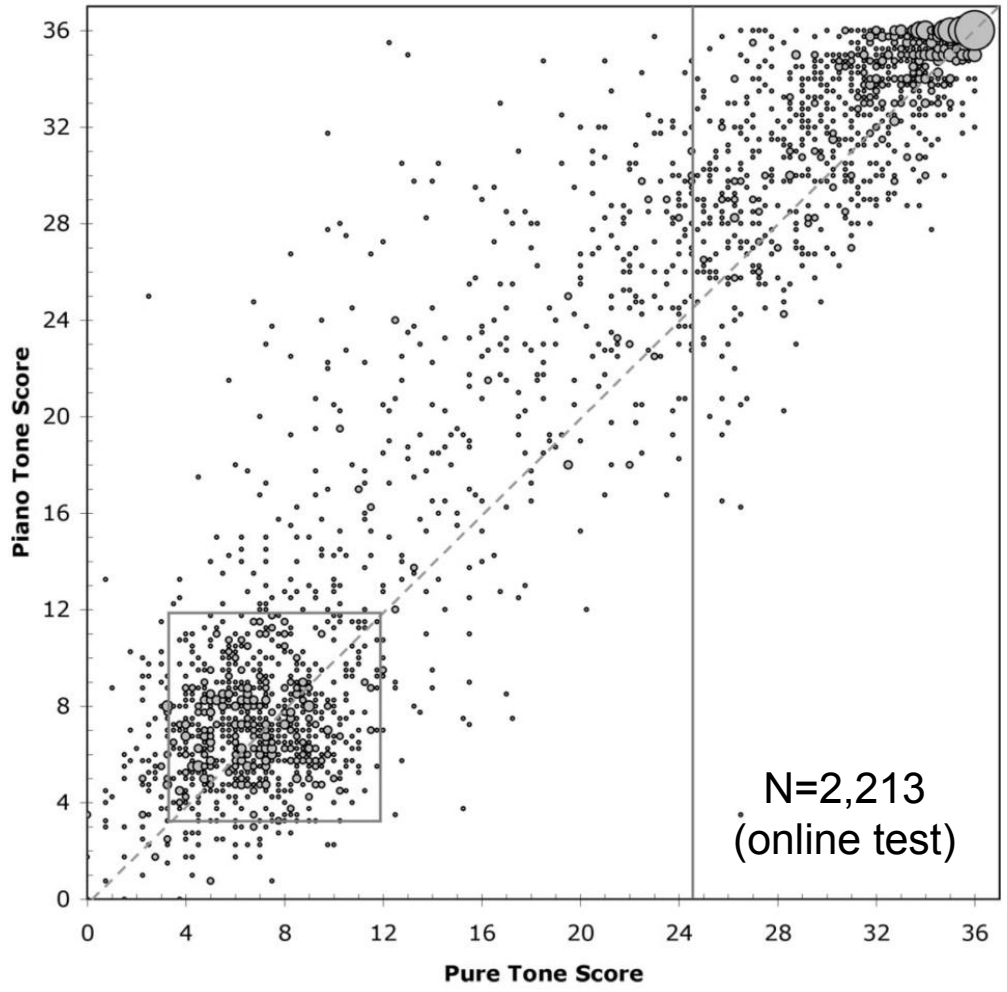
Musicality at the extremes

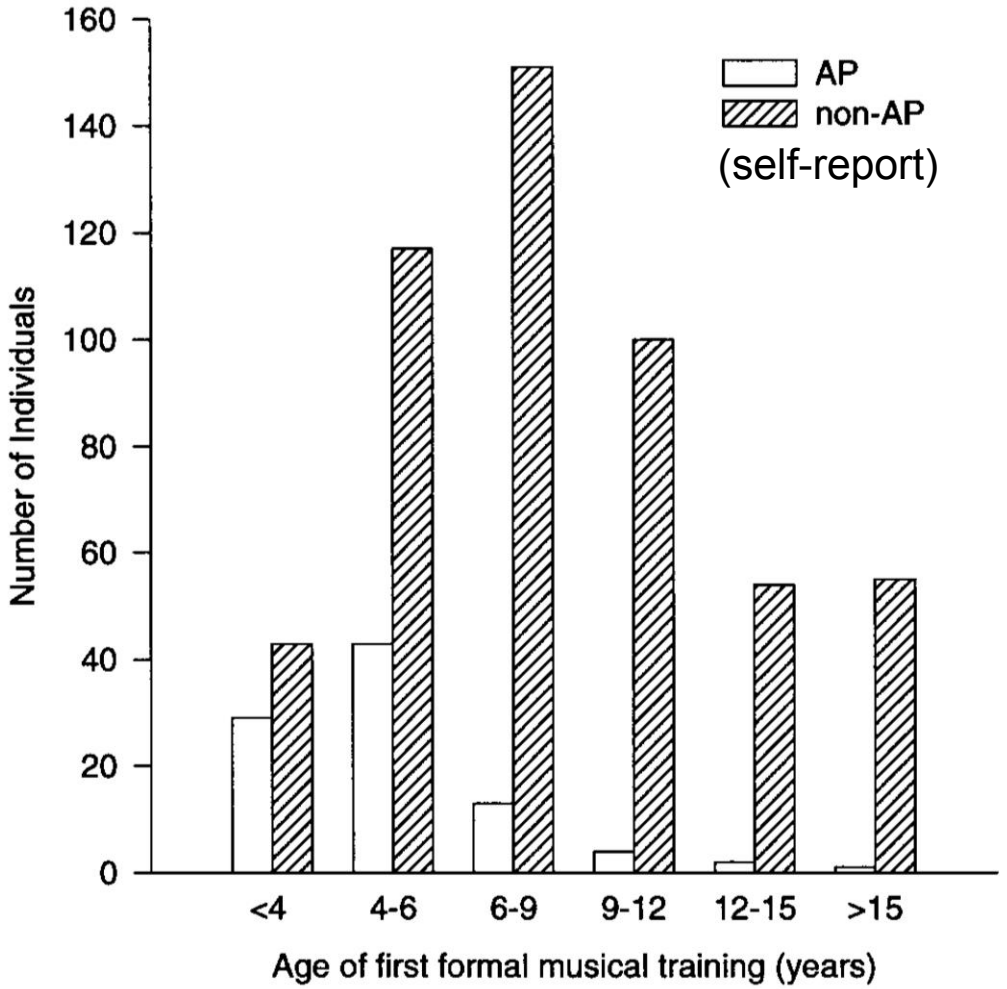


Musicality at the extremes



Absolute Pitch





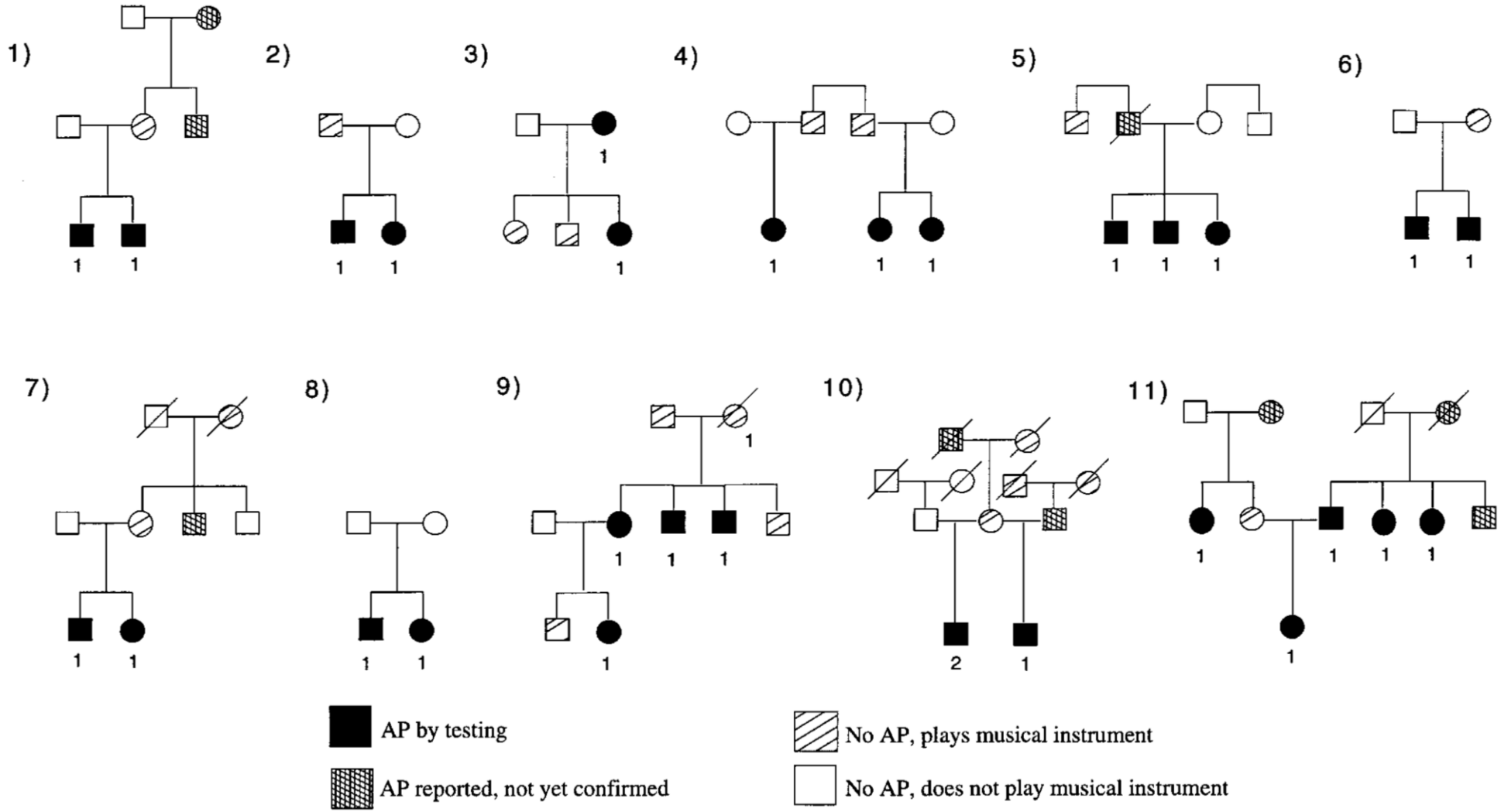
Athos et al. (2007) *PNAS* **104:** 14795-800

Baharloo et al. (1998) *AJHG* **62:** 224-31

Absolute Pitch: An Approach for Identification of Genetic and Nongenetic Components

Am. J. Hum. Genet. 62:224–231, 1998

Siamak Baharloo,[1,6] Paul A. Johnston,[2] Susan K. Service,[6] Jane Gitschier,[1,3,4,5] and Nelson B. Freimer[1,4,6]



Am. J. Hum. Genet. 65:911–913, 1999

Absolute Pitch: Prevalence, Ethnic Variation, and Estimation of the Genetic Component

PETER K. GREGERSEN,[1] ELENA KOWALSKY,[1] NINA KOHN,[2] AND ELIZABETH WEST MARVIN[3]
Division of [1]Biology and Human Genetics and [2]Biostatistics, North Shore University Hospital, Manhasset, NY; and [3]Department of Music Theory, Eastman School of Music, Rochester, NY

Prevalence of AP in Asian Music Students, Stratified by Type of Music Program

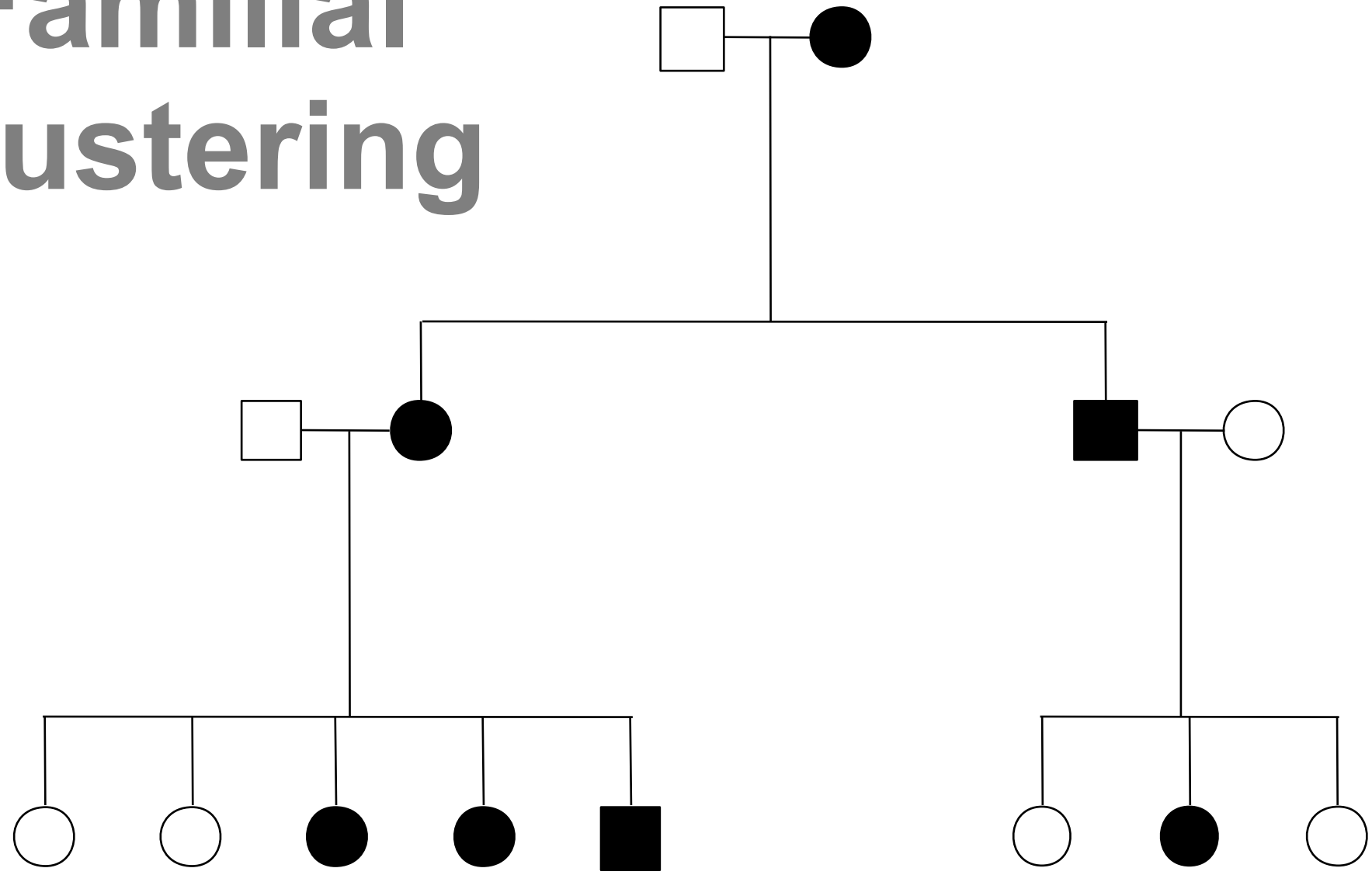
Type of Music Program (No. of Students Surveyed)	No. (%) of Students with AP
Conservatory (73)	36 (49.3)
University music program (152)	39 (25.7)
Liberal arts college (12)	1 (8.3)
All programs combined (237)	76 (32.1)

Prevalence of AP in Non-Asian Music Students, Stratified by Type of Music Program

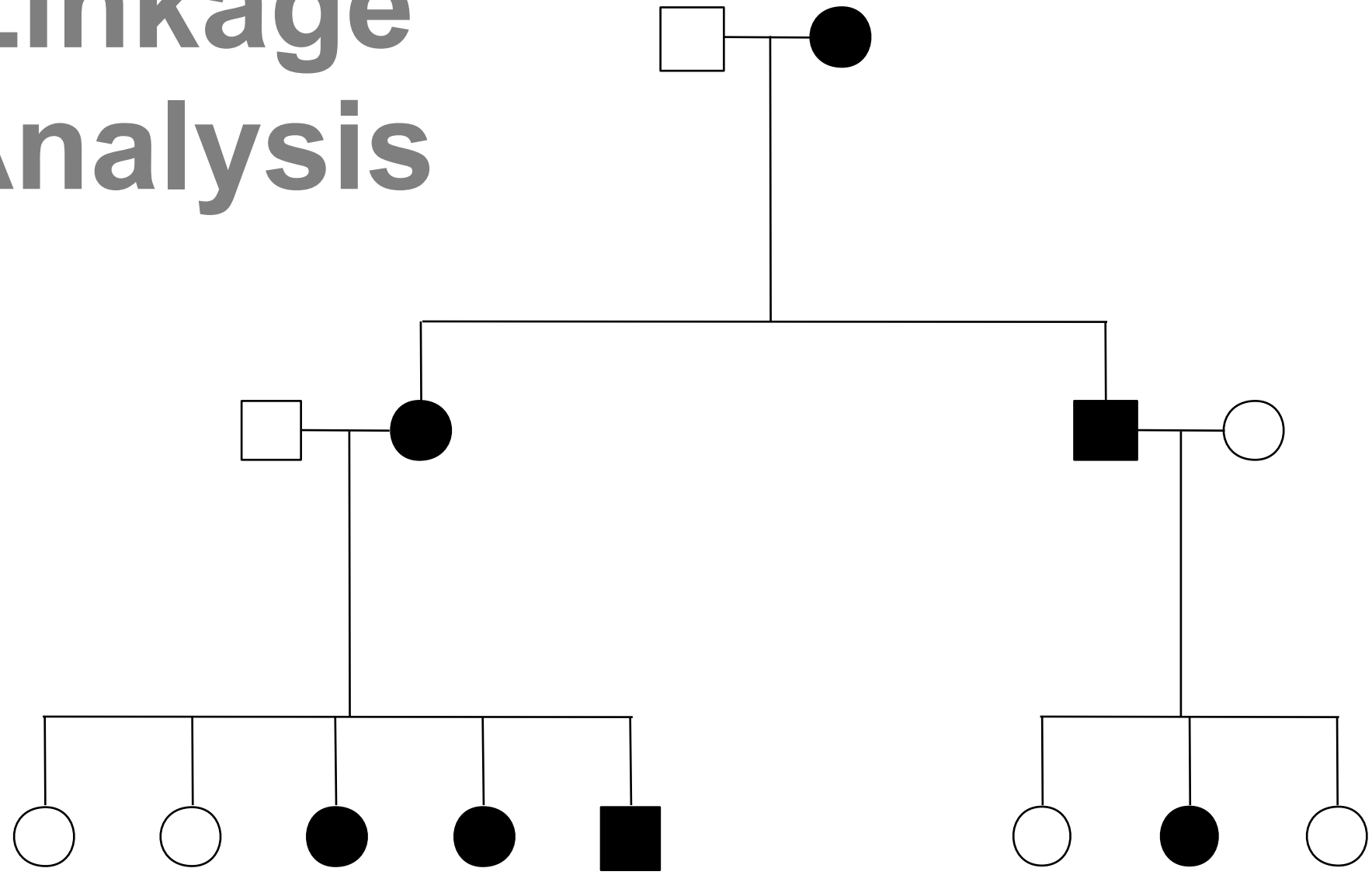
Type of Music Program (No. of Students Surveyed)	No. (%) of Students with AP
Conservatory (276)	50 (18.1)
University music program (1,844)	107 (5.8)
Liberal arts college (350)	16 (4.5)
All programs combined (2,470)	173 (7.0)

Sibling recurrence risk of ~7.5 – 15.1

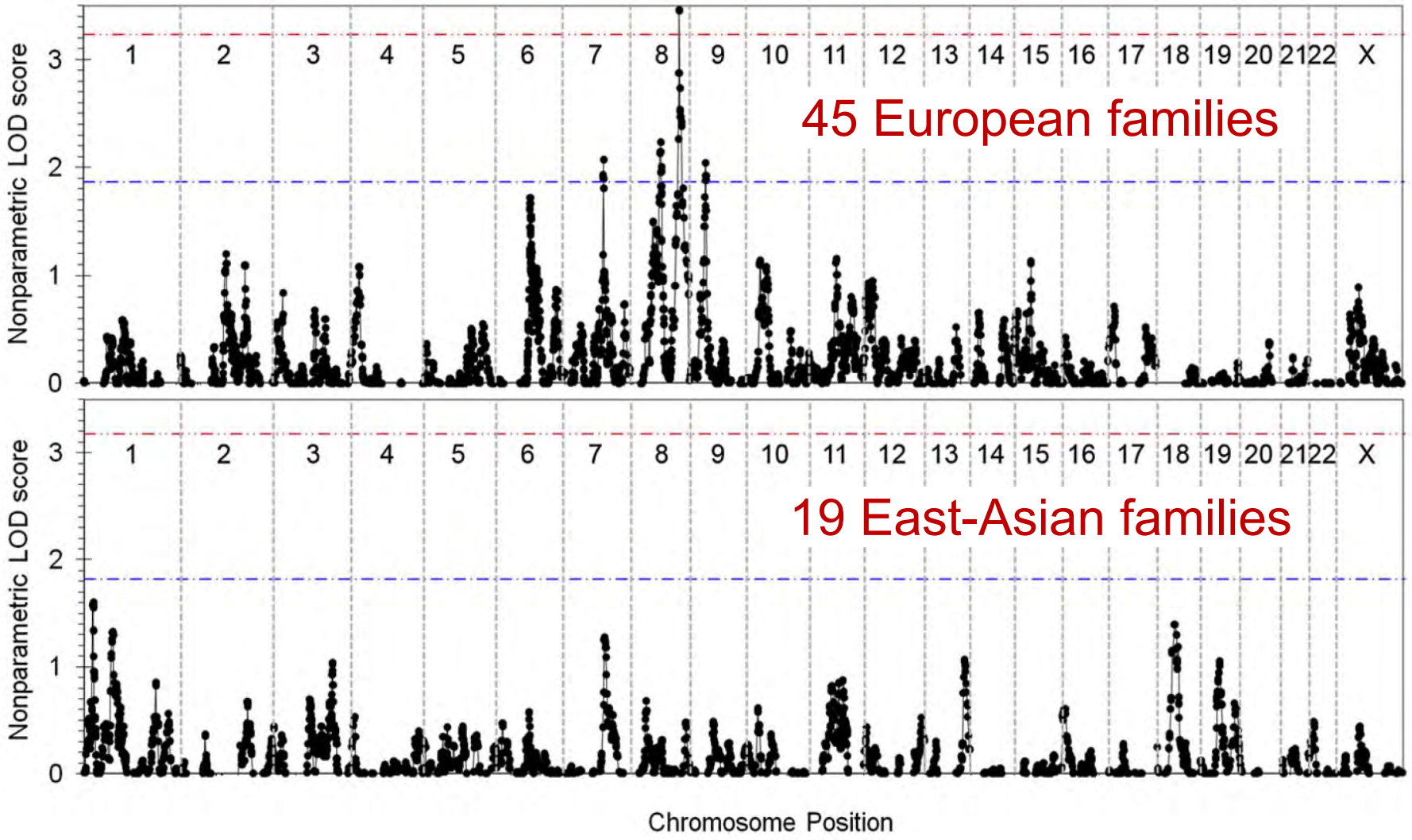
Familial Clustering



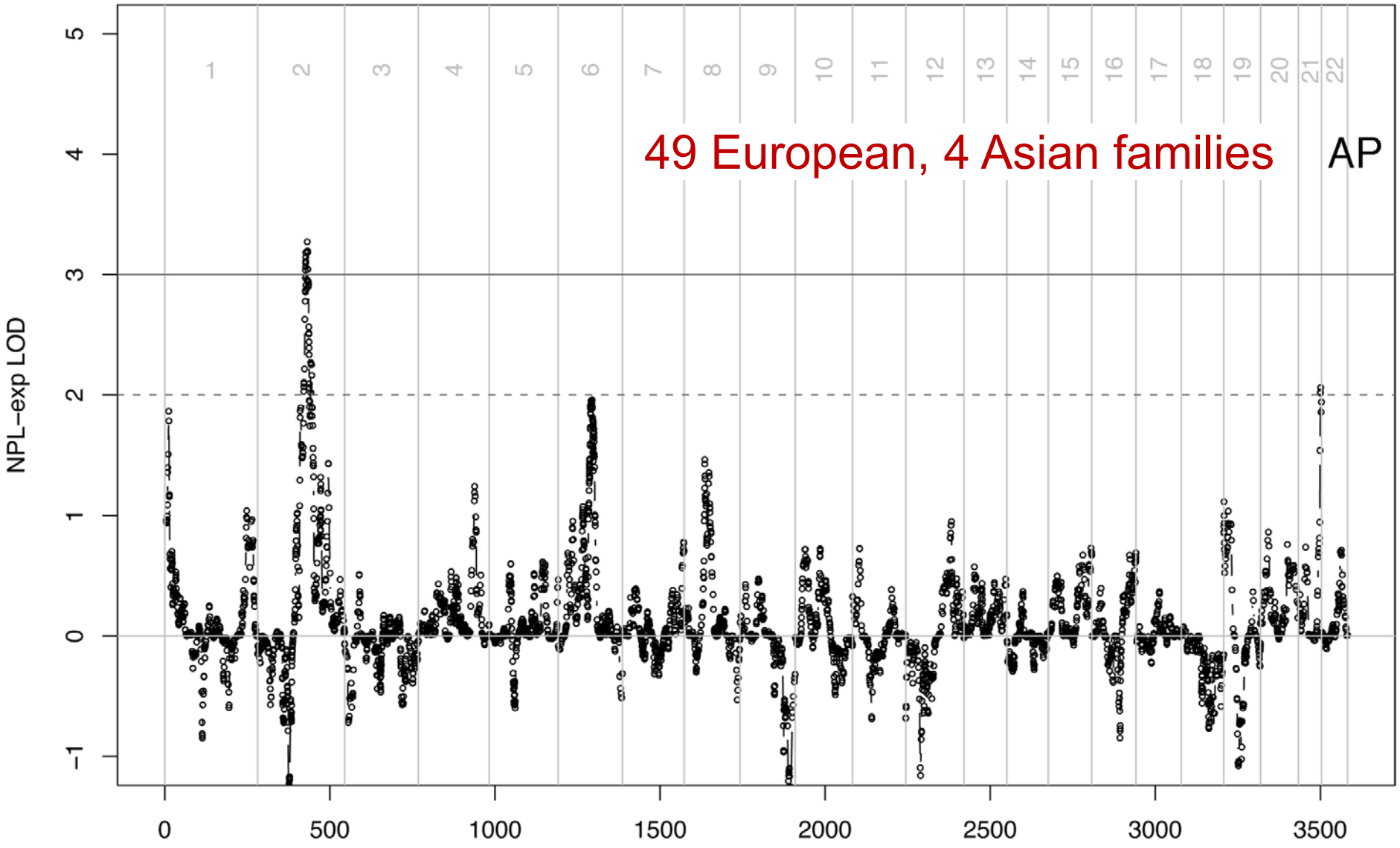
Linkage Analysis



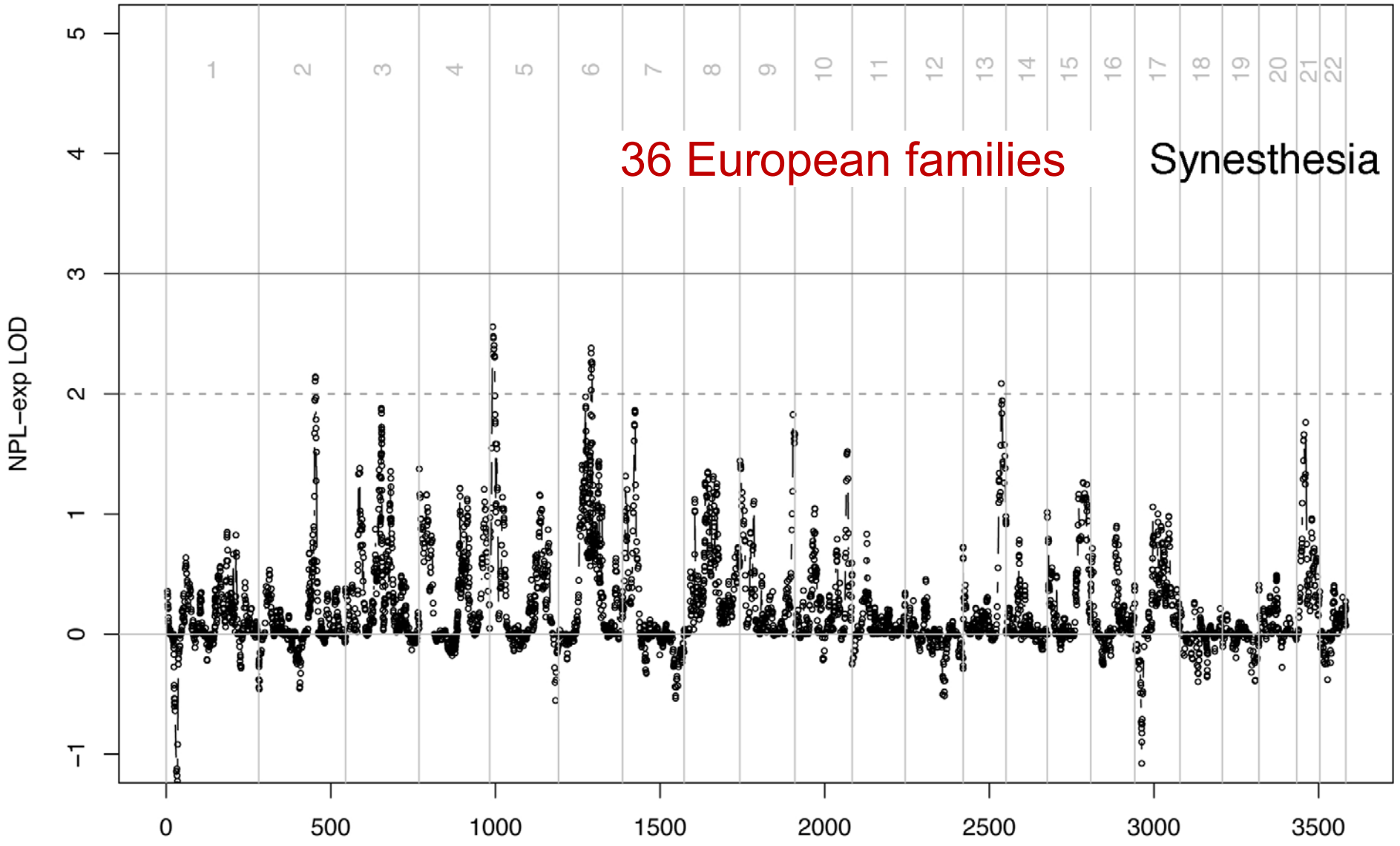
Genome-wide Study of Families with Absolute Pitch Reveals Linkage to 8q24.21 and Locus Heterogeneity



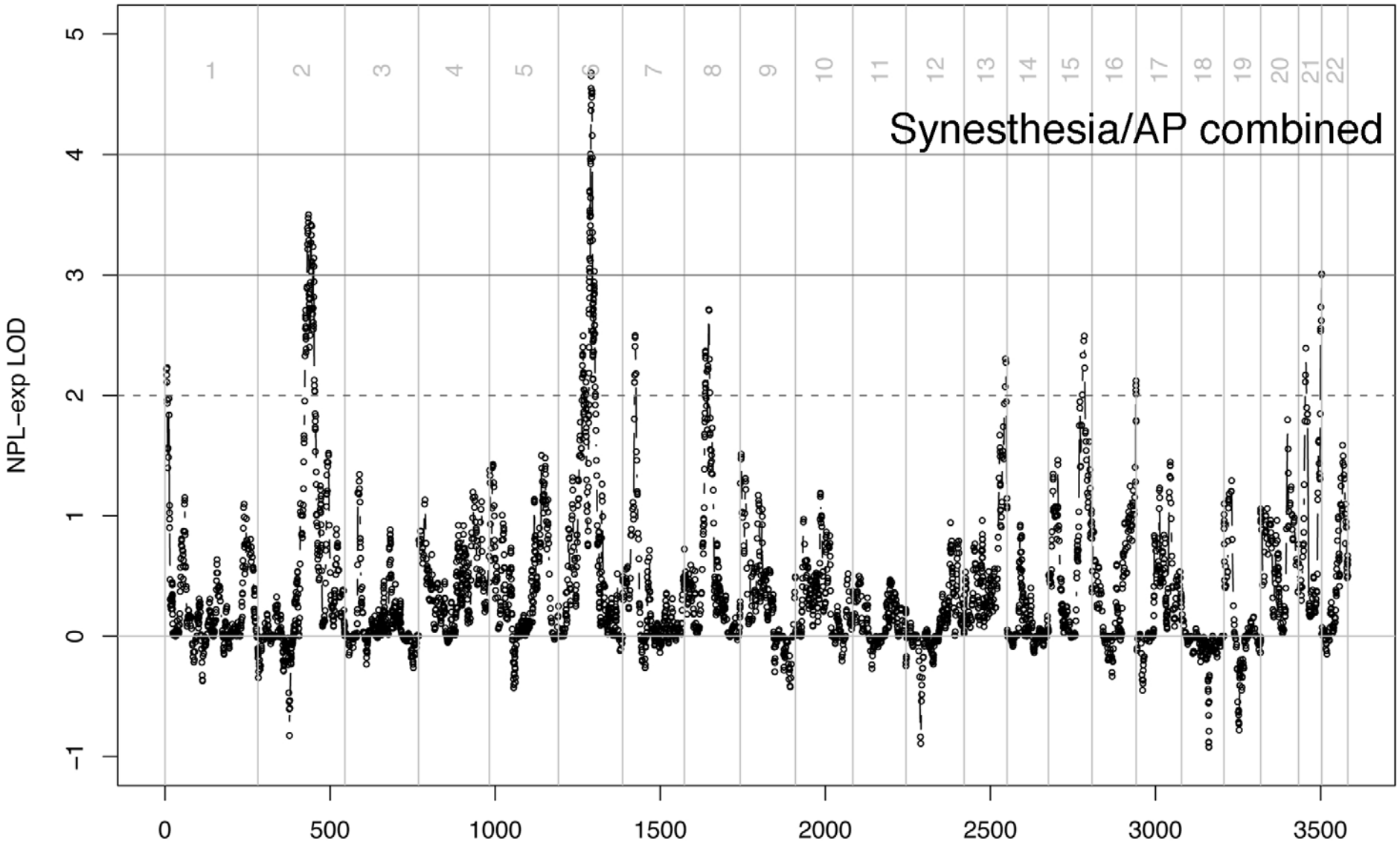
Elizabeth Theusch,[1,2] Analabha Basu,[1] and Jane Gitschier[1,2,3,*] The American Journal of Human Genetics *85*, 112–119, July 10, 2009



Gregersen et al. (2013) *Hum Mol Genet* **22:** 2097-104

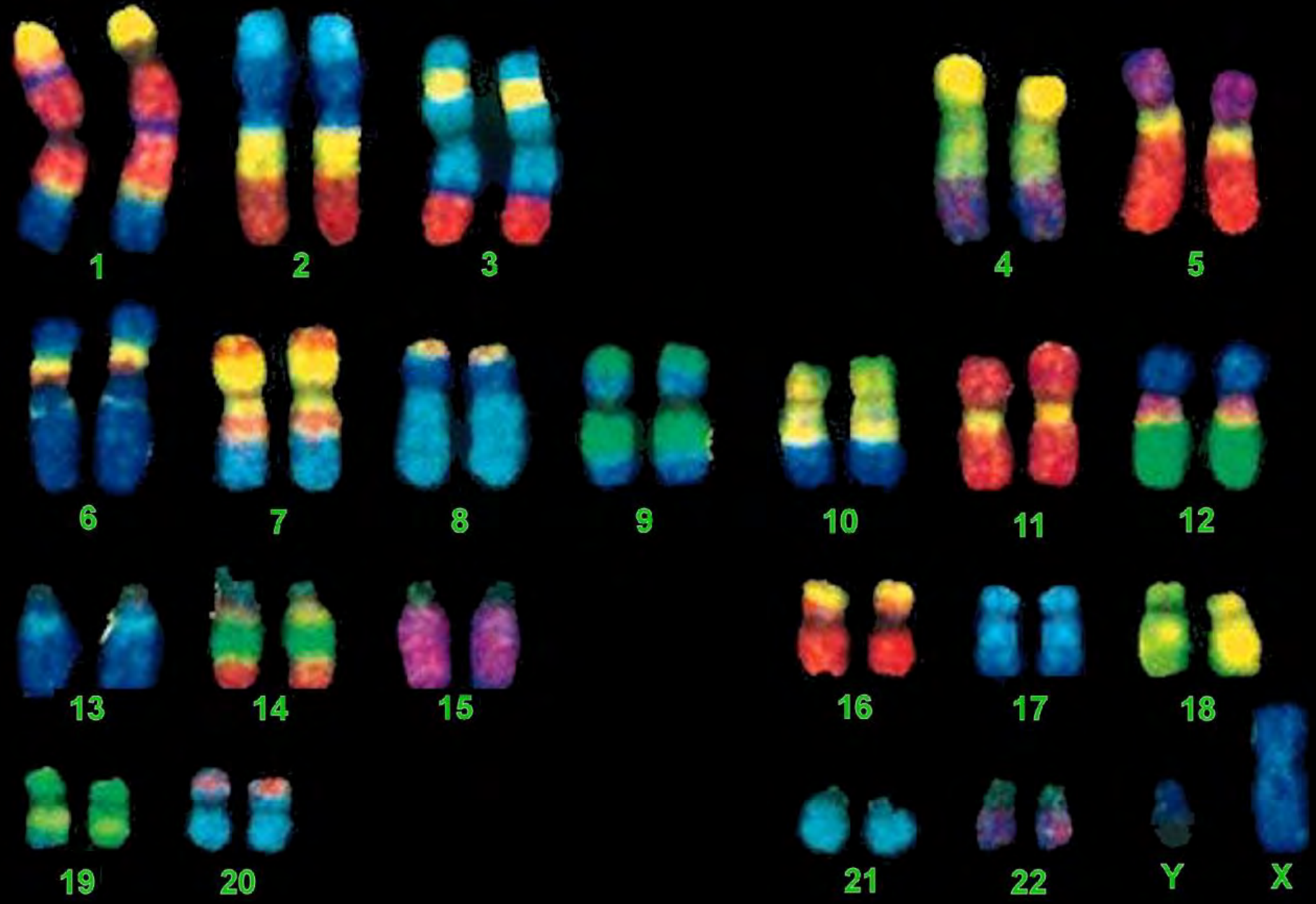


Gregersen et al. (2013) *Hum Mol Genet* **22:** 2097-104



Gregersen et al. (2013) *Hum Mol Genet* **22:** 2097-104

Molecular windows


1
2
3
4
5
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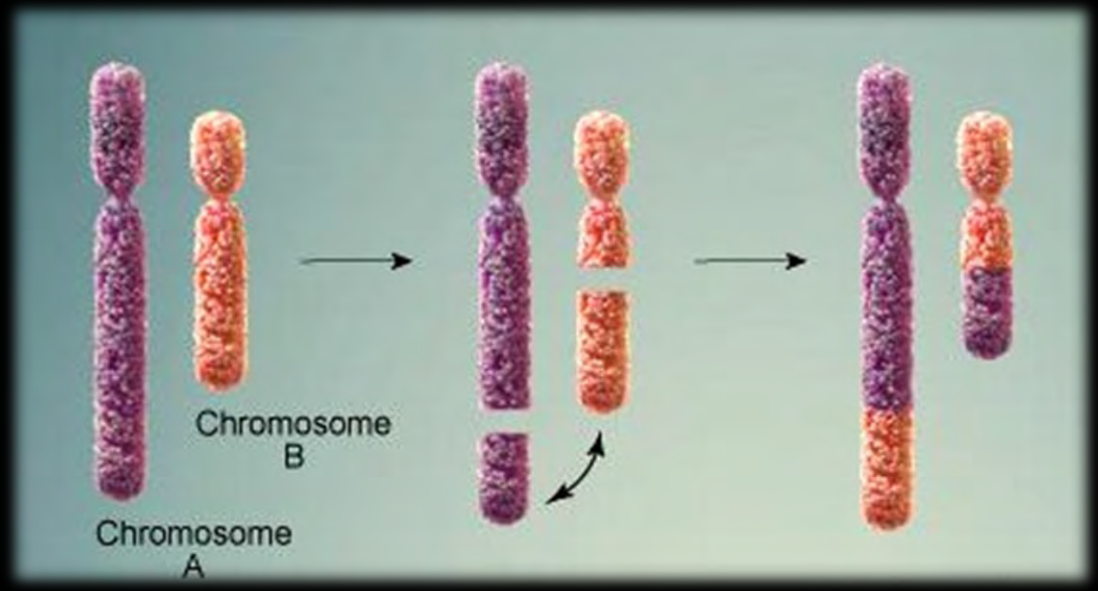
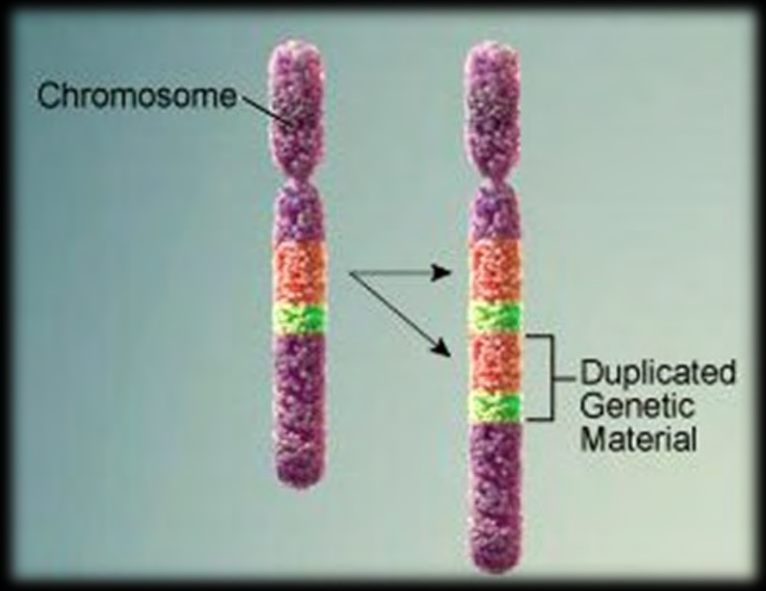
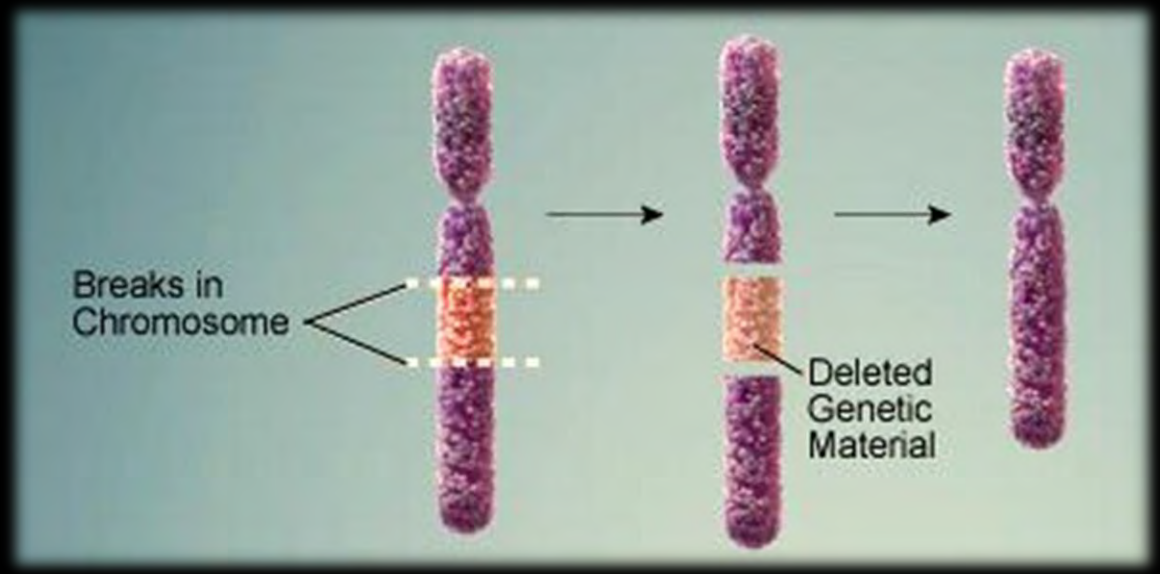
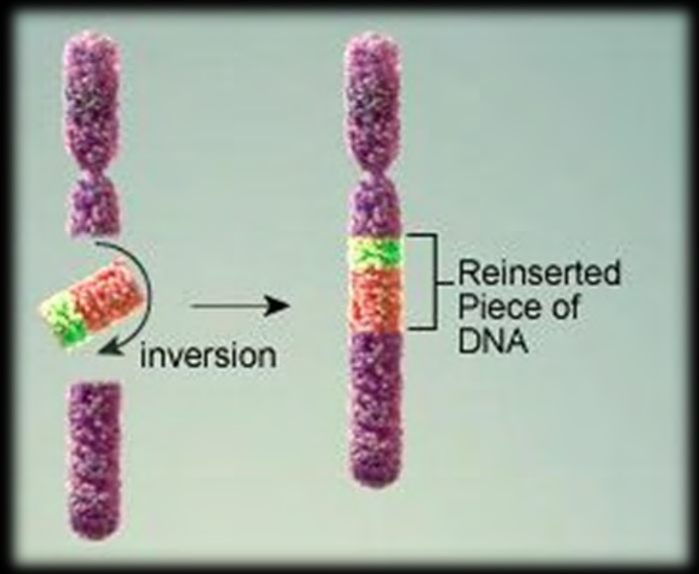
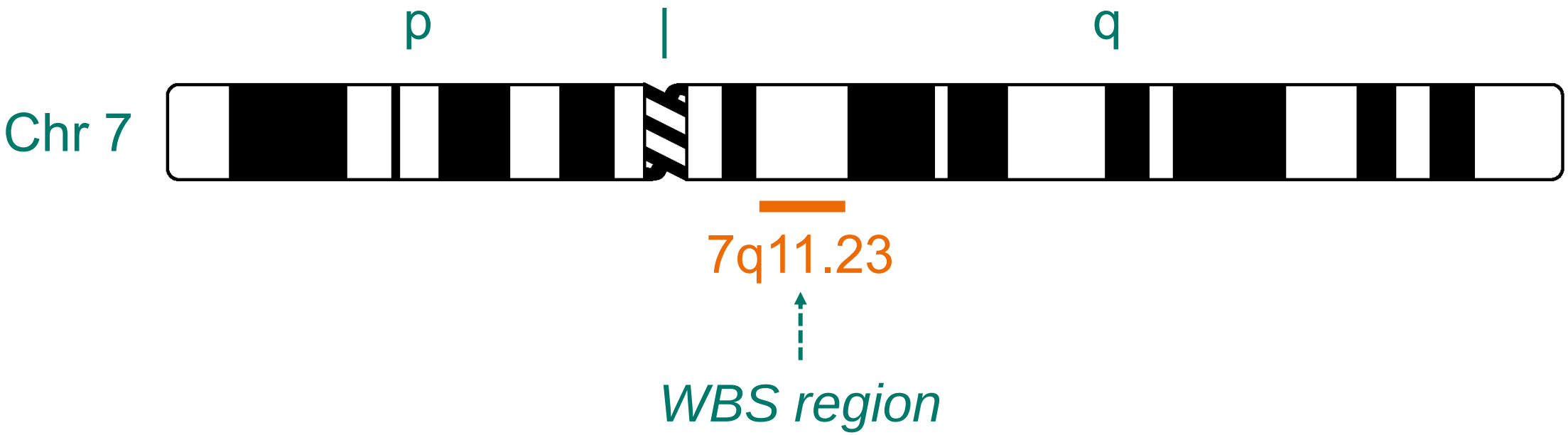
13
14
15
16
17
18
19
20
21
22
Y
X


Chromosome
B
Chromosome
A


Chromosome
Duplicated
Genetic
Material


Breaks in
Chromosome
Deleted
Genetic
Material


inversion
Reinserted
Piece of
DNA


p
|
q
Chr 7
7q11.23
WBS region

frontiers in
PSYCHOLOGY

ORIGINAL RESEARCH ARTICLE
published: 16 August 2013
doi: 10.3389/fpsyg.2013.00525

(A)musicality in Williams syndrome: examining relationships among auditory perception, musical skill, and emotional responsiveness to music

Miriam D. Lense[1,2]*, Carolyn M. Shivers[1,2] and Elisabeth M. Dykens[1,2]

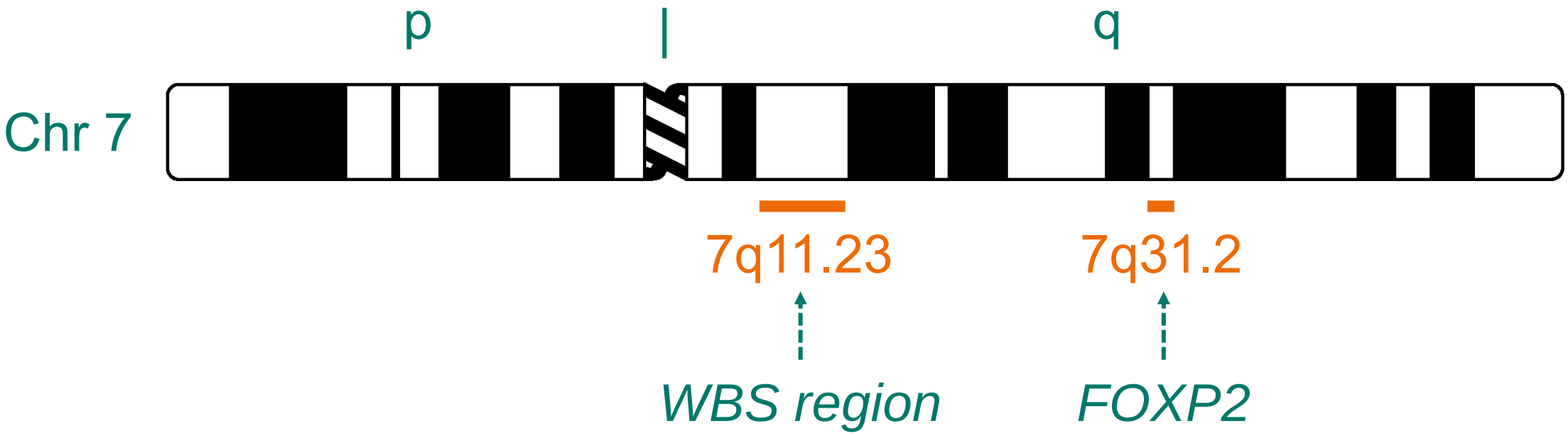
[1] *Vanderbilt Kennedy Center, Vanderbilt University, Nashville, TN, USA*
[2] *Psychology and Human Development, Vanderbilt University, Nashville, TN, USA*

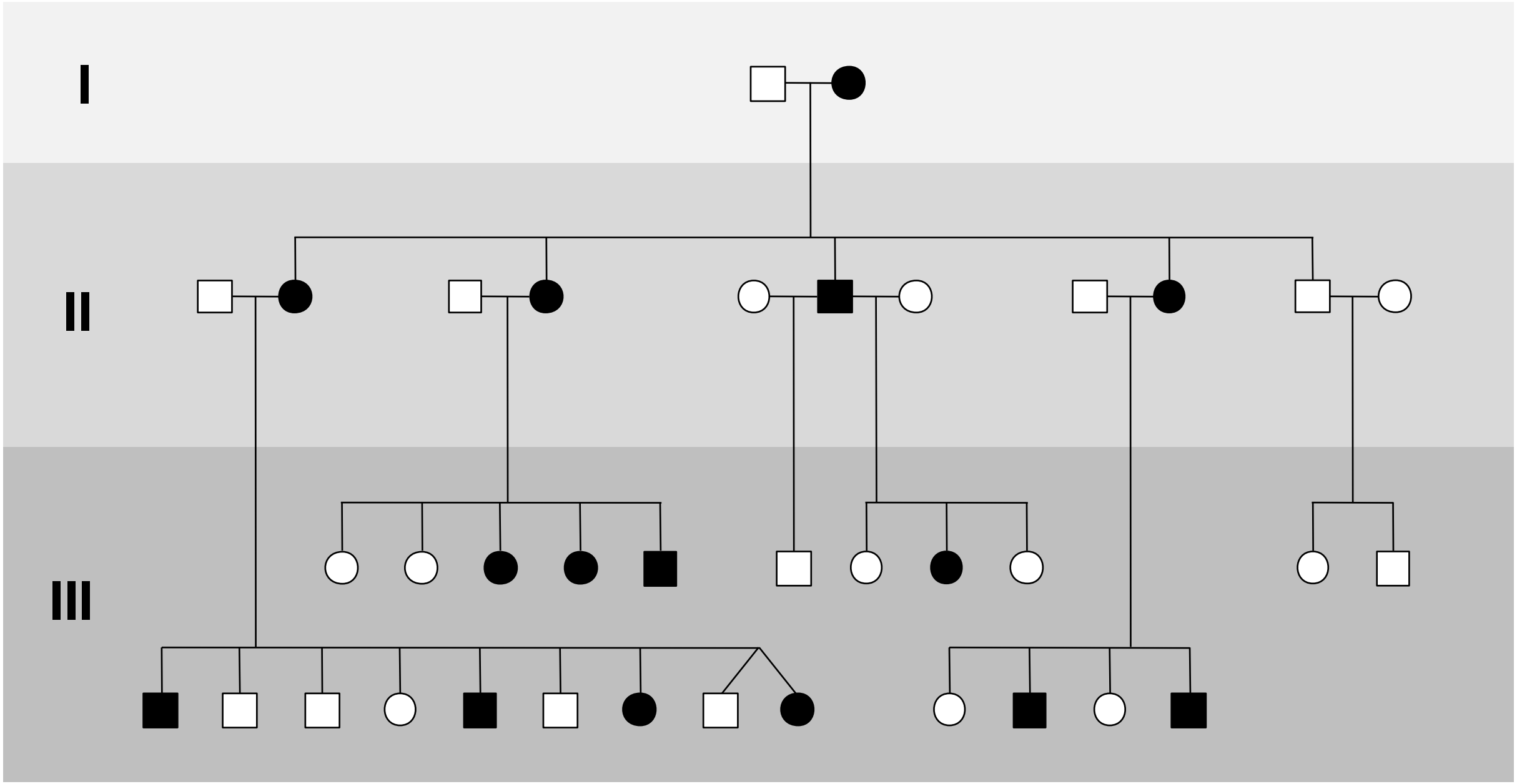
Edited by:
Sarah J. Wilson, University of Melbourne, Australia

Reviewed by:
Psyche Loui, Beth Israel Deaconess Medical Center/Harvard Medical School, USA
Marilee A. Martens, The Ohio State University at Newark, USA

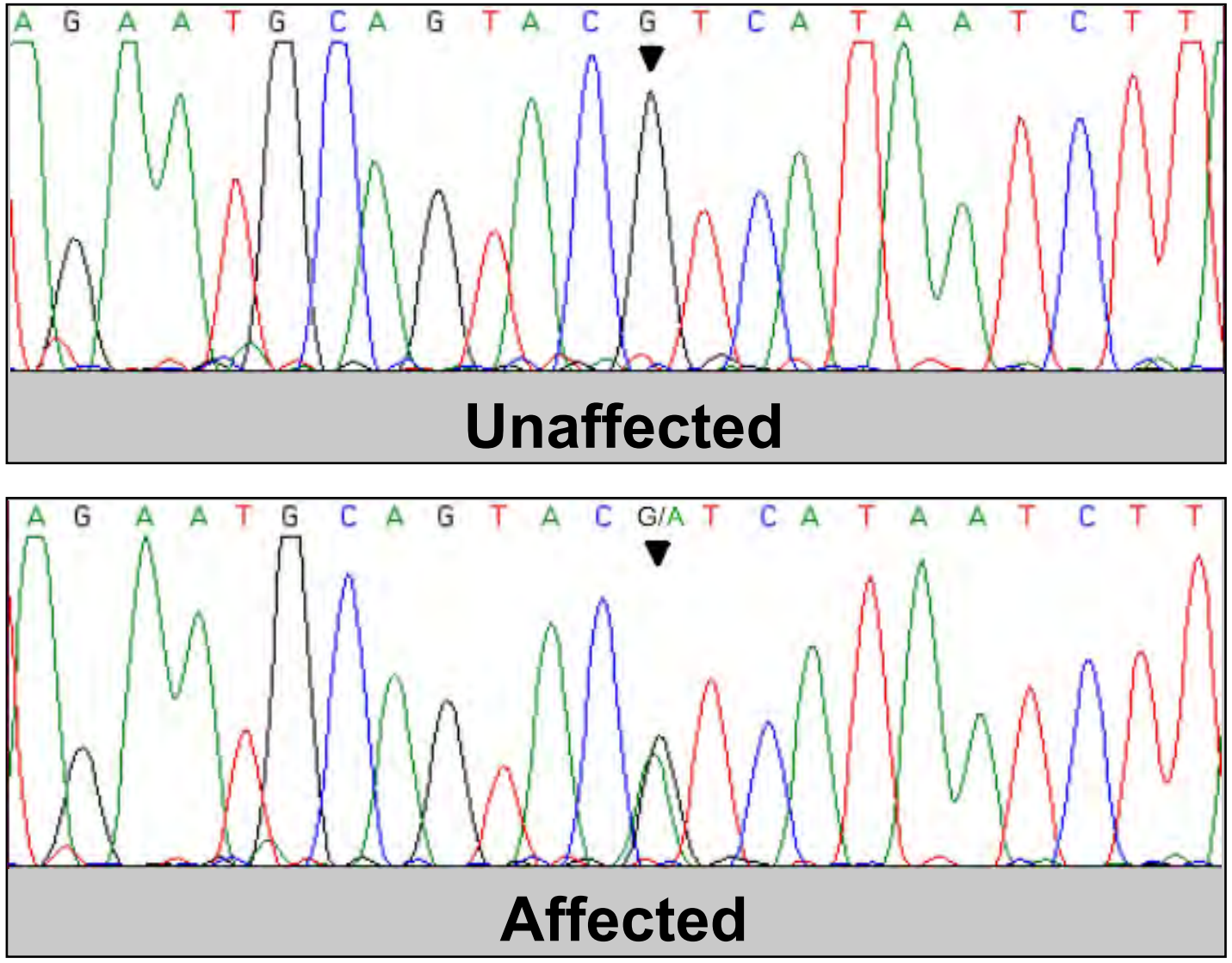
***Correspondence:**
Miriam D. Lense, Vanderbilt Kennedy Center, Vanderbilt University, Peabody Box #40, 230 Appleton Place, Nashville, TN 37203, USA
e-mail: miriam.lense@vanderbilt.edu

Williams syndrome (WS), a genetic, neurodevelopmental disorder, is of keen interest to music cognition researchers because of its characteristic auditory sensitivities and emotional responsiveness to music. However, actual musical perception and production abilities are more variable. We examined musicality in WS through the lens of amusia and explored how their musical perception abilities related to their auditory sensitivities, musical production skills, and emotional responsiveness to music. In our sample of 73 adolescents and adults with WS, 11% met criteria for amusia, which is higher than the 4% prevalence rate reported in the typically developing (TD) population. Amusia was not related to auditory sensitivities but was related to musical training. Performance on the amusia measure strongly predicted musical skill but not emotional responsiveness to music, which was better predicted by general auditory sensitivities. This study represents the first time amusia has been examined in a population with a known neurodevelopmental genetic disorder with a range of cognitive abilities. Results have implications for the relationships across different levels of auditory processing, musical skill development, and emotional responsiveness to music, as well as the understanding of gene-brain-behavior relationships in individuals with WS and TD individuals with and without amusia.

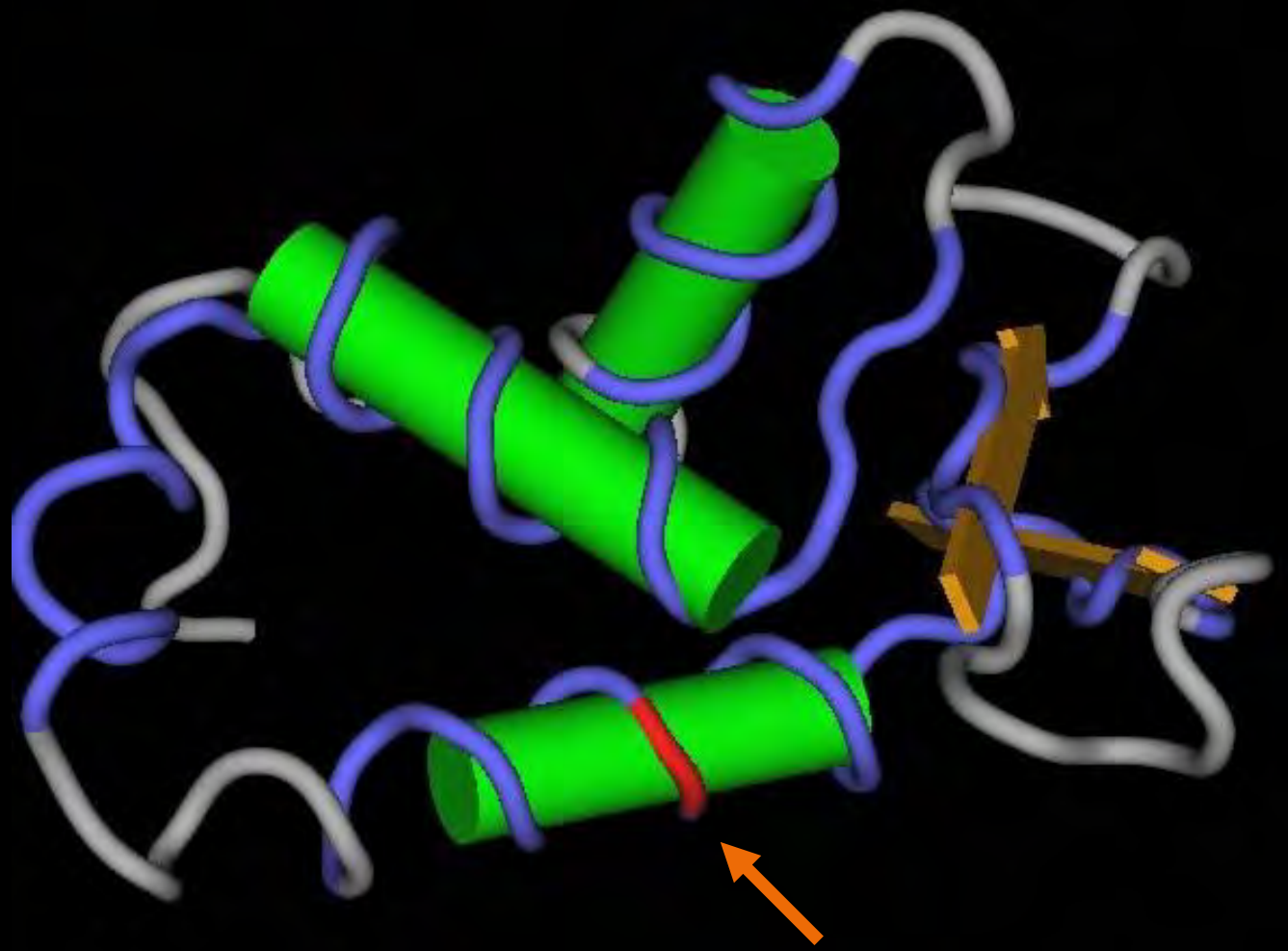

p
|
q
Chr 7
7q11.23
7q31.2
WBS region
FOXP2



Lai et al. (2001) *Nature* **413:** 519-23

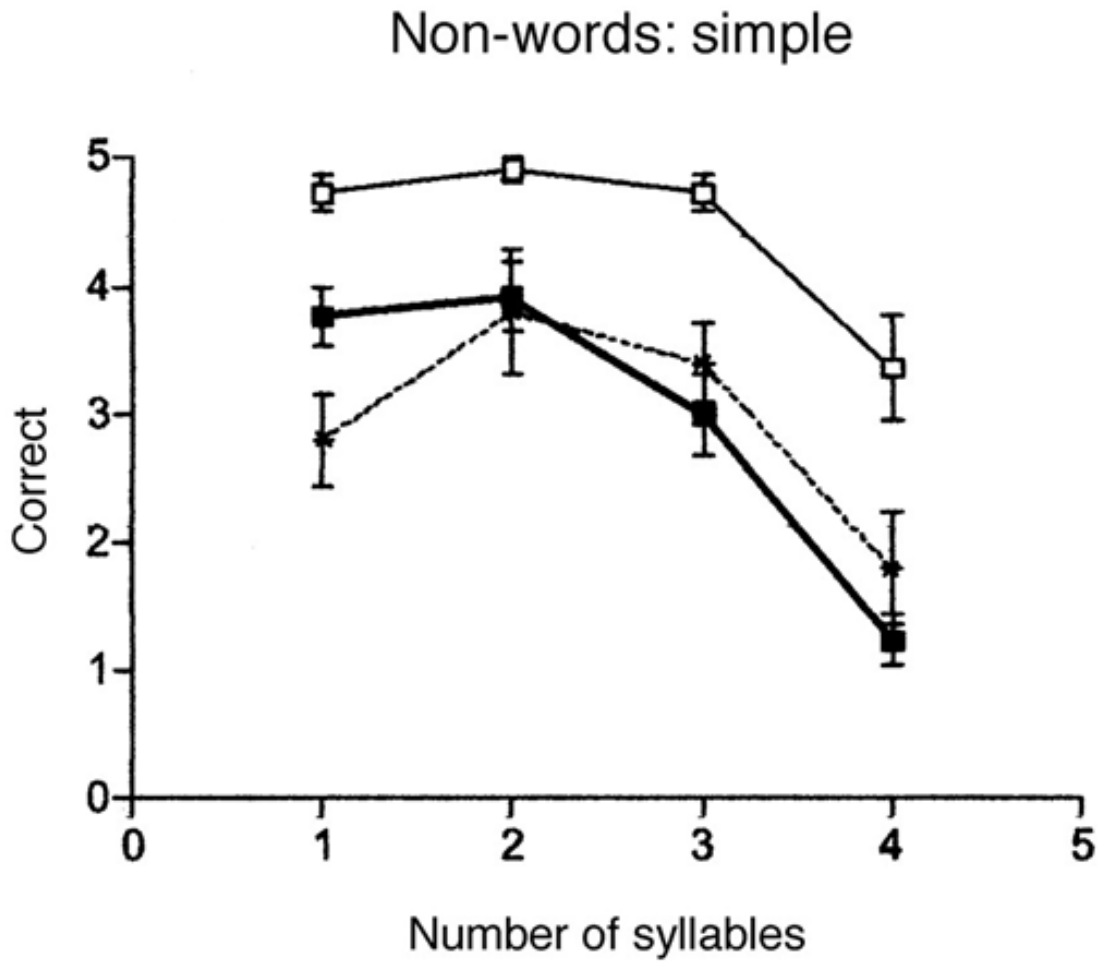


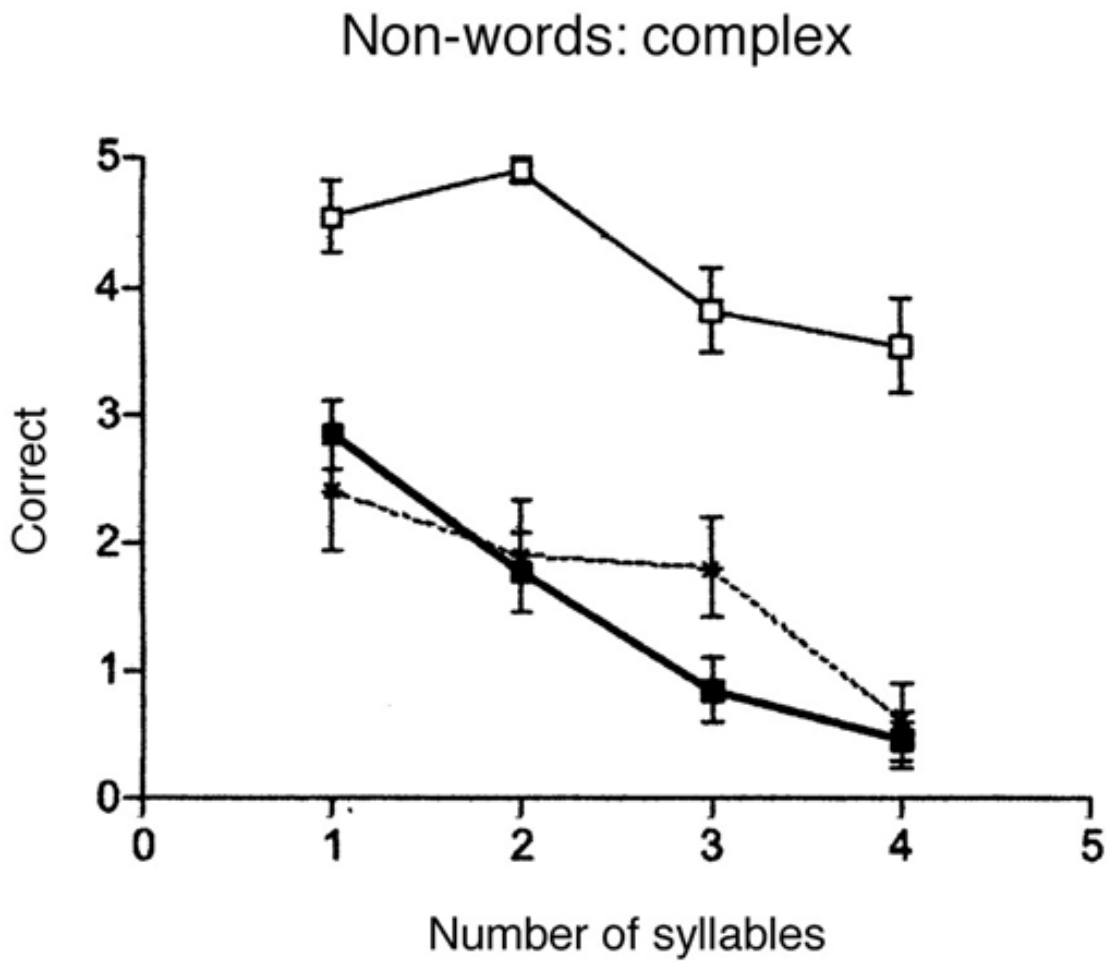
Lai et al. (2001) *Nature* **413:** 519-23



Lai et al. (2001) *Nature* **413:** 519-23

Childhood Apraxia of Speech

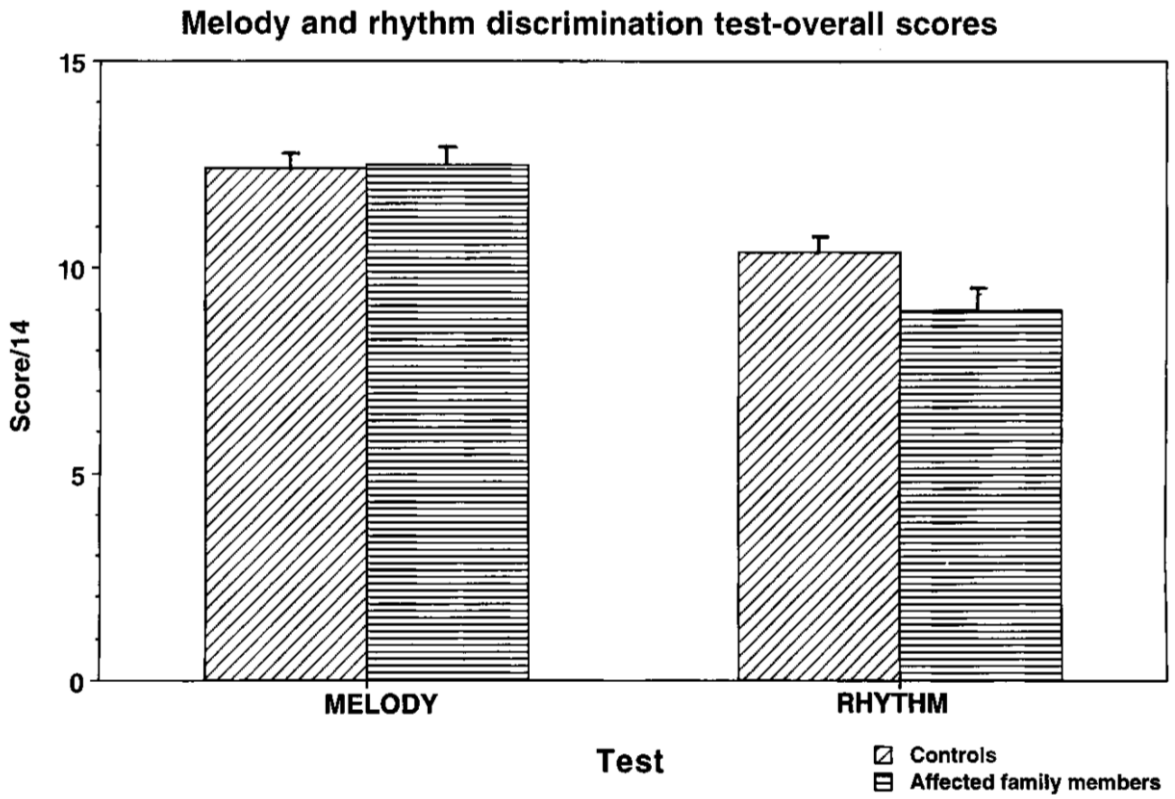


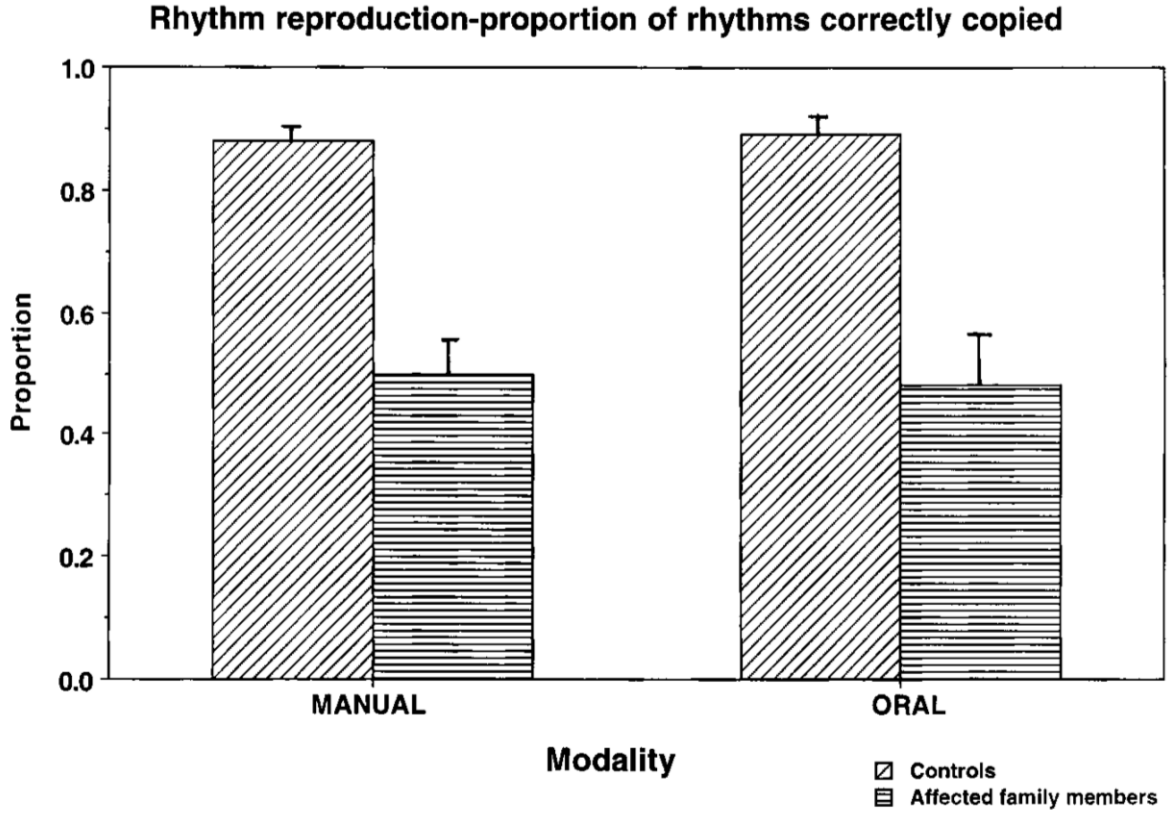


Watkins et al. (2002) *Brain* **125:** 452-64

Pitch and Timing Abilities in Inherited Speech and Language Impairment

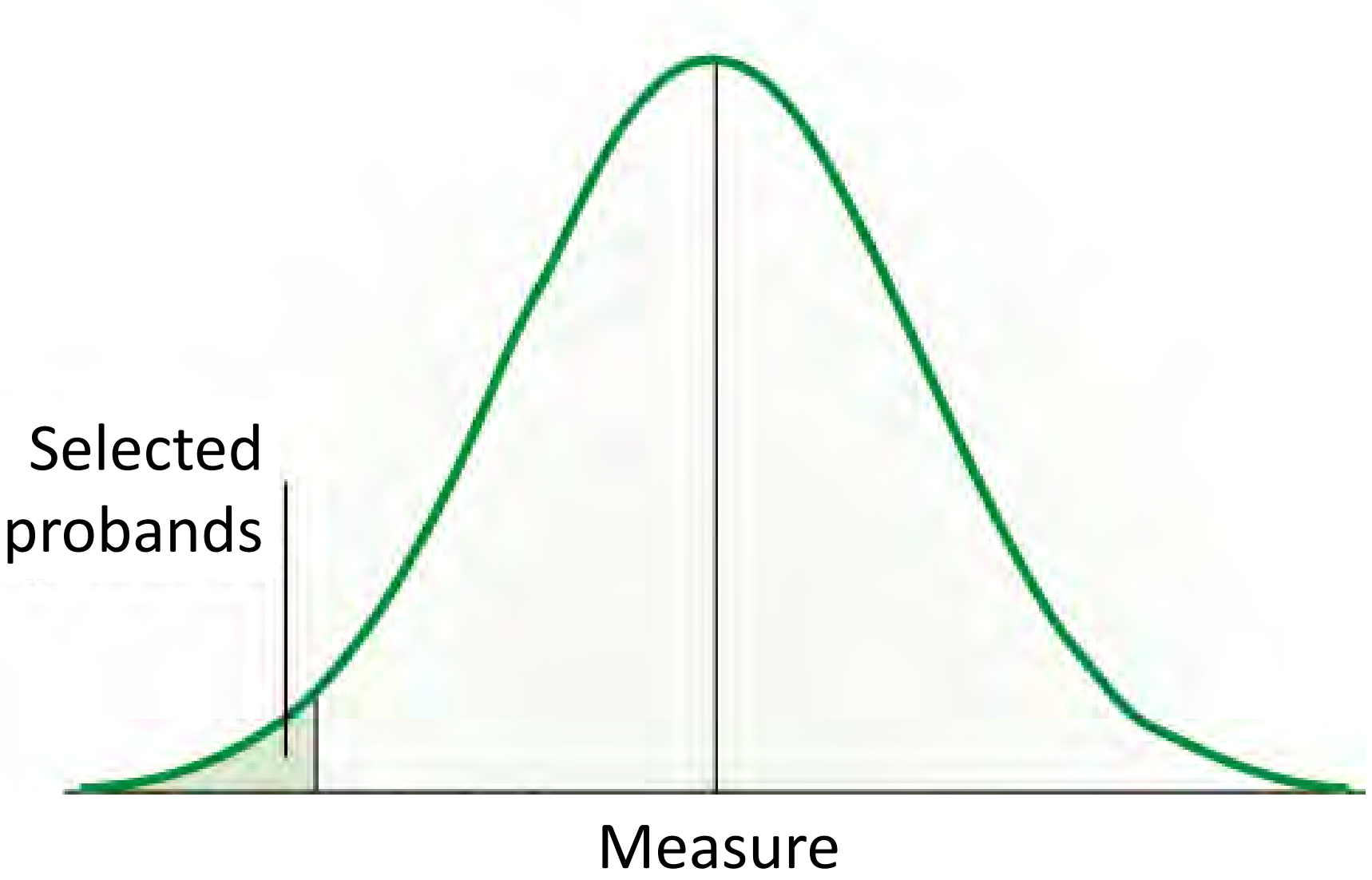
Katherine J. Alcock, Richard E. Passingham, Kate Watkins*, and Faraneh Vargha-Khadem*



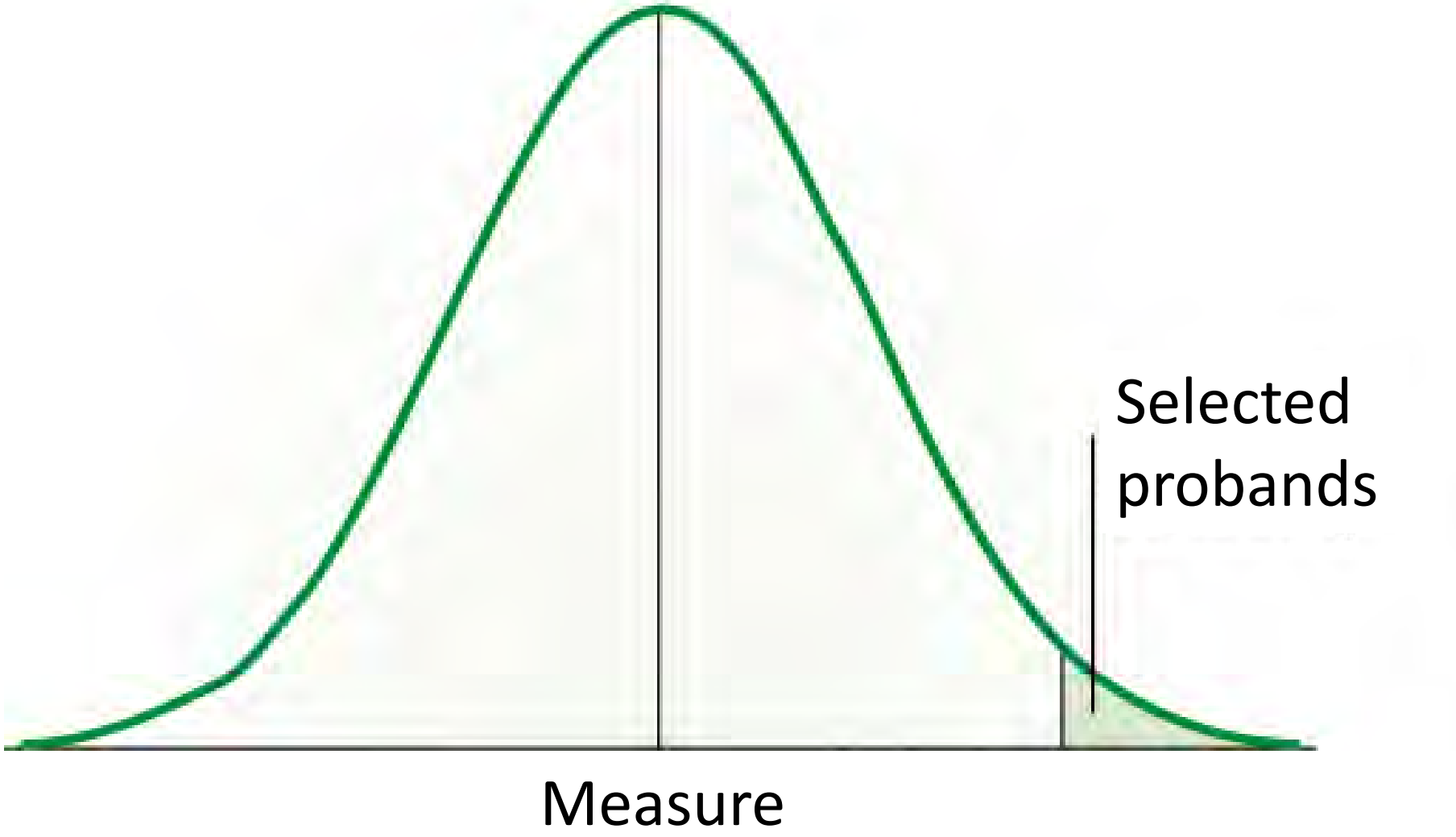


Brain and Language **75,** 34–46 (2000)
doi:10.1006/brln.2000.2323, available online at http://www.idealibrary.com on IDEAL®

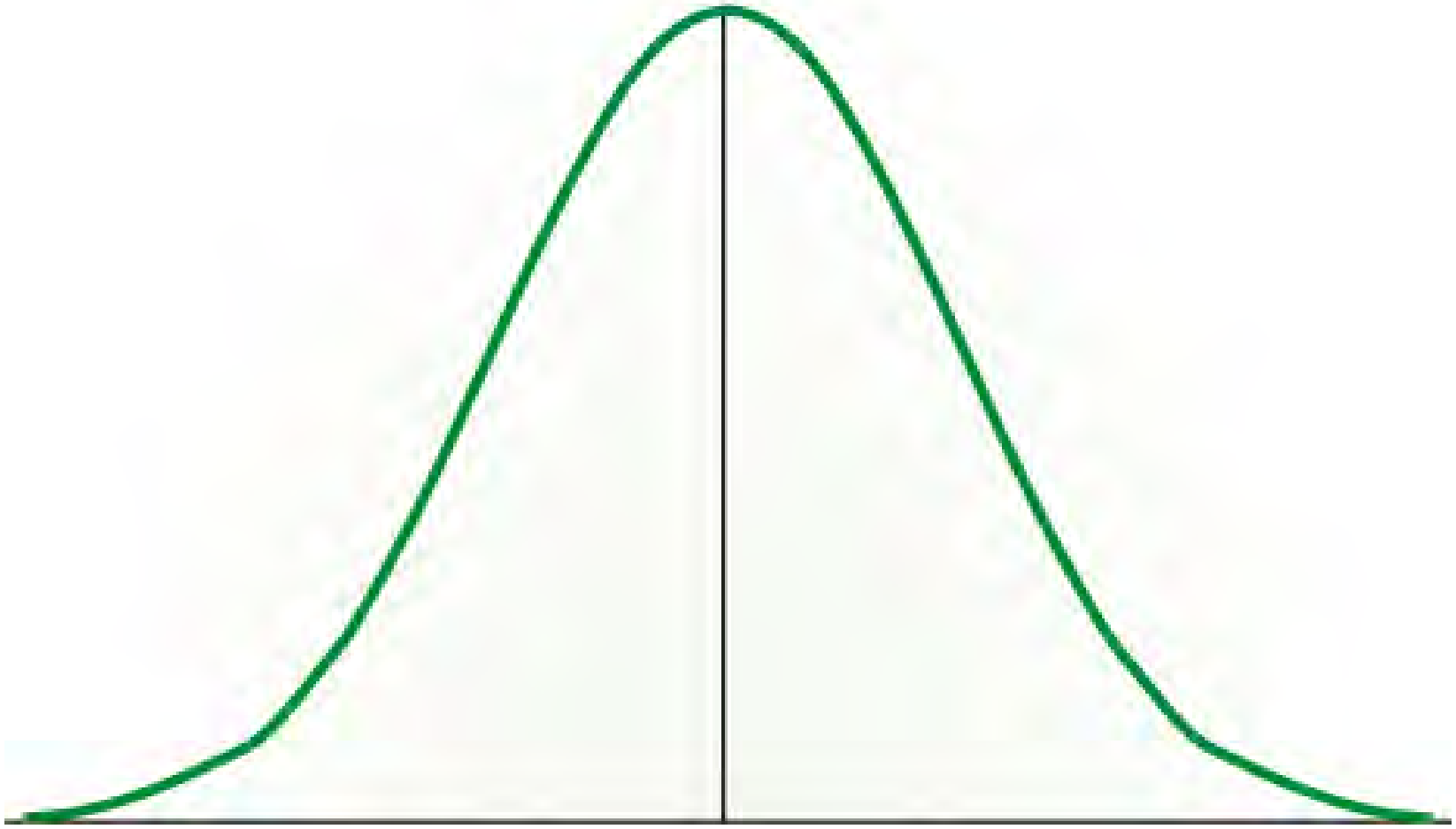
Musicality at the extremes



Musicality at the extremes



Musicality in the population



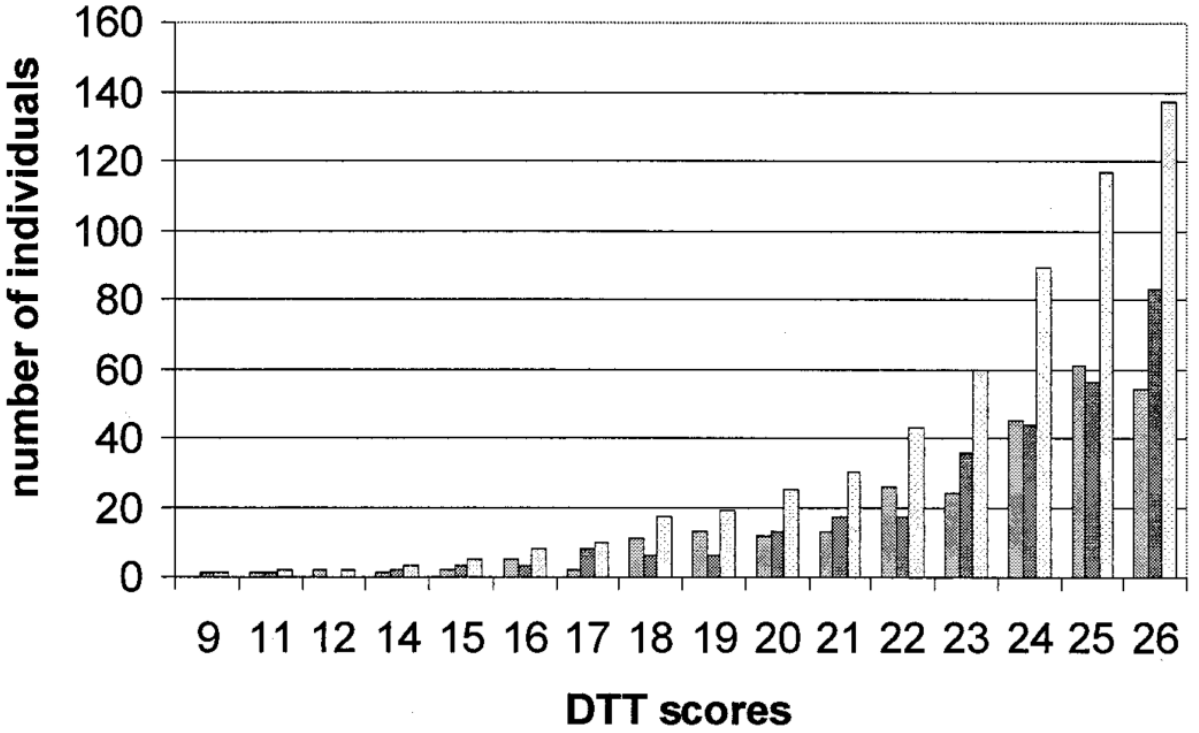
Measure


NATIONAL

Genetic Correlates of Musical Pitch Recognition in Humans

Dennis Drayna,[1]* Ani Manichaikul,[1] Marlies de Lange,[2] Harold Snieder,[2]† Tim Spector[2]

We used a twin study to investigate the genetic and environmental contributions to differences in musical pitch perception abilities in humans. We administered a Distorted Tunes Test (DTT), which requires subjects to judge whether simple popular melodies contain notes with incorrect pitch, to 136 monozygotic twin pairs and 148 dizygotic twin pairs. The correlation of DTT scores between twins was estimated at 0.67 for monozygotic pairs and 0.44 for dizygotic pairs. Genetic model-fitting techniques supported an additive genetic model, with heritability estimated at 0.71 to 0.80, depending on how subjects were categorized, and with no effect of shared environment. DTT scores were only weakly correlated with measures of peripheral hearing. This suggests that variation in musical pitch recognition is primarily due to highly heritable differences in auditory functions not tested by conventional audiologic methods.



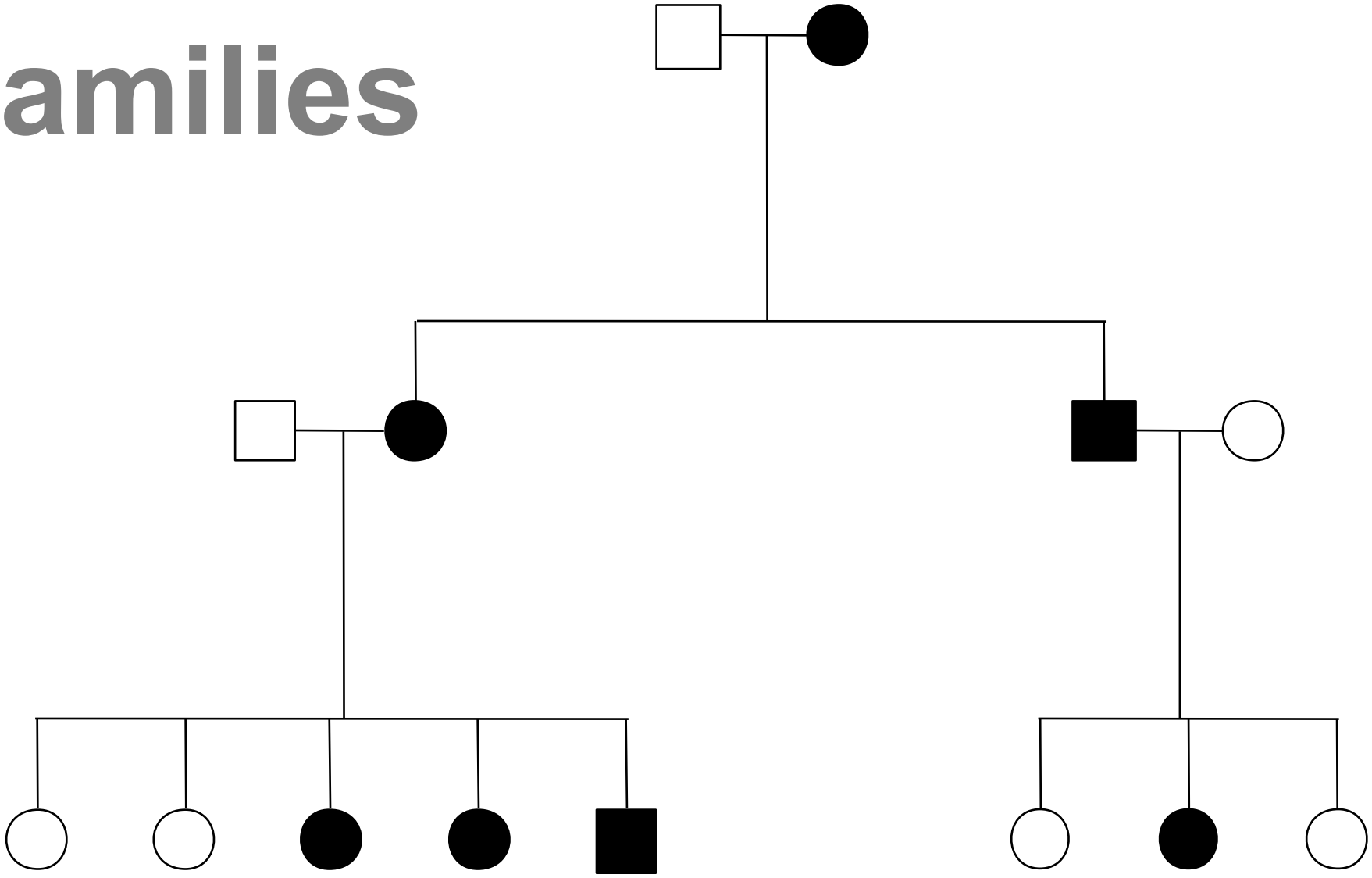
The perception of pitch requires both the ear, which receives auditory signals, and the brain, which performs substantial processing of auditory signals to produce a perceived pitch (*1*–*3*). Although the general features of human pitch processing have been well described, the precise cellular and molecular mechanisms involved remain largely obscure. One approach to understanding the mechanisms of pitch perception is to use genetic methods that exploit naturally occurring variation in pitch perception ability (*4*). If such variability is due to genetic factors, linkage and positional cloning studies could identify genes that encode the components of the pitch perception apparatus (*5*). To examine the genetic contributions to musical pitch

[1]National Institute on Deafness and Other Communication Disorders, National Institutes of Health, 5 Research Court, Rockville, MD 20850, USA. [2]Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, London, SE1 7EH, UK.

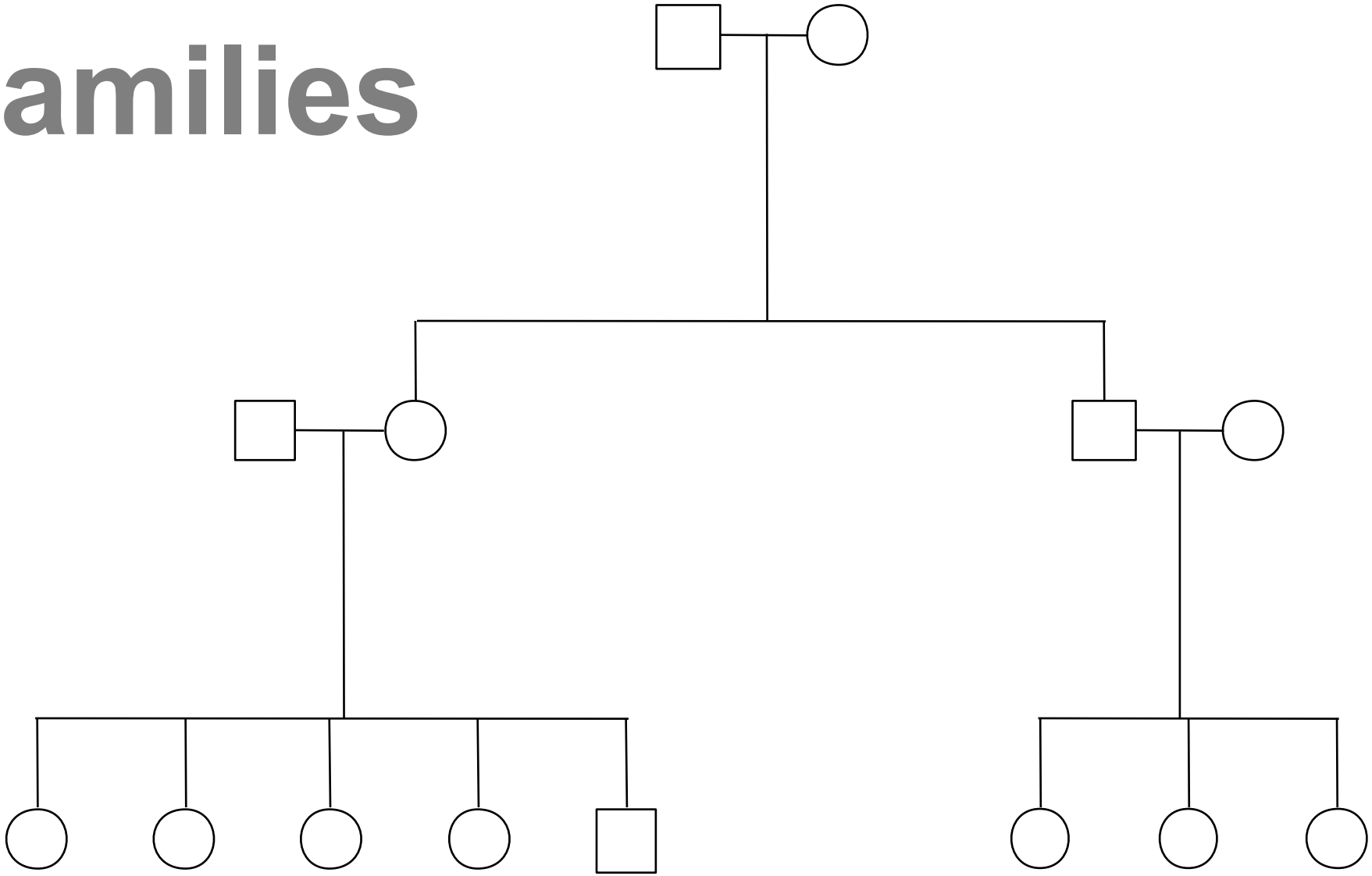
*To whom correspondence should be addressed.
†Present address: Georgia Prevention Institute, Medical College of Georgia, Building HS-1640, Augusta, GA 30912, USA.

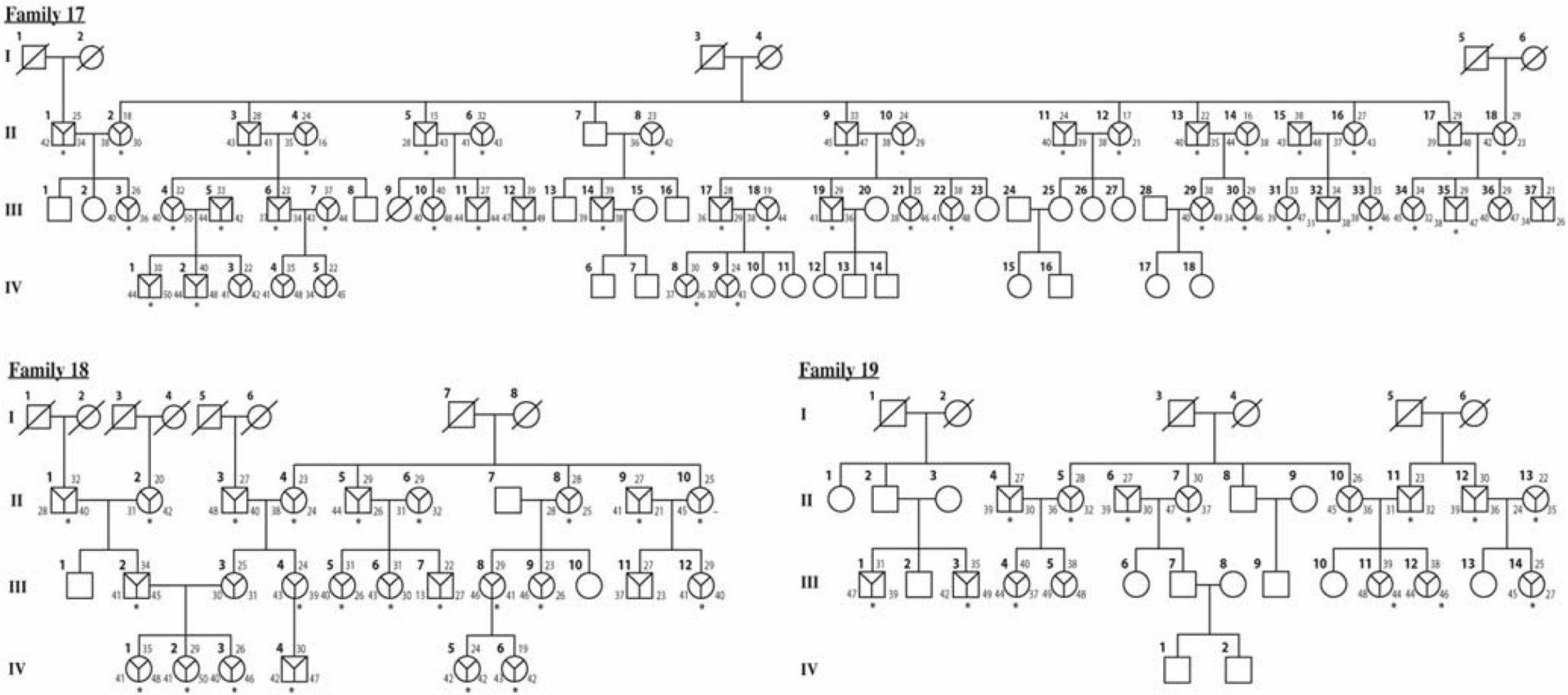
Model	Thresholds	*r*MZ	*r*DZ	h^2 (95% CI)
I	≤23	0.79	0.46	80% (65–90%)
II	≤15, actual score	0.67	0.44	71% (61–78%)

Families



Families



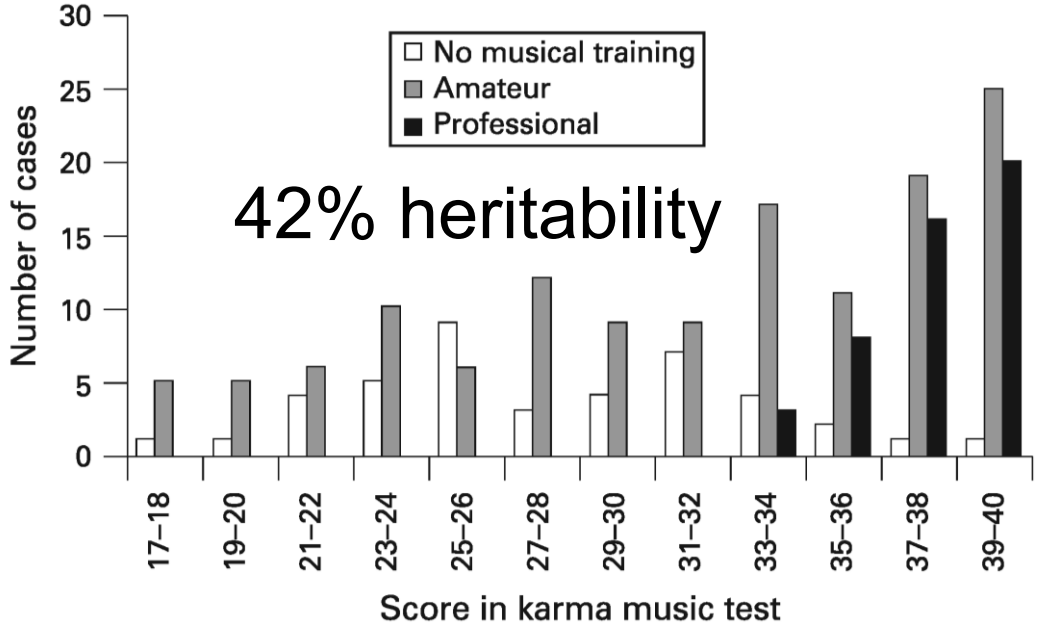


Ukkola et al. (2009) *PLoS ONE* **4:** e5534

Genome-wide linkage scan for loci of musical aptitude in Finnish families: evidence for a major locus at 4q22

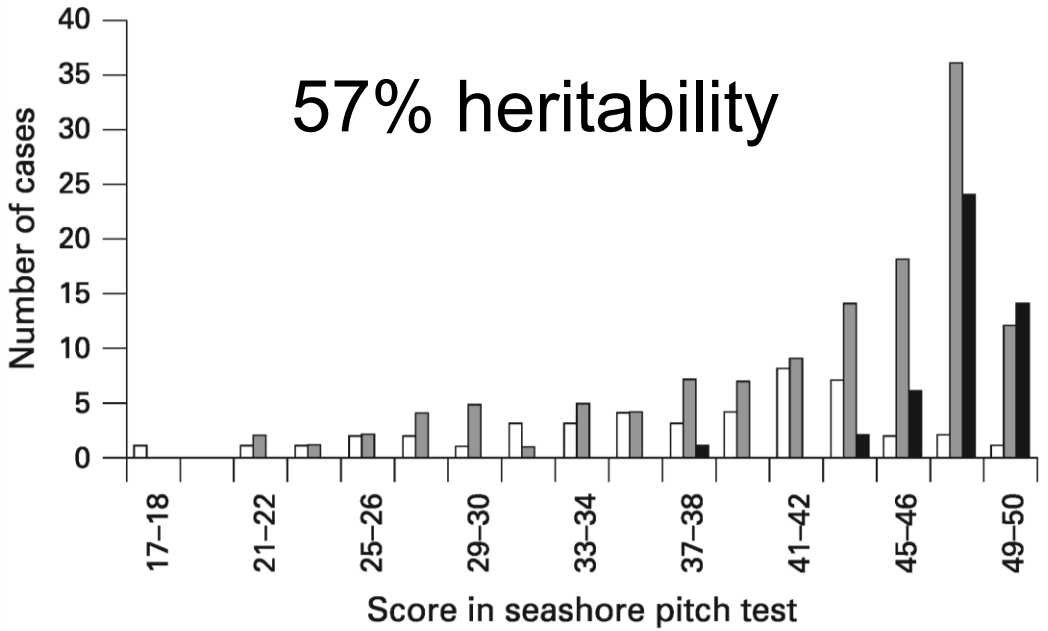
K Pulli,[1] K Karma,[2] R Norio,[3] P Sistonen,[4] H H H Göring,[5] I Järvelä[1,6]

J Med Genet 2008;**45**:451–456. doi:10.1136/jmg.2007.056366

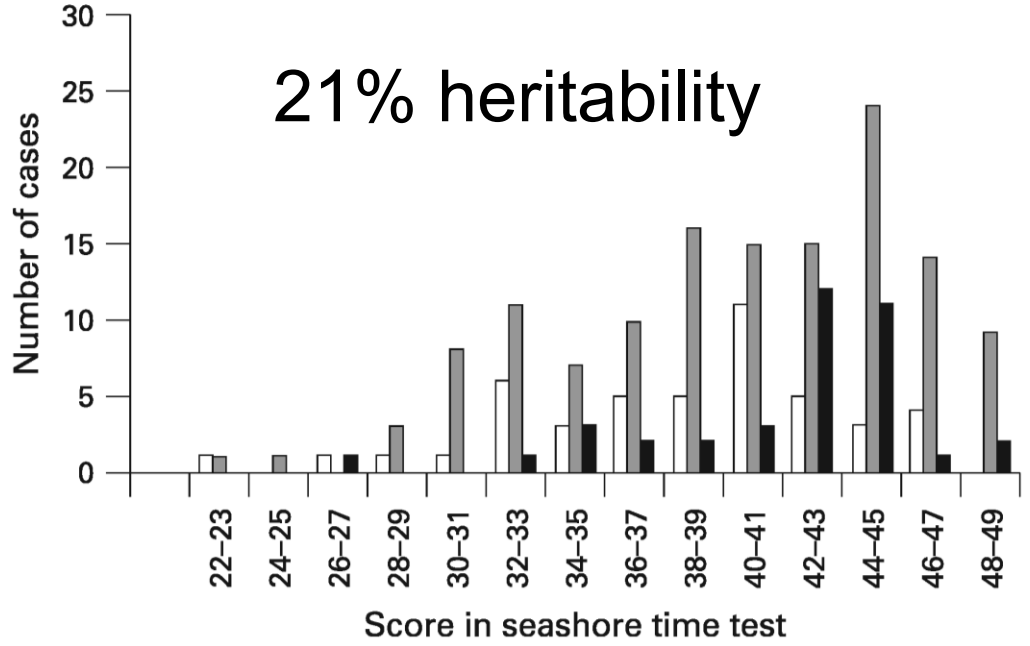


42% heritability

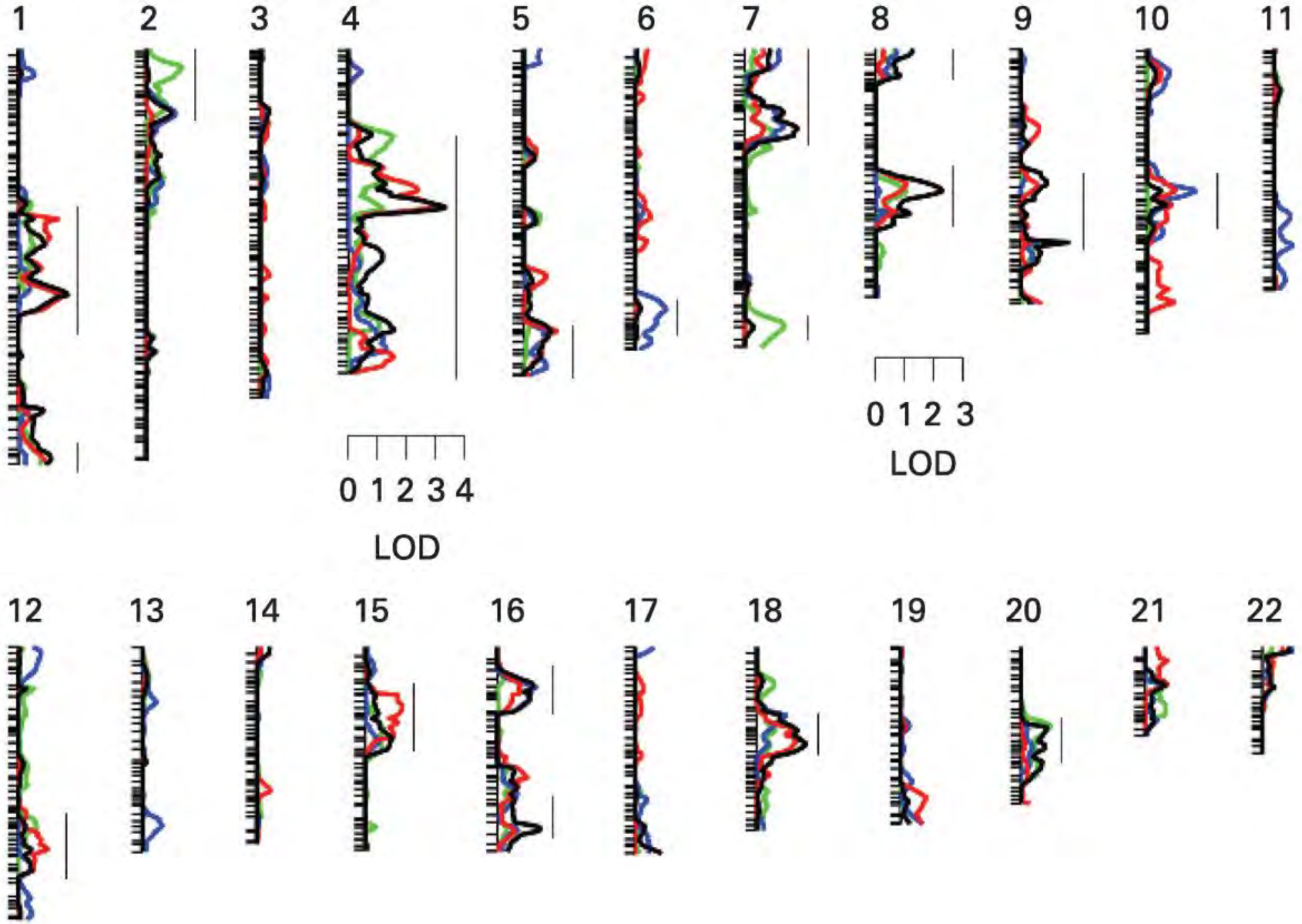
15 families (n = 234)



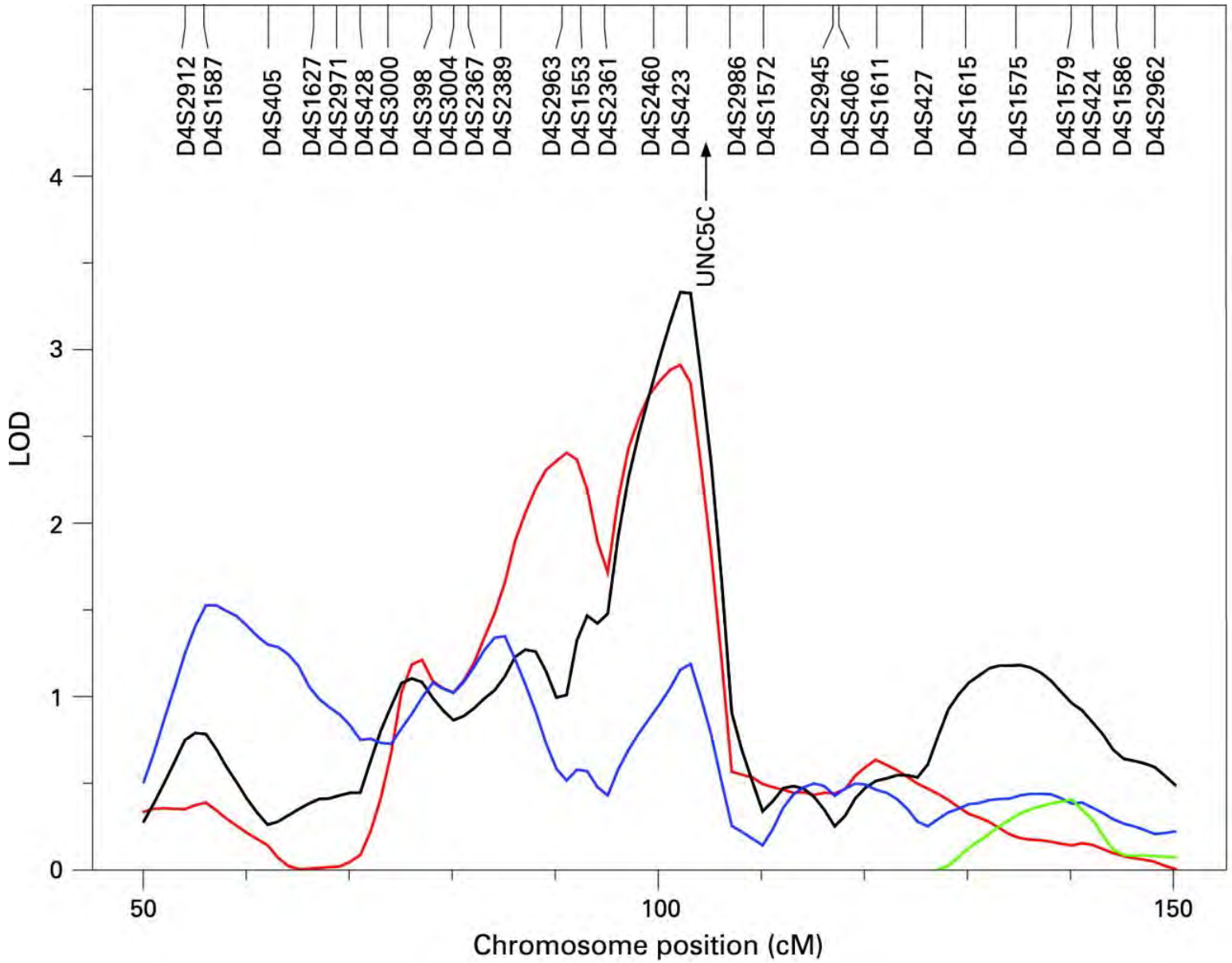
57% heritability



21% heritability



J Med Genet 2008;**45**:451–456. doi:10.1136/jmg.2007.056366



J Med Genet 2008;**45**:451–456. doi:10.1136/jmg.2007.056366

Musical Aptitude Is Associated with AVPR1A-Haplotypes

Liisa T. Ukkola[1]*, Päivi Onkamo[2], Pirre Raijas[3], Kai Karma[4], Irma Järvelä[1,5]

Trait	Gene	Polymorphism	Allele(s)	Freq./informative fam#	p	Corrected p
KMT	AVPR1A	AVR	6	0.040/17	0.00732	NS
		AVR and RS1	Overall			0.02751
		AVR and RS1	4 and 4	0.103/20		0.02751
		RS1 and RS3	Overall			0.00612
		RS1 and RS3	4 and 4	0.042/11	0.0167	0.0192
		RS1 and RS3	**4 and 5**	**0.103/21**	**0.000807**	**0.00002**
		RS1 and RS3	**5 and 4**	**0.063/10**		**0.00032**
	SLC6A4	VNTR 5-HTTLPR	12 repeats and LA	0.171/33		0.0115
SP	AVPR1A	RS3	4	0.198/45	0.0267	NS
		RS1+RS3	4 and 5	0.103/21	0.0261	0.0072
		RS1+RS3	5 and 4	0.063/10	0.0268	0.0154
ST	AVPR1A	AVR and RS1	5 and 4	0.149/28	0.0038	0.00184
		AVR and RS3	4 and 4	0.052/11	0.0352	0.00534
COMB	AVPR1A	AVR and RS1	Overall		0.0043	0.04546
		AVR and RS1	5 and 4	0.149/28	0.0083	0.00402
		RS1 and RS3	Overall		0.0104	0.06491
		RS1 and RS3	**4 and 5**	**0.103/21**	**0.0056**	**0.00060**
		RS1 and RS3	**5 and 4**	**0.063/10**	**0.0018**	**0.00064**

19 families (n = 343)

Ukkola et al. (2009) *PLoS ONE* **4:** e5534

Musical Aptitude Is Associated with AVPR1A-Haplotypes

Liisa T. Ukkola[1]*, Päivi Onkamo[2], Pirre Raijas[3], Kai Karma[4], Irma Järvelä[1,5]

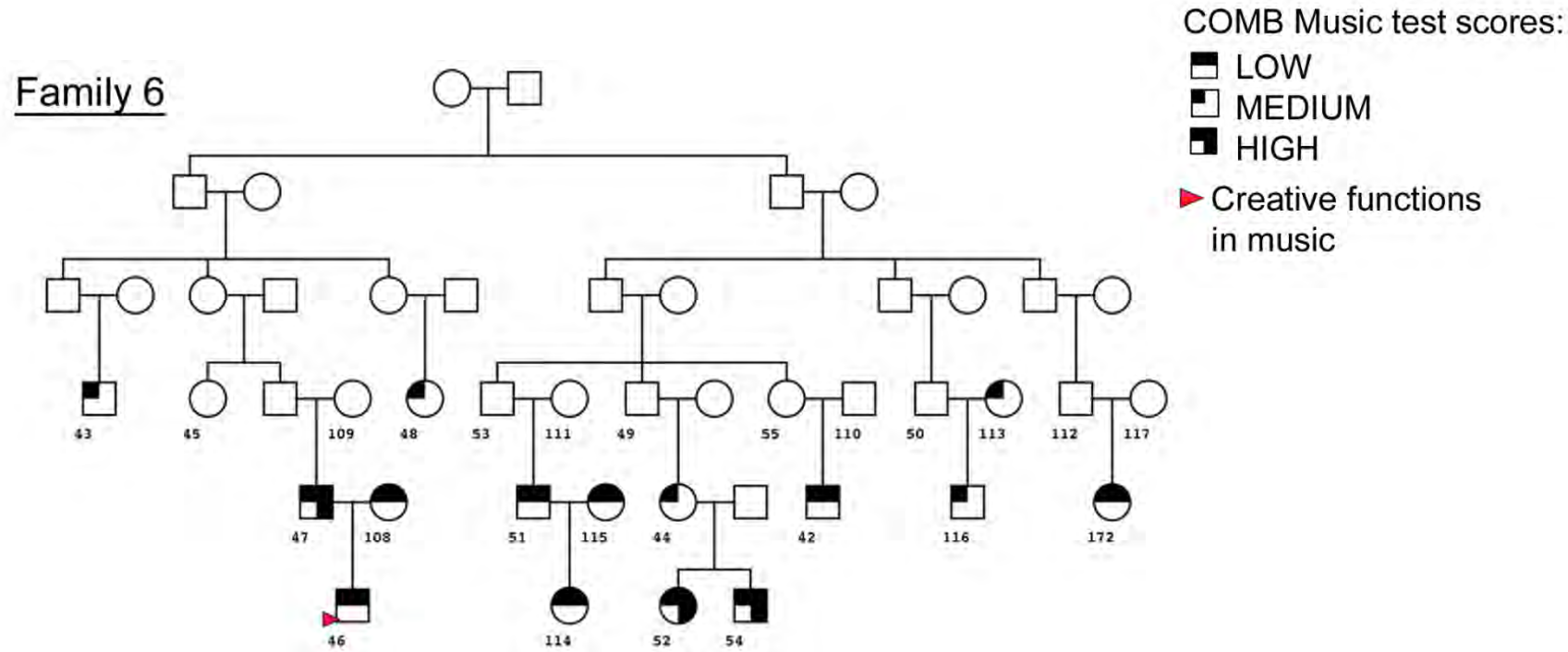
Trait	Gene	Polymorphism	Allele(s)	Freq./informative fam#	p	Corrected p
KMT	AVPR1A	AVR	6	0.040/17	0.00732	NS
		AVR and RS1	Overall			0.02751
		AVR and RS1	4 and 4	0.103/20		0.02751
SP						
ST						
COMB	AVPR1A	AVR and RS1	Overall		0.0043	0.04546
		AVR and RS1	5 and 4	0.149/28	0.0083	0.00402
		RS1 and RS3	Overall		0.0104	0.06491
		RS1 and RS3	**4 and 5**	**0.103/21**	**0.0056**	**0.00060**
		RS1 and RS3	**5 and 4**	**0.063/10**	**0.0018**	**0.00064**

Used **two** methods, **three** different modes of inheritance, and analysed multiple polymorphisms from **five** different genes. Results of one method were reported.

19 families (n = 343)

Ukkola et al. (2009) *PLoS ONE* **4:** e5534

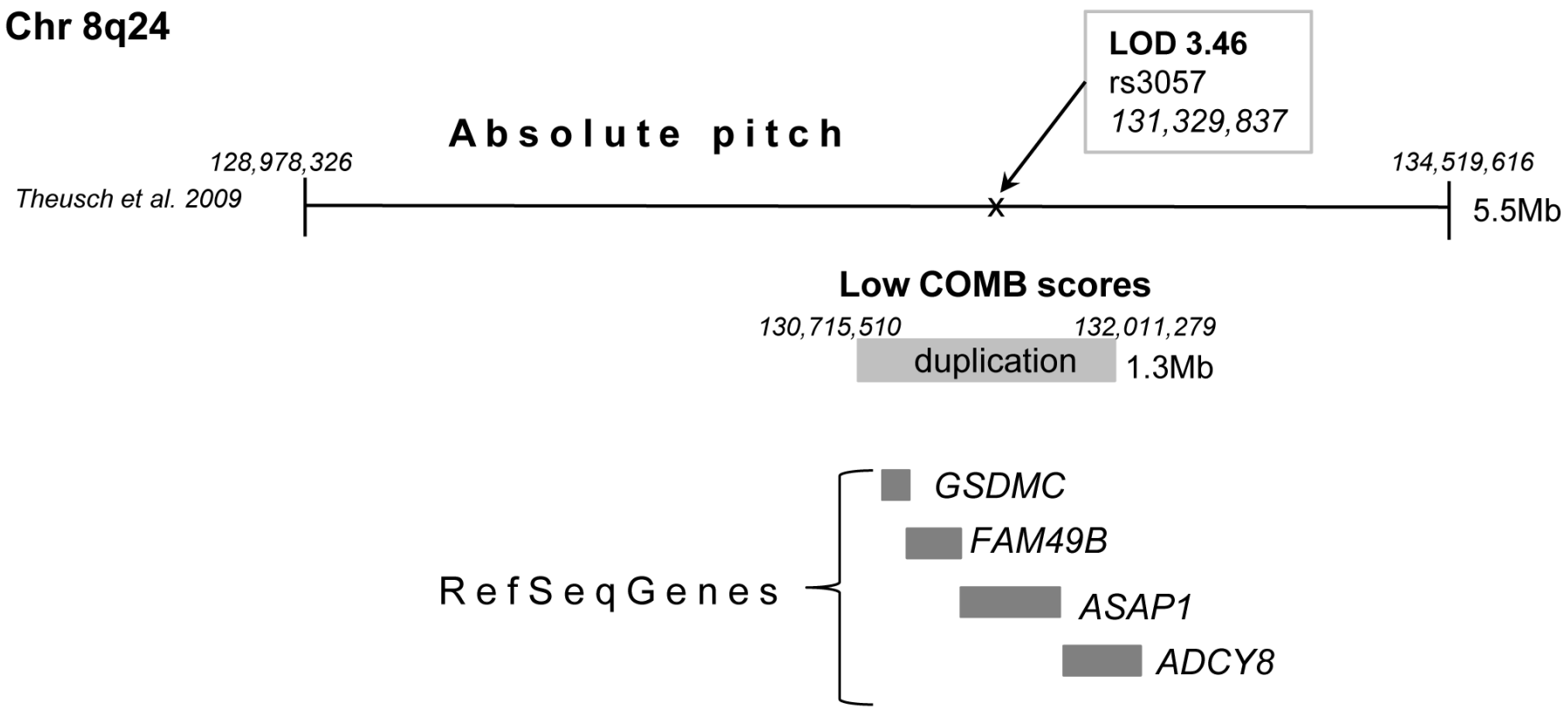
Genome-Wide Copy Number Variation Analysis in Extended Families and Unrelated Individuals Characterized for Musical Aptitude and Creativity in Music



5 families (n = 170) + 172 unrelated people

Ukkola-Vuoti et al. (2013) *PLoS ONE* **8:** e56356

Genome-Wide Copy Number Variation Analysis in Extended Families and Unrelated Individuals Characterized for Musical Aptitude and Creativity in Music



Ukkola-Vuoti et al. (2013) *PLoS ONE* **8:** e56356

Genome-Wide Copy Number Variation Analysis in Extended Families and Unrelated Individuals Characterized for Musical Aptitude and Creativity in Music

Families

	freq. in the phenotype	Chr region	Chr: start-end	Event type	Genes	Families
High COMB music test scores	67%	1q21.2	1:149039031–149388389	Loss	*FCGR1C, LOC388692*	6, 14
Low COMB music test scores	54%	5q31.3	5:140225908–140237548	Loss	*Protocadherin alpha gene cluster*	14, 15

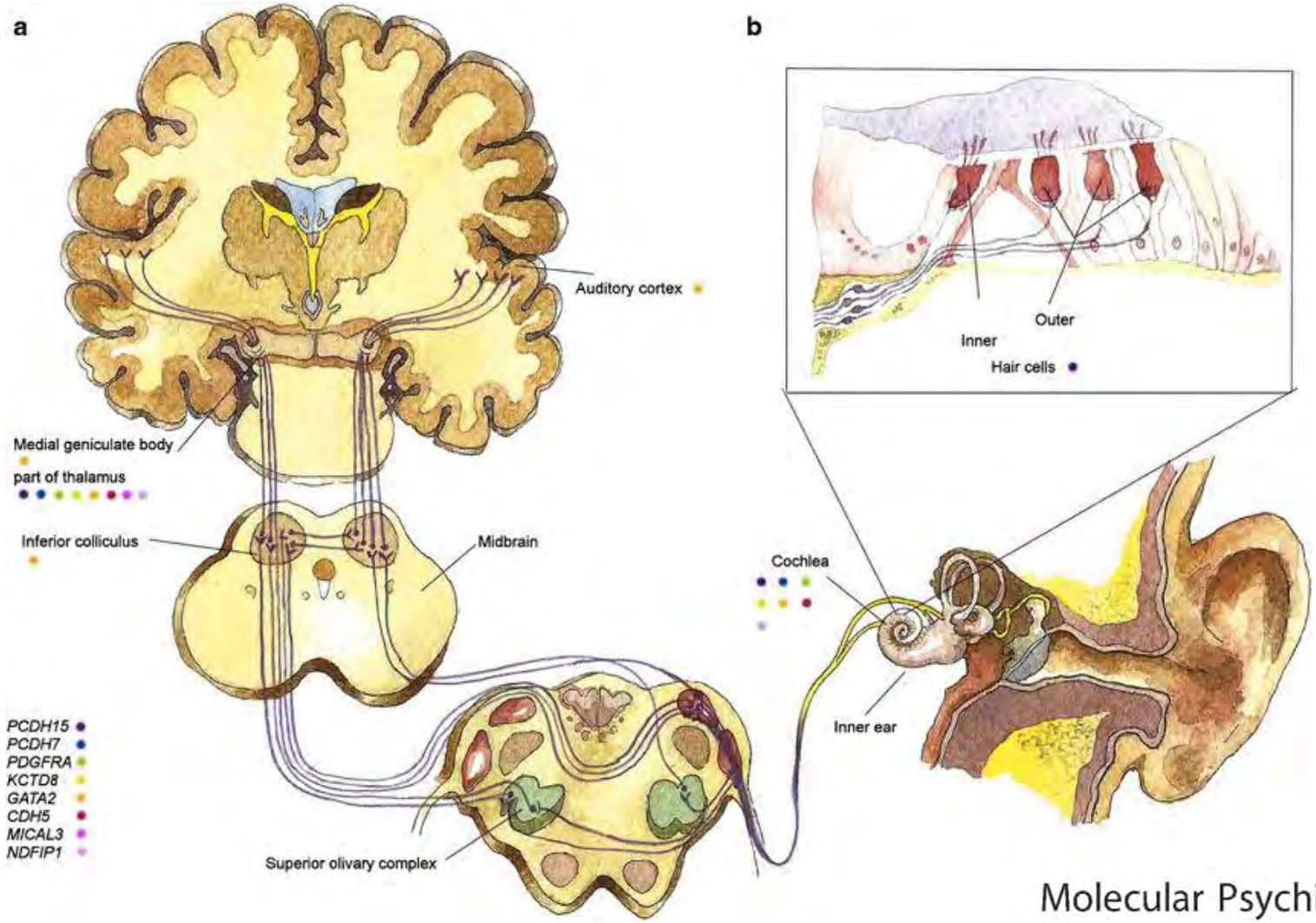
Unrelated people

High COMB (N = 40)	Low COMB (N = 28)	Chr region	Chr: start-end	Event type	Genes	p-value
8 (20%)	13 (46%)	3p14.1	3: 65191847–65214685	loss	-	0.0322
6 (15%)	0 (0%)	12p11.21	12: 31266287–31409778	gain	-	0.0385

Ukkola-Vuoti et al. (2013) *PLoS ONE* **8:** e56356

A genome-wide linkage and association study of musical aptitude identifies loci containing genes related to inner ear development and neurocognitive functions

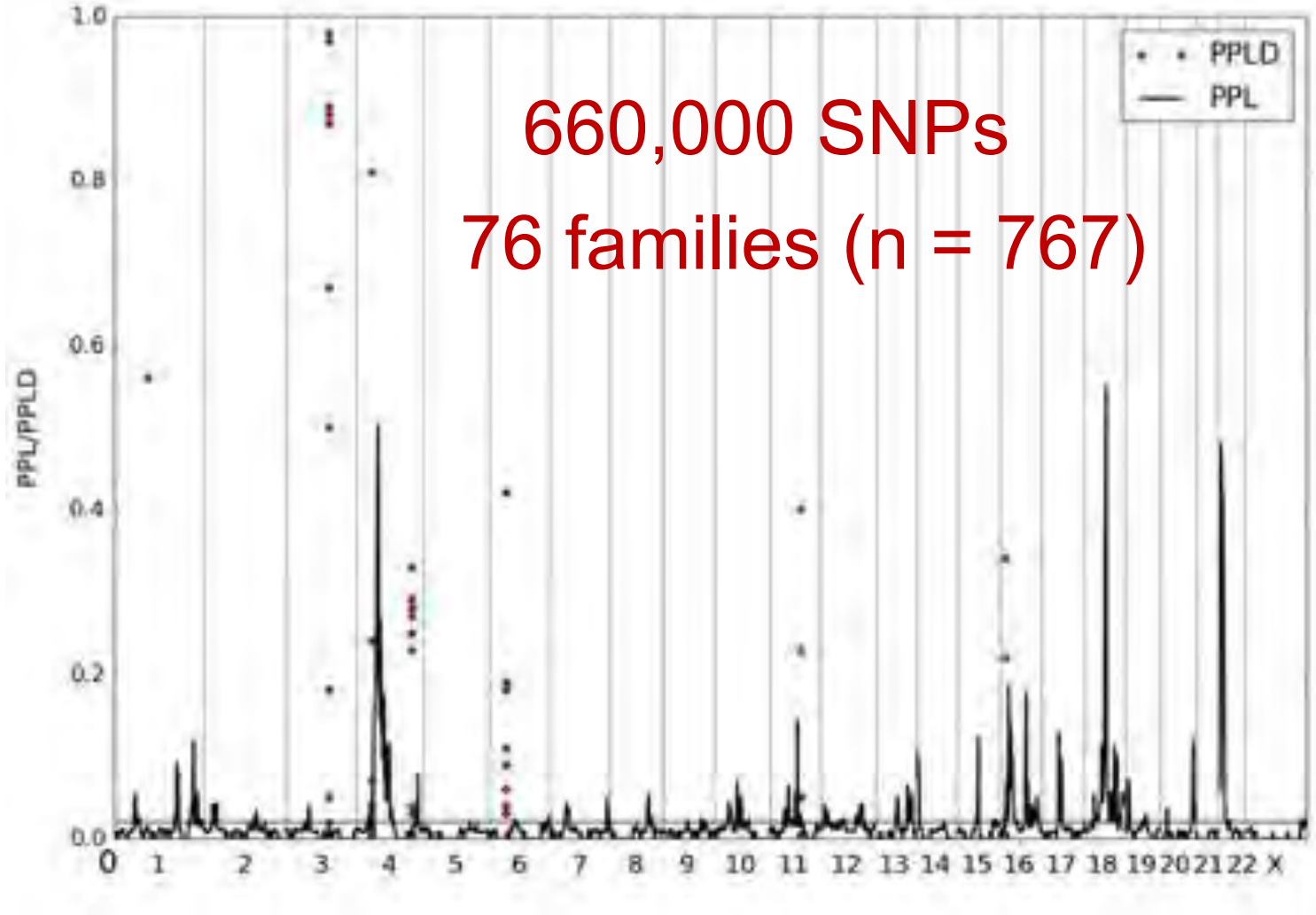
J Oikkonen[1,2], Y Huang[3], P Onkamo[2], L Ukkola-Vuoti[1], P Raijas[4], K Karma[4], VJ Vieland[3] and I Järvelä[1]



Molecular Psychiatry (2015) 20, 275–282

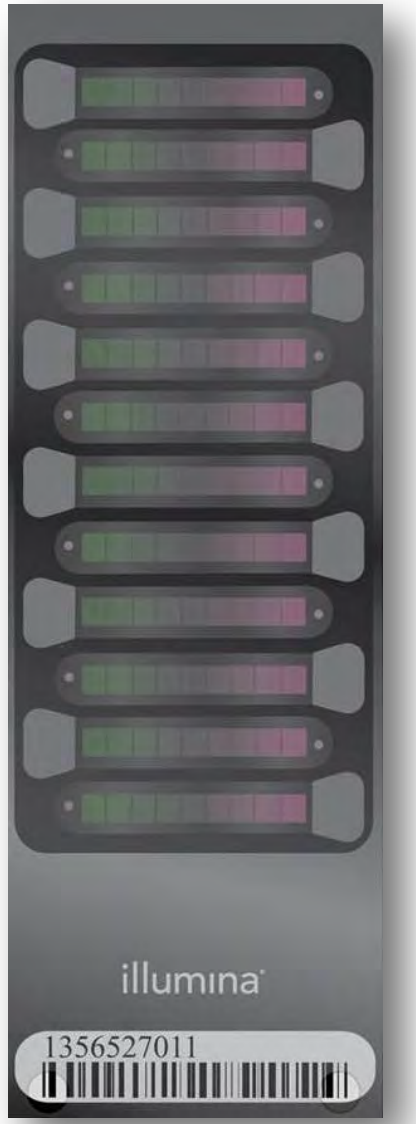
A genome-wide linkage and association study of musical aptitude identifies loci containing genes related to inner ear development and neurocognitive functions

J Oikkonen[1,2], Y Huang[3], P Onkamo[2], L Ukkola-Vuoti[1], P Raijas[4], K Karma[4], VJ Vieland[3] and I Järvelä[1]



660,000 SNPs

76 families (n = 767)



Molecular Psychiatry (2015) 20, 275–282

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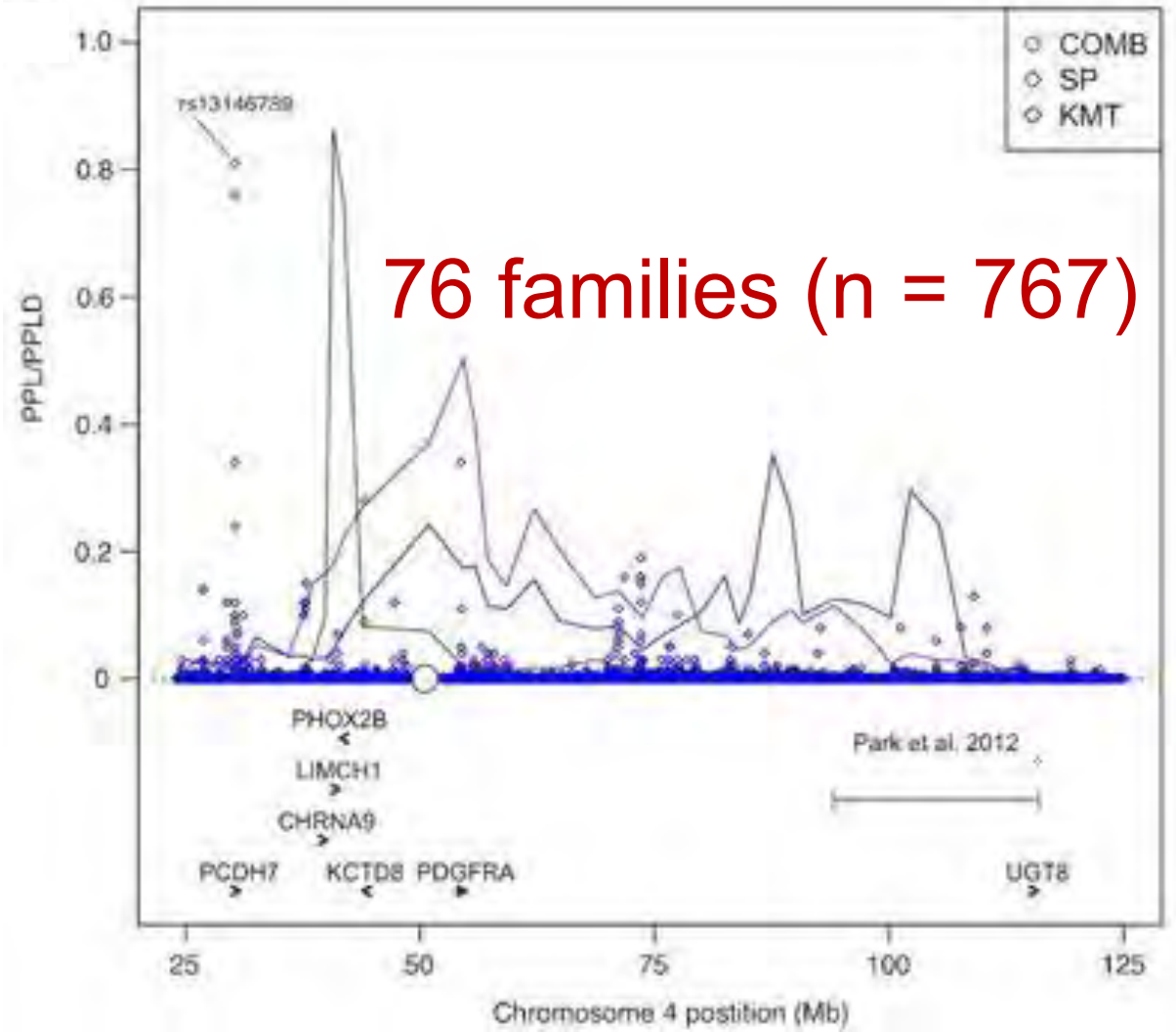

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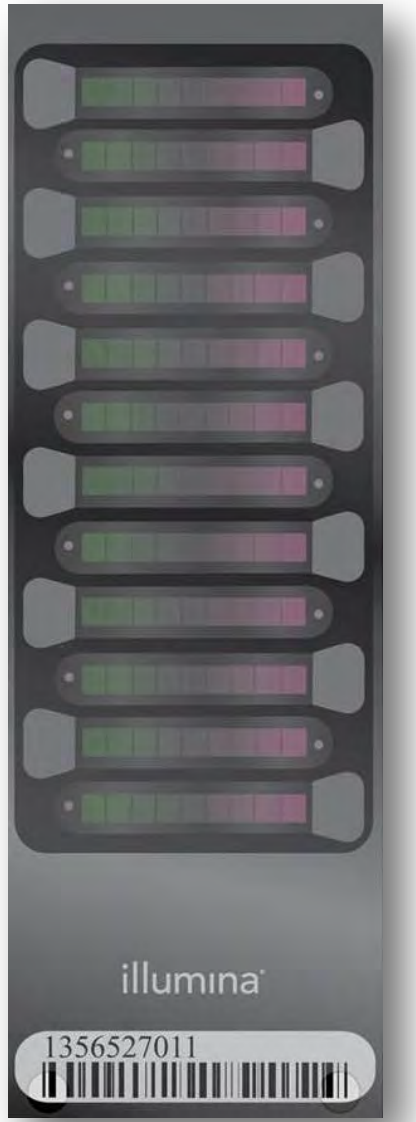

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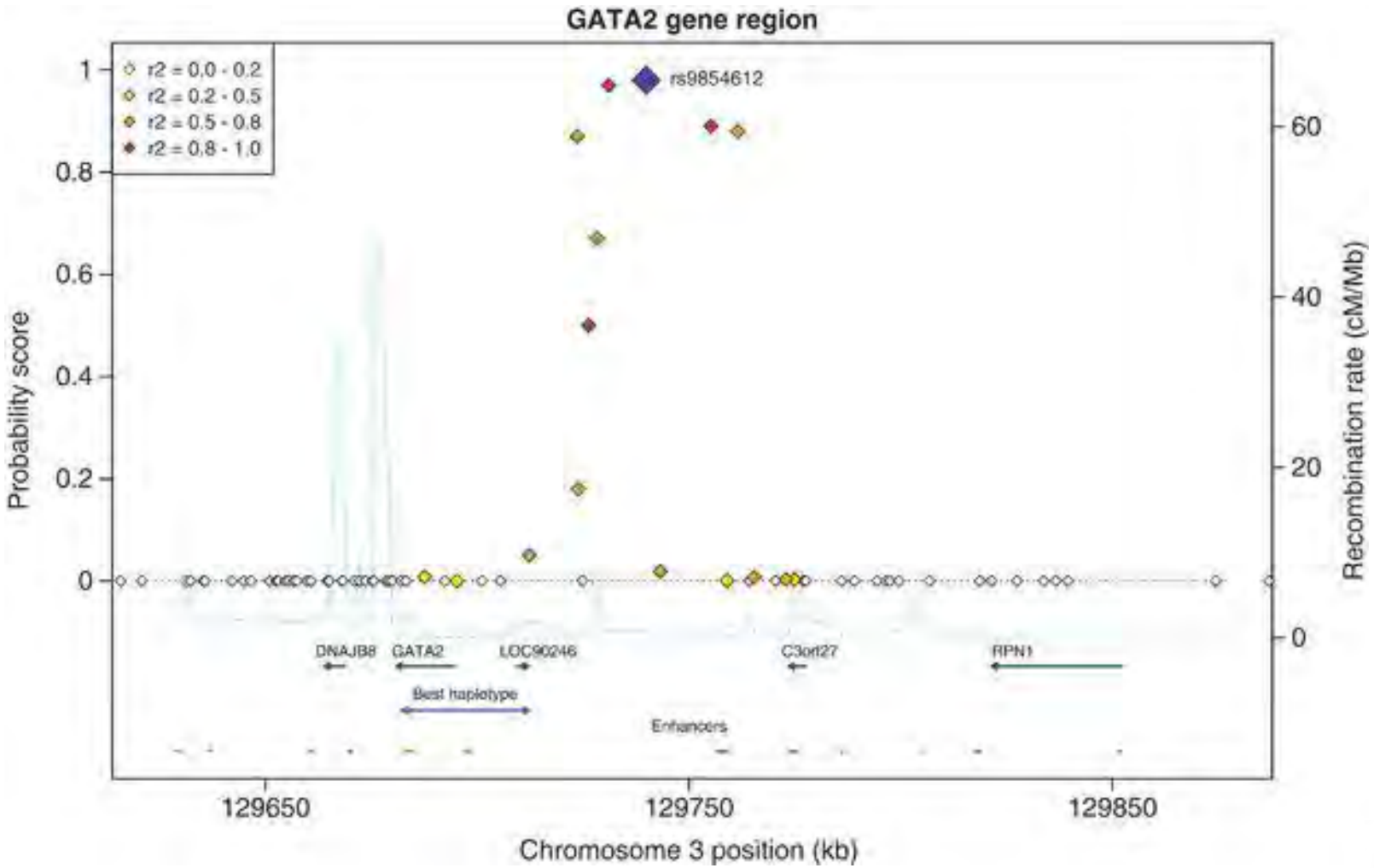

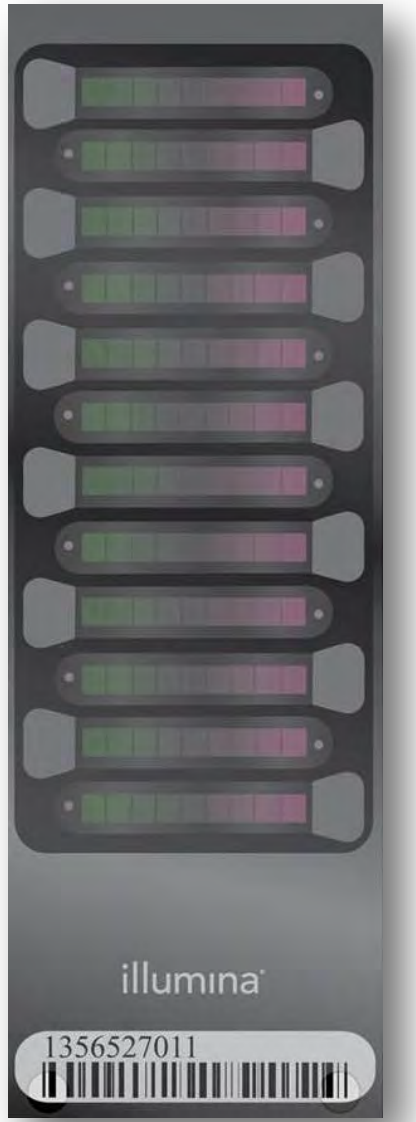

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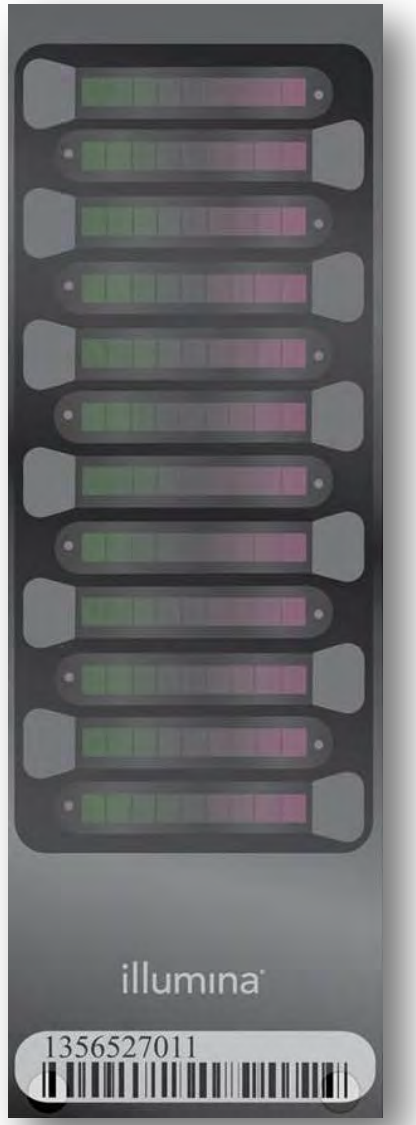
No replication of prior studies of musical (endo)phenotypes

None of the top linkage regions contained polymorphisms that showed robust evidence of association

No support for findings from prior targeted studies on candidate genes (e.g. AVPR1A)



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Molecular windows

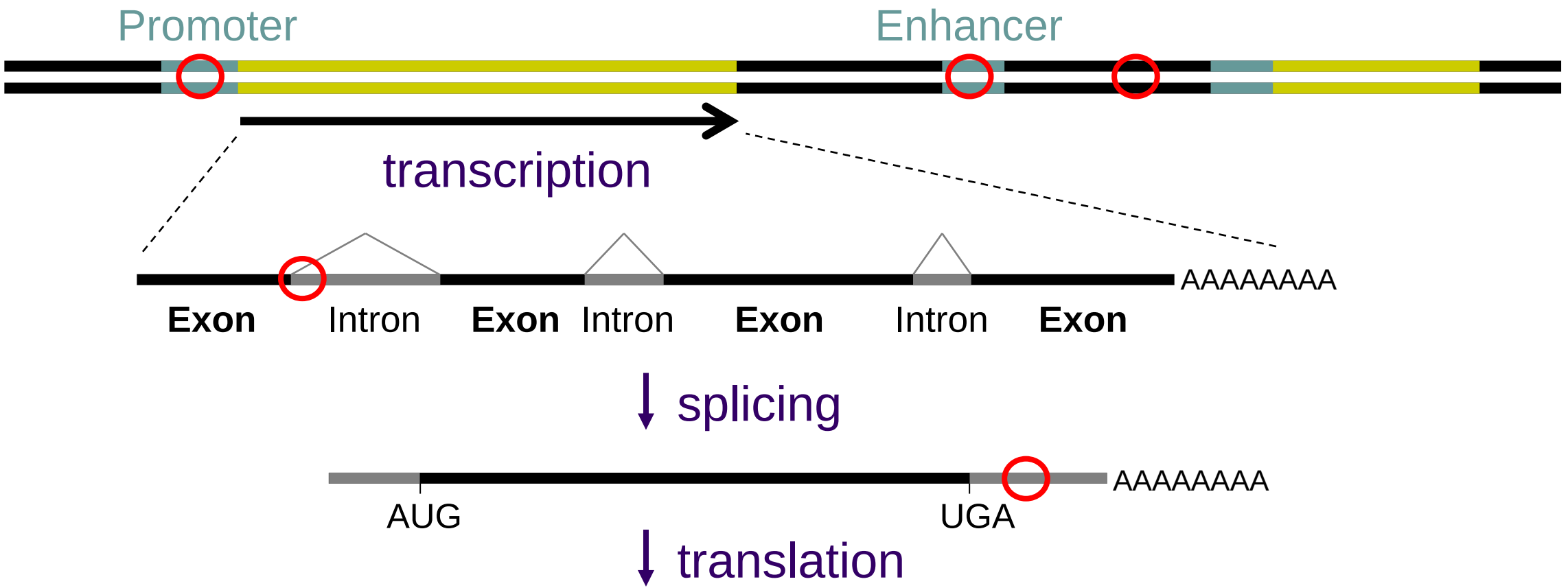
- Complex traits typically involve many genetic factors, each with tiny effect size
- Need very large samples in order to provide sufficient power to reliably detect these
- Importance of consistent replication, involving directly matching genetic markers and traits
- Small samples, multiple testing and (unintended) p-hacking increases susceptibility to false positives
- Distinguishing signals from noise is crucial
- Huge search space for plausible candidate genes

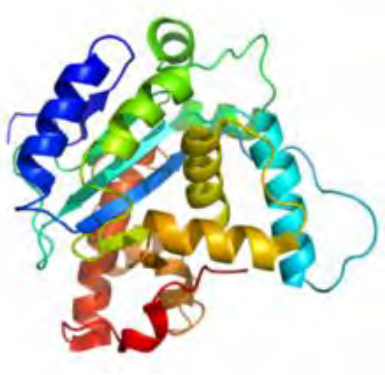
SCIENCE

A Waste of 1,000 Research Papers

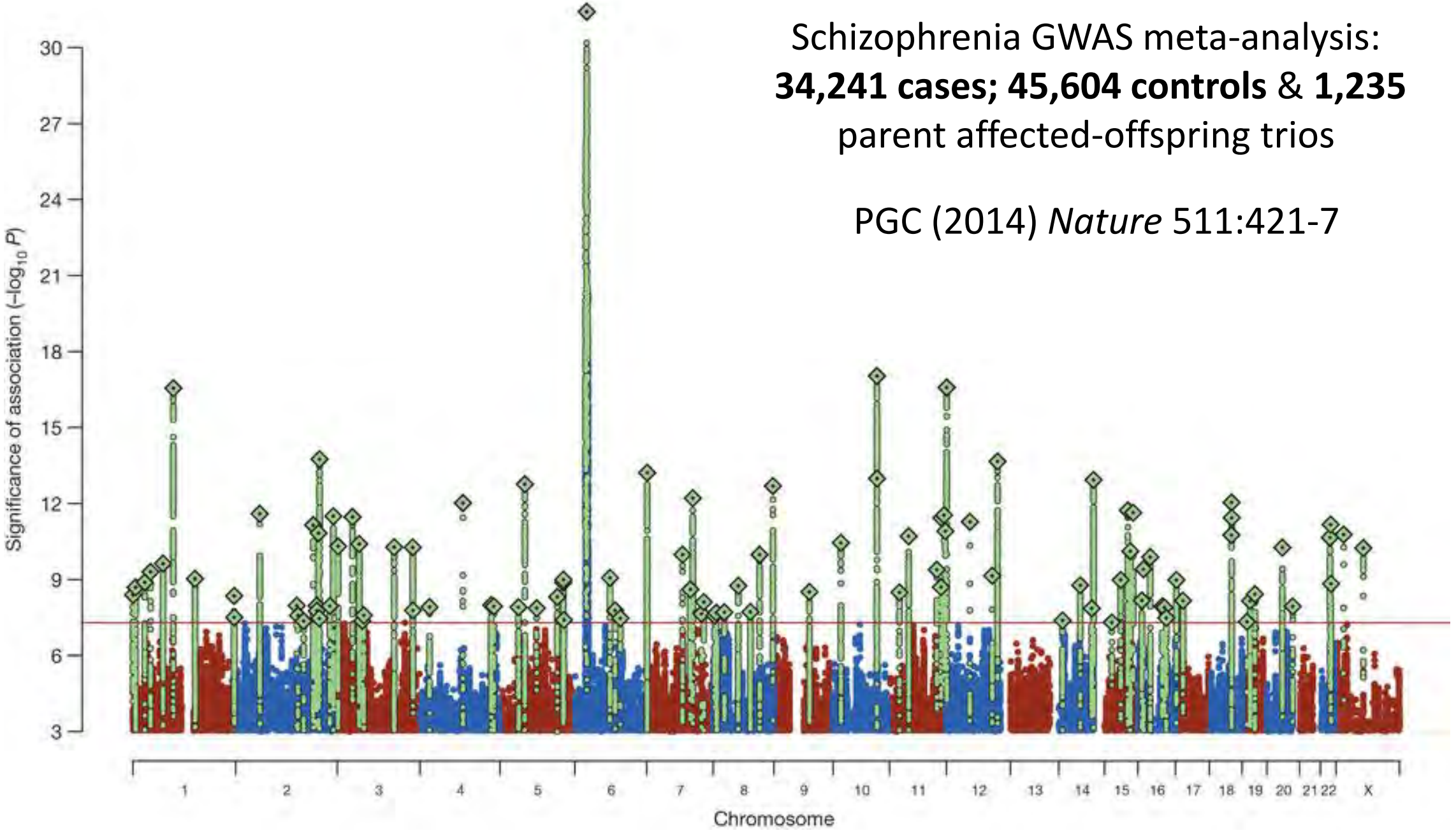
Decades of early research on the genetics of depression were built on nonexistent foundations. How did that happen?

ED YONG MAY 17, 2019


Promoter
Enhancer
transcription
AAAAAAAA
Exon
Intron
Exon
Intron
Exon
Intron
Exon
splicing
AAAAAAAA
AUG
UGA
translation



Great responsibility to ensure great power....



Schizophrenia GWAS meta-analysis:
34,241 cases; 45,604 controls & **1,235** parent affected-offspring trios

PGC (2014) *Nature* 511:421-7

- Definition of (endo)phenotype is crucial
- Complementary approaches target disorders, exceptional abilities, or general population
- Family clustering & twin studies => evidence of heritability, without pinpointing particular genes
- Linkage in families maps rough locations of genes, association studies can point to specific variants
- Insights might also be gained from observing altered musicality in known genetic syndromes
- Robust scalable phenotyping could transform field

Thank you for listening!

Email: simon.fisher@mpi.nl

Twitter: @ProfSimonFisher

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