


Lecture XV. Genetics and Human Brains:
Clues from Abnormal Function and Structure

Bio 3411
Monday
October 12, 2009

October 12, 2009 Lecture XV. Genetics and Human Brains 1

Movie - vmjr-brain.mp4



October 12, 2009 Lecture XV. Genetics and Human Brains 2

Overview

- Genetics and Humans
- MRDD (mental retardation and developmental disabilities)
- Humans
- Mice
- What's with the Brain?

October 12, 2009 Lecture XV. Genetics and Human Brains 3

Genetics and Humans

October 12, 2009 Lecture XV. Genetics and Human Brains 4

Elements

Neurons (=nerve cells) \approx 100 Billion

Glia (= glue; "supporting" cells) \approx 1 Trillion


Synapses (=clasp) $1/3,000,000^{\text{th}}$ of all stars, planets and big rocks in the universe

Genes 50% of \approx 25,000 genes in genome are expressed only in "Brain"

[70% of the balance are also expressed in the nervous system; the total is 85% of the genome]

October 12, 2009 Lecture XV. Genetics and Human Brains 5

THE BRAIN ATLAS 3rd ed, p. 20



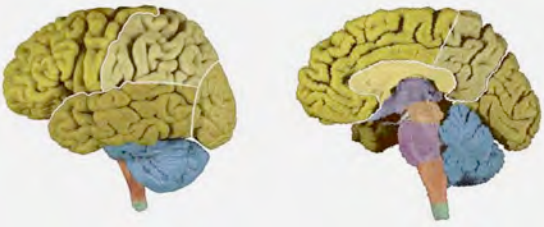
Left Lateral (side) view of the human Brain

October 12, 2009 Lecture XV. Genetics and Human Brains 6


THE BRAIN ATLAS 3rd ed, p. 9

The different regions of the brain from the lateral (side) and median section (middle) human brain. These brain regions are discernable in all vertebrates and in early embryos.


(cerebral cortex = gold; thalamus = blue/purple; midbrain = orange; pons = purple, cerebellum = blue; medulla = red/orange; spinal cord = green)



October 12, 2009 Lecture XV. Genetics and Human Brains 7



Victor A. McKusick, MD (ca 2002)




October 12, 2009 Lecture XV. Genetics and Human Brains 8

Marfan Syndrome

Marfan 1896


Tall, indented chest (pectus excavatum)
long digits, cardiovascular problems
Fibrillin – connective tissue
Autosomal dominant



Zhelli BJ 2005 Picture of the month. Arch Pediatr Adolesc Med. 2005;159:721-723.

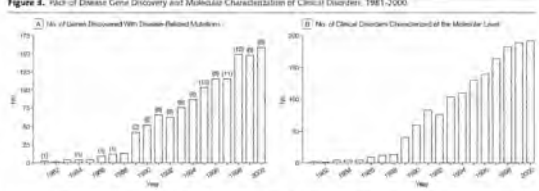
October 12, 2009 Lecture XV. Genetics and Human Brains 9

Victor McKusick organized a catalog of human inherited conditions, first published in 1966. Since then the number has grown approximately 15 fold. Of these, an increasing number of conditions has been identified as having some component related to the nervous system. From: McKusick 2007 Am J Hum Genet



October 12, 2009 Lecture XV. Genetics and Human Brains 10

Figure 3. Pace of Disease Gene Discovery and Molecular Characterization of Clinical Disorders, 1961-2000



Reprinted with permission from Palomares L, McKusick VA. Discovering human disease in the post-genomic era. Science. 2001;291:1224-1229. A: The number of disease genes discovered by the end of 2000 was 1112, including both genomic and sequence-related somatic mutations. This number does not include all the genes identified as translocation gene-fusion partners in neoplastic disorders. Numbers in parentheses indicate genes with disease-related polymorphic alleles (susceptibility genes). B: The number of clinical disorders characterized by the end of 2000 was 1430. This number does not include the many neoplastic disorders caused by translocation-related fusion genes.

From:
McKusick 2001 JAMA

October 12, 2009 Lecture XV. Genetics and Human Brains 11

Access to "Mendelian Inheritance in Man"

McKusick VA, with Antonarakis SE, Francomano CA, Hurko O, Scott AF, Smith M, Valle D, & others 1998 *Mendelian Inheritance in Man: A Catalog of Human Genes and Genetic Disorders. 12th Ed.* Baltimore: The Johns Hopkins University Press, 3972 pp.

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>

October 12, 2009 Lecture XV. Genetics and Human Brains 12

Lecture XV. Genetics and Human Brains

References

Background:

Altman L 2008 Viktor McKusick, 86, dies; medical genetics pioneer. <http://www.nytimes.com/2008/07/24/health/24mckusick.html>

Hostetler JA 1993 *Amish Society, 4th ed.* Baltimore: Johns Hopkins University Press, 435 p.

McKusick VA 2001 The anatomy of the human genome: a neo-Vesalian basis for medicine in the 21st century. *JAMA* 286:2289-2295.

McKusick VA 2007 Mendelian Inheritance in man and its online version, OMIM. *Am J Hum Genet*, 80:588-604.

Zitelli BJ 2005 Picture of the month. *Arch Pediatr Adolesc Med* 2005;159:721-723. (Marfan)

[†]Walsh CA 2001 Neuroscience in the post-genome era: an overview *TINS* 24:363-364.

[†]Stump E 2008 Victor A. McKusick, MD, wins Japan prize. *Neurol Today* May 2, p17.

[†] pdf posted on course website.

October 12, 2009 Lecture XV. Genetics and Human Brains 13

MRDD (mental retardation and developmental disabilities)

October 12, 2009 Lecture XV. Genetics and Human Brains 14

There are various causes of mental retardation, most commonly:

- Genetic conditions.
- Problems (environmental) during pregnancy.
- Problems (environmental) at birth.
- Problems (environmental) during childhood.


October 12, 2009 Lecture XV. Genetics and Human Brains 15

Partial List of Genetic Causes of MRDD

- **Trisomy 21 or Down syndrome (added 21)**
- **Williams syndrome (deletion at 7q11)**
- Fragile X syndrome
- Prader-Willi syndrome
- Smith-Magenis syndrome
- CATCH 22 syndrome
- Wolf-Hirschhorn syndrome
- Langer-Giedion syndrome
- Miller-Dieker syndrome
- Tuberosus sclerosis
- Rubinstein-Taybi syndrome
- Coffin-Lowry syndrome
- Rett syndrome
- Smith-Lemli-Opitz syndrome

October 12, 2009 Lecture XV. Genetics and Human Brains 16

Williams Syndrome

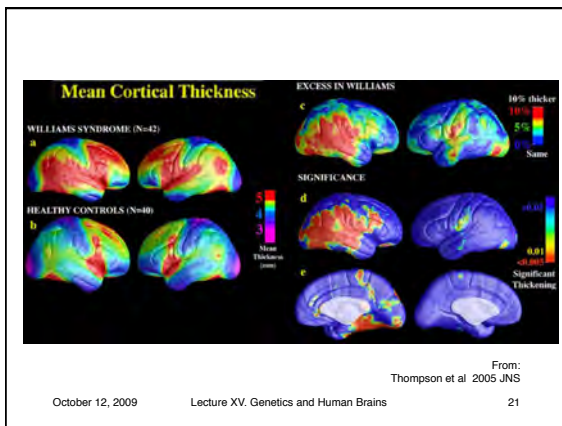
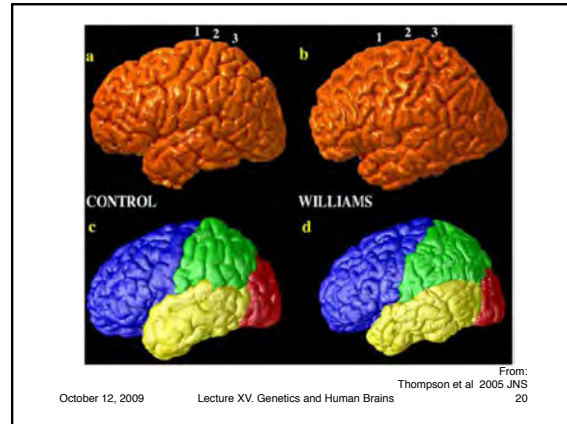
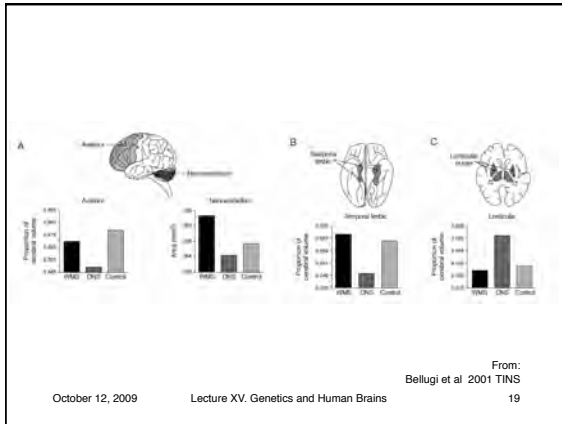


October 12, 2009 Lecture XV. Genetics and Human Brains 17

	Williams syndrome (poor on global organization)	Down syndrome (poor on internal detail)
A Free drawing of a house		
B Block-design task		
C Local-global task		

From:
Bellugi et al 2001 TINS

October 12, 2009 Lecture XV. Genetics and Human Brains 18



PBS - Williams Syndrome Broadcast 2001 with Dr. Ursula Bellugi

<http://www.pbs.org/saf/1205/video/watchonline.htm>

October 12, 2009 Lecture XV. Genetics and Human Brains 22

References

Williams Syndrome:

- Bellugi U, Lichtenberger L, Mills D, Galaburda A, Korenberg JR 1999 Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome Trends Neurosci 22:197-207.
- Thompson PM, Lee AD, Dutton RA, Geaga JA, Hayashi KM, Eckert MA, Bellugi U, Galaburda AM, Korenberg JR, Mills DL, Toga AW, Reiss AL 2005 Abnormal cortical complexity and thickness profiles mapped in Williams syndrome J Neurosci 25:4146-4158.
- Van Essen DC, Dierker D, Snyder AZ, Raichle ME, Reiss AL, Korenberg J 2006 Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses. J Neurosci 26:5470-5483.

October 12, 2009 Lecture XV. Genetics and Human Brains 23

Humans

October 12, 2009 Lecture XV. Genetics and Human Brains 24

Table 3. Pairwise Identity of ASPM Proteins

	Green Monkey	Macaque	Orangutan	Gorilla	Chimpanzee	Human
Green monkey		98.47	95.81	95.56	95.76	95.59
Macaque			96.1	95.85	96.02	95.88
Orangutan				97.72	97.86	98.3
Gorilla					98.41	99.02
Chimpanzee						99.02
Human						

Loss of the abnormal spindle protein gene (*ASPM*) correlates in humans with MRDD with small brains. This gene was present prior to the enlargement of the human brain and is thought to be upstream of genetic control of brain size. The similarities of this protein in different species is shown here.

Kouprina et al 2004 PLoS

October 12, 2009 Lecture XV. Genetics and Human Brains 25

Genes Associated With Malformations of the Human Cerebral Cortex*

Gene	Associated Disease	Gene Function
Microcephalin	Autosomal recessive microcephaly (MRCP)	Unknown; possibly DNA repair ¹
ASPM	Autosomal recessive microcephaly (MRCP)	Mitochondrial spindle ²
MST1 (nlras)	Niemann-Pick type C syndrome	DNA repair ³
EMX2	Schizencephaly	Transcription factor ⁴
TSC2 (hamartin)	Tuberous sclerosis	Tumor suppressor ⁵
TSC2 (p19)	Tuberous sclerosis	Tumor suppressor ⁶
LIS1	Lissencephaly (Miller-Dieker syndrome and isolated lissencephaly sequence)	Cytoplasmic microtubule regulator ⁷
DCX (doublecortin)	Double cortex/X-linked lissencephaly syndrome	Microtubule-associated protein ^{8,9}
RELN (reeler)	Lissencephaly with cerebellar hypoplasia	Extracellular matrix protein ¹⁰
ARX	X-linked lissencephaly with abnormal genitalia	Transcription factor ¹¹
FLNA (filamin A)	Periventricular nodular heterotopia	Actin-binding protein ¹²
PCMD (pulsin)	Fukuyama type congenital muscular dystrophy	Unknown; possibly glycosyltransferase ¹³
PSM1/PT	Muscle-eye-brain disease	Glycosyltransferase ¹⁴
PSM1/PT	Walker-Warburg syndrome	Glycosyltransferase ¹⁵

*The genes are listed along with the associated diseases and their presumed functions. Several of these genes are not discussed in the text owing to space constraints. Several genes that affect brain development but are associated with metabolic disorders or dysmorphic syndromes are omitted.

From:
Mochida & Walsh 2004 Arch Neurol

October 12, 2009 Lecture XV. Genetics and Human Brains 26

References

Humans:

- Yakovlev PI, Rakic P 1966 Patterns of decussation of bulbar pyramids and distribution of pyramidal tracks on two sides of the spinal cord. *Trans Am Neurol Assoc* 91:366-367.
- Kouprina N, Pavlicek A, Mochida GH, Solomon G, Gersch W, Yoon YH, Collura R, Ruvolo M, Barrett JC, Woods CG, Walsh CA, Jurka J, Larionov V 2004 Accelerated evolution of the ASPM gene controlling brain size begins prior to human brain expansion. *PLoS Biol* 2:0653-0663 DOI: 10.1371/journal.pbio.0020126
- Mochida GH, Walsh CA 2004 Genetic basis of developmental malformations of the cerebral cortex. *Arch Neurol* 61:637-640.
- Sun T, Patoinc C, Abu-Khalil A, Visvader J, Sum E, Cherry TJ, Orkin SH, Geschwind DH, Walsh CA 2005 Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science* 308:1794-1798.

October 12, 2009 Lecture XV. Genetics and Human Brains 27

Mice

October 12, 2009 Lecture XV. Genetics and Human Brains 28

Increasing the size of the pool of neuronal precursors in the forebrain leads to a larger more convoluted mouse brain (b & B).

From:
Chen & Walsh 2002 Science

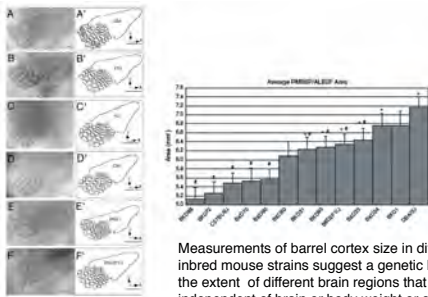
October 12, 2009 Lecture XV. Genetics and Human Brains 29

The mouse mutant "barrelless" (*brl*) was found after extensive screening. Cell bodies in the somatic normally outline the barrels (top left) that are largely absent in *brl* top right. These animals lack the gene for adenylyl cyclase 1 (lower left). Knocking out the gene for adenylyl cyclase 7 (lower right) does not affect the barrel pattern in cortex.

From:
Welker et al 1996 Science (above) and Abdel-Majid et al 1998 Nature Gen (below)

October 12, 2009 Lecture XV. Genetics and Human Brains 30

Lecture XV. Genetics and Human Brains



Measurements of barrel cortex size in different inbred mouse strains suggest a genetic basis for the extent of different brain regions that is independent of brain or body weight or size.

Li et al 2005 Somatosens Mot Res

October 12, 2009 Lecture XV. Genetics and Human Brains 31

References

Mice:

Chen A, Walsh CA 2002 Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* 297:365-369.

Welker E, Armstong-James M, Bronchti G, Qurednik W, Gheorghita- Baechler F, Dubois R, Guernsey DL, Van der Loos H, Neumann PE 1996 Modified tactile processing in somatosensory cortex of a new mutant mouse, barreless. *Science* 271, 1864-1867.

Abdel-Majid RM, Leong WL, Schalkwyk LC, Smallman DS, Wong ST, Storm DR, Fine A, Dobson MJ, Guernsey DL, Neumann PE 1998 Loss of adenylyl cyclase I activity disrupts patterning of mouse somatosensory cortex *Nature Gen* 19:289 - 291 doi:10.1038/980.


Li CX, Wei X, Lu L, Peirce JL, Williams RW, Waters RS 2005 Genetic analysis of barrel field size in the first somatosensory area (S1) in inbred and recombinant inbred strains of mice. *Somatosens Mot Res* 22:141-150.

Sun T, Patoine C, Abu-Khail A, Visvader J, Sum E, Cherry TJ, Orkin SH, Geschwind DH, Walsh CA 2005 Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science* 30:1794-1798. _____ 2008 *Allen Brain Atlas* (<http://www.brain-map.org/welcome.do>).


October 12, 2009 Lecture XV. Genetics and Human Brains 32

What's with the Brain?


October 12, 2009 Lecture XV. Genetics and Human Brains 33



The Rosetta Stone (left) permitted the translation of older Egyptian texts into Greek. Words in the former is based on a large number of unique picture based symbols each with a different meaning the latter on different arrangements of a small number of symbols (letters) which have no meaning unless arranged as words abbreviations, etc. (See add below.)



October 12, 2009 Lecture XV. Genetics and Human Brains 34



"No limit may be set to art, neither is there any craftsman that is fully master of his craft."
The Instruction of Ptahhotep

Hypothesis: The rapid enlargement of the forebrain over a virtual instant in evolutionary time may reflect the introduction of a simple, but flexible, change in the wiring of the brain and of the forebrain in particular. Rather than specifying detailed specific circuits with specific functions as may be the case in the hind brain and spinal cord the forebrain may specify simpler circuits that may be combined simply to perform different specific functions that are flexibly determined. This process may be analogous to the change from detailed and word specific writing (hieroglyphics) to a simpler more flexible representation using a few characters in different combinations to represent words old and new.

October 12, 2009 Lecture XV. Genetics and Human Brains 35


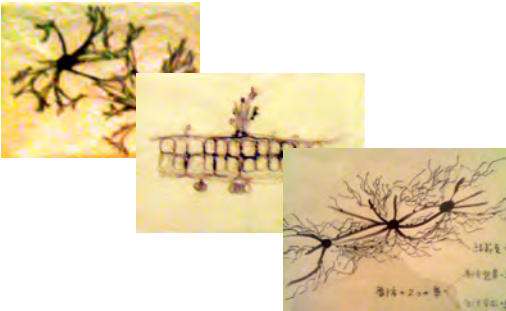


FIGURE 3.
Karnak Temple, Plan for Temple (144)
"The model showing the 'V-shaped' and the 'one and a half' temples."
Source: <http://www.egyptology.com/egyptology/egyptology.htm>

Lin, Z (2007)

October 12, 2009 Lecture XV. Genetics and Human Brains 36



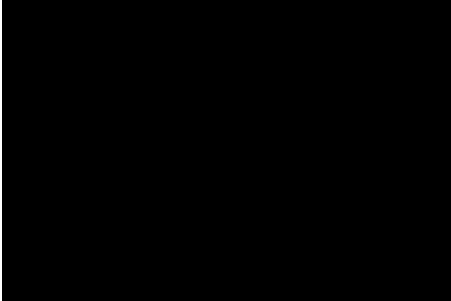
"Metabolic City." Through Jan. 4. Kemper Art Museum. 935-4523.

October 12, 2009 Lecture XV. Genetics and Human Brains 37

References


- Amadio JP, Walsh CA 2006 Brain evolution and uniqueness in the human genome. *Cell* 126:1033-5.
- LC Purchase Collection (Library of Congress). (1974). *Young Frankenstein*. United States: Twentieth Century-Fox Film Corporation, Twentieth Century-Fox Video Inc.
- Lin, Z. (2007) Urban structure for the expanding metropolis: Kenzo Tange's 1960 plan for Tokyo. *J Arch Plann Res* 24:109-124.
- Lin, Z. (2010). *Kenzo Tange and the Metabolist movement : urban utopias of modern Japan*. New York: Routledge.
- Waldrop MM 2001 *The dream machine: J. C. R. Licklider and the revolution that made computing personal*. New York: Viking, 502 p.

October 12, 2009 Lecture XV. Genetics and Human Brains 38



LC Purchase Collection
(Library of Congress), (1974)

October 12, 2009 Lecture XV. Genetics and Human Brains 39



October 12, 2009 Lecture XV. Genetics and Human Brains 40

End

October 12, 2009 Lecture XV. Genetics and Human Brains 41