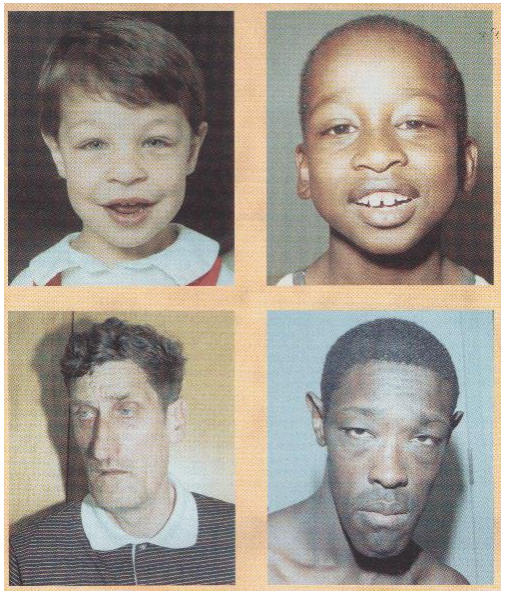
Psych 3102
Introduction to Behavior Genetics

Lecture 7

Further examples of Non-Mendelian Inheritance

Fragile-X syndrome



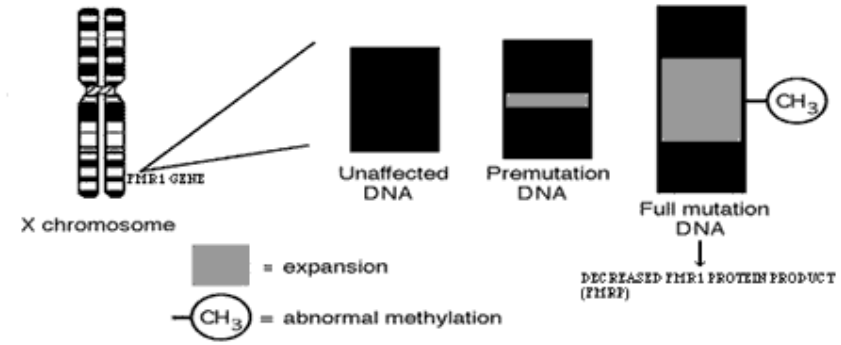
X-linked dominant with
incomplete penetrance and
variable expressivity

Prevalence:1 in 2500 males

1 in 5000 females

Phenotype: 2nd major genetic cause of mental retardation

morphological and behavioral features

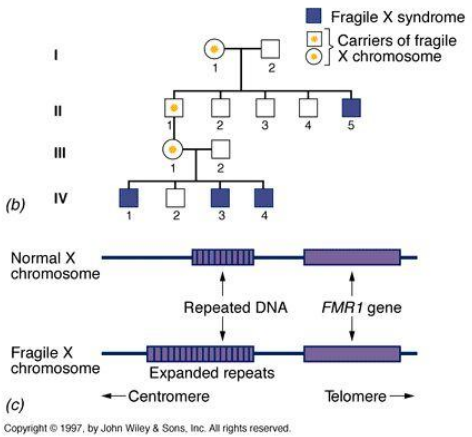


triplet repeat mutation $(CGG)_n$

n=6-52 normal

n=52-230 premutation

n=230-2000 affected



Premutation

- where a change in DNA sequence does not immediately cause a problem or disorder but predisposes offspring for a disorder

Huntington disease male expands repeat sequence more than female (due to imprinting)

11-34 CAG repeats = normal phenotype

34-36 CAG repeats = premutation, normal phenotype

37-100 CAG repeats = HD phenotype

Fragile-X syndrome female expands repeat sequence more than male (due to imprinting)

Genetic anticipation

- where expression of allele in phenotype gets more severe and/or shows at an earlier age with successive generations

Huntington disease - earlier onset, swifter progression

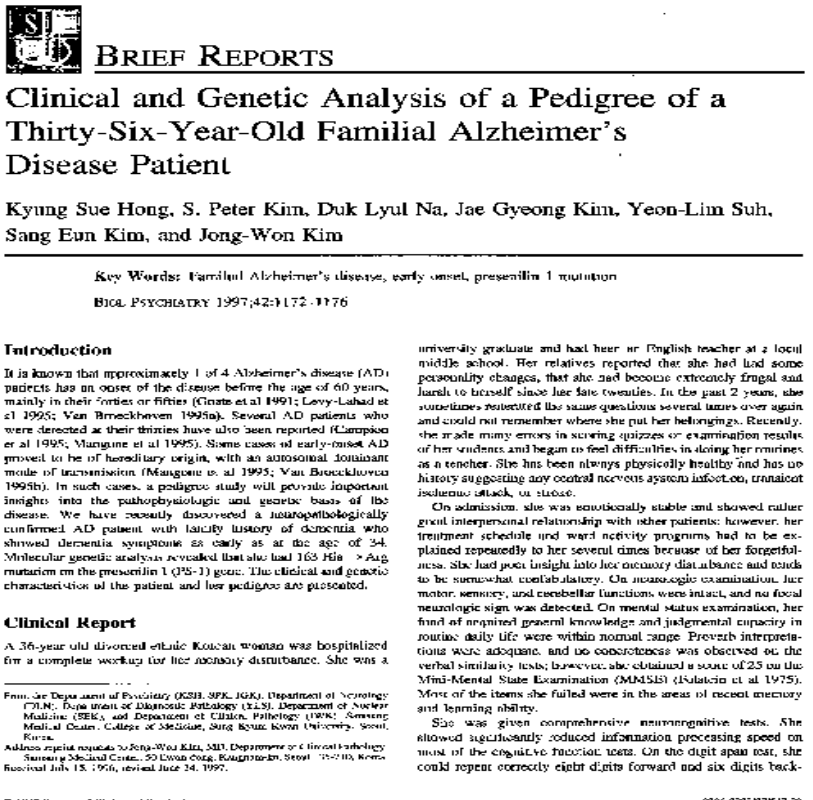
Fragile-X syndrome – greater severity

- explained by increase in number of repeats as allele is passed on

Alzheimer disease early-onset type (presenilin 1 gene)

schizophrenia manic depression ??

Early-onset Alzheimers disease presenilin 1 mutation (missense)



BRIEF REPORTS

Clinical and Genetic Analysis of a Pedigree of a Thirty-Six-Year-Old Familial Alzheimer's Disease Patient

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Key Words: Familial Alzheimer's disease, early onset, presenilin 1 mutation

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Introduction

It is known that approximately 1 of 4 Alzheimer's disease (AD) patients has an onset of the disease before the age of 60 years, mainly in their forties or fifties (Goate et al 1991; Levy-Lahad et al 1995; Van Broeckhoven 1995a). Several AD patients who were detected at their thirties have also been reported (Campion et al 1995; Mariguine et al 1995). Some cases of early-onset AD proved to be of hereditary origin, with an autosomal dominant mode of transmission (Mariguine et al 1995; Van Broeckhoven 1995b). In such cases, a pedigree study will provide important insights into the pathophysiologic and genetic basis of the disease. We have recently discovered a neuropathologically confirmed AD patient with family history of dementia who showed dementia symptoms as early as at the age of 34. Molecular genetic analysis revealed that she had 163 His → Arg mutation on the presenilin 1 (PS-1) gene. The clinical and genetic characteristics of the patient and her pedigree are presented.

Clinical Report

A 36-year old divorced ethnic Korean woman was hospitalized for a complete workup for her memory disturbance. She was a university graduate and had been an English teacher at a local middle school. Her relatives reported that she had had some personality changes, that she had become extremely frugal and harsh to herself since her late twenties. In the past 2 years, she sometimes repeated the same questions several times over again and could not remember where she put her belongings. Recently, she made many errors in scoring quizzes or examination results of her students and began to feel difficulties in doing her routines as a teacher. She has been always physically healthy and has no history suggesting any central nervous system infection, transient ischemic attack, or stroke.

On admission, she was emotionally stable and showed rather good interpersonal relationship with other patients; however, her treatment schedule and ward activity programs had to be explained repeatedly to her several times because of her forgetfulness. She had poor insight into her memory disturbance and tends to be somewhat confabulatory. On neurologic examination, her motor, sensory, and cerebellar functions were intact, and no focal neurologic sign was detected. On mental status examination, her fund of acquired general knowledge and judgmental capacity in routine daily life were within normal range. Proverb interpretations were adequate, and no concreteness was observed on the verbal similarity tests; however, she obtained a score of 25 on the Mini-Mental State Examination (MMSE) (Folstein et al 1975). Most of the items she failed were in the areas of recent memory and learning ability.

She was given comprehensive neuropsychological tests. She showed significantly reduced information processing speed on most of the cognitive function tests. On the digit span test, she could repeat correctly eight digits forward and six digits back-

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Fragile X syndrome

- X-linked
- triplet repeat mutation
- incomplete penetrance: twice as common in males as females
  50% of females with the mutation do not express any symptoms
  largely due to X inactivation
- variable expressivity : causes moderate retardation in males, mild retardation in females
- premutation 52-230 repeats (normal allele has av.30)
- genetic anticipation symptoms increase 230 -> 2000 rpt
- imprinting female has 80% chance of increasing repeats during meiosis
- pleiotropy : retardation (second genetic cause of mental impairment) physical and behavioral features:
  large protruding ears and jaw, long face, enlarged testicles,
  unusual speech, flapping hands, overactive, impulsive, inattentive

good mouse model – brain neurons affected as in humans

Drosophila model – similar synaptogenesis abnormalities

Genetic imprinting
(genomic, gametic imprinting)

- expression of an allele sometimes depends on whether it was inherited from the male or the female parent
- imprinting is a form of epigenetic inactivation via methylation
- occurs during gamete formation, the maternal or paternal copy of a gene is selectively inactivated so that only one copy of the gene is active during development after fertilization
- both male and female imprints are necessary
- original imprints are erased during germ cell development so new ones can be laid down according to sex of parent

Angelman/Prader-Willi syndromes

example of genetic imprinting

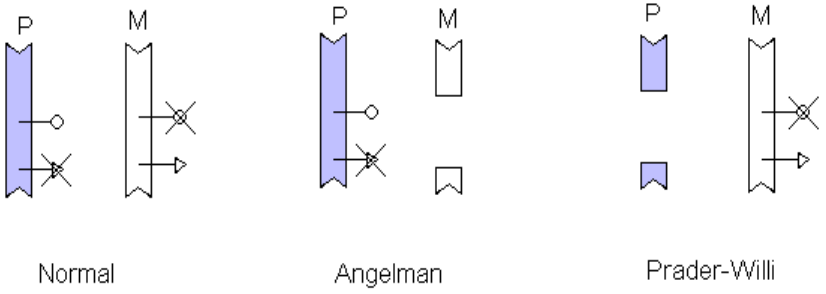
Angelman syndrome

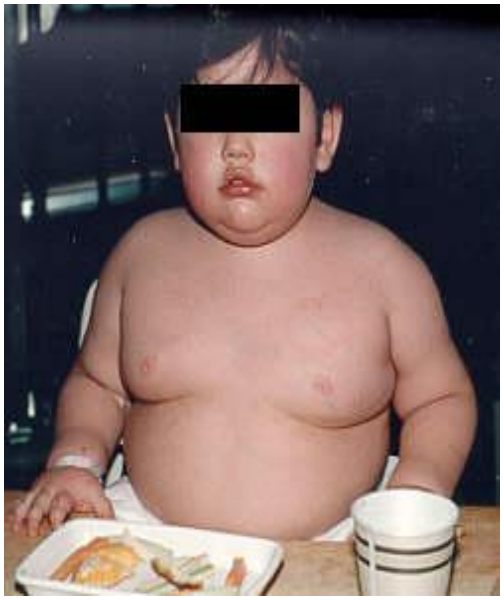
from Mom

deletion on chr 15

from Dad

Prader-Willi syndrome





Portrait of Eugenia Martinez Vallejo at Museo del Prado (Madrid)

Eugenia Martinez Vallejo was portrayed by Spanish painter Juan Carreño Miranda in 1680. It has been suggested that she had PWS [19]. At the time of the painting, she was 6 years old and in the hyperphagic (over eating) phase of the disease, which occurs after weaning. She weighed 120 pounds (~54 kg) and was portrayed with two pieces of food in her hands, which correspond to these patients' voracious appetite. Other symptoms pointing toward this disease include her short stature, almond-shaped eyes, small triangular mouth, and small hands.

LETTER

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Distinct physiological and behavioural functions for parental alleles of imprinted *Grb10*

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Imprinted genes, defined by their preferential expression of a single parental allele, represent a subset of the mammalian genome and often have key roles in embryonic development[1], but also postnatal functions including energy homeostasis[2] and behaviour[3,4]. When the two parental alleles are unequally represented within a social group (when there is sex bias in dispersal and/or variance in reproductive success)[5,6], imprinted genes may evolve to modulate social behaviour, although so far no such instance is known. Predominantly expressed from the maternal allele during embryogenesis, *Grb10* encodes an intracellular adaptor protein that can interact with several receptor tyrosine kinases and downstream signalling molecules[7]. Here we demonstrate that within the brain *Grb10* is expressed from the paternal allele from fetal life into adulthood and that ablation of this expression engenders increased social dominance specifically among other aspects of social behaviour, a finding supported by the observed increase in allogrooming by paternal *Grb10*-deficient animals. *Grb10* is, therefore, the first example of an imprinted gene that regulates social behaviour. It is also currently alone in exhibiting imprinted expression from each of the parental alleles in a tissue-specific manner, as loss of the peripherally expressed maternal allele leads to significant fetal and placental overgrowth. Thus *Grb10* is, so far, a unique imprinted gene, able to influence distinct physiological processes, fetal growth and adult behaviour, owing to actions of the two parental alleles in different tissues.

To characterize expression and investigate functions of the two parental *Grb10* alleles we have generated a mutant mouse strain (*Grb10KO*), derived by insertion of a *LacZ:neomycin*^{r} gene-trap cassette within *Grb10* exon 8 (Fig. 1a). Transmission of the *Grb10KO* allele separately through the two parental lines generated heterozygous progeny in which either the maternal (*Grb10KO*$^{m/+}$) or paternal (*Grb10KO*$^{+/p}$) *Grb10* allele was disrupted by the *β-geo* cassette and allowed us to examine *Grb10* expression in an allele-specific manner. Northern blot analysis of RNA samples prepared from whole fetuses (Fig. 1b) showed that endogenous *Grb10* transcripts were readily detected in wild-type animals and in heterozygotes that inherited a mutant *Grb10KO*$^{+/p}$ allele. In contrast, *Grb10* transcripts were found at relatively low levels in heterozygous animals with a mutant *Grb10KO*$^{m/+}$ allele, an observation consistent with previous demonstrations that most *Grb10* expression is maternally derived (for example, ref. 8). We next conducted more refined *in situ* analyses of allele-specific expression, using the integrated *LacZ* reporter gene. During fetal development, *LacZ* expression from the maternal allele was widespread in tissues of mesodermal and endodermal origin, but absent from the central nervous system (CNS) proper (Fig. 1d, f). At embryonic day (E) 14.5, expression of the maternal *Grb10* allele within the brain was seen only in the ventricular ependymal layers, the epithelium of the choroid plexus and the meninges, presumably identifying sources of maternal brain expression that have been reported by others[9–13] (Supplementary Fig. 1a, b). In contrast, expression from the paternal allele was predominant within the developing CNS, with only a few discrete sites of relatively low-level expression seen in other tissues (Figs 1e, g, 2a and Supplementary Fig. 1c, d). The CNS expression starts between E11.5 and E14.5, consistent with the onset of neurogenesis, and correlates with the brain-specific loss of a repressive histone modification (H3K27me3) from the paternal *Grb10* allele during development and during neural precursor cell differentiation *in vitro*[14]. This loss of H3K27me3 from the promoter region of the *Grb10* paternal allele-specific transcripts (see Fig. 1a) leaves a permissive histone mark on the paternal allele (H3K4me2), whereas this region of the maternal allele is constitutively associated with two repressive histone modifications (H3K9me3 and H4K20me3)[14].

Our analysis showed paternal allele expression within the developing CNS was restricted to specific regions of both the brain and spinal cord, with reporter signal identified within select areas of the dienecephalon, ventral midbrain and the medulla oblongata extending caudally along the ventral spinal cord. There was no expression detected within the presumptive neocortex, dorsal midbrain or the cerebellar primordium (Fig. 2a). Embryonic *Grb10* expression within the CNS proper was entirely paternal in origin, a fact that was not evident from previous expression studies that identified a promoter and brain-specific transcripts associated with the paternal allele, but relied on techniques involving RNA extraction from tissue homogenates[9–12]. Thus our *Grb10* expression analysis provides striking evidence of reciprocal imprinted expression from the two parental alleles in different tissues. Several imprinted genes exhibit tissue-specific and/or temporal regulation, such that their expression is biallelic (non-imprinted) at some of their sites of expression. However, the reciprocal parent-of-origin expression described here is unprecedented, suggesting new and intriguing possibilities for imprinted gene function and evolution.

Consistent with our previous studies of *Grb10Δ2–4* mice[8,15], *Grb10KO*$^{m/+}$ animals displayed a disproportionate overgrowth phenotype apparent from E12.5 onwards (Fig. 1h, i and Supplementary Fig. 2). At birth, the mean body weight of *Grb10KO*$^{m/+}$ pups was 25 ± 2.5% greater than that of wild-type littermates. The liver was disproportionately enlarged (117 ± 9.8% heavier), but there was sparing of the brain and kidney, such that the weights of these organs were not significantly different to those of wild types (Fig. 1i). The cranial sparing is consistent with limited *Grb10* maternal allele expression within the developing CNS. Body weight and proportions of *Grb10KO*$^{+/p}$ mutants did not differ from wild-type controls and no function has yet been ascribed to the paternally inherited *Grb10* allele, despite evidence of its expression within the neonatal brain[8]. Both *Grb10KO*$^{m/+}$ and *Grb10KO*$^{+/p}$ mutants were present at the expected Mendelian frequencies (χ^2 values, $P = 0.737$ and $P = 0.395$, respectively) when animals were genotyped at 3–4 weeks of age, indicating that survival to weaning was unimpaired. Observations of *Grb10KO*$^{+/p}$ pups before weaning, including analysis

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Cytoplasmic inheritance (maternal inheritance)

- genes in mitochondria (and chloroplasts) are only passed on from female parent since all cytoplasm for zygote comes from female gamete
- all offspring resemble female parent for traits influenced by mitochondrial genes

  encephalomyopathy

Alzheimer disease

Bipolar disorder

most DNA controlling MT function reside in nucleus – cannot assume problem in MT function is due to mutation on MT DNA