Distinctive patterns of memory function in subgroups of females with Turner syndrome: evidence for imprinted loci on the X-chromosome affecting neurodevelopment

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Abstract

X-monosomy is a form of Turner syndrome (TS) in which an entire X chromosome is missing. It is usually assumed that neuropsychological deficits in females with TS result from insufficient dosage of gene products from alleles on the sex chromosomes. If so, then parental origin of the single X chromosome should be immaterial. However, if there are imprinted genes on the X chromosome affecting brain development, neuropsychological development will depend on the parental origin of the single X chromosome. We contrasted verbal and visuospatial memory in females with a single paternal X chromosome (45,X\textsuperscript{p}) and those with a single maternal X (45,X\textsuperscript{m}). Neither group showed any impairment on immediate story recall; if anything, performance was above control levels. Groups did not differ on a measure of delayed recall. However, when delayed recall was considered after adjusting for level of immediate recall, 45,X\textsuperscript{m} females showed enhanced verbal forgetting relative to controls over a delay. On the Rey figure, both groups were poor at copying the figure, but, after adjusting scores for initial copy score and strategy, only the 45,X\textsuperscript{p} females showed disproportionate forgetting relative to controls. We propose there may be one or more imprinted genes on the X chromosome that affect the development of lateralised brain regions important for memory function.

Keywords: Imprinting; Verbal; Visuospatial; Monosomy; Brain; Lateralization

1. Introduction

Approximately 30\% of the human genome is expressed only in the brain, yet we understand relatively little about how such influences operate. Two approaches are available to neuropsychologists who wish to investigate genetic influences on brain development. The first is conventional behavioural genetics, which involves identifying individuals with particular neurocognitive or behavioural characteristics and considering how far genetic relatedness predicts phenotypic similarity. The second is the molecular approach in which one starts with individuals who have a known genetic anomaly and looks for neurodevelopmental consequences [30]. In this paper, we adopt the latter approach, in a study documenting aspects of the neuropsychological phenotype in Turner syndrome (TS), a chromosomal disorder in which all, or a substantial part, of one X chromosome is missing. We argue that there are subtle impairments of retention, with the profile depending on the parental origin of the single X chromosome. We conclude that a phenomenon known as genomic imprinting affects genes on the X chromosome that are involved in the development of memory systems.
1.1. The phenotype in Turner's syndrome

TS is associated with distinctive physical characteristics, the most reliable of which are short stature and low production of female sex hormones. It has been known for many years that there is a distinctive intellectual profile in TS [27]. Typically, verbal ability is in the normal range, but visuospatial skills are impaired. More recently, other characteristics have been described, including memory deficits, attentional problems, motor impairment, and difficulties in social relationships. However, although the incidence of such difficulties is increased in TS, the correlation between neuropsychological profile and genotype is far from perfect, and several authors have commented on the wide phenotypic variation seen in this syndrome [2,23]. Structural brain correlates of TS have only recently been investigated using neuroimaging, and have revealed abnormalities in the parietal lobes [20,25]. One study [20] also found that women with TS had reduced volume of the hippocampus, caudate, lenticular and thalamic nuclei, a finding that is consistent with reports of deficits in long-term memory [19,23].

1.2. Genetic basis of neurodevelopmental impairment in Turner syndrome

At first glance it is surprising that loss of an X chromosome should have neurodevelopmental consequences, because in normal females, the second X chromosome is inactivated very early in embryonic development [38]. This X-inactivation is random: in some cells the X inherited from the mother is inactivated, in others the X inherited from the father. The Y chromosome has few functions other than primary sex determination, so if X-inactivation did not occur, then normal males, with XY karyotype, would have only half as much gene product as females. X inactivation ensures equal dosage of gene product for both sexes. Thus normal females, normal males, and females with TS, all have only one activated X-chromosome. Why then should females with TS differ from those with two sex chromosomes? The conventional explanation is the haploinsufficiency hypothesis, which attributes the phenotype of TS to insufficient dosage of gene product. This explanation implicates genes on the X chromosome that are the exception to the general rule of X-inactivation [39]. Molecular studies have confirmed that there is a region of the X chromosome (the pseudoautosomal region) that escapes inactivation, so genes from both X chromosomes are active in normal females. In this region, there is evidence that males have functionally equivalent genes on the Y chromosome, so both males and females have a double dose of gene product. More recently, other regions of the X chromosome that escape inactivation have been discovered [6]. According to the haploinsufficiency hypothesis, the phenotypic abnormalities in TS, including the cognitive profile, can be explained in terms of a deficiency of gene products from a region of the X-chromosome that escapes inactivation. Adverse effects could be direct effects of genes on brain development, or more indirect consequences of the hormonal deficiencies that result from the genetic deficit.

Recently, we suggested that a phenomenon known as genomic imprinting might play a role in determining the phenotype associated with TS. Genomic imprinting is another mechanism whereby one member of a pair of alleles is inactivated, but in this case, the inactivation is not random, but is determined by the parental origin of the chromosome. The phenomenon of imprinting is a relatively recent discovery, which has been investigated both experimentally and clinically, with a focus mainly on autosomal rather than sex chromosomes (see Keverne [12] for a review). It is possible to create mice that carry a duplicated gene from one parent, rather than the normal complement of one gene from each parent. Such animals show serious developmental disturbances, reflecting the fact that certain genes are silenced unless they come from a specific parent. Clinically, our understanding of imprinting has been advanced by the study of genetic disorders in which there is deletion on chromosome 15, in the region q11-13. When such a deletion affects the maternally derived chromosome, the result is Angelman’s syndrome, with a phenotype of severe mental handicap, lack of speech, and other physical and behavioural abnormalities. When it is the paternally derived chromosome that is deleted, the very different clinical picture of Prader–Willi syndrome is observed, characterised by hypotonia and hypothalamic dysfunction in the context of mild mental handicap. The relevant region of chromosome 15 has been mapped with gene markers, to reveal a region where only maternal alleles are transcribed, and an adjacent region where only paternal alleles are transcribed. Imprinted genes have distinctive effects on brain development, and Keverne postulated that they might have been important for remodelling of the brain during mammalian evolution.

Imprinted X-linked genes have recently been identified in humans [21] as well as autosomal imprinted genes that are expressed in the brain [12,18,28]. We argued that if humans had imprinted genes affecting neurodevelopment on the X chromosome, then we would expect to see neurocognitive differences between females with a single X chromosome (i.e., monosomic TS), depending on the parental origin of the X chromosome [29,33]. Suppose there were an X-linked gene that was expressed only when inherited from the father. Females with a single maternal X chromosome would lack the relevant gene product, whereas those...
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