Epilogue

VI

Spain, 1981, Salvador Dalí.

Salvador Dalí (1904 - 1989), the eccentric Catalan artist who is best known for his surrealist work, prepared this portrayal of the complex structure of neurons and the interactions of their axonal and dendritic extensions for a celebration in memory of Santiago Ramón y Cajal (1852 - 1934).

X-linked mental retardation. Is it really on the X?

Although a male excess in MR has long been recognised[42], its magnitude is still ambiguous. It is estimated to be between 25 – 45% for the moderately and severely retarded[44,80,839,840]. Owing to difficulties in determining a reliable prevalence for mild MR[1173], the male excess among those with IQs between 50 and 70 remains largely elusive. A meta-analysis resulted in an average male:female ratio of 1.9 for patients with mild MR[840]. Originally, mental deficit, and with that the observed male excess, was believed to be based on social, societal and ascertainment biases. Penrose, who conducted the famous Colchester Survey on mental defect in 1938[44], was among the early proponents of the belief that MR was biologically, not only socially, determined[43,1174,1175]. However, Penrose did not believe that the 24.5% male excess he observed at Colchester was due to a *predominance* of genes on the X chromosome. In 1963, referring to his survey, he wrote: '... in general, the genes on the X chromosome do not play any *greater* part in the causation of mental defect that might be supposed from the fact that there are 22 autosomes to one sex chromosome in man' and 'The conclusion may be drawn that there is no *outstanding* tendency for sex-linked genes to influence the genetics of mental deficiency'[1175] [italics mine]. Incomprehensibly, several eminent geneticists, including Turner, Partington, Neri and Opitz, interpreted these statements as if Penrose thought there were *no* genes on the X chromosome involved in MR[839,1176] (Dr. M. Partington, personal communication), thereby implying that Penrose had overseen the publication of the many pedigrees showing clear X-linked inheritance of mental deficit[45,56,841,1177]. Given the calibre of Penrose's work, the '*Quandoque dormitat Homerus*' of Neri and Opitz may be a little disrespectful[1176], and it is much more likely that Penrose did not believe there was a *preponderance* of X-linked genes in MR and that the male excess he had observed had a different reason.

In the late 1960's, Lehrke audaciously hypothesised *major* loci for intelligence on the X chromosome that, when mutated, would result in MR. He estimated that such mutations would underlie 25 – 50% of all forms of mental impairment[1178]; the basis for his theory has been outlined under I.A.3.2.3. When an abridged version of his work was later published in the American Journal of Mental Deficit[46], rather sharp responses followed, essentially stating

that the male excess observed in institutions for the mentally handicapped must be due to ascertainment bias[1179,1180]. This is inexplicable, as the 1890 US census, in part published 75 years before Lehrke's work, already clearly showed a 24% male excess with regard to MR in the general population[42]. However, the discussants were right in that Lehrke's theory was an over-interpretation of the available data, which should also have been appreciated at the time. Most importantly, it should have been evident that the proposed 6.5 – 20-fold higher rates of X-linked mutations in MR compared to autosomal alterations, which is implied by Lehrke's XLMR prevalence estimates and considers the fact that X-chromosomal DNA only contributes ~5% to the total genome, is absurd given the small differences between male and female intelligence in the general population. Moreover, there was no evidence to support the notion that a genetic basis for MR equals the existence of intelligence genes. Nevertheless, Turner, who, with Partington, restated Lehrke's hypothesis and stressed the importance of NS-MR in the study of cognition[1181], vehemently supported the hypothesis of a *principal* involvement of X-linked genes in intelligence. It is unfortunate that she, almost without exception, peppered her publications with non-scientific, personal views[a], highlighting the lack of evidence supporting the thesis of a *major* contribution of the X chromosome to intelligence[839,1181-1185].

In summary, there were two schools of thought: one did not believe in a disproportionately large involvement of X-linked genes in MR and the second stated that most, if not all, of the male excess observed in MR was due to X-linked mutations.

Interpretation of recent data suggests that, as perhaps should have been expected, the truth likely lies in the middle. There appears to be a preponderance of genes involved in XLMR, but their importance in the male excess among mentally impaired individuals seems to be less than anticipated.

In 2004, Mandel and Chelly estimated that < 10% of all male MR is accounted for by XLMR, suggesting that less than half of the male excess is due to mutations in X-

[a] From the 'Turner archive'; a small collection of comments, which I regard as inappropriate to scientific communication:
'If the main genetic source of intelligence resides on the X chromosome, man, at least, should have organised the matriarchial society with the polyandrous mating system. Perhaps we are still paying for the mistake of organising the patriarchial society of kings and dukes.'[1181]
'A T-shirt with a wider application might be one that gives thanks to mothers from their children for her X chromosomes for their major contribution to their intelligence' and 'In day-to-day practical evolutionary terms for our new millennium the male needs to remember that his primitive urges in mate selection are coded in his genome, and that they target current ideals of sexual attractiveness and youth. His frontal cortex should interpose reminding him that his sons' intelligence, if that is important to him, is solely dependent on his partner, and that is mirrored in both her parents. The female has more freedom of choice; she may be driven to mate by her partner's physique but the brightness of her children lies mainly within her'[1182].
'I am delighted that Hook has taken up the gauntlet; from his difficulties in embracing the flavour of this essay I know that he could only be male!'[1183]

chromosomal genes. Their calculations were based on a mutation frequency in *ARX* that is much higher in pedigrees with clear X-linked inheritance of MR compared to that observed in sporadic MR cases[84]. Additional research comparing *ARX* mutation frequencies between XLMR families and affected brother pairs essentially reached the same figures[168]. Ropers and Hamel also arrived at a similar conclusion when using the frequency of Fragile X syndrome[70]. Finally, it should be pointed out that the involvement of X-linked genes in MR may even be smaller than is presently believed. This is so because the studies that estimated the prevalence rates for XLMR were all conducted in societies where consanguineous marriage is uncommon[80,839,1186] and, hence, it could be expected *a priori* that preferentially X-chromosomal defects will show up. Autosomal recessive forms of MR, which may explain part of the affected sister pairs observed in those studies, are rarer. In societies where consanguineous marriage is routinely practiced, it is likely that a higher rate of autosomal recessive forms of MR will be encountered, thereby decreasing the relative importance of XLMR. Although still not ideal, the reduced genomic complexity in pedigrees from such societies may be the closest we can get to test the hypothesis that X-linked genes indeed contribute disproportionately to human intelligence.

Importantly, the decrease in significance of XLMR was paralleled by an increase in the estimated number of NS-XLMR genes from 7 – 19 [80] to ~100 [69]. A conservative estimate, employing extrapolation of the allelism that is apparent from Table I-3 but excluding the genes in which mutations cause both S- and NS-MR, yields ~70 unique genes involved in NS-XLMR[a]. Although the exact number of NS-XLMR genes may not be known yet, it will essentially preclude the existence of one or a few *major* intelligence loci on the X chromosome as postulated by Lehrke[46] (Table VI-1). Indeed, when comparing the human and chimpanzee genomes, the absence of human-specific loci became apparent[1187]. This finding is in line with the idea that evolution invented new functions for old vertebrate genes[1188,1189] and with the contemporary concept of many QTLs underlying intelligence[830].

Of course, two exceptionally intriguing questions remain. First, why should sex-specific genes be important in intelligence? Second, if not genes, what else can explain the remaining male excess seen in MR? Several theories, which offer plausible answers to these intertwined questions, have emerged from the field of evolutionary biology.

[a] Thirty-one unique genes for 44 cloned entries, yields 73 genes for a total of 103 entries.

Table VI-1 | **Estimates of XLMR prevalence rates and number of NS-XLMR genes during the past ~35 years**

Period	Involvement of XLMR in male MR (IQ < 50)[§]	Refs.	Period	Estimated number of NS-XLMR genes	Refs.
1968 – 1996	25 – 35% 100%	80,839,1178,1184	1978 – 1996	7 – 25	79,80,1190,1191
2002 – 2006	5 – 15% ~50%	70,84,168,1192	2000 – 2005	~100	69,82,83

[§] Top, fraction of severe male MR assigned to XLMR; bottom, fraction of male excess in severe MR explained by XLMR.

Speciation, which leads to an interbreeding population that is reproductively isolated from co-existing populations[1193], involves mechanisms that play at the pre-mating and post-mating stage.

It is self-evident that pre-mating systems such as mate choice operate in the human population. As in mammals, including humans, mate choice is dictated through the female's preference with whom she will produce offspring[1194], and the characteristics governing her choice should leave their traces on and act through the genome, especially the X chromosome. The disproportionate influence of the X chromosome on cognitive ability may indicate that masculine intelligence is a factor influencing feminine mate choice. Since cognitive function directs behaviour, this seems a likely assumption[1195]. Moreover, correlations between spouses for intelligence are ~4-fold higher than for other personality traits[1196] which is in agreement with cognition as a factor affecting mate choice. Additional appeal for this assumption comes from the fact that such exceptional coupling of sexual selection (mate choice) and natural selection (individual survival) in humans has the potential to explain the extraordinarily rapid evolution of the human brain, which has tripled in volume in the past 2.5 million years[1197]. In other species, male ornaments, such as a peacock's tail, are always a trade-off between courtship display (sexual selection) and predatory pressure (natural selection)[1198,1199].

Post-mating mechanisms are exemplified by fertility and viability of the offspring. A rule central to speciation theory states that when one sex in an interspecific hybrid is sterile (or inviable) it is almost always the hetero-gametic sex[1200]. Given the incidence of male sterility and the decline of the male:female ratio from 140:100 at conception to 106:100 at birth, it is clear that post-mating speciation mechanisms are still active in humans[1195]. Support comes from the observation that the X chromosome is roughly fifteen-fold enriched for male germ cell-specific, spermatogonially expressed genes[1201] and for placentally expressed genes[1202]. Together with the preponderance of X-chromosomal intelligence genes, this observation fits

well with the hypothesis of coupled sexual and natural selection: if alleles leading to suboptimal intelligence exert a detrimental effect on fertility, this would efficiently select against such alleles. The high rate of urogenital problems and infertility seen in XLMR syndromes[1203] and the simultaneous expression of genes in brain and testis during development[1195,1204] lend support to this attractive possibility. Human social and societal behaviour further limits reproduction of mentally impaired individuals.

Taken together, the preponderance of genes involved in cognition and reproduction on the X chromosome may have driven speciation and could explain the rapid evolution of human intelligence.

Still, the question remains how the small genomic differences between great apes and humans[1205] translated into a considerable disparity in intelligence. It is reasonable to assume that some sort of snowball effect must have occurred. Neuroactive hormones such as the sex and thyroid hormones constitute an appealing possibility for mediating such snowballing.

As may be expected from the similarity in genetic make-up, the basic body plans of great apes and humans are not very different. However, evolutionary divergence is apparent[1206]. Apart from intellectual capacity, major disparities include differences in hair growth, more pronounced secondary sexual characteristics in humans and human full-time sexual receptivity, all of which involve testosterone and/or oestrogen[1207-1211]. Indeed, sex hormone metabolism differs significantly between humans and great apes[1212,1213].

The importance of sex hormones on brain development and function[1214-1217] is well documented and seems to be mediated at the molecular[1218,1219] as well as anatomical[1220-1223] level. Moreover, many links between sex steroids and intellectual performance have been reported[1224-1228]. Interestingly, sex hormones may be the agents governing the coupling of sexual and natural selection described earlier, as they not only exert an influence on the brain and cognition, but also play a significant role in mate choice[1229-1231]. The most direct link between sexual selection and intelligence involving sex hormones comes from the observation that symmetry, which is a measure for attractiveness[1232], is correlated with intelligence[1233] and hormonal levels[1234].

It should be noted that other hormonal metabolisms that also differ between primates and humans, such as that of thyroid hormones[1235], have important functions in the brain[1236]. Indeed, iodine deficiency is one of the leading causes of MR[1237,1238], especially in third-world countries[1239]. Therefore, thyroid hormones are also candidates for the potentiation of higher intelligence[1240,1241].

The sex hormones that may have shaped hominid evolution are an excellent alternative to X-linked genes to explain part of the male excess observed in MR. As Lubs pointed out, the greater male variability in IQ that is often quoted as evidence for XLMR only applies to certain subsets of abilities and is unidirectional[1242]; that is, while males excel at non-verbal skills, such as science and mathematics, females are better at verbal skills, such as reading and writing[1243], and, hence, sex hormones are a much more straightforward explanation than genetic variants[1242]. One example to support the involvement of sex hormones in cognitive disparities between males and females is the observation that women who were exposed to abnormally high androgen levels *in utero* score significantly higher than controls on tests of spatial ability[1244], which seems to be indicative of a masculinisation of their brains. Perhaps it is not only coincidence that the androgen receptor is coded for by a gene ... on the X[1245].

Certainly, many more factors could be envisaged to explain part of the sex-specific incidence observed in MR. In fact, sexual dimorphisms of the brain[1246-1248], autosomal[1249] and X-linked parent-of-origin specific imprinting[1250,1251], gender roles[1252], sex-specific selective pressures[1253], gender-specific differences in constitution[1254] and sex-specific gene expression[1255] may all represent candidates for such factors.

In conclusion, given the lack of evidence at present supporting the idea that the greater majority of male excess observed among the mentally handicapped is due to the involvement of X-chromosomal genes, I propose that it may be more correct to refer to ‘gender-specific MR’. The term XLMR should be reserved for those instances in which the mental handicap actually segregates with the X chromosome.