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Evolutionary neuropathology and Down syndrome: An analysis of the etiological and phenotypical characteristics of Down syndrome suggests that it may represent an adaptive response to severe maternal deprivation

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Summary This paper will suggest that the Down syndrome phenotype would have been well suited, physiologically, for a deprived environment and that it may represent a predictive, adaptive response to severe maternal deprivation. A trisomy of the 21st chromosome, prior to, or at conception is responsible for Down syndrome and is known to increase in incidence with advanced maternal age. One out of 11 mothers over the age of 50 conceives a Down syndrome baby, compared to one in one thousand at age 30. This article emphasizes that an older mother is more likely to die before she is able to provide the parental investment necessary to produce an ecologically self-sufficient offspring. Prolonged maternal investment is known to be essential for hunter-gatherers to master the skill intensive food procurement techniques that they will need in order to become independent of their mothers. Because Down syndrome individuals are much more likely to be born to older mothers, they must have been routinely deprived of maternal investment in the human environment of evolutionary adaptedness. This consistent paring of maternal deprivation to trisomy 21 conceptions, over time, may have caused natural selection to favor genes responsible for the energy conserving traits seen in modern day Down syndrome. These traits include muscle hypotonia, decreased cerebral metabolism, decreased hippocampal volume, a strong propensity for obesity and growth hormone and thyroid hormone paucity. Such a "thrifty phenotype" may have allowed Down syndrome individuals to become independent of their mothers at a far earlier age and allowed them to forgo the skill intensive ecological niche that non-trisomic humans are phenotypically suited for in order to take up a less cognitively and physically rigorous one.

Introduction

Contrary to the current view of Down syndrome (DS) as disease, this article presents a scenario in

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which DS played the role of a protective mechanism within the human or protohuman ancestral environment. To be more specific, the phenotypic traits characteristic of DS individuals might have allowed them relative independence of maternal investment and thereby increased the incidence of the trisomy 21 and its close relationship to advanced maternal age. Like other forms of predictive, adaptive responses, the propensity for DS is genetic [1,2] with increased likelihood of DS birth associated with combined maternal and paternal proclivity.

This would not be the first hypothesis to claim that non-disjunction (or chromosomal aneuploidy) in an animal chromosome has been made more frequent by natural selection. The soil nematode, *Caenorhabditis elegans*, is a species that reproduces through self-fertilizing hermaphrodites, yet can produce functional males by means of chromosomal non-disjunction [3—5]. *C. elegans* is thought to have adopted the male dimorphism as a vehicle that allows sexual reproduction and thus increased allelic diversity. The qualities of the DS dimorphism, as proposed here, are analogous to those of the *C. elegans* male in that they respond to specific environmental contingencies utilizing non-disjunction to provide an adaptive advantage.

The clinical entity known as Down syndrome was recognized [6] many years before its etiology was determined to be related to chromosomal non-disjunction, more specifically to an extra chromosome 21 within all cellular nuclei [7]. Advanced maternal age remains the most conspicuous risk factor in non-disjunction [8] although several others have been reported in the last few decades. It is important to note that the biological mechanisms that produce non-disjunction errors in meiosis (I and II) are not well understood [9].

DS is a highly prevalent disorder that affects millions of individuals throughout the globe. It is the most common identifiable cause of intellectual disability and it accounts for nearly one third of all diagnosed cases. With an incidence of 1—2 in 1000 births [10], DS, otherwise known as trisomy 21, is the single most frequent of the autosomal trisomies in liveborns, and also the most frequent chromosomal abnormality in children. It is clear that DS is associated with disability in the modern environment and thus its relative prevalence is inexplicable under evolutionary theory — unless one is to propose that the genes that create the propensity for DS conferred some benefit.

The role of maternal age in Down syndrome

The literature provides overwhelming evidence for a relationship between maternal age and proclivity for DS [1]. As a mother grows older, her propensity to conceive and deliver children with DS increases very quickly, from one in one thousand at age 30 to one in 11 at age 50 [11]. It is clear that an older mother is more likely to die before she is able to provide the parental investment necessary to produce a socially and ecologically self-sufficient offspring. It is well recognized in anthropological literature that the human foraging niche is both extremely cognitively demanding and skill intensive and that self-sufficiency absolutely requires maternal care and instruction [12]. This maternal age effect may have proved an apposite vehicle for the DS dimorphism because it provides a precocial and energy efficient phenotype for children that are statistically likely to be born to a mother who will not live to provide sufficient investment.

The following table presents the frequencies of trisomy 21 with respect to maternal age. Please note that the frequency of trisomy 21 increases with maternal age at a rate that is faster than the sum of all the other chromosomal abnormalities. This relative rate increase is consistent with the assertion that trisomy 21 might be a preferentially selected trait.

Maternal age	Frequency of Down syndrome	Frequency of any chromosomal abnormality
20	(1/1667)	(1/526)
24	(1/1250)	(1/476)
30	(1/952)	(1/384)
35	(1/385)	(1/192)
40	(1/106)	(1/66)
45	(1/30)	(1/21)
48	(1/14)	(1/10)
49	(1/11)	(1/8)

Source: [11,13].

It is also interesting to note that the maternal age effect does not increase after age 49 [10]. This suggests a reproductive strategy for the following reason: The year of abatement in the maternal age effect seems to correspond with both the average age of menopause, 50—52 years [14] and the average life expectancy for modern hunter-gatherer groups as seen in the table below. In other

words, mothers in the ancestral environment died around age 50, so there would be no selective pressure to further increase the rate of DS conceptions after this age. If DS was simply pathological, and due to increasing germ cell mutations over time, we might expect the frequency of trisomy 21 to continue to increase after age 49, but it does not.

Life history parameters for human hunter-gatherers

Life history parameters for human hunter-gatherers

Group	Terminal age
Hadza, female	54.7
Hadza, male	52.4
Hiwi, female	51.3
Hiwi, male	51.3
Kung, female	56.5
Kung, male	56.5

Sources: [15—17].

The following table presents the frequency of trisomies for each chromosome, among both spontaneous abortions and live births. This table shows that trisomy 21 is by far the most frequently occurring trisomy among live births.

Chromosomal trisomy	Number among spontaneous abortions	Number among live births
1	0	0
2	159	0
3	53	0
4	95	0
5	0	0
6—12	561	0
13	128	17
14	275	0
15	318	0
16	1229	0
17	10	0
18	223	13
19—20	52	0
21	350	113
22	424	0

Source: [18].

It is also important to note that it has been shown that the trisomies associated with maternal age may not be due to germ cell mutations or increased rate of non-disjunctions during conception. A review of studies on the effects of maternal age on trisomy 21 conceptions written by Raymond Kloss and Randolph Ness suggests that the origin of the trisomies lies not with an increase in the number of non-disjuctions, but with a decrease in rejection of trisomy zygotes. The authors state that this finding suggests that the pronounced association between trisomy 21 and maternal age is indicative of a "reproductive strategy," because it is not simply due to the accumulation of germ cell mutations with age [19].

Additional risk factors that may be environmental cues in the programming of DS

Other risk factors, aside from maternal age, link DS etiology with maternal deprivation. A cluster investigation reported that short pregnancy interval is implicated as a risk factor for DS [20]. It is logical to conclude that mothers who have more than one baby in a short time interval would be statistically less likely to provide sufficient maternal care because their time and resources would be divided. Furthermore, one would expect that a mother providing sufficient care to the baby that she has already invested in previously, might not be able to provide sufficient care to subsequent offspring.

Other reports have strongly associated anovulatory activity followed quickly by conception with increased occurrence of DS [21,22]. These findings can be interpreted in a similar way. Anovulatory activity, or amenorrhea, is usually caused by either pregnancy or lactation, and it is conceivable that this effect may have been selected for because of the difficulty associated with allocating maternal investment to two closely spaced infants. This epidemiological data frames the DS dimorphism as part of a quantitative reproductive strategy.

Additional maternal factors that may be associated with maternal deprivation are linked with DS conception. For instance, mothers of Down syndrome children have been shown to have more significant illnesses before conception, especially psychological illnesses [23]. A mother that is suffering from anxiety or a psychological illness is probably more likely to deprive her offspring of sufficient maternal care.

Another interesting pattern is derived from reports that have found an association between risk of DS and advanced age of the maternal (yet not paternal) grandmother at the mother's birth (after correction for maternal age) [24,25]. There is growing consensus in the anthropological literature that the presence of a maternal grandmother, yet not a paternal one [26,27], has a variety of positive

effects on a forager child's survival likelihood, rate of productivity and life expectancy [28,29]. If the maternal grandmother is very old at her daughter's conception then it follows logically that she is likely to be quite old at the time of her grandchild's conception. It would also follow logically that an older grandmother would be less likely to provide grandparental investment before she dies. Thus DS may be an adaptive response to diminished maternal and grandmaternal investment.

It is also important to mention that Prader—Willi syndrome, a form of neuropathological disease, is known to be caused by a uniparental chromosomal disomy which increases in frequency with advanced maternal age. This disorder also features a tendency toward obesity and low metabolic rates.

The protective functions of Down syndrome

DS babies have a very low metabolism which might have conferred them an ability to conserve calories and thus avoid starvation in the environment of evolutionary adaptedness (EEA). Reports have shown that the resting metabolic rate of both children and adults with Down syndrome is significantly lower than those of matched, non-trisomic individuals [30,31]. DS is strongly associated with decreased muscle tone which may partially explain the lowered metabolic rate. Decreased thyroid hormones observed in DS [32] may also be responsible. Low metabolism is thought to partially explain the high proclivity for obesity in DS groups as observed in modern times [33]. This genetic propensity for energy conservation probably only translates into obesity in modern times and may have protected DS individuals from starvation in ancestral times.

An objection to the present hypothesis might point out that DS individuals are "weak" and "non-intelligent" and thus would have been conspicuously defenseless in savage, prehistoric times. Australopithecines, a vastly successful hominid group that survived for over two million years despite their tiny frames and small brains, would have had skull cases far smaller than those of DS individuals.

"It is clear from the study of their fossil remains that, anatomically speaking, the Australopithecines were peculiarly defenseless creatures."
-William Le Gros Clark

It is well established that the brain and nervous tissue in general are very metabolically expensive [34]. In fact, the mass specific metabolic rate of brain tissue is over 22 times the mass specific metabolic rate of skeletal muscle [35]. The small brain size seen in DS individuals may in fact be an advantageous decrease in this metabolically expensive organ. Brain volume and weight are well documented to be diminutive throughout the maturational timeline in DS individuals [36,37]. A study limited to adults determined that the average brain weight in DS adults is 76% of normal [38]. The decrement in cognitive function that accompanies such a diminution in brain size may have allowed DS individuals to inhabit an ecological niche similar to that inhabited by less encephalized, ancient, hominid groups — groups that are thought to have depended far less on maternal investment.

The volume of the hippocampus is significantly smaller in DS subjects than in normal comparison subjects even when total brain volume is controlled for [39—42]. Decreased hippocampal volume in DS may be evidence of an adaptive neuroanatomical alteration to decreased ecological demands encountered by DS individuals in the EEA. The hippocampus is known to respond plastically to ecological demand in both mammals and birds and decrements in its size are consistently interpreted as predictive, adaptive responses to food scarcity and environmental deprivation [43—45].

DS and many other heritable forms of mental retardation are associated with increased distance between the eyes [46], also known as hypertelorism. It makes sense that an MR individual would be less susceptible to ambush if they had wider peripheral vision. Wider set eyes should prove valuable for a vigilance strategist and it is clear that many vigilance strategists like mammalian herbivores, reptiles, amphibians and fish also exhibit hypertelorism — their eyes are near the opposite sides of their heads. We know that DS humans have working memory and attention deficits and so it makes sense that they might forgo the benefits of hypotelorism (closely set eyes), because they would be less likely to benefit from chase hunting, tool making or close perceptual work.

It is also interesting to note that DS individuals have a few strange phenotypic traits that may have analogues, or homologues in chimpanzee morphology. DS individuals are much more likely to have small noses and flat faces, two characteristics of both apes and ancestral hominids. They are also known to have a larger space between big and smaller toes [46]. This space is known as the sandal gap — and is similar to the large space that apes have between their prehensile big toe and the smaller toes. Perhaps even more intriguing, DS individuals are much more likely to have a simian crease in their hand [46], which all monkeys and

apes but very few non-trisomic humans have. DS individuals also have anomalous dentition, characterized by smaller teeth [47] which may be evidence of a frugivorous or insectivorous diet. Analysis of the genes for morphological traits like these may help researchers estimate when the DS dimorphism arose since the time that humans diverged from the common ancestor that they share with chimpanzees. Also, these atavistic traits and the genes that are responsible for them may have paleoanthropological significance with implications for phylogeny and systematics.

The Chinese Human Genome Center has spent much time studying the genomic divergence between humans and primates primarily because, as they assert, it "may provide insight into the origins of human beings and the genetic basis of human traits and diseases". They chose to compare the genes located on the 21st chromosome in humans to the corresponding genes of chimpanzees, orangutans, gorillas and macaques. The findings of one study [48] identified the number of nucleotide differences, and the differences in coding promoter, and exon—intron junction regions between humans and the aforementioned apes. Using a bioinformatics based approach, they concluded that the discrepancies between the genes found on human chromosome 21 and the genes found on the homologous regions in chimpanzees suggest that chromosome 21 arose due to the presence of "purifying selection". They do not fail to point out that the genes responsible for DS are located on the 21st chromosome, a very small chromosome that seems to contain a relatively small number of genes.

Obesity, heart disease and the thrifty phenotype

DS individuals are susceptible to specific pathological disorders apart from neuropathology. The close association of fitness compromising diseases, including diabetes [49], heart disease [50—52] and obesity [53—55] with DS may well have influenced some researchers to reject the idea that DS may be an adaptive phenotype. I have three arguments against such criticism. First, the disabilities are not all that potent. Medical experts advise parents raise DS children in much the same way that they would raise non-DS children. DS children are screened for certain diseases that they seem to be more susceptible to, such as heart disease, but most DS individuals can expect to live a moderately healthy life. Second, the DS phenotype may have produced adaptive benefits for a more ancient ancestor (such as ancestral hominids) and since this time the phenotype may not have been exposed to equally purifying, selective processes — allowing the accumulation of deleterious mutations. It is interesting to mention that trisomy 13 and 18 (the other two highly prevalent trisomies in humans) are also associated with mental retardation, but individuals with these phenotypes usually die before early childhood [56]. These trisomies may have produced adaptive benefits earlier in the Pliestocene, but since have been selected against.

My third response to the anticipated criticism points out that the "pathological" disorders that regularly accompany DS today may have actually increased reproductive success for DS individuals in the EEA. These disorders — diabetes, heart disease and obesity — are the three facets of the thrifty phenotype phenomenon [57,58]. According to the thrifty phenotype hypothesis, phenotypes that are programmed prenatally (by nutritional deprivation) to express low metabolic rates are thought to enjoy a survival advantage under deprived circumstances; however, if such a thrifty fetus is born into an environment marked by nutritional abundance it will face increased risk of negative health consequences including diabetes, heart disease and obesity [59].

The genes that cause DS individuals to be susceptible to diabetes, heart disease and obesity in modern times may have protected them from starvation and famine, during ancestral times, via the mechanisms proposed by Neel [60,61] and Barker [62—64]. DS individuals are also known to have suppressed immune systems and a susceptibility to respiratory infections [65], yet this may be adaptive for their niche. A great deal of "embodied capital" or scarce resources are invested in the immune system and the less active immune system seen in DS individuals may be another example of bioenergetic thrift.

Reproduction in Down syndrome individuals

It is very difficult to find precise information about DS reproductive fertility yet it is well known that the majority of DS females are fertile and the majority of DS males are subfertile [66]. These findings make sense in terms of evolutionary and sociobiological theory. DS males might dedicate less energy to fertility because, in the EEA, they would have faced a higher risk of being rejected by females through the exercise of female choice and sexual selection. However, a DS mother would be able to increase her reproductive fitness, and

the reproductive fitness of a normal male, if she carried his baby to term. Furthermore, half of such conceptions would be normal — without trisomy 21. For these reasons it is reasonable to assume that DS males would encounter some difficulty finding receptive females whereas DS females probably would not encounter difficulty in finding receptive males. This is evidenced by the fact that DS females in modern times are frequently preyed upon sexually by non-trisomic males [67,68]. One study reports that 72% of sexual abuse victims that are mentally retarded are women, and that the majority, 88%, of perpetrators are men [69].

These facts imply that DS females might have been the driving force behind the selection for trisomy 21, because their progeny would have carried genes for increased proclivity. The less fertile males though, may still have been able to increase their reproductive fitness and thus the human proclivity for DS, by aiding their close kin (inclusive fitness), alloparenting, or by achieving covert copulations (similar to the alternative reproductive strategy of jack salmon [70]).

Importantly, DS males may not have been subfertile in the EEA. The low testicular mass, or hypogonadism, seen in DS males may make them more susceptible to the fertility reducing properties of obesity which is widespread in modern DS populations. Many forms of syndromic mental retardation, including DS [66], are associated with hypogonadism, which is thought to be related to the reductions in fertility seen in some of these groups. Testosterone, the hormonal product of the male gonads, is well known to be a powerfully anabolic hormone and, as we have seen, DS physiology seems to feature diminished anabolism in the form of insulin resistance [49] and growth hormone paucity [71]. It is known that rodents, responding plastically to starvation in order to reduce energy expenditure, often diminish their use of anabolic hormones. One way they accomplish this is by suppressing gonadal function which reduces the energy spent on fertility and reduces the anabolic effects of the sex hormones [72,73]. The suppression of gonadal function in DS may be an analogous, adaptive trait. The widespread, almost ubiquitous obesity seen in DS males, which surely would not have been present in the EEA, may be exacerbating the susceptibility to diminished fertility that is due to hypogonadism. In fact, obesity is well known to decrease testosterone levels and is a significant risk factor for infertility in non-trisomic males [74—76].

Conclusion

The concept of the thrifty phenotype has become an increasingly emergent theme in medical science and it has deeply impacted the viewpoints assumed by pathologists. It has become well accepted that certain disorders can be programmed by differential gene expression resulting in a phenotype that is parsimonious with energy expenditure. The association with advanced maternal age, along with the metabolically conservative traits seen in individuals with DS, imply that it may well represent an adaptive, thrifty phenotype. It is evident, though, that much more work is needed to define the parameters of the relationship between DS and human reproductive strategy.

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