

Body Maps on the Human Genome

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The human genome possesses large-scale structure: In particular, body tissue genes map somatotopically onto the complete chromosome set. The synoptic picture is that genes highly expressed in particular tissues are not randomly distributed on the genome. Rather, they form a "genome homunculus": a multi-dimensional, genome-wide body representation extending across chromosome territories (each chromosome's preferred nucleus locale) of the entire spermc cell nucleus. The antero-posterior axis of the body corresponds to the head-tail axis of the nucleus, and the dorso-ventral body axis to the central-peripheral nucleus axis. Somatotopic maps in cerebral cortex have been reported for over a century. This pervasive genome mapping merits further attention.

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The human genome may be a clutter, but it seems to have a global landscape, with large-scale patterns encompassing all chromosomes together. Tissue-specific genes of the adult human body appear to map somatotopically onto the genome, in multiple dimensions. The holistic

arrangement of tissue gene-sites in the complete chromosome set mirrors the antero-posterior, and dorso-ventral, configuration of the tissue-loci in the body. Unlike hox complexes (McGinnis et al, 1984) or collinearity phenomena (Lewis, 1978), this anatomical mapping includes thousands of genes in the entire chromosome set of the genome. Such a multi-chromosomal bodymap may help as a navigation guide in uncovering genes involved in pathologies of corresponding tissues.

There appears to be little prior study of this extensive structure. Danchin et al (2000) discussed such a mapping idea for the prokaryotic chromosome. Caron et al (2001) described clustering on human chromosomes of highly expressed genes into regions of increased gene expression. In a survey of gene expression in human tissues, Shyamsundar et al (2005) reported gene clustering on single chromosomes according to anatomic locations or types of tissues (e.g., "lymphoid tissues", including thymus, spleen, etc.); but not any higher-order pattern of whole-organism, or whole-genome, mapping.

The map results here are based on combining published data about tissue-specific gene expression levels, and about chromosome territory locations in the nucleus. The chromosome territory model of the nucleus is that chromosomes are not randomly sited, but rather each have preferred loci (Cremer et al, 1982; Cremer & Cremer, 2001). A notable result is that, using fluorescent tag techniques, Bolzer et al (Fig. 1, 2005)

depict territory locations for all chromosomes in one human fibroblast nucleus.

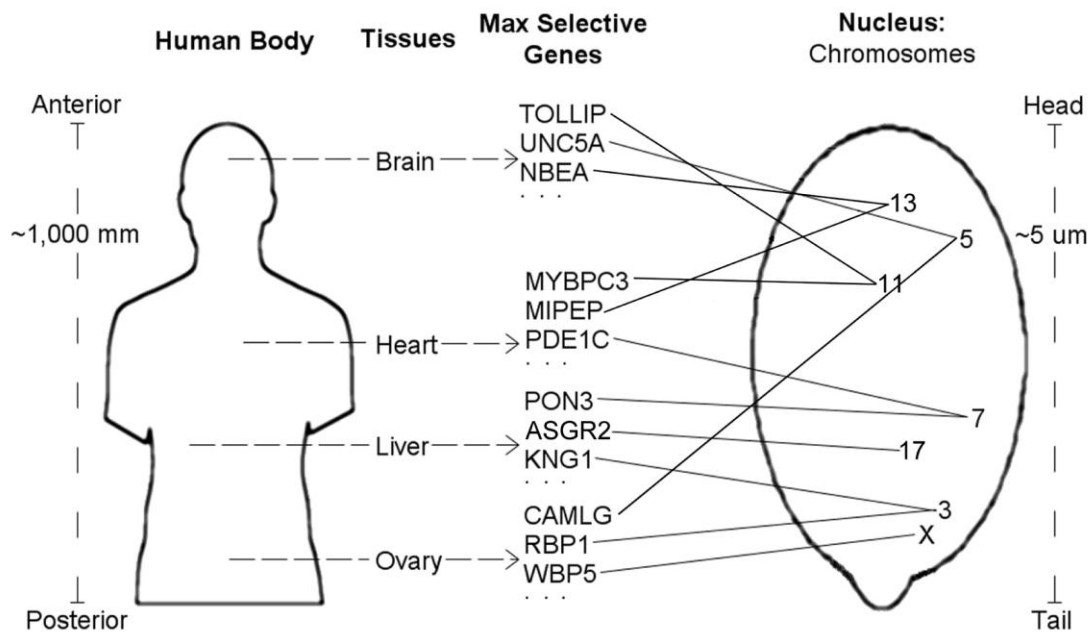


Fig. 1 Mapping the human body onto its genome: Antero-posterior axis. Four organs are illustrated. A few of the maximally selective genes for each tissue are listed (from Liang et al, 2006). Each gene is then assigned to its chromosome. In the sperm cell nucleus, each chromosome has a specific territory. Some of these chromosome sites are also illustrated (from Manvelyan et al, 2008).

Thus: tissue → genes → chromosomes → genome locations.

Methods

For mapping one structure to another, topological interrelations among loci in the one structure must be preserved among loci in the other structure. Here, the two structures are the mature human organism with its tissue sites, and its genome -- i.e., a complete set of

chromosomes, each in its territory in the cell nucleus. The topological interrelations between the tissues examined here are their spatial orderings -- for example, along the antero-posterior axis, the brain is above the heart, etc. So, for each given tissue locus on a body axis, there would be a corresponding preferred zone on the chromosome set for genes expressed in that tissue. (See Fig. 1.)

For this analysis, nine normal tissues were selected; unlike many in the Shyamsundar et al (2005) study, each is compact and localizable (as opposed to, e.g., skin or blood). They each also have the largest number of tissue-specific genes of all compact tissues analyzed (see below). For the approximate centroid of each organ, the antero-posterior order of positions in the body is: brain, thymus, heart, liver, spleen, pancreas, kidney, ovary, testis. Thus, tissues were sampled across different organ systems -- nervous, endocrine, circulatory, digestive, excretory, and reproductive.

The antero-posterior and dorso-ventral axes were each analyzed separately. Because of bilateral symmetry in the vertebrate bodyplan, the lateral (left/right) body axis has a more limited set of distinct tissue loci. For instance, brain, thymus, kidney, ovary, testis all have lateral centroids approximately at the midline; as opposed to heart, liver, spleen, pancreas.

For each tissue, its set of maximally-selective genes was chosen from data of Liang et al (2006). This study included one of the largest sets of tissue-specific genes for brain. Using

Tukey HSD tests on U133A and U133B DNA microarray results, the study identified nearly 4,000 genes that are preferentially expressed in few tissue types. (A supporting finding for this methodology is Zou et al (Fig. S2, 2008), which associates high pleiotropy with low expression levels in C. elegans genes.) A tissue's genes are not in general entirely exclusive to that tissue; shared genes tend to decrease contrast between tissues, and to blur any bodymapping. The count of high-contrast tissue-selective genes for each tissue on each chromosome was compiled (e.g., 98 brain tissue genes on chromosome 1); see Table S1 in the Supporting Information. Table S2 lists for each chromosome and tissue the ratio of such tissue specific genes to the chromosome's combined total tissue specific genes for all tissues in the Liang study (e.g., for brain genes in chromosome 1, the high proportion 0.153).

Chromosome territories were mapped with data derived from a comprehensive study by Manvelyan et al (2008) of sperm cell nuclei. Chromosome architecture in sperm cells has a distinctive packing, with the chromosomes condensed, that is, tightly coiled. Manvelyan et al employed multicolor banding techniques to obtain information on all 24 chromosome loci; each chromosome was observed in 30 nuclei. (Because of its smaller size, the Y chromosome is excluded from the analyses here.) Their Fig. 4 summarized distribution of chromosomes on the "head" - "tail" axis, i.e., from apex to base of nucleus. The location of each chromosome in the 30 sampled had only been classified in terms of

head, middle, or tail zones of the nucleus. We transformed the head - middle - tail distribution of each chromosome into a position score $i = h*1 + m*2 + t*3$. The Manvelyan Fig. 2 includes corresponding chromosome location data for the orthogonal "central" - "peripheral" axis of the nucleus. Measurements from each figure were compiled to determine a mean position-score of each chromosome on each axis. For example, chromosome X occupies the first position at the tail of the nucleus, and chromosome 13 the last position at the head; chromosome 7 is in the first position at the periphery, and chromosome 22 is in the last position, at the center. Tables S3 and S4 present these loci for the entire chromosome set in the head-tail and central-peripheral axes, respectively.

Results

Of course, genes of each of the nine localized tissues are not mainly concentrated on a single particular chromosome (see Table S1). At the opposite extreme, genes of each tissue also are not approximately uniformly distributed on all chromosomes. For instance, the proportion of brain genes ranges from 36.7% in chromosome 13, to 1.8% in chromosome 21 (see x-axis of Fig. 2). Similarly, the highest mean proportion of tissue genes in all chromosomes combined is 17.0% brain genes, while the lowest mean proportion is 2.4% pancreas genes.

However, tissue gene distributions on the chromosomes show a significant intermediate division of labor. For instance, genome-wide positions of genes that express most strongly in

brain, heart, kidney, ovary, etc. respectively tend significantly to correspond to the antero-posterior order of those organs in the body. In particular, for anterior organs (e.g., brain), the gradient of their tail-to-head gene distribution in the spermcell nucleus is increasing (see Fig. 2): That is, the more anterior the tissue, the greater the proportion of its genes in chromosomes of the nucleus head. For mid-positioned organs (e.g., heart), their gene distribution slope shifts from increasing to flat. Then, for posterior organs (e.g., ovary), the relation reverses to decreasing (see Fig. 3).

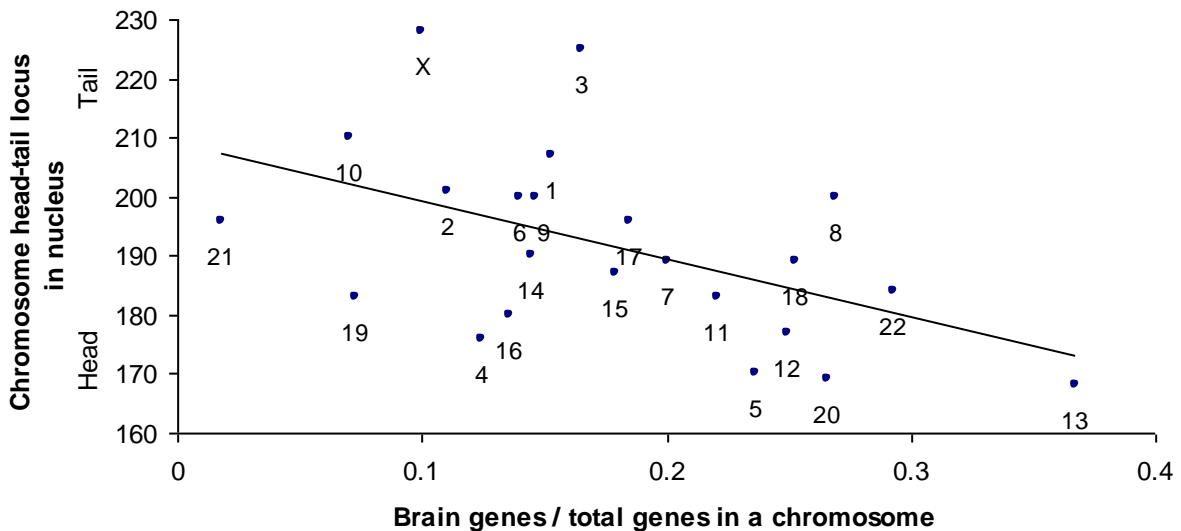


Fig. 2. Brain gene gradient in genome. More braingene-rich chromosomes tend significantly to concentrate at head end of cell nucleus, rather than tail end. ($r^2 = 0.25$; $p < 0.01$, nondirectional.) Each datapoint is labeled with its chromosome number.

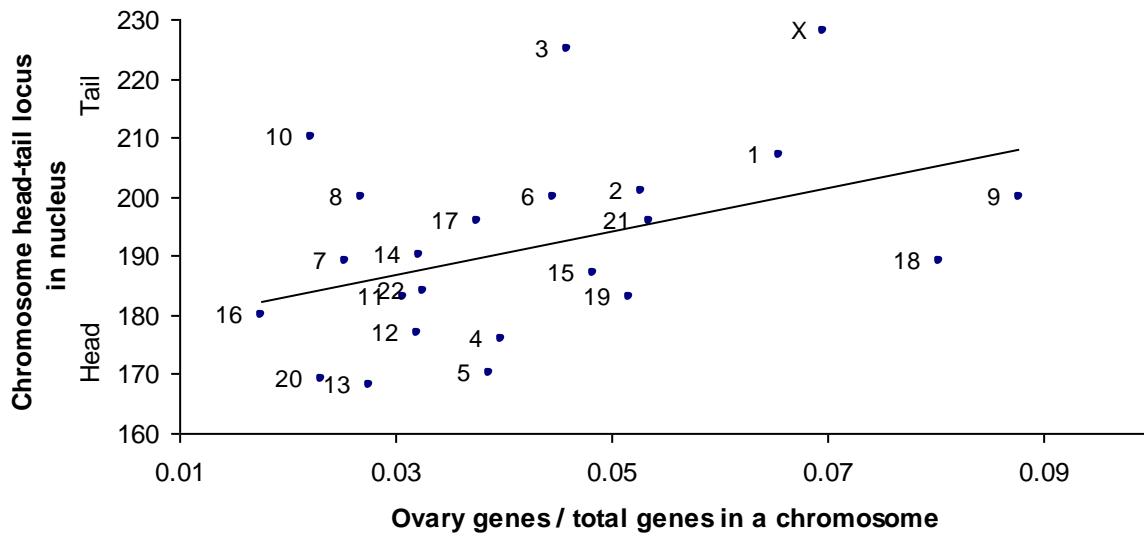


Fig. 3. Ovary gene head-tail distribution in genome. In contrast to maximally-selective brain genes, genes of the posteriorly-positioned ovary show an opposite gradient: They tend to be located more in the tail than in the head of the nucleus. ($r^2 = 0.18$; $p < 0.04$, nondirectional.)

Thus, the set of tissue-slopes itself has a meta-pattern. There is in turn an antero-posterior progression, a "trend of trends". Fig. 4 includes the brain genes distribution of Fig. 2, and the ovary genes distribution of Fig. 3, along with the other tissue gene antero-posterior gradients. The relationship between tissue-loci in the body and gene-loci in the genome significantly fits a simple linear model.

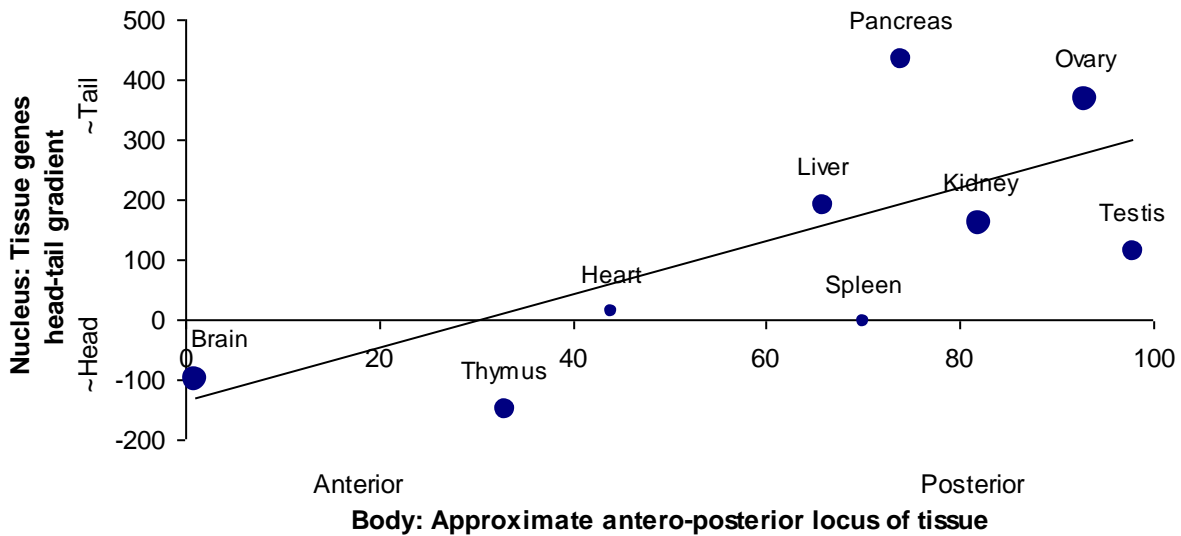


Fig. 4. Antero-posterior "gradient of gradients" in nucleus. Tissue position in body correlates significantly with tissue genes position in cell nucleus. (For datapoints each weighted by their own significance, $r^2 = 0.62$; $p < 0.01$, nondirectional.) The more forward-placed a tissue in the body, the more forward-placed its genes on chromosomes in nucleus. -- The head of the genome homunculus is at the head of the nucleus. Approximate loci of tissues on the antero-posterior axis of body are on a normalized 100-point scale.

Thus, the set of tissue-slopes itself has a meta-pattern. There is in turn an antero-posterior progression, a "trend of trends". Fig. 4 includes the brain genes distribution of Fig. 2, and the ovary genes distribution of Fig. 3, along with the other tissue gene antero-posterior gradients. The relationship between tissue-loci in the body and gene-loci in the genome significantly fits a simple linear model.

The dorso-ventral axis of the body similarly maps to the central-peripheral axis of the nucleus. The more dorsally-positioned a tissue in the body, the more centrally-placed its

genes on chromosomes in the cell nucleus. See Fig. 5. Tissue location on the dorso-ventral axis of the body is in terms of the order of the tissues. For the human body, the aspect ratio of the antero-posterior vs dorso-ventral axes exceeds 5:1 ; consequently, dorso-ventral tissue loci are only resolved on a scale of 10.

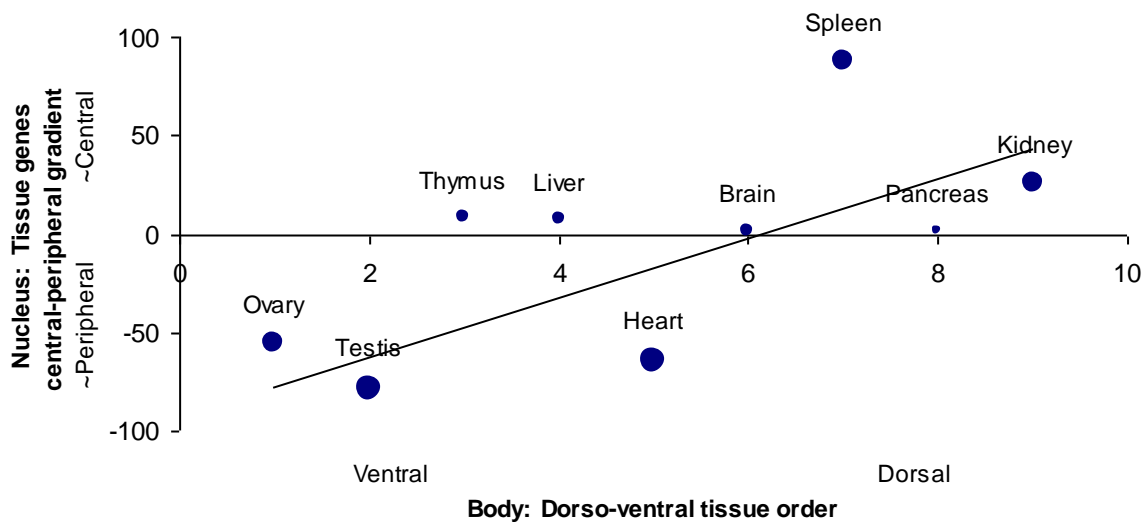


Fig. 5. Dorso-ventral "gradient of gradients" pattern. Similarly to the antero-posterior axis, tissues positioned more dorsally in the body tend to have their genes concentrated on chromosomes sited more toward the center of the nucleus. (For weighted datapoints, $r^2 = 0.47$; $p < 0.04$, nondirectional.) -- In the nucleus, the genome homunculus is facing outward.

The two body axes were each also cross-tested for goodness of fit to the two nucleus axes. There is a contrast: For unweighted data, when the antero-posterior body axis is evaluated instead for correlation with the central-peripheral nucleus axis, r^2 drops appreciably, from 0.49 to 0.09 . Similarly, for the

dorso-ventral body axis correlation with the head-tail nucleus axis, its r^2 again diminishes markedly, from 0.40 to 0.09 . As mentioned, data for lateral (left/right) body axis is limited; its correlation with each nucleus axis is similarly poor.

There is also evidence of mapping of brain subregions, e.g., telencephalon and metencephalon, extending from head to tail of the nucleus like the brain genes gradient of Fig. 2 above. These subregion gradients have the same antero-posterior orientation as the brain gradient; that is, telencephalon and metencephalon genes concentrate more on chromosomes at the head than tail of the nucleus. In addition, we have found a significant pattern of bodymaps on individual chromosomes. This constitutes further convergent support for a genome homunculus hypothesis.

Discussion

The perspective shift here is to view the whole genome as a unified system with its chromosomes meshing together, instead of as isolated, separate components. This approach yields evidence of a genome-wide map of the human body.

The correlation of dorso-ventral tissue positions with tissue genes' central-peripheral nucleus sites can be compared with models of chromosome location on the central-peripheral axis. One is that more gene-dense chromosomes tend to locate more toward the nucleus center (Croft et al, 1999). Another is that chromosomes with more active genes tend to locate more toward the center (Gilbert et al, 2001).

Somatotopic maps have long been observed in mammal sensorimotor cortex (Fritsch & Hitzig, 1870; Penfield & Rasmussen, 1950). One possible function or design rationale for a genome homunculus might be to help minimize message-passing costs by shortening interconnections among related genes in genetic regulatory networks. The question then is whether information transmission is not cost-free even within a cell, nucleus, or genome. Similar connection optimization has been observed in nervous system wiring (Cherniak et al, 2004). -- Thus: Genome as "nanobrain".

This work raises natural next questions concerning prevalence of genome body maps. Does the genome, like the cortex, contain multiple maps -- e.g., "motor" output vs input maps, or overlapping submaps? Does the familiar antero-posterior polarity of the egg cell in fact also resolve into a body-tissue ordering, and a mapping, when the large scale chromosome territory structure of the genome is taken into account? As opposed to haploid germ cells, how much of this bodyplan modeling do specialized, mature somatic cells retain? And, in contrast to ontogenetic development, from a phylogenetic perspective, does this type of genome bodymap already appear for simpler eukaryotes -- for example, plants? (For another organism that also has a bodyplan with longitudinal and radial axes, Alexandrova et al (2003) report chromosome territories like those of mammal nuclei in the polyp Hydra.)

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Supporting Material:

Tables S1 to S4

Supporting Information

Table S1. Human genome: Maximally-selective tissue genes. Counts of genes expressed for each of 9 topologically compact tissues. Compiled from: Liang et al (2006). For 83 normal tissue groups.

| Chromo | Brain | Thymus | Heart | Liver | Spleen | Pancreas | Kidney | Ovary | Testis | Other | Totals |
|--------|-------|--------|-------|-------|--------|----------|--------|-------|--------|-------|--------|
| 1 | 98 | 66 | 60 | 38 | 27 | 17 | 56 | 42 | 18 | 218 | 640 |
| 2 | 44 | 39 | 32 | 20 | 6 | 10 | 43 | 21 | 20 | 163 | 398 |
| 3 | 54 | 31 | 13 | 32 | 5 | 11 | 32 | 15 | 21 | 112 | 326 |
| 4 | 25 | 27 | 13 | 21 | 6 | 4 | 14 | 8 | 10 | 73 | 201 |
| 5 | 61 | 20 | 30 | 10 | 6 | 2 | 33 | 10 | 16 | 70 | 258 |
| 6 | 44 | 36 | 6 | 23 | 15 | 9 | 42 | 14 | 14 | 111 | 314 |
| 7 | 55 | 27 | 18 | 13 | 4 | 7 | 12 | 7 | 16 | 116 | 275 |
| 8 | 50 | 10 | 4 | 9 | 3 | 4 | 14 | 5 | 13 | 74 | 186 |
| 9 | 30 | 13 | 13 | 21 | 3 | 6 | 14 | 18 | 10 | 77 | 205 |
| 10 | 19 | 15 | 20 | 28 | 4 | 8 | 33 | 6 | 10 | 128 | 271 |
| 11 | 86 | 20 | 16 | 14 | 8 | 11 | 38 | 12 | 22 | 163 | 390 |
| 12 | 70 | 32 | 18 | 18 | 7 | 5 | 18 | 9 | 16 | 88 | 281 |
| 13 | 40 | 12 | 3 | 7 | 3 | 1 | 8 | 3 | 2 | 30 | 109 |
| 14 | 27 | 20 | 3 | 18 | 3 | 3 | 23 | 6 | 14 | 69 | 186 |
| 15 | 26 | 15 | 17 | 9 | 5 | 2 | 14 | 7 | 5 | 45 | 145 |
| 16 | 31 | 22 | 5 | 14 | 8 | 11 | 25 | 4 | 6 | 102 | 228 |
| 17 | 54 | 20 | 4 | 15 | 8 | 3 | 30 | 11 | 13 | 134 | 292 |
| 18 | 22 | 6 | 7 | 6 | 1 | 1 | 0 | 7 | 8 | 29 | 87 |
| 19 | 24 | 26 | 14 | 18 | 13 | 6 | 19 | 17 | 17 | 175 | 329 |
| 20 | 46 | 13 | 6 | 6 | 3 | 5 | 7 | 4 | 17 | 66 | 173 |
| 21 | 1 | 3 | 4 | 3 | 0 | 0 | 9 | 3 | 4 | 29 | 56 |
| 22 | 36 | 9 | 6 | 8 | 1 | 4 | 11 | 4 | 6 | 38 | 123 |
| X | 20 | 15 | 13 | 9 | 7 | 6 | 27 | 14 | 19 | 71 | 201 |
| Totals | 963 | 497 | 325 | 360 | 146 | 136 | 522 | 247 | 297 | 2181 | 5674 |

Table S2. Ratios of counts of tissue genes / total genes, for each chromosome. Based on Table S1.

| Chromo | Brain | Thymus | Heart | Liver | Spleen | Pancreas | Kidney | Ovary | Testis | Other |
|--------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| 1 | 0.153125 | 0.103125 | 0.09375 | 0.059375 | 0.042188 | 0.026563 | 0.0875 | 0.065625 | 0.028125 | 0.340625 |
| 2 | 0.110553 | 0.09799 | 0.080402 | 0.050251 | 0.015075 | 0.025126 | 0.10804 | 0.052764 | 0.050251 | 0.409548 |
| 3 | 0.165644 | 0.095092 | 0.039877 | 0.09816 | 0.015337 | 0.033742 | 0.09816 | 0.046012 | 0.064417 | 0.343558 |
| 4 | 0.124378 | 0.134328 | 0.064677 | 0.104478 | 0.029851 | 0.0199 | 0.069652 | 0.039801 | 0.049751 | 0.363184 |
| 5 | 0.236434 | 0.077519 | 0.116279 | 0.03876 | 0.023256 | 0.007752 | 0.127907 | 0.03876 | 0.062016 | 0.271318 |
| 6 | 0.140127 | 0.11465 | 0.019108 | 0.073248 | 0.047771 | 0.028662 | 0.133758 | 0.044586 | 0.044586 | 0.353503 |
| 7 | 0.2 | 0.098182 | 0.065455 | 0.047273 | 0.014545 | 0.025455 | 0.043636 | 0.025455 | 0.058182 | 0.421818 |
| 8 | 0.268817 | 0.053763 | 0.021505 | 0.048387 | 0.016129 | 0.021505 | 0.075269 | 0.026882 | 0.069892 | 0.397849 |
| 9 | 0.146341 | 0.063415 | 0.063415 | 0.102439 | 0.014634 | 0.029268 | 0.068293 | 0.087805 | 0.04878 | 0.37561 |
| 10 | 0.070111 | 0.055351 | 0.073801 | 0.103321 | 0.01476 | 0.02952 | 0.121771 | 0.02214 | 0.0369 | 0.472325 |
| 11 | 0.220513 | 0.051282 | 0.041026 | 0.035897 | 0.020513 | 0.028205 | 0.097436 | 0.030769 | 0.05641 | 0.417949 |
| 12 | 0.24911 | 0.113879 | 0.064057 | 0.064057 | 0.024911 | 0.017794 | 0.064057 | 0.032028 | 0.05694 | 0.313167 |
| 13 | 0.366972 | 0.110092 | 0.027523 | 0.06422 | 0.027523 | 0.009174 | 0.073394 | 0.027523 | 0.018349 | 0.275229 |
| 14 | 0.145161 | 0.107527 | 0.016129 | 0.096774 | 0.016129 | 0.016129 | 0.123656 | 0.032258 | 0.075269 | 0.370968 |
| 15 | 0.17931 | 0.103448 | 0.117241 | 0.062069 | 0.034483 | 0.013793 | 0.096552 | 0.048276 | 0.034483 | 0.310345 |
| 16 | 0.135965 | 0.096491 | 0.02193 | 0.061404 | 0.035088 | 0.048246 | 0.109649 | 0.017544 | 0.026316 | 0.447368 |
| 17 | 0.184932 | 0.068493 | 0.013699 | 0.05137 | 0.027397 | 0.010274 | 0.10274 | 0.037671 | 0.044521 | 0.458904 |
| 18 | 0.252874 | 0.068966 | 0.08046 | 0.068966 | 0.011494 | 0.011494 | 0 | 0.08046 | 0.091954 | 0.333333 |
| 19 | 0.072948 | 0.079027 | 0.042553 | 0.054711 | 0.039514 | 0.018237 | 0.057751 | 0.051672 | 0.051672 | 0.531915 |
| 20 | 0.265896 | 0.075145 | 0.034682 | 0.034682 | 0.017341 | 0.028902 | 0.040462 | 0.023121 | 0.098266 | 0.381503 |
| 21 | 0.017857 | 0.053571 | 0.071429 | 0.053571 | 0 | 0 | 0.160714 | 0.053571 | 0.071429 | 0.517857 |
| 22 | 0.292683 | 0.073171 | 0.04878 | 0.065041 | 0.00813 | 0.03252 | 0.089431 | 0.03252 | 0.04878 | 0.308943 |
| X | 0.099502 | 0.074627 | 0.064677 | 0.044776 | 0.034826 | 0.029851 | 0.134328 | 0.069652 | 0.094527 | 0.353234 |
| Means | 0.169722 | 0.087593 | 0.057279 | 0.063447 | 0.025731 | 0.023969 | 0.091999 | 0.043532 | 0.052344 | 0.384385 |
| | [Fig 2] | | | | | | | [Fig 3] | | |

Table S3. Human sperm cell. Chromosome location in nucleus, on Head / Tail axis. Derived from Manvelyan et al (2008), Fig. 4, p. 5. 30 nuclei sampled for each chromosome. (HMT score range: 100 for all observed loci in head; 300 for all in tail.)

| Chromo | Cell Head% | Cell Mid% | Cell Tail% | HMT Index | Hd/TI Order | |
|--------|------------|-----------|------------|-----------|-------------|------|
| 1 | 30 | 33 | 37 | 207 | 4 | |
| 2 | 30 | 39 | 31 | 201 | 5 | |
| 3 | 20 | 35 | 45 | 225 | 2 | |
| 4 | 34 | 56 | 10 | 176 | 15 | |
| 5 | 37 | 56 | 7 | 170 | 16 | |
| 6 | 17 | 66 | 17 | 200 | 6 | |
| 7 | 23 | 65 | 12 | 189 | 9 | |
| 8 | 17 | 66 | 17 | 200 | 6 | |
| 9 | 17 | 66 | 17 | 200 | 6 | |
| 10 | 17 | 56 | 27 | 210 | 3 | |
| 11 | 20 | 77 | 3 | 183 | 12 | |
| 12 | 23 | 77 | 0 | 177 | 14 | |
| 13 | 41 | 50 | 9 | 168 | 18 | Head |
| 14 | 27 | 56 | 17 | 190 | 8 | |
| 15 | 23 | 67 | 10 | 187 | 10 | |
| 16 | 30 | 60 | 10 | 180 | 13 | |
| 17 | 17 | 70 | 13 | 196 | 7 | |
| 18 | 34 | 43 | 23 | 189 | 9 | |
| 19 | 30 | 57 | 13 | 183 | 12 | |
| 20 | 44 | 43 | 13 | 169 | 17 | |
| 21 | 17 | 70 | 13 | 196 | 7 | |
| 22 | 23 | 70 | 7 | 184 | 11 | |
| X | 17 | 38 | 45 | 228 | 1 | Tail |
| Means | 25.6 | 57.2 | 17.2 | 191.7 | 9.2 | |

Table S4. Chromosome position in nucleus, on Central / Peripheral axis. Derived from Manvelyan et al (2008), Fig. 2, p. 4. “% probability” of location: 30 cells sampled for each chromosome.

| Chromo | % Ctrl | Ctrl/Prph Order | |
|--------|--------|-----------------|------------|
| 1 | 30 | 5 | |
| 2 | 34 | 6 | |
| 3 | 20 | 2 | |
| 4 | 20 | 2 | |
| 5 | 27 | 4 | |
| 6 | 60 | 12 | |
| 7 | 17 | 1 | Peripheral |
| 8 | 27 | 4 | |
| 9 | 34 | 6 | |
| 10 | 37 | 7 | |
| 11 | 37 | 7 | |
| 12 | 44 | 8 | |
| 13 | 50 | 10 | |
| 14 | 73 | 14 | |
| 15 | 46 | 9 | |
| 16 | 54 | 11 | |
| 17 | 63 | 13 | |
| 18 | 23 | 3 | |
| 19 | 80 | 15 | |
| 20 | 30 | 5 | |
| 21 | 34 | 6 | |
| 22 | 83 | 16 | Central |
| X | 23 | 3 | |
| Mean | 41.1 | 7.3 | |