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Editorial: A matter of ingredients

Fig. 1 shows a work of art by Marzia Migliora. The two skeletons reproduce the burial of a man and a woman who lived and died together, sometime during the Neolithic Age, and were dug near present day Mantua. This scene, spelling love and mutual commitment beyond the boundaries of physical existence, is highly emotional. But then, who is he, who is she, in the couple? Any science scholar knows how to answer this question: details in the shape of our bones differ between males and females, and contribute to the overall difference in appearance between the genders. Difference in the shape of the bones, most notably of chest and pelvis, is just one feature of sexual dimorphism. The main anatomic distinction obviously involves the gonads together with the internal and external genitals and the endocrine apparatus with its physiological and behavioral effects. But many aspects are involved, at different levels of complexity/integration.

Together with physiology, anatomy addresses the highest level of biological complexity; the possibility to differentiate individuals by sex on the basis of morphological dimorphism – a procedure that we apply endlessly and unthinkingly to animals of all species – is a most logical consequence of the compound influence of all the traits peculiar to either gender. However, the possibility to differentiate genders still holds when addressing the lowest level of complexity: Fig. 2 shows the separation between male and female rats afforded by compositional dimorphism as assessed by the quantitation of > 200 small molecular weight substances in plasma.

The results in Fig. 2 belong to the field of metabolomics, namely the comprehensive study of the collection of all metabolites in a biological cell, tissue, organ or organism, which are the end products of cellular processes; accordingly, metabolic profiling provides an instantaneous snapshot of the physiology of that cell, tissue, organ, or organism. Metabolomics is just one of the omics, the branches of biological research aiming at the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of a biological entity. As shown by Fig. 3, differences between sexes have been investigated with all of such comprehensive omics approaches, and the results are published in a large number of scientific papers. More evidence is expected to be provided by future endeavor as such a leading funding agency as the National Institutes of Health (NIH) requires that grant proposals submitted after January 2016 include sex or gender in study designs, or explain why not (NIH Notice Number: NOT-OD-15-102).

By far the largest number of reports in the scientific literature deals with nucleic acids, either at the DNA (genomics, epigenomics) or at the RNA (transcriptomics) level. The relevance of sex-specific investigations in this area directly stems from the sheer evidence of dimorphic sex chromosomes (in mammals, females are homogametic (XX), males heterogametic (XY)) and reflects the hierarchy between informational and non-informational molecules. Omics studies started earlier in this than in other fields of research and progressed faster, thanks to technical development with extensive automation for genome-wide analyses.

Fundamental research has dealt with origin and evolution of the sex chromosomes themselves, in Fig. 4, and of the regulatory networks controlling sex determination, in Fig. 5 [2–5]. The cascades triggering gender differentiation in different phyla extensively differ at the level of master genes whereas the downstream components are conserved throughout evolution and appear to converge on the regulation of a few common effectors. SRY is the master male sex regulator of all therian mammals; it most likely arose as the result of two events that redirected the biological role of existing genetic elements: a dominant mutation in the SOX3 allele, and the fusion with regulatory sequences from another gene already on the X chromosome. The proto-Y was born.

Advances in sequencing technology allowing for genome-wide assessments have shown that the patterns of germline mutation - the source of all evolutionary adaptations - are definitely non-random. Among species, an inverse relationship holds between neutral substitution rates and generation time; within each species, between mutation size and incidence. Three fourths of the new mutations originate in the paternal lineage and increase with paternal age (∝ number of mitoses before meiosis). They occur more frequently in early-replicating, genic regions (∝ CpG dinucleotides) and show signatures of transcription-coupled repair. Mutations within clusters include a lower number of transitions and a higher number of transversions than isolated mutations. The mutation rate is itself a product of evolution and in primates, including our species, it is likely to have changed over time [6–8].

In humans, two continuous linkage groups are carried by a single sex. The Y chromosome, in its non-recombinant portion, is only passed from father to son (patrilineality); mitochondrial DNA (mtDNA) can only be passed to the next generation by females (matrilineality) [9]. Data on Y chromosome and on mtDNA are being used by molecular anthropology to establish evolutionary links between ancient and modern human populations [10,11], as well as among contemporary species [12].

Current view about sexual differentiation (through an organizational-activational mechanism) maintains that sex chromosome genes/gene products, hormones and sex-specific environments, all have independent as well as synergistic differentiating effects. This applies to all tissues, but has been more extensively characterized for CNS; sexual differentiation of the brain pervasively impacts on such traits as gender identity and sexual orientation [13], as provocatively epitomized by the

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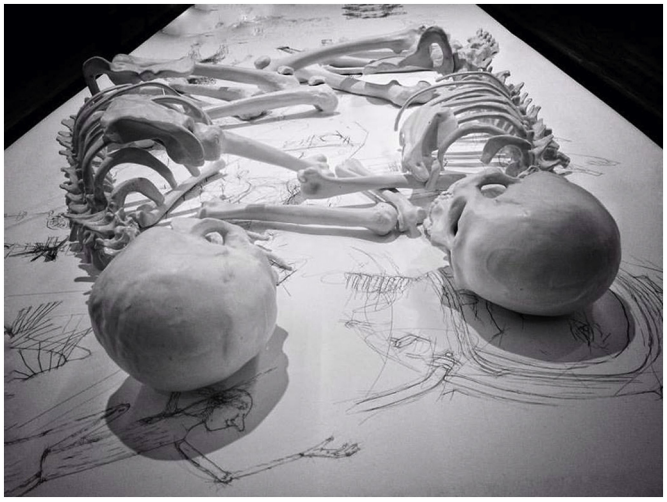

Fig. 1. “La morte tornò a letto, si abbracciò all'uomo e, senza ben capire quello che le stava succedendo, lei, che non dormiva mai, sentì che il sonno le faceva calare dolcemente le palpebre. Il giorno seguente non morì nessuno” by Marzia Migliora, recently shown at Fondazione Prada, Milano (http://www.fondazioneprada.org) as part of the exhibition “To the Son of Man Who Ate the Scroll” designed by Goshka Macuga. This work of art reproduces the Valdaro's Lovers, the everlasting hug between two skeletons from the Neolithic Age.

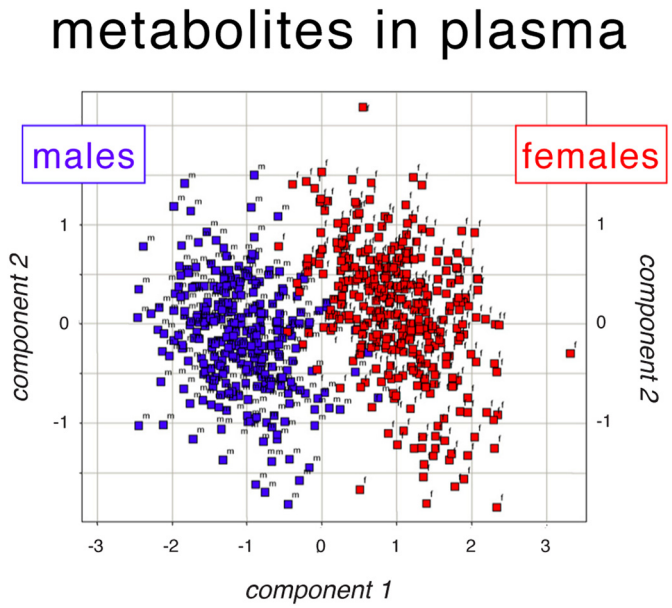

Fig. 2. Distribution in the space of the first two principal components from a PCA analysis of the plasma metabolite profiles (215 compounds being quantified, with a molecular weight between 80 and 1000 Da) for some hundreds of rats (670 in total) across multiple experiments (11) performed within one year. Males (blue) and females (red) are clearly separated. Modified from Fig. 1 in [1]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

question: “Is it useful to view the brain as a secondary sexual characteristic?” [14]. Compensatory sex-specific factors have been recognized as well, influencing the degree to which brain regions are masculinized or feminized in one individual; in a population this implies extensive variance among individuals of the same sex as for relative maleness or femaleness [15]. Among the cellular and molecular mechanisms of sexual differentiation (which include differences in cell genesis, migration and death, and in their neurochemical and morphological phenotype [16], with a specific timing for sensitivity to hormones [17]), epigenetic modifications play a most relevant role [18]. DNA and histone PTM are believed to account for the long-term effects of short-term stimuli, sometimes restricted to phases of the embryonic/fetal development. Indeed, the complex between estradiol and its nuclear transcription factor receptor (ER) recruits histone acetyl transferases and modifies the activity of DNA methyl transferase [19,20].

In a symmetrical situation to the abundance of papers investigating nucleic acids, the smallest number of omics reports deals with the smallest chemical entities, metal ions. This includes a provocative point of view by A. De Loof about “the essence of female-male physiological dimorphism” that he identifies in the differential homeostasis of calcium ions, dubbed calcigender [21]. In this perspective, the high amount of Ca^{++} in spermatic fluid and in egg shells (non-mammals) or milk (mammals) should be regarded as a way to extrude a potentially toxic metal (Ca^{++} at concentrations above 10 mM). Due to the different balance of reproduction-related hormones (sex steroids), females need to pump off their cells and eventually extrude off their bodies more Ca^{++} than males.

Few reports deal as well with interactomics. Two of them are worth mentioning here as addressing disease conditions. One investigates

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