Evolution favors the females but with exceptions - 46,XY DSD, a gold medal, and autoimmune diseases

A sports event and an example of why to care especially for women

The hope for another gold medal in women's boxing for Thailand during the Olympic Games in Paris was shuttered by an Algerian man. He was born with some faulty developments of his sexual organs, claiming to be a female. The saddened Thai Ms. Jamjaem Suwannapheng finally made it to a bronze medal in one of the female boxing categories. The Algerian is genetically a man, looks like a man, and boxes like a man. He hit all the female competitors, strong like a man, and proudly presented a gold medal.

Previously, this blog mentioned the threat that sports for women would be impaired and emphasized the danger of neglecting the female sex in research and medicine (1). The scandal during this infamous Parisian game clearly shows the face of the bizarre ideology claiming that sex is a social construct.

Sex chromosomes identify ciswomen and cismen

Eventually, after finishing high school, one knows that mankind consists of only females and men. Both sexes are easily identified by the chromosomes of the 9th category: an individual with the setting XX as female and XY as male. Nowadays, if one wants to publish in Western ideology-dominated publications, such as the science magazines 'Nature' or 'Science', one better term, the preceding sentence, such as 'sex bias has to distinguish between ciswomen and cismen', demonstrating that you are totally in trend to believe in a multitude of the LGBTQ+ genders.

46, XY DSD - Disorder of sex development

Professionals in medicine know that there is hardly any process in the setting up of our organs without the possibility that something goes wrong. That applies too also during fetal development. The Algerian male boxer, enjoying hitting females, is probably the victim of a disorder of sex development (DSD). As disclosed in the media, the Algerians carried the XY chromosomes. He probably is a patient with '46,XY DSD.' The gene NR5A1 has a significant role in the development of sex organs, and mutation of the gene can interfere with normal sex organ development, such as for a patient with 46,XY DSD. The abnormality, 46,XX DSD, also might distort sexual development, so this person appears like a man but is genetically a female (2, 3). Both are extremely rare diseases and by no means is it justified to use pathological incidents trying to muddle up the importance of distinguishing between males and females and substitute it with gender indoctrination. Evolution chose for mammals, including homo sapiens, bisexual reproduction.

Evolution decided for humans to involve women and men in reproduction

The decision was made about 200 to 300 million years ago. Besides mammals, other species choose bisexual reproduction as well, such as birds, fish, and amphibians (4). During evolution, the genus mammals split from the monotremes. These are species that lay eggs.

The arrangement to relay for reproduction to males and females, chosen for homo sapiens, is somewhat complex and termed genetic redundancy, but it seems to enhance reproductive success (5, 6). Females are carrying most of the burden of assuring that the species homo sapiens survive. So, it's not surprising that evolution favored females over males in certain aspects. The death rate for males during their lifetime is 20% higher after conception up to 73 years old, changing only after that advanced age because there are more surviving females compared to males (7).

It depends on the male whether a girl or boy is born

The gametes in the ovary contain only one X, while the sperm carry either the X or the Y (8)(see pages 77 – 86). Whether a male or a female is finally born depends on the father, not the mother. During meiosis, the mother can only contribute one X. If the other X is derived from the father, a daughter is born. For a son, it's the Y that comes from the father (9). Maybe once a historian sums up the fate of those unfortunate royal women in history, being condemned, dispelled, and wrongly blamed for the dynasties to vanish because they did not 'produce' a follower for the throne. Fortunately, it is proved that the royal power also of females determined the shape of whole periods in history for the betterment of nations, such as Queen Victoria for Great Britain.

Gonadal development

While it was believed until recently that if the male determining Y chromosome from the father didn't make it through the meiosis after fertilization, more or less automatically, in the presence of the X from the mother and the X from the father, the progression towards the female sex, as a 'default process,' continues. More advanced technologies, such as single-cell RNA sequencing (scRNA-seq), proved that the process is quite complicated not only for the XY pair but also for the XX chromosome pair (10, 11).

Gonadal development set off around the fourth gestational week. It starts from a bipotential group of cells within the growing embryo named adreno-genital primordium (AGP). Coelomic epithelial cells are transformed into mesenchymal cells expressing genes such as SRY for male development. Progenitor cells cause cell differentiation into male-determining Sertoli and Leydig cells or the granulosa and theca cells for females. From here, development leads to germ cells and the function of the sexual endocrine system, and finally, the descent of the testis and the development of the ovary (10).

Not all genes on the X chromosome have a role in reproduction

The two sex chromosomes are not only different in size, but the X chromosome is significantly larger than the Y chromosome. Therefore, females have 23 homologous pairs of chromosomes, and males have 22 pairs. Recently, investigations into genetic linkage have mainly focused on the X chromosome. The non-homologous part of the sex chromosomes is involved in the

meiosis. Despite what happens during meiosis, 867 coding genes on the X chromosome are involved in developing the neural system, bone, blood, liver, kidney, retina, ear, heart, skin, and teeth. These genes mainly have no role in reproduction (9).

Sequencing the Y chromosome

Sequencing the the human Y chromosome proved to be almost impossible because of 'repetitive and inverted stretches of DNA', which made it extremely difficult to identify coding genes. It was the human chromosome, out of which half was missing. That changed last year when the result of the consortium Telomere-to-Telomere (T2T) published in Nature the complete sequence not only from one but from several men from different countries. It was found that the number of genes, to a great extent, varied from man to man. Forty-one formerly unknown coding genes were found, and numerous errors in important gene families were corrected (12).

Diseases linked to the X chromosome are more severe in men

In the future, very interesting, complex interrelationships between sexes will be found to explain and combat Y-linked diseases. So far, it is known that at least 533 X-linked diseases are, in the majority, more harmful for men than for women (7). Most of these diseases are known to the clinical specialist by their phenotypes, and names are derived from the physicians who described the syndrome. Only more recently did the genetic background become known. An exhaustive list of hundreds of such diseases has recently been spread over more than 11 pages of a review publication (7).

Women are spared a greater risk of acquiring X chromosome-linked diseases depend on different variant alleles of their two X chromosomes. Females, like men, have only one active X chromosome. This is achieved by describing only one of the two X chromosomes, a process called X-inactivation. Females usually have two kinds of cells in their tissue: those active from their maternal- and those inactive from the paternal side. In 46 XY male tissues, the maternal X is active in every cell; in females, it is only in 50% of the cells. Yet, the damaging variant is not expressed in all of her cells. That results in many disorders of the X chromosome type; females have less severe clinical manifestations (7). But there is no rule with an exception.

Exception - autoimmune diseases affect more females than men

It has been known for quite some time that major autoimmune diseases of almost 80% affect women over men. In the United States, it is the third most common group of illnesses besides heart diseases and cancer, with 5% to 8% of the population. Diseases of this group are known, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis, and myocarditis. Almost every organ can be involved, like the thyroid, the connective tissue, the gastrointestinal tract, the heart, the skin, and the kidney (13).

Autoantibodies are not necessarily harmful and are widely distributed in the average population. Two main classes of antinuclear antibodies (ANA) are directed to DNA, histones, and nuclear material. The physiological role is to clear cellular debris due to inflammation or wounds inflicted. Diseases occur when ANA binds to self-antigens inducing complement, causing

cytotoxicity or a pathological immune complex in damaging tissues of various organs. Together with the symptoms of different autoimmune diseases, autoantibody titers are used for the diagnosis (14, 15). Unfortunately, the diagnostic properties of DNA antibodies are not as specific as those of RNA-binding proteins, and frequent testing is necessary to follow up on the course of diseases such as SLE (16). The initiating reasons for autoimmune diseases and certain infectious diseases have been intensively discussed. Why, in particular, women are prone to suffer from the diseases remained unclear (13).

The Xist ribonucleoprotein complex

This changed recently! It was suspected that the offender's preference for SLE and those other diseases for the fairer sex could be found in connection with the X chromosome. An important paper published in the scientific journal Cell hints at the X-chromosome inactivation in females, which dampens one X chromosome in XX cells. This is to adjust their action of X-linked genes to match the XY situation in man (17).

Inactivation is achieved through the non-coding RNA (lncRNA) Xist. Xist is only transcribed from the ‘quiet’ X chromosome in females and is missing in males. Every cell in females inactivates one of the two X chromosomes through the Xist ribonucleoprotein (RNP) complex. Xist wraps around the entire inactive X chromosome, together with 81 binding proteins forming a ribonucleoprotein (RNP) complex, out of which ten complexes interact directly with RNA proteins, the rest is indirectly expressed in somatic cells.

Not all of the genes on the silent X chromosome might stay inactivated, and the Xist RNA complexes can act as autoantigens. T cells from the innate immune system can be activated from those autoantibodies, and atypical B cells formed in females. In a mouse model, this course of events could initiate SLE. In the sera from patients with autoimmune diseases protein complexes such as Xist RNP are target by autoabtibodies and this also was observed in the mouse model. Animals expressing Xist had higher autoantibody compared to those that didn’t. Ultimately, tissue and organs are attacked, resulting in those symptoms known to be autoimmune diseases. Naturally, women with their XX chromosome are more prone to suffer from autoimmune diseases than men (17, 18).

Future investigation in Xist of benefit also for Africa and Asia

The group of diseases is not only a major cause of morbidity and mortality in the USA. SLE, for instance, seems more common in populations of Asian and African origin. So far, Thailand's morbidity and mortality statistics for autoimmune diseases do not seem available yet. In Hong Kong, the prevalence was estimated to be 58.8 per 100.000 inhabitants. Chinese patients display more serious progressions of the diseases, especially concerning the kidneys (19). Autoimmune diseases, such as SLE, are characterized by very unspecific symptoms in the early phases, difficulties in coming to a valid diagnosis, and therapies against the ‘B-cell depletion’ do not always work (20). Future studies about the role of Xist RNP in autoimmunity are promising to enhance a better understanding of the disease (18).

Conclusion

In the future, it might be worthwhile for public health to join clinicians in concentrating on the importance of diseases for women. Through the primary health care of the Thai public health system, methods could be tested and implemented to improve secondary prevention.

The short notice about the investigation into the Xist RNP in the science magazine NATURE found it necessary to say sorry for drawing attention to the two sexes in plain words by writing: 'This article uses 'women' and 'female' to describe people with two X chromosomes and no Y chromosome, reflecting the language of the study, while acknowledging that gender identity and chromosomal make-up do not always align' (17). This excuse should not be necessary. Investigating the molecular background of diseases, especially those that strike women, illustrates the importance of considering the differences between sexes in health and disease. Regarding how meiosis works, we can easily grasp that mankind consists of only two sexes. To argue on very rare diseases in the development of sexual organs to nebulize the obvious should be questioned.

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