Revisiting the Shbg genes evolution across vertebrates supports a much earlier origin than previously hypothesized

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Influence of chronic Sodium valproate treatment on cytochrome P450 aromatase gene of male Sprague-Dawley rats

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Sodium valproate is known and well defined for anticonvulsant activity. Its mode of action mediated through effects on the function of brain gamma-amino butyric acid (GABA). One of its side effects is the negative effect on reproductive functions but its influence on cytochrome p450 aromatase gene is not known. The P450 aroma in testis and ovary is known to be regulated via. the proximal promoter II. Androgen, estrogen and related hormones to reproductive functions play an important role in testis and epididymis and also act as important parameters for maintaining male fertility. In present study sodium valproate were fed orally to Sprague Dawley rat for 90 days to understand its chronic effects on cytochrome P450 aromatase gene and hormones related to male reproductive functions. Present study registered decrease in weight of testis and epididymis with decrease in sperm count and sperm motility with significantly increase registered in FSH and estrogen level with decreased in LH and testosterone levels. Enzyme β-Glucuronidase and Hyaluronidase activity registered significant decrease in testis and epididymis. SNP analysis was conducted by standard procedure on testis tissue upon completion of treatment tenure. SNP report compared with normal gene sequence indicates chromosomal aberrations in the Exon I and Exon II of cytochrome P450 aromatase gene. The mutations i.e. insertation, deletion and mismatch observed before the start of translation site (ATG) and present within the Exon I and Exon II. The mutations were also seen in the proximal promoter II region of the aromatase gene. Chromosomal aberrations indicate mutations after the chronic treatment of this compound.

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In vertebrates, two different sex hormone-binding globulin (*Shbg*) genes have been characterized: *Shbga* and *Shbgb*. The *Shbga* gene has been shown to be conserved in most vertebrate lineages, from chondrichthyes to mammals. The protein encoded by this gene is mostly secreted by the liver and released in the blood circulation where it binds androgens and estrogens and regulates their access to target tissues. To date, the *Shbgb* gene has only been reported in salmonids. It has been demonstrated that the *Shbgb* transcript is mainly expressed in the ovary, suggesting a local mediation of the sex steroids effects by the Shbgb protein. In addition to exhibit totally different tissue distributions, the two Shbg share very low identity percentages as shown in rainbow trout (*Oncorhynchus mykiss*) with 26% identity at the amino acid level. However, as salmonid ancestor has experienced a specific whole genome duplication (Ss4R), the Shbg diversity has been considered as resulting from this particular event, after which *Shbgb* would have experienced a functional shift.

The increasing amount of genomic and transcriptomic data has enabled us to revisit the evolutionary history of *Shbg* among vertebrates. Investigating the transcriptomes of 24 actinopterygian species (including 22 teleosts) and vertebrate genomes, we identified previously non-reported *Shbg* genes. Performing phylogenomic analyses, we characterized orthologs of *Shbgb* in a wide variety of non-salmonid vertebrate species, including European eel (*Anguilla anguilla*), arowana (*Osteoglossum bicirrhosum*), spotted gar (*Lepisosteus oculatus*) and frog (*Xenopus tropicalis*). Those results support a much earlier origin of the *Shbg* diversity in vertebrates than first hypothesized. Our analyses demonstrate that this diversity results from one of the two first whole genome duplication rounds (1R & 2R) that occurred at the beginning of the vertebrate evolution. Our results also suggest independent losses of Shbgb among teleosts reflecting different evolutive and reproductive strategies in this lineage.

Using quantitative PCR and next generation sequencing approaches, we characterized the expression profiles of *Shbga* and *Shbgb* transcripts for all the 24 investigated actinopterigyan species. Our results confirm that *Shbga* expression is mainly detected in the liver and highly conserved among actinopterygians. They also suggest that *Shbgb* expression pattern could have evolved from a gonadic-specific expression pattern, in non-teleost actinopterygians, to an ovarian-specific pattern in current teleosts.

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