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Transcriptomic analysis reveals transgenerational effect of hypoxia on the neural control of testicular functions

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ABSTRACT

There are over 400 hypoxic zones in the ocean worldwide. Both laboratory and field studies have shown that hypoxia causes endocrine disruption and reproductive impairments in vertebrates. More importantly, our recent study discovered that parental (F0) hypoxia exposure resulted in the transgenerational impairment of sperm quality in the F2 generation through the epigenetic regulation of germ cells. In the present study, we aim to test the hypothesis that the brain, as the major regulator of the brain-pituitary-gonad (BPG) axis, is also involved in the observed transgenerational effect. Using comparative transcriptomic analysis on brain tissues of marine medaka *Oryzias melastigma*, 45 common differentially expressed genes caused by parental hypoxia exposure were found in the hypoxic group of the F0 and F2 generations, and the transgenerational groups of the F2 generation. The bioinformatic analysis on this deregulated gene cluster further highlighted the possible involvement of the brain in the transgenerational effect of hypoxia on testicular structure, including abnormal morphologies of the epididymis and the seminal vesicle, and degeneration of the seminiferous tubule. This finding is concordant to the result of hematoxylin and eosin staining, which showed the reduction of testicular lobular diameter in the F0 and F2 generations. Our study demonstrated for the first time the involvement of the brain in the transgenerational effect of hypoxia.

1. Introduction

Aquatic hypoxia arises when the dissolved oxygen concentration in the water falls below 2.8 mg/L (Diaz and Rosenberg, 1995). The main cause for aquatic hypoxia is eutrophication caused by excessive nutrients being discharged into the water from human activity, leading to algal blooms, which increase oxygen demand and reduce oxygen levels. Over 400 hypoxic zones (dead zones) have been identified worldwide, and this number is likely to further increase in the coming years (Diaz and Rosenberg, 2008). Both laboratory and field studies have shown that hypoxia causes endocrine disruption, leading to reproductive impairments in vertebrates (Wang et al., 2016; Bomhard and Gelbke, 2013; Shang and Wu, 2004). For instance, carp exposed to hypoxia showed disturbances in sex hormones, reduced gonad sizes, retarded gametogenesis, and lower fertilization success and hatching rates (Wu et al., 2003). Zebrafish exposed to hypoxia and Atlantic croaker harvested from the Gulf of Mexico Dead Zone showed altered testosterone and estradiol levels and impaired gametogenesis (Shang et al., 2006; Thomas and Rahman, 2009). Male Wistar rats kept under hypoxia showed lower levels of luteinizing hormone (LH) and testosterone than their normoxic counterparts (Farias et al., 2008), and significant reductions in spermatogenic epithelial cells, Sertoli cells, and Leydig cells were found in rats after exposure to acute hypoxia (Shevantaeva and Kosyuga, 2006). Hypoxia also affects the sex differentiation in zebrafish and freshwater medaka, leading to a male-biased F1 generation, even though the latter carries a sex-determining gene (DMY) similar to humans (Shang et al., 2006; Cheung et al., 2014). Our recent study further discovered that parental exposure to hypoxia can lead to impairment in sperm quality in F2, despite these offspring having never been exposed to hypoxia. The observed transgenerational effects suggest that hypoxia

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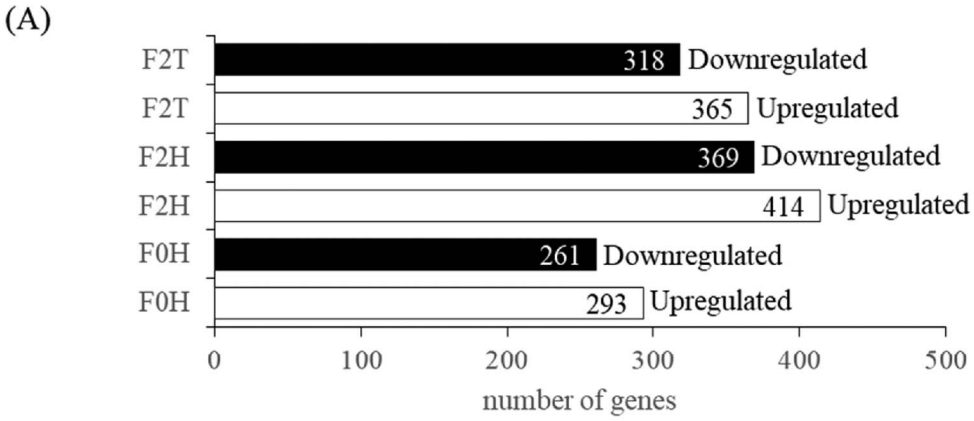

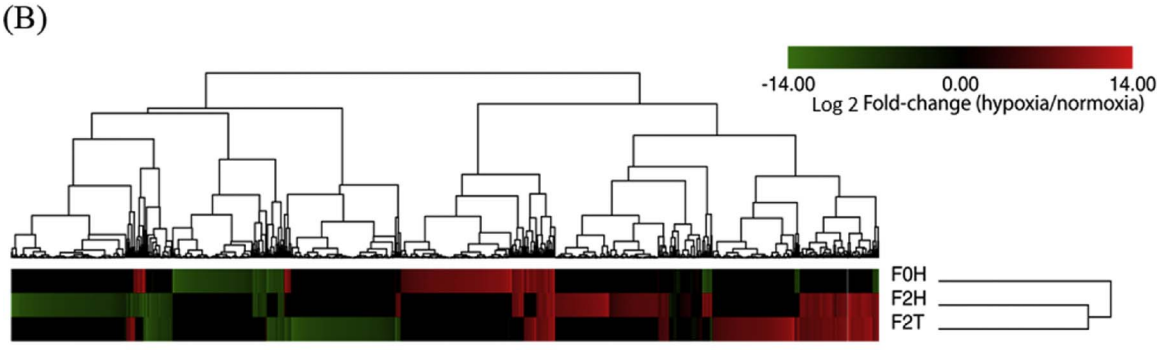

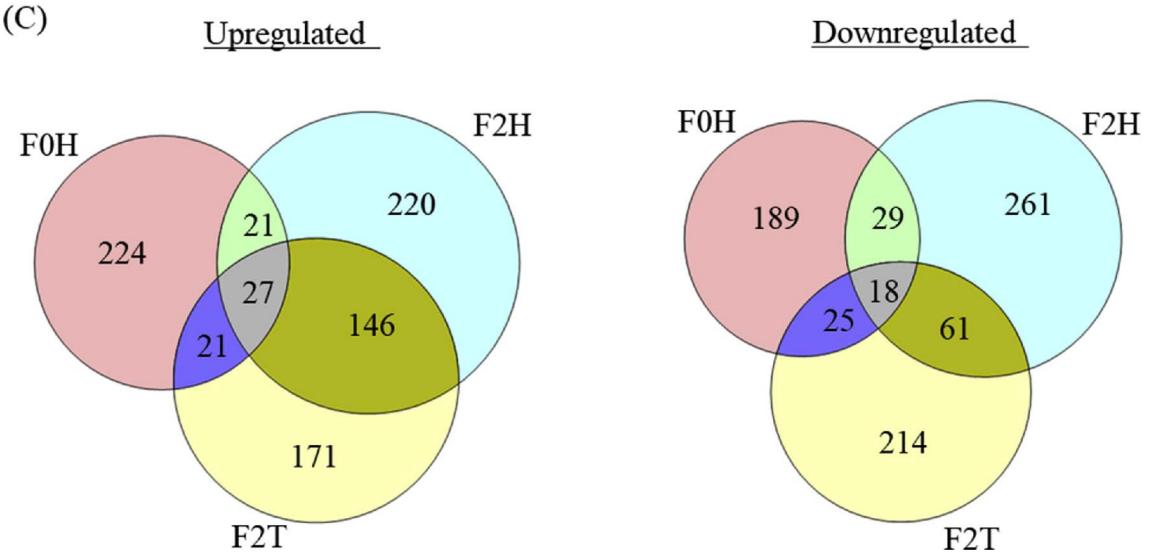

Fig. 1. Hypoxia exposure causes differential gene expression in the male brains of F0 and F2 generations. (A) Number of differentially expressed genes found in the F0H, F2H and F2T groups. X-axis represents the number of differentially expressed genes. Y-axis represents the treatment groups in different generations. (B) Hierarchical clustering heat map. The color scale represents the fold-change in the $\log_2$ ratio. Red and green bars indicate upregulation and downregulation, respectively. (C) Venn diagram of the overlapping significantly upregulated or downregulated genes shared among the F0H, F2T and F2H groups compared to the corresponding normoxic groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)