Functional transcriptome analysis of the postnatal brain of the Ts1Cje mouse model for Down syndrome reveals global disruption of interferon-related molecular networks

ABSTRACT

Background: The Ts1Cje mouse model of Down syndrome (DS) has partial triplication of mouse chromosome 16 (MMU16), which is partially homologous to human chromosome 21. These mice develop various neuropathological features identified in DS individuals. We analysed the effect of partial triplication of the MMU16 segment on global gene expression in the cerebral cortex, cerebellum and hippocampus of Ts1Cje mice at 4 time-points: postnatal day (P)1, P15, P30 and P84. Results: Gene expression profiling identified a total of 317 differentially expressed genes (DEGs), selected from various spatiotemporal comparisons, between Ts1Cje and disomic mice. A total of 201 DEGs were identified from the cerebellum, 129 from the hippocampus and 40 from the cerebral cortex. Of these, only 18 DEGs were identified as common to all three brain regions and 15 were located in the triplicated segment. We validated 8 selected DEGs from the cerebral cortex (Brwd1, Donson, Erdr1, Ifnar1, Itgb8, Itsn1, Mrps6 and Tmem50b), 18 DEGs from the cerebellum (Atp5o, Brwd1, Donson, Dopey2, Erdr1, Hmgn1, Ifnar1, Ifnar2, Ifngr2, Itgb8, Itsn1, Mrps6, Paxbp1, Son, Stat1, Tbata, Tmem50b and Wrb) and 11 DEGs from the hippocampus (Atp5o, Brwd1, Cbr1, Donson, Erdr1, Itgb8, Itsn1, Morc3, Son, Tmem50b and Wrb). Functional clustering analysis of the 317 DEGs identified interferon-related signal transduction as the most significantly dysregulated pathway in Ts1Cje postnatal brain development. RT-qPCR and western blotting analysis showed both Ifnar1 and Stat1 were over-expressed in P84 Ts1Cje cerebral cortex and cerebellum as compared to wild type littermates. Conclusions: These findings suggest over-expression of interferon receptor may lead to over-stimulation of Jak-Stat signaling pathway which may contribute to the neuropathology in Ts1Cje or DS brain. The role of interferon mediated activation or inhibition of signal transduction including Jak-Stat signaling pathway has been well characterized in various biological processes and disease models including DS but information pertaining to the role of this pathway in the development and function of the Ts1Cje or DS brain remains scarce and warrants further investigation.

Keyword: Mouse; Down syndrome (DS); Mouse chromosome 16 (MMU16); Disrupted molecular pathways