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Editorial

Reversing intellectual disabilities in Down syndrome: Hopes or hypes?

Down syndrome (DS) is a chromosomal disorder resulting from the complete or partial triplication of human chromosome 21 (HSA21), affecting approximately 1 in 800 live births[1]. DS is the leading genetic cause of intellectual disability (ID), and DS individuals face over 90 per cent lifetime risk of developing dementia bearing neuropathological evidence for Alzheimer's disease (AD) by the age of 40 yr[2]. DS brains exhibit reduced volumes and hypocellularity in several brain regions, most notably the hippocampal formation. While several hypotheses have been postulated to explain these discrepancies, ID among DS individuals remains an area that is not fully understood. Given these complex neuropathological features, researchers continue to explore the underlying mechanisms contributing to cognitive impairment in DS individuals. As such, addressing the root cause of ID remains a popular topic in the field of DS research[1].

Neuroinflammatory damage may be one of the several reasons behind the neuropathogenesis of ID in DS. The increased expression of various inflammatory markers in brain tissues[1] marks heightened neuroinflammation from the developmental period to adulthood. Neuroinflammation in DS is multifaceted and has several potential mechanisms, though it is most directly attributed to increased HSA21-localised gene dosages[3]. DS individuals exhibit heightened sensitivity towards inflammatory responses due to increased expression of inflammatory signalling components, such as interferon (IFN) receptors and NF-κB[4]. Besides, DS brains are also seen with aberrant microglia activation and increased astrogliosis, both of which contribute to AD progression among DS individuals and their subsequent cognitive deficit[5]. Mitochondrial dysfunction further imposes oxidative stress *via* the unregulated production of reactive oxygen species[6]. Furthermore, triplication of the amyloid-beta precursor protein (*APP*) gene and other modulatory genes on HSA21 leads to early deposition of the neurotoxic amyloid-beta (Aβ) plaques and phosphorylated-tau protein, thereby accelerating neurodegeneration and contributing to early-onset AD[2]. The existing damage is further exacerbated by impaired autophagy mechanisms and proteo-stasis pathways that ultimately lead to neurotoxic substances and neuronal demise accumulation[4]. These interwoven mechanisms create a persistent neuroinflammatory landscape in DS, imposing continuous stress on neurons and driving progressive neurodegeneration in early development.

Another point of view postulates that the reduction in neuronal number in DS brains may not solely be caused by neuronal loss due to inflammation but also an imbalance in neuronal production by neural stem cells (NSC). NSC in DS brains has been shown to bear a higher tendency to differentiate along the astroglia lineages in contrast to neuronal lineages, a phenomenon known as a neurogenic-to-gliogenic shift[7]. Current evidence points to a dysregulated signalling network that contributes to this shift. On the one hand, NSC in DS brains exhibits reduced neurogenesis capacity that stems from Sonic Hedgehog (SHH) signalling deficit due to overproduction of APP proteins. On the other hand, NSC exhibits increased astrogliogenesis due to an upregulated JAK-STAT signalling that is attributable to either: (*i*) an increased cell-surface IFN receptor expression, (*ii*) an increase in dual specificity tyrosine phosphorylation regulated kinase 1A (*DYRK1A*) activity, or (*iii*) a functional disruption in upstream regulators like repressor element-1 silencing transcription factor (REST)[7]. The observed gliogenic shift depletes available NSC for astrocyte production instead of neurons, leading to an overall decrease in neuronal number. Such JAK-STAT signalling upregulation also induces recommitment of oligodendrocyte precursor cells (OPC) into astrocytes instead of oligodendrocytes, leading to hypomyelination[8]. Ultimately, this imbalance in signalling pathways results in a disproportionate increase in astrocytes at the expense of neurons and oligodendrocytes, which may underlie the observed ID in DS.

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The triplication of dosage-sensitive genes is a key hypothesis in understanding DS pathology development and driving researchers to explore therapies targeting these genes. One hotspot gene of interest is *DYRK1A*, located at 21q22.13, which is triplicated in DS and consistently associated with DS impairments in neurodevelopment and neuronal functions[9]. Although *DYRK1A*-targeted inhibitors have been widely researched, their safety and efficacy remained suboptimal due to their widespread expression in various tissues, which reduces inhibitor specificity and the challenge of crossing the blood-brain barrier[9]. Additionally, four out of six IFN receptor genes, including *IFNAR1, IFNAR2, IFNGR2* and *IL10RB*, are located on HSA21 and contribute to neuroinflammation and IFN hypersensitivity in DS. Notably, genetic correction of these genes has shown promise in ameliorating immune responses, heart malformations, neurodevelopment, cognitive functions and craniofacial formations, highlighting the therapeutic potential of targeting dosage-sensitive genes[10]. Furthermore, *APP* and β-secretase 2 (*BACE2*), both located on HSA21, are strongly associated with the early onset of Alzheimer's disease in DS individuals. This connection makes DS models a valuable tool for studying therapies for AD and identifying early diagnostic markers, which could prevent or delay the progression of AD-related neuropathology.

While there is no cure for Down syndrome, groundbreaking advancements in chromosomal therapy and genome editing are making strides toward correcting the gene dosage imbalance. Sophisticated technologies such as CRISPR/Cas9, zinc finger nucleases (ZFNs) with X-inactive specific transcript (XIST), transcription activator-like effector nucleases (TALENs) and Cre/loxP system have been used to target the HSA21 precisely[11]. These technologies can induce double-strand breaks or inactivation to completely or partially remove the extra chromosome. Additionally, research has discovered an exciting phenomenon known as trisomy rescue, where DS somatic cells reprogrammed into induced pluripotent stem cells (iPSCs) unexpectedly restored to a disomic state. While the mechanism behind this rescue remains unclear, these corrected stem cells hold significant potential for autologous stem cell regenerative therapies in DS individuals[11]. These groundbreaking technologies offer hope for potential DS treatments, though their safety and ethical implications require further exploration.

Amplified developmental genome instability is another important hypothesis explaining the dysregulation of non-HSA21 genes leading to a wide variety of DS clinical symptoms' severity and manifestation. Epigenetic changes in DS have attracted significant attention as they are associated with genome-wide gene dysregulation and their potential as a 'modifiable' therapeutic opportunity[12]. Triplicated *DYRK1A* suppresses an epigenetic histone modifier, REST, which targets approximately 50 per cent of human protein-coding genes and plays an important role in nervous system development, function, and stress resilience[13]. REST downregulation has been consistently seen in various DS models. REST restoration using cost-effective lithium has successfully rescued the neurogenic-to-gliogenic shift in DS neural progenitor cells and alleviated oxidative stress in DS neurons[7,14,15]. In summary, epigenetic treatment demonstrates tremendous potential to ameliorate DS neuropathogenesis by targeting transcription factors that can simultaneously address multiple downstream effects.

Even with the advent of gene, chromosome, and genome editing technologies, the most current practical interventions for DS individuals remain symptom-oriented to improve cognitive health, motor skills, and overall well-being *via* special education, supplementation, and physical therapies. Personalised learning strategies, including Individualized Education Programs (IEPs), enhance literacy, numeracy, and communication skills, while inclusive education fosters social and cognitive development[16]. High-tech augmentative and alternative communication (AAC) tools and multisensory teaching methods improve learning outcomes[17]. Applied Behaviour Analysis (ABA) and occupational therapy aid in motor and adaptive skill development[18]. Oxidative stress and mitochondrial dysfunction in DS have driven research into antioxidant supplementation, including coenzyme Q10, green tea extract (EGCG), and omega-3, which have shown cognitive benefits[6]. Physiotherapy strengthens muscles, improves balance, and enhances mobility, while occupational and speech therapy supports fine motor control and communication[19]. Other therapies, such as hippotherapy and aquatic therapy, contribute to functional independence[20,21], robotic-assisted therapy improves proprioception and gait[22] and neuromodulation techniques such as transcranial direct current stimulation (tDCS) offer non-invasive cognitive interventions[23]. With ongoing research refining these strategies through genetic insights and rehabilitation technologies, a multidisciplinary approach integrating education, supplementation, and

therapies will significantly enhance the quality of life for DS individuals.

More than a century after John Langdon Down first described Down syndrome and over six decades since Jerome Lejeune identified its genetic cause, we are yet to develop a cure or an effective treatment to counteract ID or cognitive impairment in DS[24]. While symptomatic treatments, special education, supplementation, and physical therapies have significantly improved DS individuals' quality of life and cognitive function, do we risk becoming complacent? Have these interventions, though practical, led to a lack of urgency in pursuing a true cure? Is there a cure in the first place? Funding and research efforts have primarily focused on symptom management rather than addressing the underlying genetic cause. This raises an uncomfortable but essential question: Have we, as a society, accepted the status quo rather than attempted transformative breakthroughs in DS treatments? DS individuals face a broad spectrum of medical conditions affecting nearly every system in their bodies. While current treatments help mitigate these issues, emerging research into gene therapy, regenerative medicine, and targeted pharmacological interventions offers glimpses of potential cures or at least significant disease-modifying strategies. Are we satisfied with simply palliative care and settle for what is currently available when promising treatments exist as better alternatives?

So, what is our role? As researchers, clinicians, policymakers, and advocates, we must push for a balanced approach that continues to support effective symptom management while driving investment into curative research. The responsibility does not lie solely with the scientific community but extends to governments, healthcare organisations, and society. Funding allocation, policy direction, and advocacy efforts must reflect the urgency of finding long-term solutions rather than settling for incremental improvements. We must challenge ourselves to do more – not just to improve cognitive function in DS but to reverse it for every individual with DS worldwide: hope on the horizon or just another illusion? The answer depends on the choices we make today.

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