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Insights on the structural determinants of proBDNF V66M variant, a modifier in neuropsychiatric disorders severity.

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The human genetic variant BDNF (V66M) represents the first example of neurotrophin family member that has been linked to psychiatric disorders. In order to elucidate structural differences that account for the effects in cognitive function, this hproBDNF polymorph was expressed, refolded, purified and compared directly to the WT variant for the first time for differences in their 3D structures by DSF, limited proteolysis, FT-IR and SAXS measurements in solution. Our complementary studies revealed a deep impact of V66M polymorphism on hproBDNF conformations in solution. Although the mean conformation in solution appears to be more compact in the V66M variant, overall, we demonstrated a large increase in flexibility in solution upon V66M mutation. Thus, considering that plasticity in IDR is crucial for protein function, the observed alterations may be related to the functional alterations in hproBDNF binding to its receptors p75NTR, sortilin, HAP1 and SorCS2. These effects can provoke altered intracellular neuronal trafficking and/or affect proBDNF physiological functions, leading to many brain-associated diseases and conditions such as cognitive impairment and anxiety. The structural alterations highlighted in the present study may pave the way to the development of drug discovery strategies to provide greater therapeutic responses and of novel pharmacologic strategy in human populations with this common polymorphism, ultimately guiding personalized medicine for neuropsychiatric disorders [1].

[1] S, Covaceuszach, L.J. Peche, P.V. Konarev, J. Grdadolnik, A. Cattaneo, D. Lamba. IJMS, under revision, 2022

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