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# Structural investigation of the ubiquitylation effects on the human Bardet-Biedl Syndrome (BBS) complex through Coarse-Grained Molecular Dynamics simulations

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Bardet-Biedl syndrome (BBS) is a ciliopathy genetic disorder characterized in most cases by obesity, polydactyly, renal dystrophy and cystic kidneys. BBS is strictly related to the hetero-octameric protein complex named as BBSome. The recruitment of BBSome into cilia membranes is mediated by the binding with the GTP binding protein ARL6, which binds at the interface between the BBS1 and BBS7 subunit of BBSome [1]. Specifically, the ARL6 binding occurs only in the active state of BBSome, characterized by an open conformation bewteen the BBS1 and BBS7 β-propeller subunits [2], while in absence of ARL6 (apo form), BBS1 is arranged in a more closed conformation. Additionally, the most promising structural and functional properties, are exerted by the BBSome core complex formed by the BBS1, 4, 8, 9 and 18 subunits, with the latter having remarkable stabilizing effect on the complex [3]. Experimental data, revealed the ubiquitination at K143 residue of BBS1 by the E3 ligase praja2 positively regulates the binding to ARL6, but a detailed structural mechanism of action is still unknown, probably because of the large size of the system, which requires long-time scale simulations. We have undertaken this challenge using microseconds-long Coarse-Grained Molecular Dynamics (CG-MD) simulations on both the homology models of the human sequence of BBSome (wt-hBBSome) and the K143 monoubiquitinated form (Ub-hBBSome), followed by essential motion analyses. The CG description, in fact, allows building a simplified representation of systems, resulting in the possibility to increase the orders of magnitude in the simulated time and length scales. Our advanced computational approach provided structural insights for the comprehension of the Ubiquitin (Ub) role on the BBSome subunits, representing a valuable therapeutic approach for ciliopathy disorders.

1. Yang S.; Bahl K.; Chou H.T et al. eLife 2020;9:e55954
2. Klink U.B.; Gatsogiannis C.; Hofnagel O. et al. eLife 2020;9:e53910
3. Klink U.B.; Zent, E.; Juneja P. et al. eLife 2017;6:e27434.

## Department

Department of Pharmacy

**Primary author(s) :** Dr. MORACA , Federica (Department of Pharmacy University “Federico II” of Naples); Dr. CONFLITTI , Paolo (Faculty of Biomedical Sciences, Institute of Computational Science, Università della Svizzera italiana (USI)); Dr. CATALANOTTI , Bruno (Department of Pharmacy, University “Federico II” of Naples)

**Presenter(s) :** Dr. MORACA , Federica (Department of Pharmacy University “Federico II” of Naples)