

## Abstract

Bardet-Biedl Syndrome (BBS) is a rare genetic disease categorized under ciliopathies; a group of diseases linked to primary cilia dysfunction. Primary cilia, also known as cellular antennae, play a vital role in sensing extracellular stimuli and transducing them through various signalling cascades. Proper cilia function and signalling depends on multiple ciliary proteins, with eight of them forming a BBSome complex. The BBSome is involved in the transport of proteins into and out of the cilia. Mutations in genes encoding BBSome complex lead to BBS. Among these genes, *BBS1*, which encodes the BBS1 subunit of the BBSome, is notably highly mutated compared to others.

This thesis focuses on the BBS1 subunit and aims to investigate the molecular mechanisms underlying three specific BBS patients' mutation located in *BBS1*: M390R, E224K, R160Q. In the first part, we validated the expression of these selected BBS1 variants and examined their effects on the expression of other BBSome subunits. We observed decreased expression levels of BBS4 and BBS5 subunits in the presence of M390R and E224K mutations. Secondly, we assessed BBSome assembly in the context of these mutations, showing that R160Q mutation did not impair BBSome assembly, whereas assembly was severely disrupted in the presence of M390R variant, and partially impaired with the E224K variant. In the third part, we investigated how these variants affect the transport of signalling proteins. Our findings indicate that each BBS1 variant led to the same phenotype – accumulation - suggesting impaired ciliary export of BBSome cargo.

In summary, this study elucidates the molecular mechanisms underlying selected BBS1 mutations. These mechanisms were unique to each BBS1 variant analysed and correlated with the severity of BBS symptoms observed in patients with the respective mutations. This research enhances our understanding of how specific mutations contribute to the development of BBS symptoms.

## Key words

Bardet-Biedl Syndrome, ciliopathy, cilia, BBSome, BBS1, protein transport, BBS1-R160Q, BBS1-E224K, BBS1-M390R