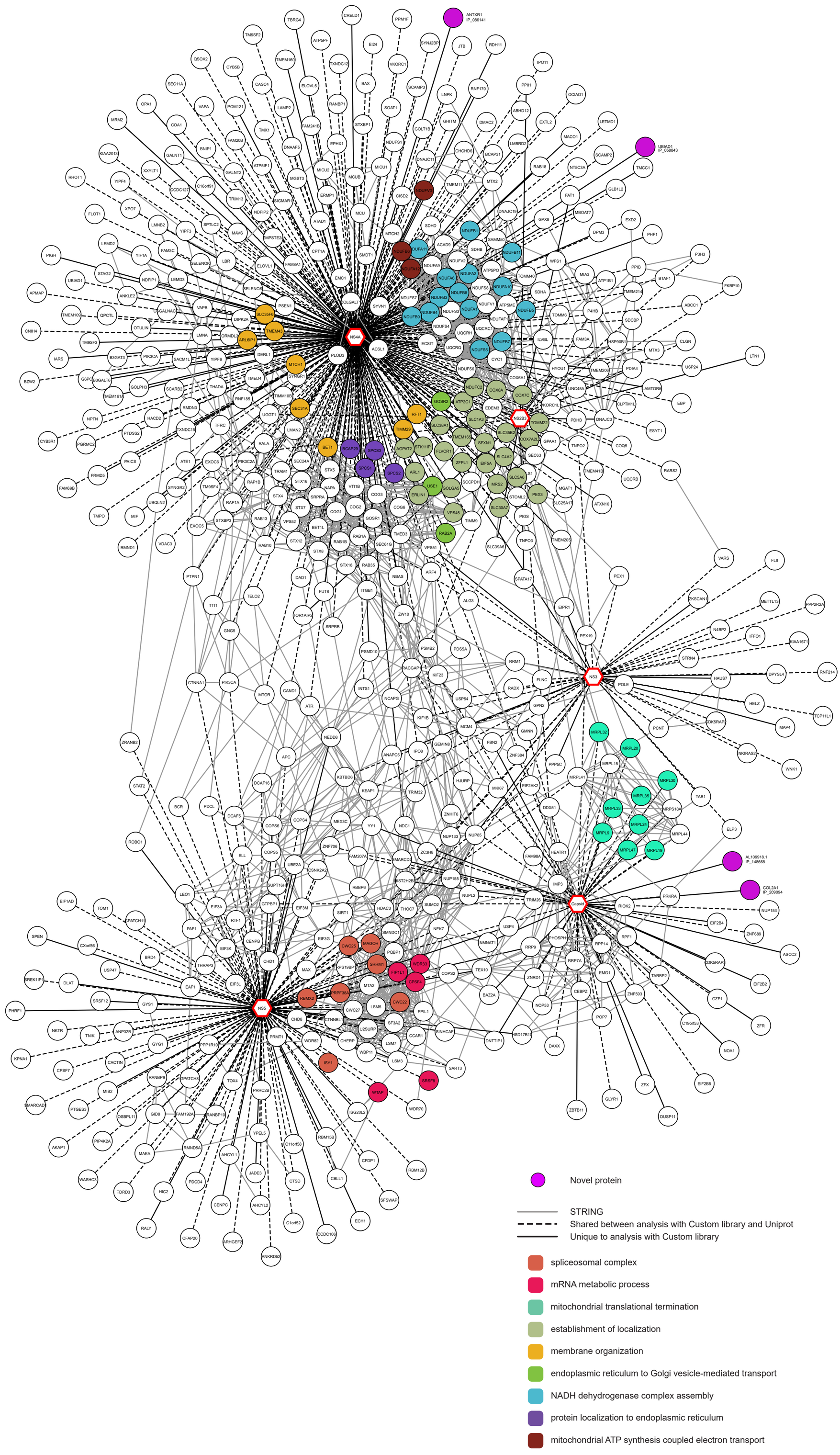Supplementary Fiure 4