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# PROTEIN KINASE 2 CATALYTIC SUBUNITS A1/A2 OF THE SSU PROCESSOME'S UTP-C SUB-COMPLEX REGULATES GROWTH LIKELY THROUGH RIBOSOME BIOSYNTHESIS

**James Cluff**, Brandon University, Children's Hospital Research Institute of Manitoba; **J. Michael Charette**, Brandon University, Children's Hospital Research Institute of Manitoba

**Background:**
The nucleolus, the site of ribosome assembly, is a diagnostic/prognostic marker of cancer, with cell growth being dependent on the rate of ribosome biosynthesis. Ribosome assembly defects (ribosomopathies) are associated with many cancers. The Small Subunit Processome (SSUP) is a large ribonucleoprotein complex responsible for the assembly of the SSU of the ribosome. It consists of five sub-complexes, one of which (UTP-C) likely contains the protein kinase CK2 complex, consisting of catalytic CKa1/CKa2 and regulatory CKb1/CKb2 proteins. CK2 is a ubiquitous and constitutively active serine/threonine kinase implicated in many cellular processes including growth, differentiation, and neoplasia. CK2 regulates all three RNA polymerase and coordinates ribosomal protein production with ribosome assembly.

**Objective:**
Demonstrate that the CK2 protein complex is a *bona fide* member of the SSUP with a regulatory role in ribosome assembly and cellular growth.

**Methods:**
Using a yeast model, we determined the role of CK2 in the regulation of ribosome assembly by genetically depleting cells of individual/pairs of CK2 subunits using a galactose inducible/glucose repressible promoter. As growth is directly correlated to ribosome assembly, growth curves were used as a surrogate for ribosome assembly. Membership of CK2 in the SSUP was confirmed by co-IP of each individual CK2 proteins with known SSUP components.

**Results:**
Genetic depletion of individual catalytic subunits CKa1 and CKa2 results in a reduction in growth while depletion of both catalytic subunits is lethal as seen in growth curves. Northern analysis of pre-rRNA processing will be used to identify defects in pre-rRNA processing in these strains. Co-IPs of CK2 components with known SSUP components confirm, for the first time, CK2 membership in the SSUP.

**Conclusion:**
We have shown that single and double depletion of the two catalytic CK2 proteins has a major impact on cell growth, likely through a dysregulation of ribosome assembly, and CK2 membership in the SSUP.

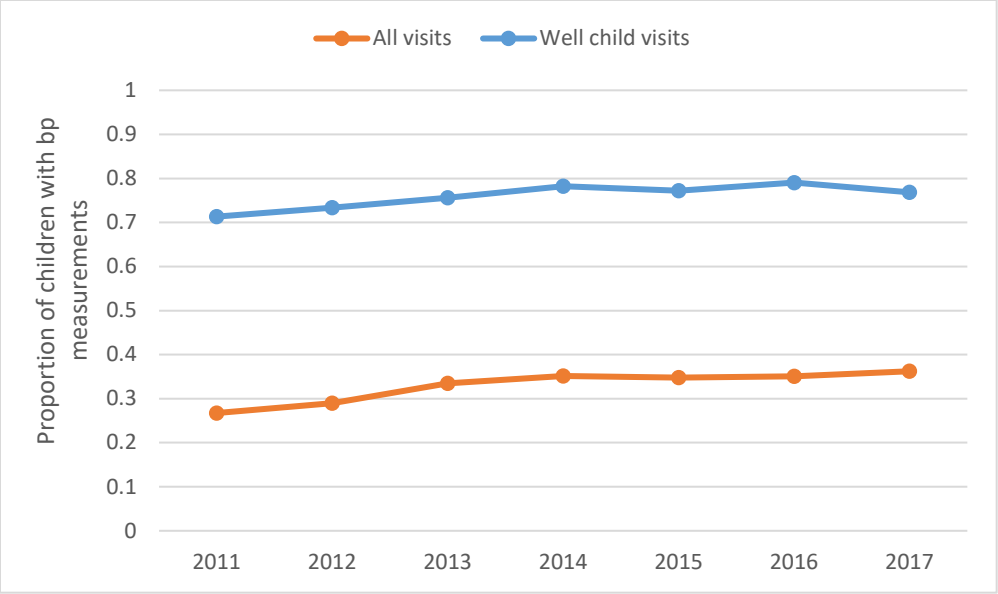


Figure 1. Percentage of children with at least one documented blood pressure (bp) for all pediatric visits and well child checks, from 2011 – 2017.

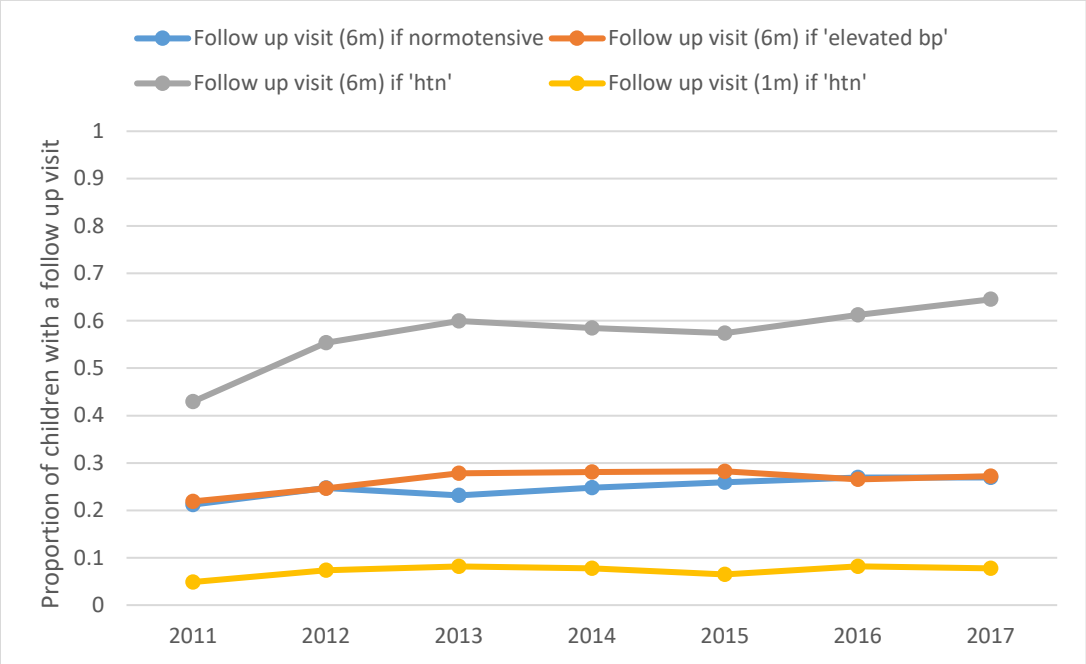


Figure 2. Percentage of children with normal blood pressure and elevated bp with follow up blood pressure measurement in six months (6m). Percentage of children with blood pressure above hypertension threshold with follow up blood pressure measurement in one (1m) and six months (6m).

Table 1 – Multivariate regression model of patient and provider characteristics associated with increased blood pressure screening

| Variable | Adj odds ratio | 95% confidence interval | P value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Patient characteristics | | | |
| Sex (female vs male) | 1.00 | 0.97-1.03 | 0.93 |
| First encounter age | 1.03 | 1.02 – 1.03 | <0.0001 * |
| Overweight | 2.19 | 2.11 – 2.26 | <0.0001 * |
| Hyperlipidemia | 1.00 | 0.88 – 1.13 | 0.97 |
| Pediatric diabetes | 1.88 | 1.51 – 2.33 | <0.0001 * |
| Chronic kidney disease | 0.96 | 0.82 – 1.11 | 0.58 |
| Social deprivation index (5=most vs 1= least deprived) | 1.34 | 1.29 – 1.40 | <0.0001 * |
| Urban vs rural residence | 1.09 | 0.98 – 1.21 | 0.10 |
| Provider characteristics | | | |
| Sex (female vs male) | 1.40 | 1.36 – 1.44 | <0.0001 * |
| Age group (>median 43 years vs ≤ 43 years) | 1.40 | 1.36 – 1.44 | <0.0001 * |