

Loss of TBCK alters bone cell homeostasis resulting in altered bone morphology

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TBCK Syndrome
OVERVIEW, SYMPTOMS + HEALTH IMPACTS

TBCK SYNDROME IS A VERY RARE NEUROGENETIC DISEASE THAT WAS FIRST DESCRIBED IN MEDICAL LITERATURE IN 2016. MOST OF THE PATIENT POPULATION IS CHILDREN + YOUNG ADULTS.

<100 ESTIMATED NUMBER OF PATIENTS DIAGNOSED GLOBALLY

24 AGE OF OLDEST KNOWN PATIENT

BRAIN + EPILEPSY
Seizures are a common symptom, which families often note as the number one health concern. Neuro-degeneration is possible in some patients.

COMMUNICATION
Most patients have speech delay and/or require support for communication. Many utilize augmentative and alternative communication (AAC) devices and methods.

INTELLECTUAL DISABILITY - GLOBAL DEVELOPMENTAL DELAY
Most diagnosed patients require assistance with activities of daily living as well as motor, cognitive, speech/language, and personal/social skills.

ENDOCRINE SYSTEM
Patients often have metabolic abnormalities and thyroid dysfunction.

RESPIRATORY SYSTEM
Due to hypotonia (low tone) basic respiratory illnesses can be severe. Some patients require a tracheostomy.

VISION IMPAIRMENT
Majority of patients have vision impairment. Many have strabismus.

CRANIOFACIAL DYSMORPHIA
Aberrant cranial form can be found in most patients.

AUTISM
Families often seek support for non-verbal, sensory and communication.

DIVERSE POPULATION
Patient population includes 25 ethnicities, most patients identify as a person of color. High variability in variants means most mutations are unique to an individual. Founders mutation identified in the Caribbean: Boricua Mutation.

AUTOSOMAL RECESSIVE DISEASE

PHYSICAL DISABILITY + HYPOTONIA
Most patients have severe hypotonia. Low muscle tone contributes to musculoskeletal issues (osteoporosis + scoliosis).

GASTRO-INTESTINAL (GI)
GI issues are common. GI-tubes are very common for patients due to feeding and dysphagia.

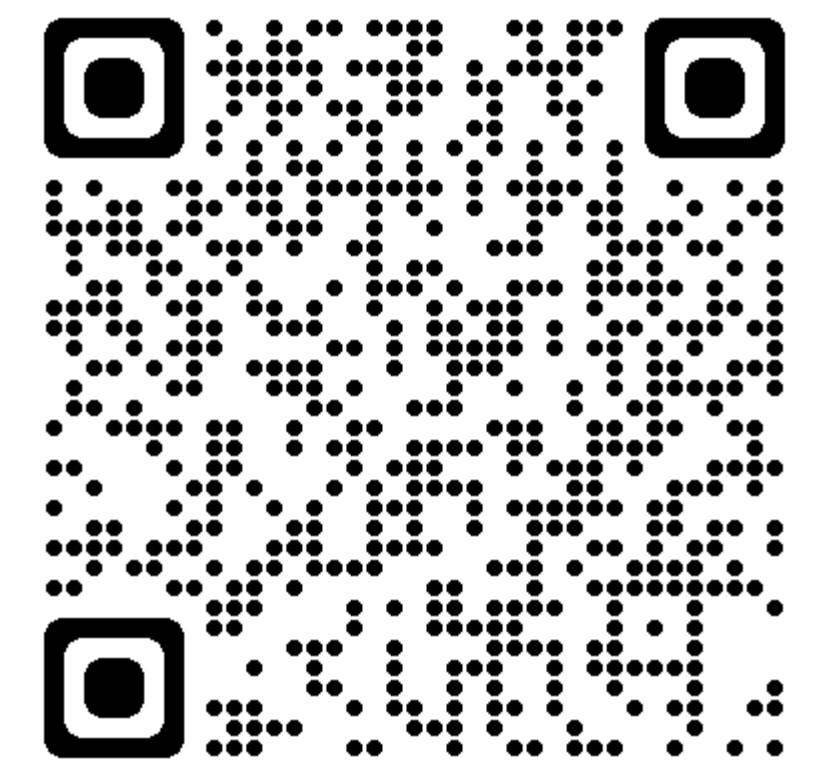
TBCK

Hypothesis: Loss of TBCK negatively impacts bone health

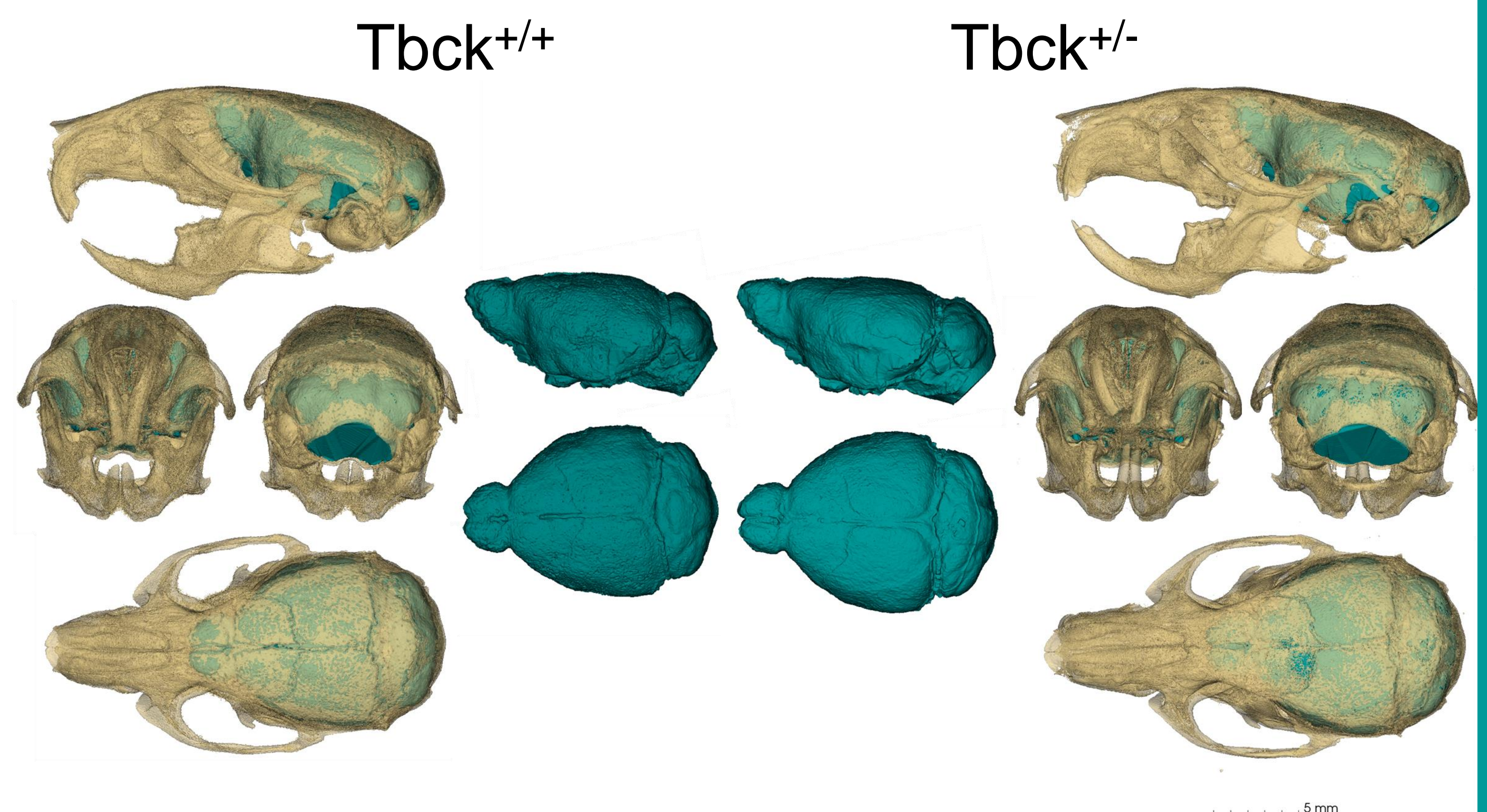
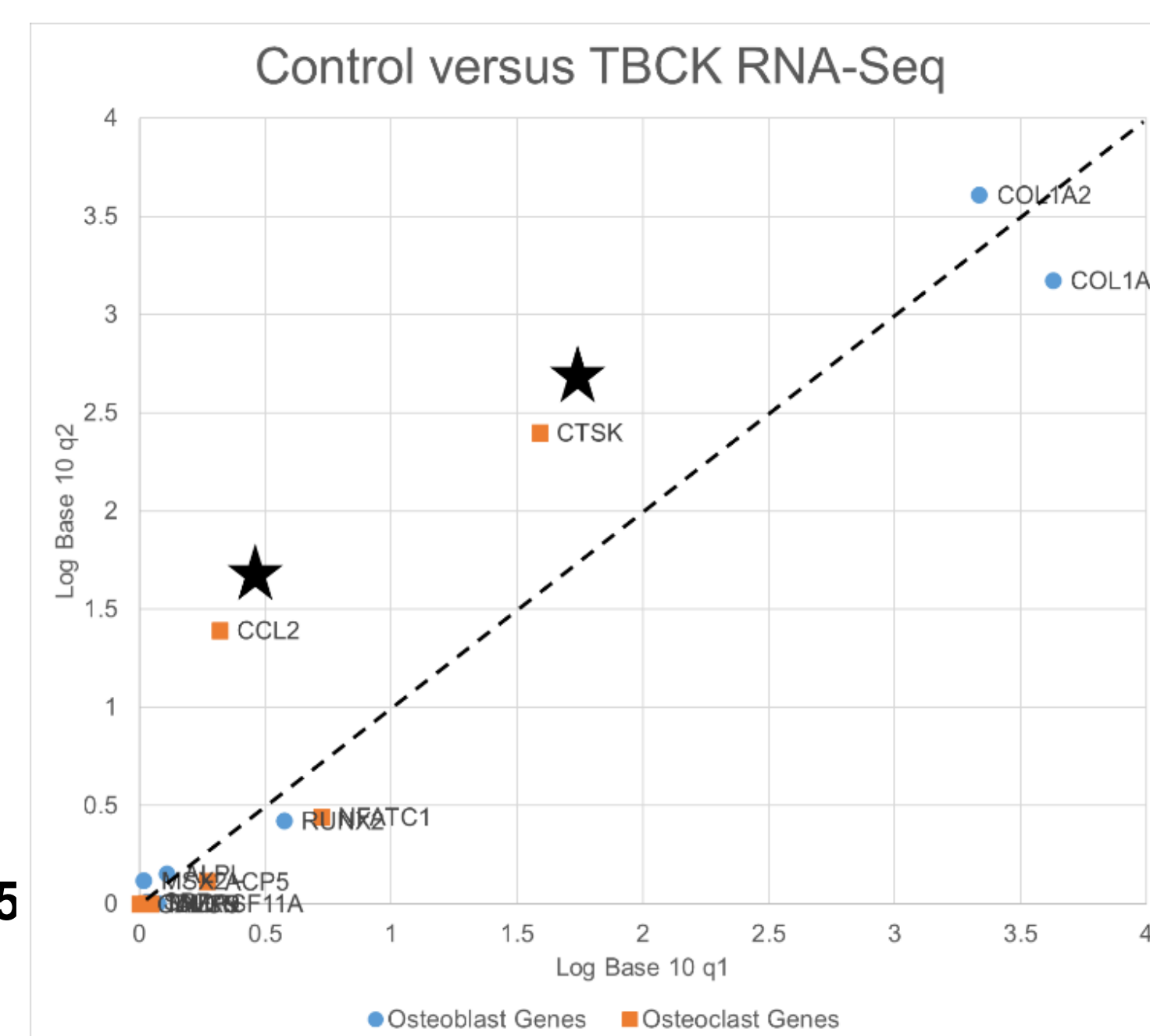
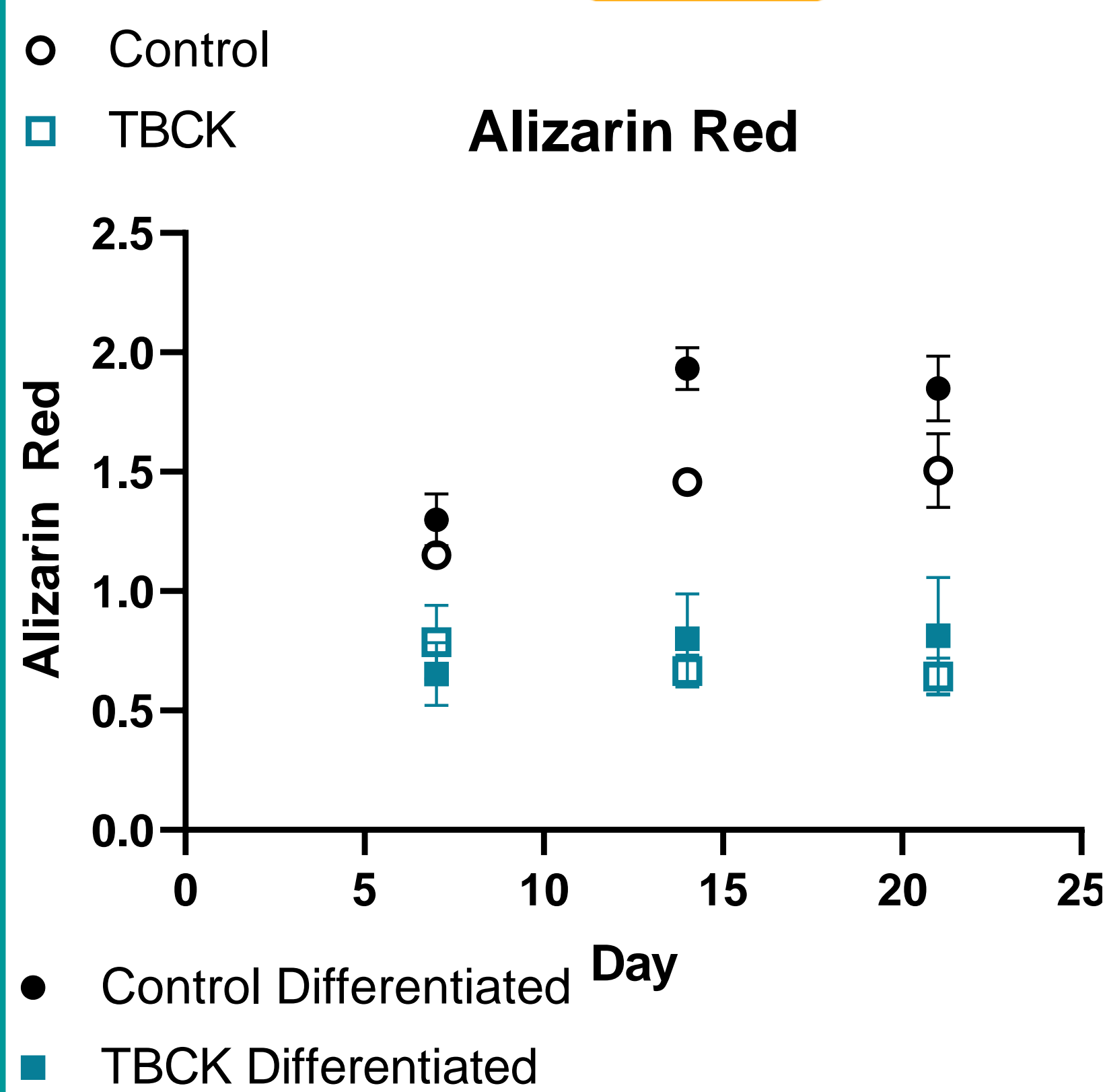
Methods:

- ❖ Differentiate patient derived fibroblasts
- ❖ Compare gene expression
- ❖ 89wk *Tbck*^{+/+} & *Tbck*^{+/-} mice n=7/group
- ❖ Micro CT endocast and cephalometrics
- ❖ Histology suture morphometrics

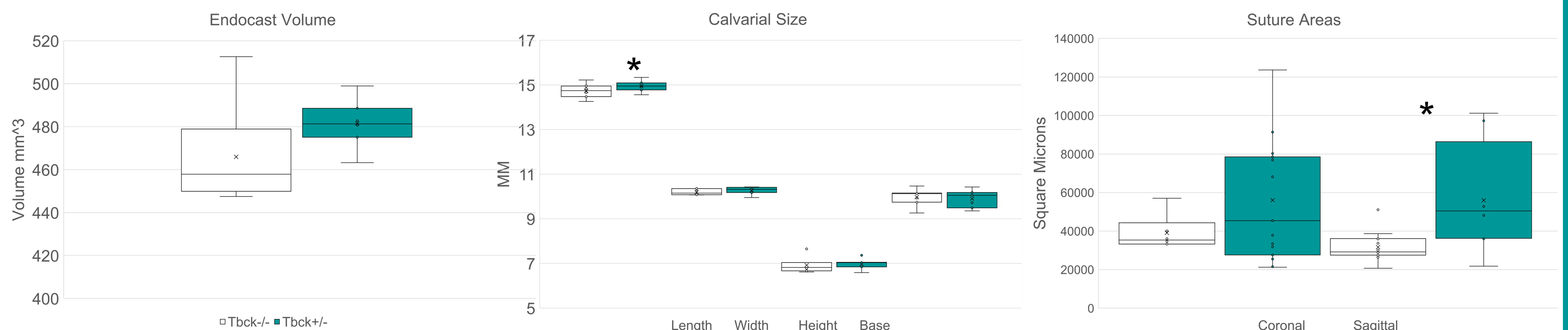
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TBCK syndrome: a rare multi-organ neurodegenerative disease
Durham et al 2023



TBCK deletion has system-wide effects specifically on bone



Figures: Top Left. Differentiation of patient derived fibroblasts using osteogenic media. n = 3 **Top Center.** Scatterplot of bone related gene expression in Control and TBCK samples. Stars highlight significantly differentially expressed osteoclast related genes. Genes along the dotted line indicate similar (unaffected by TBCK deficiency) gene expression. **Top Right.** 3D reconstructions of *Tbck*^{+/+} (left) and *Tbck*^{+/-} (right) skulls and endocasts (center) in left lateral (top), anterior (middle left), posterior (middle right), and superior (bottom) views. Note longer, less domed calvarium in *Tbck*^{+/-} individuals. Also note incisor defects and skeletal malformations leading to malocclusion in *Tbck*^{+/-} mice. n = 7/genotype Scale = 5 mm **Bottom Left.** Endocast volume, calculated using 3DSlicer and Wrap Solidify, did not identify significant differences between genotypes which does not preclude potentially significant differences in brain shape. **Bottom Center.** Cephalometric assessment of calvaria determined *Tbck*^{+/-} mice have an elongated calvarium (p=0.044) as compared to *Tbck*^{+/+} mice. No other measure used identified shape differences between genotypes perhaps indicating a need for a more global form assessment. **Bottom Right.** Skull growth site histomorphometrics indicated a significant increased in sagittal suture area (width p≤0.001, height p=0.047) perhaps indicating changes to calvarial growth patterns. n = 3/genotype for histology.

