Loss of function in RBBP5 is associated with a neurodevelopmental disorder

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Background

RBBP5 is a core member of the SET domain histone H3K4 methylation protein complex, which is a key regulator for activating gene expression. To date, RBBP5 has not been associated with a human disease.

Study aim

To characterize a new genetic disorder resulted from a loss of function mutation in RBBP5.

Methods

To recruit candidate patients with RBBP5-related disorder, we conducted a search in whole exome sequencing databases through an international collaboration. The common clinical features of candidate patients were examined.

The impact of the RBBP5 mutations in the function of the histone H3K4 methylation were investigated in a cell line expressed wild type and mutant RBBP5.

Protein structural analysis was performed to assess the functional implication of the structural difference caused by the mutation.

Transgenic drosophila model is created to provide in vivo evidence for the pathogenesis of RBBP5-related disorder.

Table 1

Patient ID	Patient 1	Patient 2
Age (year)	16	2
Gender	Male	Female
Variant (c and p position)	c.695C>T, Thr232Ile	c.919C>T, Arg307X
De novo or inherited	De novo	
Other variant of interest	No	
Other CNVs of interest	No	
Gestational age	40 wk	
Abnormal prenatal findings	SGA	IUGR
Stature	Short stature, delayed bone age	Short stature
Microcephaly	No	Yes
Height (%tile and SD)	152cm, -2.42 SD	
Weight (%tile and SD)	38.6KG, -2.65 SD	
HC (%tile and SD)	53.5cm, 17%ile	
Feeding difficulty	Yes	
Failure to thrive	Yes, G tube	Yes
Hypotonia	Yes	No, Bilateral hypertonia of LE
Developmental delay	Yes, global	Yes, global
Intellectual disability	Yes, severe	Yes
Dysmorphic facial features	Hypertelorism, high arched eyebrow, long eyelash, synophrys, board nasal tip, and retrognathia, R ear tag	R microtia, dysmorphic features
Hearing loss	Yes, mild bilateral SNHL	Yes, Profound bilateral SNHL
Neurological symptoms	Reduced sensation to pain and temperature	Febrile seizure
Cardiovascular anomaly	Two superior vena cava	
GI issues	Chronic vomiting, abdominal pain, constipation, GERD	
Urogenital anomaly	Cryptorchidism	
Recurrent infection	Yes, low IgG	
Abnormal hematological findings	No	
Musculoskeletal anomaly	Bilateral 5th finger clinodactyly, prominent fingertip pad, hyperextensible joints	
Abnormal skin findings	Cutis marmorata	
Behavior or mental illness	Autism, ADHD	
Other clinical features	Lacrimal duct stenosis, Y-shaped gluteal cleft	Lacrimal duct stenosis

Table 1 clinical features of candidate patients

Figure 1

Figure 1 Dysmorphic features of proband

Figure 2

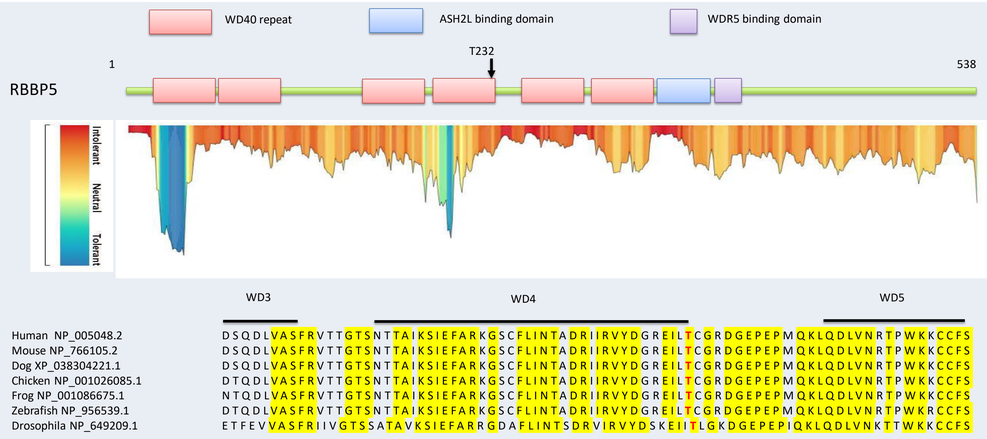


Figure 2 In Silico analysis of candidate variant

Figure 3

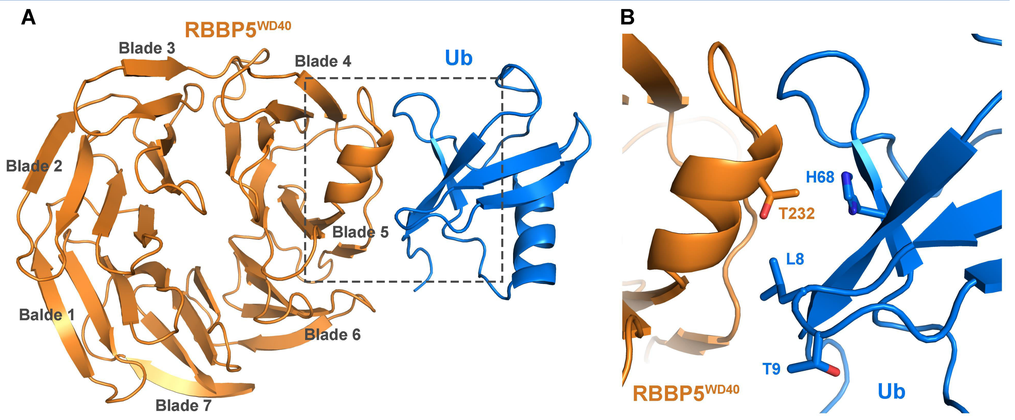


Figure 3 Cryogenic electron microscopy protein structural analysis. Thr232Ile: at the interface of RBBP5 and H2B-K120-conjugated ubiquitin and might affect the interaction between RBBP5 and H2B-ub.

Figure 4

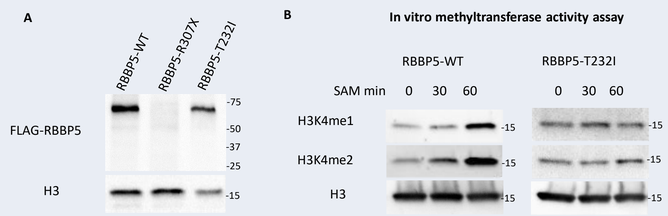
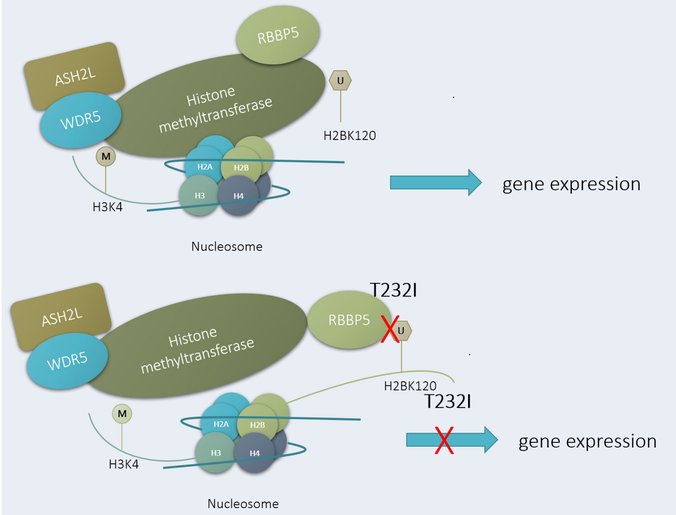


Figure 4 Loss of function in RBBP5 reduces H3K4 methylation

Figure 5



Proposed molecular mechanism for RBBP5-related disorder

Conclusion

1. Patients with loss of function variants in RBBP5 present with a board range of clinical features including FTT, GDD, ID, SNHL, and dysmorphic facies.

2. Missense variant T232I reduces H3K4 methylation and potentially interferes the interaction between RBBP5-ubiquitinated nucleosome.

3. Loss of function in RBBP5 affects many essential biological processes.

Acknowledgements

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