HYPK in Humans: The First Characterization of a New Neurodevelopmental Syndrome

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Objective: We report the first known case of a de novo HYPK variant (R70I) presenting with developmental delay, autism, and facial dysmorphia.

Introduction and Background

- HYPK (Huntingtin-Interacting Protein K) is a modulator of the NatA complex, which is involved in N-terminal protein acetylation (Figure 1)
  - NATA complex = NAA10, NAA15, and HYPK (among other proteins)
  - Variants in NAA10 (Ogden Syndrome) and NAA15 (NAA15-related neurodevelopmental syndrome) are known to cause global developmental delay, cardiac dysfunction, hypotonia, and more
- Variants in HYPK have not been phenotypically characterized prior to this report
- The HYPK N-terminus interacts with the NatA active site to inhibit enzymatic activity, an effect that was overcome by the ribosome-associated nascent polypeptide associated complex (NAC) during cotranslational nascent chain Nt-acetylation (Lentzsch et al., Nature 2024)

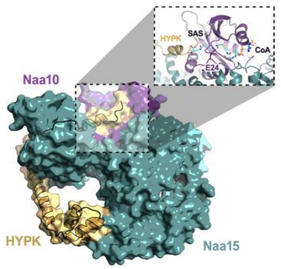

Figure 1. HYPK on NatA complex (Gottlieb et al., 2018)

Methods

- Case report of a male proband identified with a de novo HYPK variant
- Clinical evaluation of developmental milestones, cognitive function, facial dysmorphology, and symptom evolution over time
- Biochemical analyses were performed to evaluate the impact of the variant on NatA-mediated N-terminal acetylation

FIGURE 2 (a–e). Images of the facial phenotype of HYPK_1 at age 4 years (a) and 23 years (b–e). Cardinal facial features include broad nasal bridge, flattened philtrum, button nasal tip, down-slanting eyebrows, and prognathism.

Age	Motor	Global Development	Cognitive / Testing
Birth (38 weeks GA) - 6 months	Unremarkable	Developmentally appropriate	–
6-12 months	Emerging delay	Early concerns begin	–
1 year	Crawling at 12 months (delayed)	Clear developmental delay	–
5 years	–	Severe global delay	Battelle: - Attention: 1y3m - Perception: 1y4m - Social: 1y4m - Adult Interaction: 2y5m
Childhood → Adolescence	Persistently delayed	Non-regressive course	Severe intellectual disability
Adolescence → Adulthood (current)	Severely impaired (3y4m)	Persistent global impairment (6y10m)	Stable IQ ~44-50 Adaptive function: - Personal: 8y9m - Community: 9y6m - Broad independence: 6y10m

Results

- This proband exhibited developmental delay, features of autism spectrum disorder, and distinct facial dysmorphia (Figure 2) with a broad nasal bridge, flattened philtrum, button nasal tip, down-slanting eyebrows, and prognathism
- Biochemical data revealed that the pathogenic HYPK R70I mutation resulted in more stable interaction of HYPK with NatA, and thus enhanced enzymatic inhibition compared to wild type HYPK
- This is the first phenotypic characterization of a pathogenic HYPK mutation in the literature

Conclusions

- A de novo HYPK variant can cause a neurodevelopmental syndrome characterized by intellectual disability, developmental delay, and dysmorphic features, similar to that seen in NAA10- and NAA15-related neurodevelopmental syndrome
- The variant's effect on NatA inhibition indicates a molecular basis for the observed phenotype
- These results expand clinical and molecular understanding of the role of HYPK and, in cases with similar presentations, should be considered in the differential

Future Directions

- Systematic collection of additional cases with HYPK variants to better define genotype-phenotype correlations
- Functional molecular studies to explore how HYPK affects NatA activity and how NatA activity affects neurodevelopmental pathways
- Investigation of potential therapeutic targets that can modify NatA activity or compensate for dysregulation within it

Limitations

- Single case report of this ultra-rare condition massively limits generalizability
- Additional functional validation outside the biochemical assays is needed to confirm the pathogenic mechanism of HYPK dysregulation
- Limited longitudinal follow up data on developmental progression limits prognostication