Supplementary Information for:

UBR5 loss-of-function variants in autism spectrum disorder and intellectual disability: Case series and review of the literature

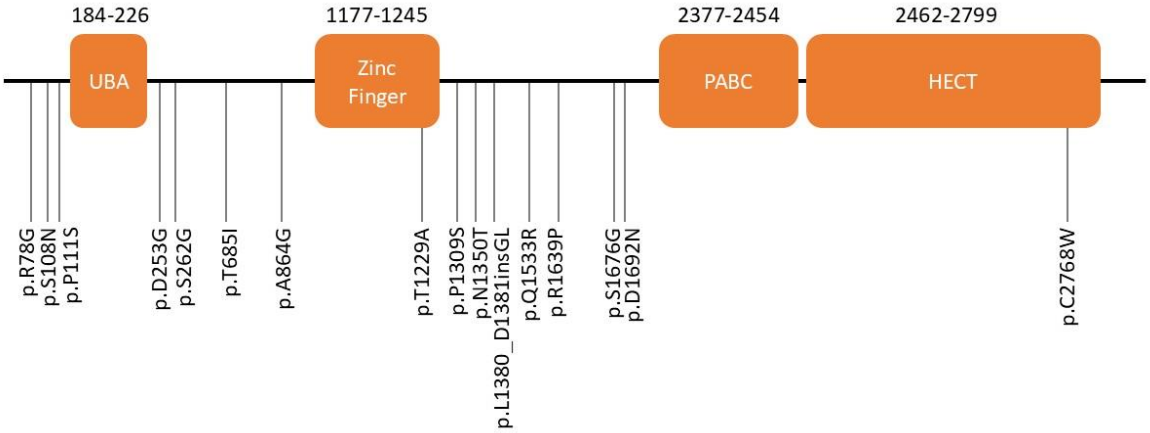
Miriam S. Reuter, Nelson Bautista Salazar, Jennifer L. Howe, Ny Hoang, Ege Sarikaya, Thanuja Selvanayagam, Marla Mendes de Aquino, Astrid M. Vicente, Guiomar Oliveira, Christine M. Freitag, Bhooma Thiruvahindrapuram, Brett Trost, Stephen W. Scherer

Supplementary Table S1: *De novo* missense/in-frame variants in *UBR5* (NM_015902.6).

Study cohort, Method	Variant	gnomAD AF	Domain, REVEL score	Phenotype
Fu et al. 2022	c.232A>G; p.(Arg78Gly)	0	NA, 0.40	ASD
Viggiano et al. 2024	c.323G>A; p.(Ser108Asn)	0	NA, 0.08	ASD
Wang et al. 2023	c.331C>T; p.(Pro111Ser)	0	NA, 0.23	ASD, Moderate ID (IQ 40)
Decipher	c.758A>G; p.(Asp253Gly)	0	NA, 0.48	Abnormalities of head or neck, ear, integument, musculoskeletal system, nervous system
Decipher	c.784A>G; p.(Ser262Gly)	0	NA, 0.35	Abnormality of the nervous system
Sabeh et al. 2025	c.2054C>T; p.(Thr685Ile)	6.20e-6	NA, 0.15	ASD, ID
MSSNG (AU3154301), Trost et al. 2002	c.2591C>G; p.(Ala864Gly)	0	NA, 0.38	Female with ASD, ADHD, first single words 23 m, phrases 42 m, 7.4 yr: HC 52 cm, height 127 cm, weight 22.4 kg. Raven1 nonverbal IQ 108, Full scale IQ 80 (Stanford Binet) (7.5 yr)
MSSNG, Trost et al. 2022	c.3685A>G; p.(Thr1229Ala)	0	Zinc finger domain, 0.63	ASD
Qaiser et al. 2021	c.3925C>T; p.(Pro1309Ser)	0	NA, 0.09	Lennox-Gastaut Syndrome (Age at seizure onset 17 days), developmental delay (motor, speech and language), hypotonia, DR, dysmetria and dysdiadokokinesia, severe ID and an ASD diagnosis, non-ambulatory, non-verbal, fed through a G-tube
Zhou et al. 2022, Lim et al. 2017, Krumm et al. 2015	c.4049A>C; p.(Asn1350Thr)	0	NA, 0.14	ASD
Sabeh et al. 2025	c.4136_4141dup; p.(Leu1380_Asp1381insGlyLeu)	0	NA	ASD, ID, DD, epilepsy
Sabeh et al. 2025	c.4598A>G; p.(Gln1533Arg)	0	NA, 0.21	ASD, ID, DD
Zhou et al. 2022, MSSNG	c.4916G>C; p.(Arg1639Pro)	0	NA, 0.29	ASD, Female with IQ Wechsler performance 125, verbal 109,

3-0114-000 (Trost et al. 2022)				full scale 118, ASD (ADOS module 3: 2), speech delay (first words 26m, phrases 40 m), walking unaided 11 m
Zhou et al. 2022	c.5026A>G; p.(Ser1676Gly)	0	NA, 0.23	ASD
Sabeh et al. 2025	c.5074G>A; p.(Asp1692Asn)	0	NA, 0.23	ID, DD, epilepsy, movement disorder, genital anomalies
Sabeh et al. 2025	c.8304C>G; p.(Cys2768Trp)	0	HECT, 0.93	ID, DD, genital anomalies

Abbreviations: ASD, autism spectrum disorder; DD, developmental delay; ID, intellectual disability.



Supplementary Figure S1: Putative structure of UBR5 (NM_015902.6) consists of ubiquitin-associated (UBA) domain, Zinc finger domain, poly(A)-binding protein C-terminal domain (PABC), and HECT domain (https://www.uniprot.org/). Location of de novo missense/in-frame variants without functional evidence. Genomic size: 160,428 nucleotides, exon count: 59, Protein: 2799 amino acids, 18,734 - 158,954 nucleotides (multiple isoforms spanning 12-59 exons).