

Supplementary Table 2.- Mutant neuronal and retinal phenotypes in different animal models and human listed per DUB family and gene.

ND- Not determined (The list of bibliography is included at the end)

JAMM							
<i>D. melanogaster</i> [1]			<i>D. rerio</i> [2]		<i>M. musculus</i>		<i>H. sapiens</i>
Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype
AMSH	ND	ND			Loss of neurons in the hippocampus and cerebral cortex [3]	Microcephaly-capillary malformation syndrome (OMIM)	
AMSH-Like							
BRCC36	ND	ND					
CSN5					-/- homozygotes die soon after implantation and exhibit growth-retardation, decrease in cell proliferation, and an increase in cell apoptosis.		
CSN6	Pupal death		1dpf: cns necrosis , fused somite; 4dpf: small size and short body, small head, pericardial edema, unconsumed egg yolk with no yolk extension, shorten notochord length , dysmorphic axis, underdeveloped tail	4dpf: small eyes	-/- homozygotes are embryonic lethal [4]		
EIF3H	Pan-neural knockdown is developmentally lethal						
JAMM2							
JAMM3							
MYSM1	ND	ND	1dpf: cns necrosis , curled tail developed; 3dpf: narrow head; closed otoliths, abnormal yolk shape with short yolk extension, abnormal notochord shape , slightly curled tail, ratty caudal fin	3dpf: funny eyes shape			
POH1	Larval death						
PRPF8						Retinal degeneration in heterozygotes, more severe in homozygotes [4]	autosomal dominant retinitis pigmentosa
PSMD7			1dpf: serious cns necrosis ; 2dpf:		-/- homozygotes are embryonic		

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	small and short body, underdeveloped head, preicardial edema, shorten notochord , thin trunk, fused somite, shorten and fatty tail, shorten yolk extension	lethal [4]	
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MJD

<i>D. melanogaster</i>		<i>D. rerio</i>		<i>M. musculus</i>		<i>H. sapiens</i>	
Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype
ATX3	ND	ND	1dpf: cns necrosis , fused somite; 3dpf: reduced body length, dysmorphic axis development, malformed and shorter tail			Neurodegenerative disease SCA3 [5]	
JOSD1	ND	ND	1dpf: serious cns necrosis , slightly trunk and tail necrosis, fused somite, shorten tail; 3dpf: small head, strange yolk shape, abnormal notochord shape , irregular floorplate, hemorrhage at tail region, fused somite, shorten and curled tail	3dpf: funny eyes shape, abnormal retinotectal projection			
JOSD2			1dpf: abnormal head shape, fused somite; 4dpf: small and short body, strange head shape, tectum enlarged, pericardial edema, unconsumed egg yolk, fat and short yolk extension, dysmorphic axis development, abnormal notochord shape , curled tail				
JOSD3	ND	ND	ND	ND			

OTU

<i>D. melanogaster</i>		<i>D. rerio</i>		<i>M. musculus</i>		<i>H. sapiens</i>	
Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype
OTUB1			1dpf: cns necrosis , fused somite; 2dpf: small and short body, round				

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			yolk shape with thin yolk extension, thin trunk, curled tail		
OTUB2	ND	ND	ND	ND	
OTUD1	ND	ND	ND	ND	
OTUD3	ND	ND	1dpf: slightly cns and trunk necrosis, fused somite; 3dpf: serious dysmorphic development of axis and notochord, curled tail		
OTUD4			1dpf: underdeveloped trunk; 3dpf: small and short body, reduced pigmentation, cns necrosis , dysmorphic notochord shape, thin trunk, slightly curled tail (Tse)	3dpf: undeveloped eye (Tse). Reduction in size of the optic tecta and cerebellum (Margolin 2013)	Mutated, together with RNF216, in cerebellar ataxia and hypogonadotropic hypogonadism (Gordon Holmes syndrome) [6]
OTUD5			1dpf: cns necrosis , fused somite; 3dpf: reduced pigment, small and short body, pericardial edema, thin and short yolk extension, slightly bent body		Abnormal embryo turning and developmental patterning [4]
OTUD6a	ND	ND	ND	ND	
OTUD6b					
OTUD7a	ND	ND			
OTUD7b	ND	ND	ND 1dpf: underdeveloped trunk and notochord , fused somite; 3dpf: small and short body, slightly trunk necrosis, fused and curled tail	ND	
PARPF11			1dpf: cns necrosis , fused somite; 4dpf: strange head shape, small and short body, dysmorphic axis shape, thin trunk curled tail, ratty caudal fin		
TNFAIP3	ND	ND	1dpf: trunk and tail necrosis; 4dpf: abnormal head shape, pericardial edema, axis and notochord problems , thin trunk, unconsumed egg yolk with no yolk extension, short and curled tail		
VCPIP1	ND	ND	1dpf: underdeveloped trunk and notochord , shorten and fused tail;	4dpf: small eyes	

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		4dpf: small and small body, small head, thin trunk, abnormal somite shape, curled and thin tail		
YOD1		No early phenotype; 3dpf: short and edema body, pericardial edema, unconsumed egg yolk with fat and shorten yolk extension, underdeveloped liver and gut, abnormal axis and notochord shape , fused somite, short and curled tail		
ZRANB1	Pharate adult and young adult death (Sokol)	1dpf: fused somite, curled tail developed; 3dpf: shorten body length, abnormal notochord shape , no yolk extension, curled tail		

UCH

<i>D. melanogaster</i>		<i>D. rerio</i>		<i>M. musculus</i>		<i>H. sapiens</i>	
Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype
BAP1		1dpf: serious cns and trunk necrosis , fused somite; 4dpf: hemorrhage in head, unconsumed egg yolk, abnormal notochord shape , curled tail		-/- homozygotes are embryonic lethal(Clague)			
UCL1	ND			Gracile axonal dystrophy [5]		Linked to PD and other diseases [5]Childhood-Onset Neurodegeneration With Optic Atrophy: Progressive visual loss due to optic atrophy at around age 5 years, followed by spasticity, cerebellar ataxia, peripheral neuropathy, and myokymia, consistent with systemic neurodegeneration and deficits at the neuromuscular junction (OMIM)	
UCL3		1dpf: slightly trunk necrosis, fused somite; 3dpf: small and short body, pericardial edema, fat and short yolk	3dpf: reduced eye pigment	Learning and working memory deficits [5]	Retinal degeneration [5]		

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		extension, abnormal notochord shape , curled and malformed tail				
UCHL5	Pupal and pharate adult death (FUNC: NEUROGENESIS)	1dpf: cns necrosis , abnormal head shape, fused somite; 4dpf: thick looking jaw, enlarged otolith, pericardial edema, thin yolk extension, slightly body bent and curled tail, ratty caudal fin		Prenatal lethality, severely abnormal brain development [4]		
USP						
<i>D. melanogaster</i>		<i>D. rerio</i>		<i>M. musculus</i>		<i>H. sapiens</i>
	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype	Neuronal phenotype	Retinal phenotype
USP 1	(Neuronal) Slower Adults		No early phenotype; 3dpf: abnormal notochord development , body bent, thin trunk and curved tail		Elevated perinatal lethality, male infertility. Fancony anemia [4]	
USP 2	Pan-neuronal knockdown leads to reduced locomotion and earlier adult death [5]					Upregulated in high-grade gliomas [5]
USP 3	ND	ND	1dpf: serious cns necrosis , fused somite; 2dpf: small and short body, underdeveloped head, reduced pigmentation, enlarged tectum, thin trunk, body bent, abnormal notochord development , curled and fused tail	2dpf: underdeveloped eyes		
USP 4	ND	ND	ND 1dpf: cns necrosis ; 2dpf: small and short body, small head, unconsumed yolk with thin extension, notochord problem, curled tail	ND 2dpf: small eyes		
USP 5	Pupal death(Sokol)		1dpf: slightly cns necrosis , undeveloped trunk, fused tail; 2dpf: small and short body, abnormal head shape, percardial edema, dysmorphic axis shape, shorten notochord, trunk and tail necrosis,	2dpf: underdeveloped small eyes	-/- homozygotes are embryonic lethal [4]	

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		short and curled tail			
USP 6	ND	ND	ND	ND	
USP 7	Pharate adult death		1dpf: slightly cns damage ; 2dpf: small and short body, small head, reduced pigment, "bud" on head, abnormal notochord development , fused tail, ratty caudal fin, ; 3dpf: close otoliths, slightly percardial edema, unconsumed yolk in pear shape	2dpf: small eyes	-/- homozygotes are embryonic lethal(Clague). Brain specific knockdown causes brain malformation and neonatal lethality, due at least in part to p53-dependent mechanisms. [5]
USP 8	Larval death		1dpf: serious cns and trunk necrosis , fused somite; 3dpf: small body, slightly cns necrosis , percardial edema, abnormal notochord development , fused somite, curled tail with ratty caudal fin		Brain development deficiencies in brain targeted knockout (Hausp fl/fl nes-Cre) mice
USP 9X	Fat facets		ND	ND	reduction in axonal length and arborisation, decrease in neuronal migration [7] Involved in neuronal fate specification and NMJ function.(Sokol?) patients with multiple myeloma overexpressing USP9X have a poor prognosis [8]
USP 9Y	ND	ND	ND	ND	
USP 10			1dpf: cns necrosis , fused somite; 2dpf: small and short body, reduced pigment, thin trunk, body bent ventrally, curled tail, ratty caudal fin		
USP 11	ND	ND			
USP 12	ND	ND	1dpf: cns and tail necrosis ; 4dpf: slightly edema body, percardial edema, unconsumed yolk, abnormal yolk shape with thin yolk extension, dysmorphic notochord and axis shape , curled tail		
USP 13	ND	ND	1dpf: cns necrosis , fused somite; 2dpf: small and short body, reduced pigment, thin trunk, dysmorphic notochord shape , percardial edema, slightly curled tail		
USP 14	(Neuronal)Slower				Mutations in intron leads to

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	adults, early death (Sokol)				reduced USP14 levels. Tremors, abnormal brain morphology, altered synaptic transmission and increased apoptosis. [4]	
USP 15	ND	ND	1dpf: cns necrosis , fused somite; 2dpf: underdeveloped head and trunk, axis and notochord problems , pericardial edema, fused somite, short and slightly curled tail; 4dpf: unshaped head; body edema, round shape unconsumed yolk, underdeveloped liver and gut, tail slightly necrosis	2dpf: small eyes 4dpf: unshaped eyes		
USP 16	ND	ND			reduces the self-renewal of hematopoietic stem cells and the expansion of mammary epithelial cells, neuroprogenitors, and fibroblasts [9]	overexpression of USP16 reduces the expansion of normal fibroblasts and postnatal neural progenitors, whereas downregulation of USP16 partially rescues the proliferation defects of Down syndrome [9]
USP 17	ND	ND	ND	ND		
USP 18	ND	ND	1dpf: cns and tail necrosis , fused somite; 2dpf: underdeveloped trunk, tail necrosis; 3dpf: small and short body, small head, thin trunk, shorten notochord length , serious pericardial edema, unconsumed yolk with short yolk extensions shorten, short and curved tail	3dpf: small eyes	Tremors, seizures, abnormal nervous system, death [4]	
USP 19	ND	ND	1dpf: slightly cns necrosis , fused somite; 2dpf: small and short body, reduced pigmentation, small head, shorten notochord length , pericardial edema, short and curled tail with slightly necrosis (with "buds"),	2dpf: small eyes		
USP 20	Earlier adulthood death		1dpf: cns necrosis , fused somite; 2dpf: small and short body, reduced pigment, "buds" on the pericardial and yolk area, tail necrosis; 3dpf: small head, pericardial edema, "buds" (necrosis) on the pericardial	3dpf: small eyes		

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			area, unconsumed yolk with short extension, curled tail with slightly necrosis at the end		
USP 21	ND	ND	1dpf: mild necrosis throughout the body; 3dpf: underdeveloped head, small head, abnormal axis and notochord development , trunk necrosis, pericardial edema, roundly and unconsumed yolk with no yolk extension, no tail	3dpf: small eyes	
USP 22		Axonal projection of photoreceptor cells [5]	No early phenotype at 1dpf; 2dpf: inflated brain		-/- homozygotes are embryonic lethal [4]
USP 24	ND	ND	1dpf: body necrosis, fused somite; 2dpf: small and short body, cns necrosis became more seriously, abnormal notochord development , thin trunk, fat and short yolk extension, curled short tail with necrosis	2dpf: abnormal eyes	May be involved in PD susceptibility [5]
USP 25	ND	ND	1dpf: cns and tail necrosis ; 2dpf: small and short body, unshaped head, cns necrosis , bulging forebrain, thin trunk, fused somite, tail necrosis	2dpf: unshaped eyes	Overexpressed in Down Syndrome brains [5]
USP 26	ND	ND	ND	ND	
USP 27	ND	ND	ND	ND	
USP 28	ND	ND	1dpf: head damage, fused somite; 2dpf: serious cns necrosis , reduced pigment, notochord and axis underdevelopment , thin trunk, shorten and curved tail	ND	
USP 29	ND	ND	ND	ND	
USP 30	Knockdown of Usp30 in dopaminergic neurons protects flies against paraquat toxicity in vivo, ameliorating defects in				

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	dopamine levels, motor function, and organismal survival. [10]				
USP 31	ND	ND			
USP 32					
USP 33	ND	ND	1dpf: cns necrosis ; 3dpf: small and short body, small head, notochord development problem , curled tail	3dpf: small eyes	in cultured mouse embryonic commissural axons and was required for growth cone collapse in response to Slit exposure [11]
USP 34	Pan neuronal knockdown is developmentally lethal [5]				
USP 35		ND	ND		
USP 36	Larval death		1dpf: slightly cns necrosis ; 3dpf: small and short body, reduced pigment, very thin trunk, pericardial edema, funny yolk shape with fat yolk extension, curled tail		
USP 37	ND	ND	1dpf: cns necrosis ; 3dpf: small and short body, small head, tectum enlargement, pericardial edema, round yolk shape, thin trunk, notochord problem , shorten and slightly curled tail	3dpf: small eyes	
USP 38	ND	ND			
USP 39	Larval death		1dpf: cns and tail necrosis , 2dpf: small and short body, small head, slightly pericardial edema, dysmorphic notochord development, fused somite, curled tail	2dpf: small eyes	
USP 40	ND	ND			May be involved in PD susceptibility [5]
USP 41	ND	ND	ND	ND	
USP 42	ND	ND	1dpf: slightly cns necrosis , fused somite; 3dpf: inflated hindbrain, slightly pericardial edema and body bent		
USP 43			1dpf: slightly cns necrosis , fused somite; 2dpf: small and short body,	2dpf: small eyes	

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			reduced pigment, small head, bulging forebrain , pericardial edema, curled tail		
USP 44	ND	ND	1dpf: abnormal development, cns and tail necrosis , fused somite; 3dpf: very small and short body, underdeveloped head and trunk, shorten notochord length , axis development problem, serious pericardial edema, unconsumed round yolk with short yolk extension, short and curled tail		
USP 45	Pupal, pharate adult and young adult death		1dpf: cns necrosis ; 2dpf: reduced pigment, a bit smaller head, close otolith distance, slightly pericardial edema, thin yolk extension	2dpf: reduced eyes	
USP 46					role in the GABAergic neurotransmission [12]
USP 47					
USP 48	ND	ND	No early phenotype; 3dpf: small and short body, reduced pigment, small head, pericardial edema, body bent, slightly tail necrosis	3dpf: small eyes	
USP 49	ND	ND	ND	ND	
USP 50	ND	ND	ND	ND	
USP 51	ND	ND	ND	ND	
USP 52			ND	ND	
USP 53	ND	ND	No early phenotype at 1dpf; 3dpf: small and short body, reduced pigment, small head, inflated brain, notochord problem , curled tail	3dpf: small eyes	
USP 54	Pharate adult and young adult death				
CYLD			1dpf: cns necrosis ; 2dpf: small and short body, strange head shape, thinner mid/hidbrain boundary, midbrain enlargement , round yolk shape with thin extension, slightly axis and notochord problem, curled tail 1dpf: cns necrosis , trunk necrosis;	1dpf: small eyes (CylDb)	

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	2dpf: small and short body, small head, necrosis spread through the body, pericardial edema, thin trunk, notochord problem , body bent		
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