Validation of gene causality for neurological disorders by WES/WGS analyses in a diagnostic setting

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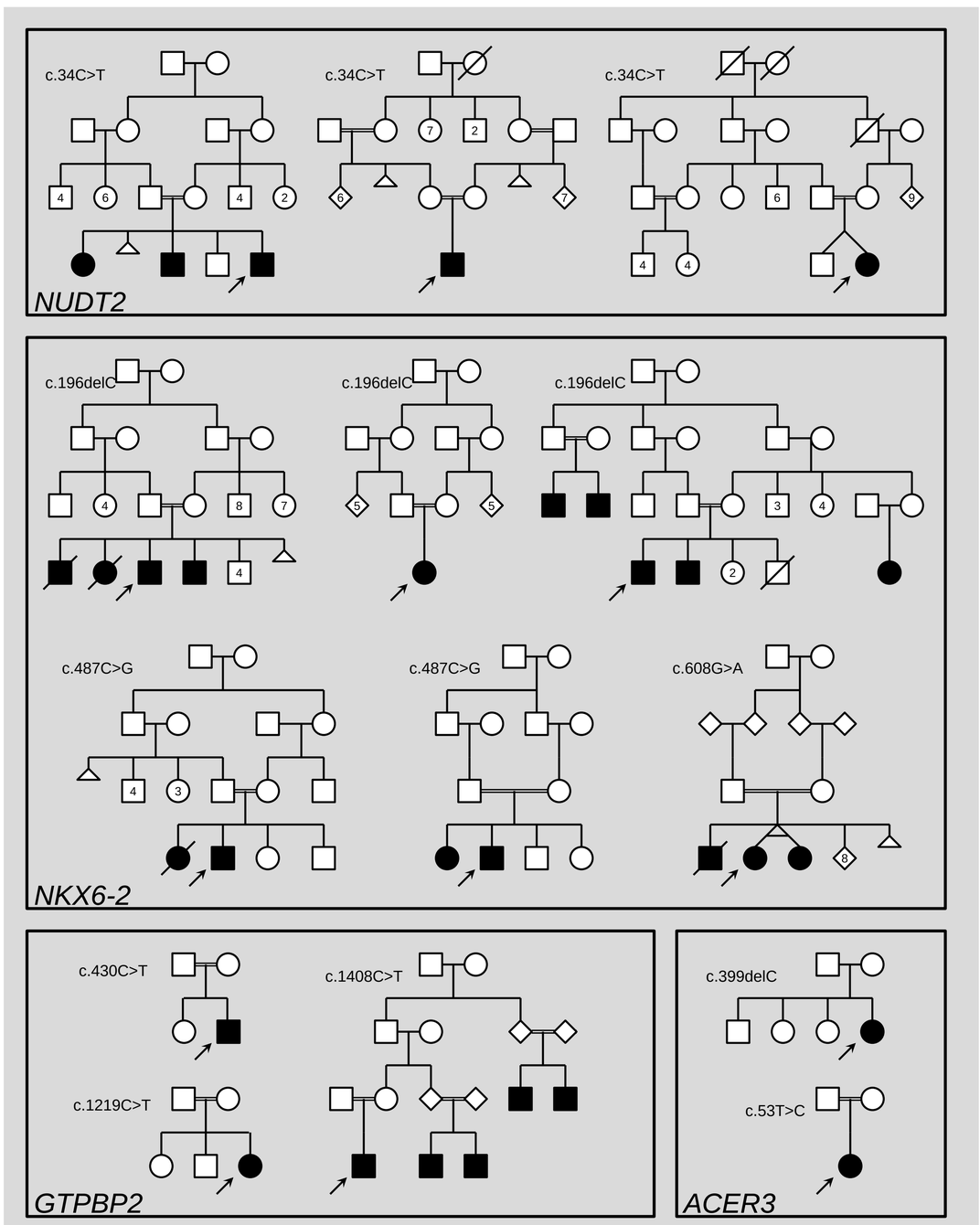

Figure 1: Novel pedigrees as identified in our proprietary database CentoMD© for the indicated recessive disease genes

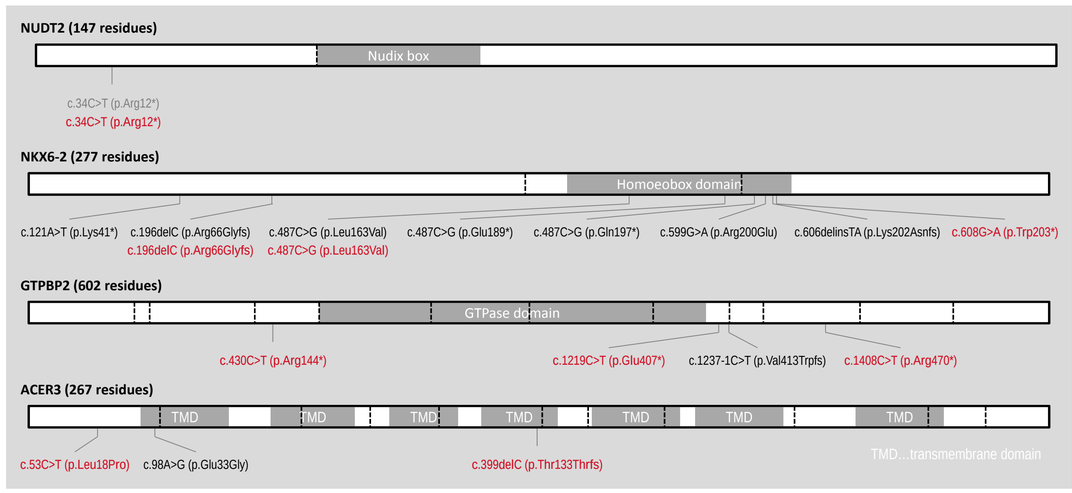

Figure 2: To-scale schemes of coding sequences (exon boundaries as stippled lines), critical protein domains, and pathogenic variants identified previously (black) and in CentoMD© (red)

Table 1: Origins of patients

Gene	Previously described patients	Patients from CentoMD© (**bold=novel**)
NUDT2	Saudi Arabia	Saudi Arabia
NKX6-2	India; Kenya/Tanzania; Morocco; Saudi Arabia	**Kuwait; Oman**; Saudi Arabia; **United Arab Emirates**
GTPBP2	Iran	**Kuwait; Saudi Arabia**
ACER3	Israel	**India; Saudi Arabia**

Table 2: Phenotypic features

Gene	Described previously	Novel in CentoMD©-listed patients
NUDT2	Intellectual disability	**Low birth weight and height, muscular hypotonia, delayed motor and language development**
NKX6-2	Hypomyelinating dystrophy, spastic ataxia	**Mild dysmorphism, seizures, clinical regression**
GTPBP2	Dystonia, ataxia, cognitive dysfunction; motor neuropathy, retinal abnormalities, sparse hair, brain iron accumulation	**Skeletal anomalies, extra-neurological presentations, lack of clinical progression, no evidence for brain iron accumulation**
ACER3	Progressive leukodystrophy (truncal hypotonia, appendicular spasticity, dystonia), short stature, late onset macrocephaly, facial dysmorphism	**Underweight, lactic acidosis; delayed myelination; brain atrophy**

Table 3: Summary of novelties as extracted from CentoMD©

Gene	Previous studies on an association of the investigated genes with monogenic disease	# families previously published	# families listed in CentoMD©	# patients previously published	# patients listed in CentoMD©	# pathogenic variants previously published	# pathogenic variants listed in CentoMD©	Extension of geographic origin of patients	Extension or refinement of phenotype	Centogene publication
NUDT2	Anazi et al., 2017a	1	3	2	5	1	1	no	yes	Yavuz and Bertoli-Avella et al., *in press*
NKX6-2	Chelban et al., 2017; Dorboz et al., 2017; Anazi et al., 2017b	7	6	15	12	7	3	yes	yes	Baldi and Bertoli-Avella et al., 2018
GTPBP2	Jaberi et al., 2016	1	3	3	5	1	3	yes	yes	Bertoli-Avella et al., 2018
ACER3	Edvardson et al., 2016	1	2	2	2	1	2	yes	yes	*in preparation*
total	**2016 - 2017**	**10**	**vs. 14**	**22**	**vs. 24**	**10**	**vs. 9**	**yes for 3 of 4**	**yes for 4 of 4**	

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Disclosure of conflict of interest:

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