Ataxies congénitales ou à début très précoces : épidémiologie génétique et corrélations génotype-phénotype à partir d'une série de 812 patients

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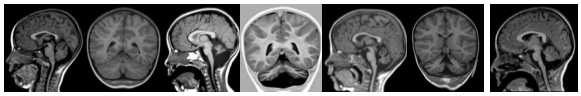
Aim of the study

- Describe the genetic epidemiology in our cohort of patients with congenital and very-early-onset ataxia
- Patients
  - Mainly children, but also adults from our reference center or french national network
  - Presence of Ataxia before 2 years old, with or without evidence of congenital disease
  - Non progressive at the time of inclusion
- Exclusion criteria
  - Ataxia clearly progressive
  - Diagnostic suggested by MRI:
    - Joubert Syndrome (molar tooth)
    - other pathognomic MRI images (VLDLR, LAMA1, Tubulinopathies)

Patients

- 812 patients / 756 propositus
- 58 multiplex families
  - 30 « autosomal recessive » (two affected siblings M/F or 2F)
  - 5 AR or X-linked (2 affected male)
  - 23 autosomal dominant (parent/child or children)
- Sex ratio 1/1 (380 female/376 male)
- MRI normal / cerebellar atrophy (vermis or hemispheres) /abnormal foliation



Strategy

- NGS gene panel as first line analysis
  - 3 different panels since 2016
- If negative: pangenomic analysis WES/WGS
- Genetic analysis in our local diagnostic lab or at the national genomic platform
- Validation of the pathogenicity
  - Segregation analysis in the families
  - Frequency in databases (gnomAD)
  - Classical prediction softwares (CADD, Polyphen2, revel, alphamissense, ..)
  - RNAseq and/or RTPCR (splicing variants)

Last panel design 247 genes

ACTB	CASK	ERCC5	HPCA	NGLY1	PPT1	SLC2A1	TMEM106B	UBTF
ADAR	CC2D2A	ERCC6	HPRT1	NKX2-1	PREM13	SLC30A10	TMEM151A	UNC13A
ADCY5	CEP120	EXOSC3	HSPD1	NKX6-2	PRKCG	SLC39A14	TMEM17	VAC14
ADPRS	CEP290	EXOSC5	INPP4A	NPC1	PRKN	SLC52A2	TMEM216	VLDLR
AFG3L2	CEP41	EXOSC7	INPP5E	NPC2	PRKRA	SLC52A3	TMEM231	VPS13D
AHI1	CEP78	EXOSC8	ITPR1	NPHP1	PRPS1	SLC5A3	TMEM237	VPS16
AFM1	CHMP1A	EXOSC9	KATNIP	NUS1	PRRT2	SLC6A5	TMEM237	VPS41
ABP1	CLDN11	FA2H	KCNA2	OFD1	PUM1	SLC9A1	TMEM240	WARS2
ALDH5A1	CLN6	FGF14	KCNC3	OPHN1	RARS2	SLC9A6	TMEM63A	WDR45
AMPD2	CLP1	FITM2	KCND3	PACS1	RNF220	SNAP25	TMEM67	WDR73
ANO3	COASY	FOLR1	KCNMA1	PACS2	RNU4ATAC	SNX3	TOE1	WDR81
AOPEP	COL4A3	GBA2	KCTD17	PANK2	ROBO3	SNX14	TOR1A	YY1
APTX	COQ8A	GCDH	KCTD3	PCYT2	RORA	SPR	TPK1	
ARMC9	CPLANE1	GCH1	KIAA0586	PDE10A	RPGRIP1L	SPTAN1	TPP1	
ATAD1	CSPP1	GEMIN5	KIAA0753	PDE2A	SACS	SPTBN2	TRAPPC6B	
ATAD3A	CTBP1	GLB1	KIF1A	PIBF1	SART3	SRY	TRAPPC9	
ATM	CWF19L1	GLRA1	KIF7	PIGG	SCN1A	STUB1	TRPM3	
ATP13A2	DDC	GLRB	KIF9	PIGK	SCN2A	STXBP1	TSEN15	
ATP1A3	DHDDS	GM2A	KMT2B	PIGS	SCN8A	SUFU	TSEN2	
ATP8A2	DEGS1	GNAL	LAMA1	PIGT	SCYL1	SYT1	TSEN34	
B3D1	DNAJC12	GNAO1	MBP	PLA2G6	SEPSECS	TAR1S2	TSEN54	
B3D2	DNAJC16	GNB1	MECP2	PMM2	SERAC1	TBC1D23	TSPOAP1	
BCAP31	DNAJC6	GPAA1	MECR	PMPCA	SETX	TBC1D24	TTPA	
BRAT1	DYRK1A	GRIN2	MED17	PNKP	SGCE	TCTN1	TUBA1A	
C19ORF12	EBP3	GRIA2	MORC2	POLR1C	SGCE	TCTN2	TUBB	
C2CD3	ECHS1	GRIA3	MNPP1	POLR3A	SIL1	TCTN3	TUBB2A	
CACNA1A	EIF2AK2	GRID2	MKS1	POLR3B	SKOR2	TH	TUBB2B	
CACNA1G	EMC1	GRIK2	MRE11	POLR3K	SLC18A2	THAP1	TUBB3	
CACNA2D2	ERCC1	HEXA	MTHFS	PPP2CA	SLC19A3	THG1L	TUBB4A	
	ERCC2	HEXB		PPP2R1A	SLC25A46	TIMM8A	UBA5	

Cerebellar disorders
Non progressive congenital ataxia
Early onset ataxia
Joubert syndrome
Pontocerebellar hypoplasia
Cerebrocerebellar atrophy
Other cerebellar congenital anomalies

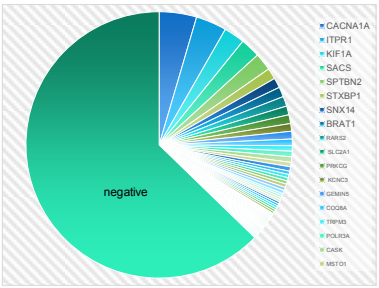
Movement disorders

106 genes congenital/VEO ataxia

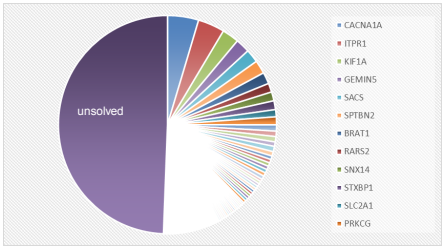
All the patients were analysed with at least one panel

Panel analysis - Results

Positive molecular diagnosis : 35%



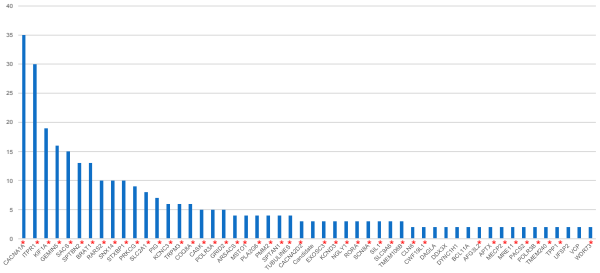
Total study (panel +WES/WGS) – Results (On going)



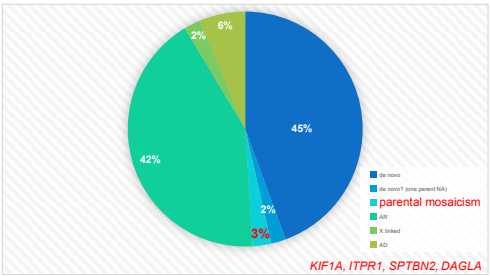
101 exomes
30 genomes

Diagnosis rate > 50%

Genes



Inheritance

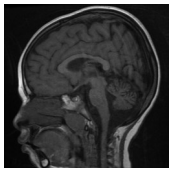


KIF1A, ITPR1, SPTBN2, DAGLA

Metabolic disorders - Atypical forms or diagnosis before regression

- female, 4 years old
  - No neonatal hypotonia
  - but early psychomotor delay noticed by the mother
  - Walking at 21 months, unstable
  - Language delay
  - Mild static and cinetic ataxia
  - No regression
  - MRI : cerebellar ataxia

  Panel => homozygous CLN6 variant p.(Val133Cysfs*18) , pathogenic



Metabolic disorders identified using the panel in patients with congenital or very-early onset ataxia:
- 4 CLN6 patients
- 2 CLN2 patients
- 2 siblings with atypical mild Menkes disease mimicking very early onset ataxia
- 2 unrelated patients with MSTO1 variants (mitochondrial myopathy and ataxia)

Why perform targeted panel sequencing in 2024?

- Speed and simplicity, even without parental samples
- Good yield (35%, perfectible)
- Good sensitivity for
  - Mosaicism =>
  - Exonic deletion/duplication =>
- Avoids incidental findings
- limits data storage issues

FGF14 deletion exons 2 and 3