

GENETYKA
dla NIE-GENETYKÓW
„OMIKA” - NOWA DZIEDZINA DIAGNOSTYCZNA
Nie tylko choroby rzadkie.

**NIEODPŁATNE
KURSY**
dla lekarzy, diagnostów
i innych specjalistów
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GENETYKA DLA NIE-GENETYKÓW

„OMIKA” NOWA DZIEDZINA DIAGNOSTYCZNA

Nie tylko choroby rzadkie.

„Choroby genetycznie uwarunkowane – edukacja i diagnostyka”
Program Operacyjny Wiedza Edukacja Rozwój – 2019 - 2021



Fundusze
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Rzeczpospolita
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Instytut
Matki i Dziecka

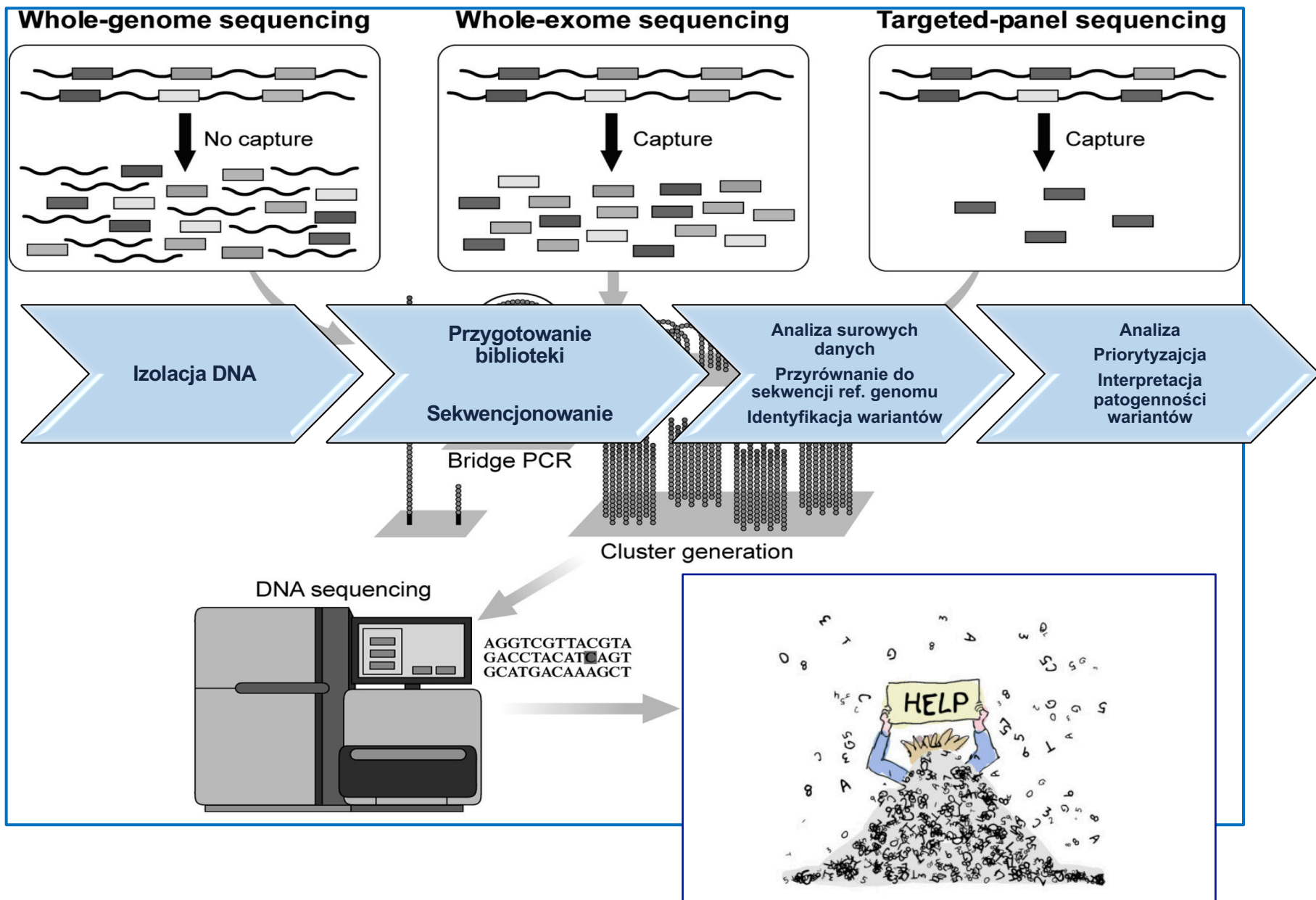
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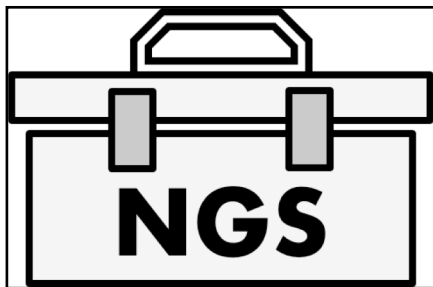




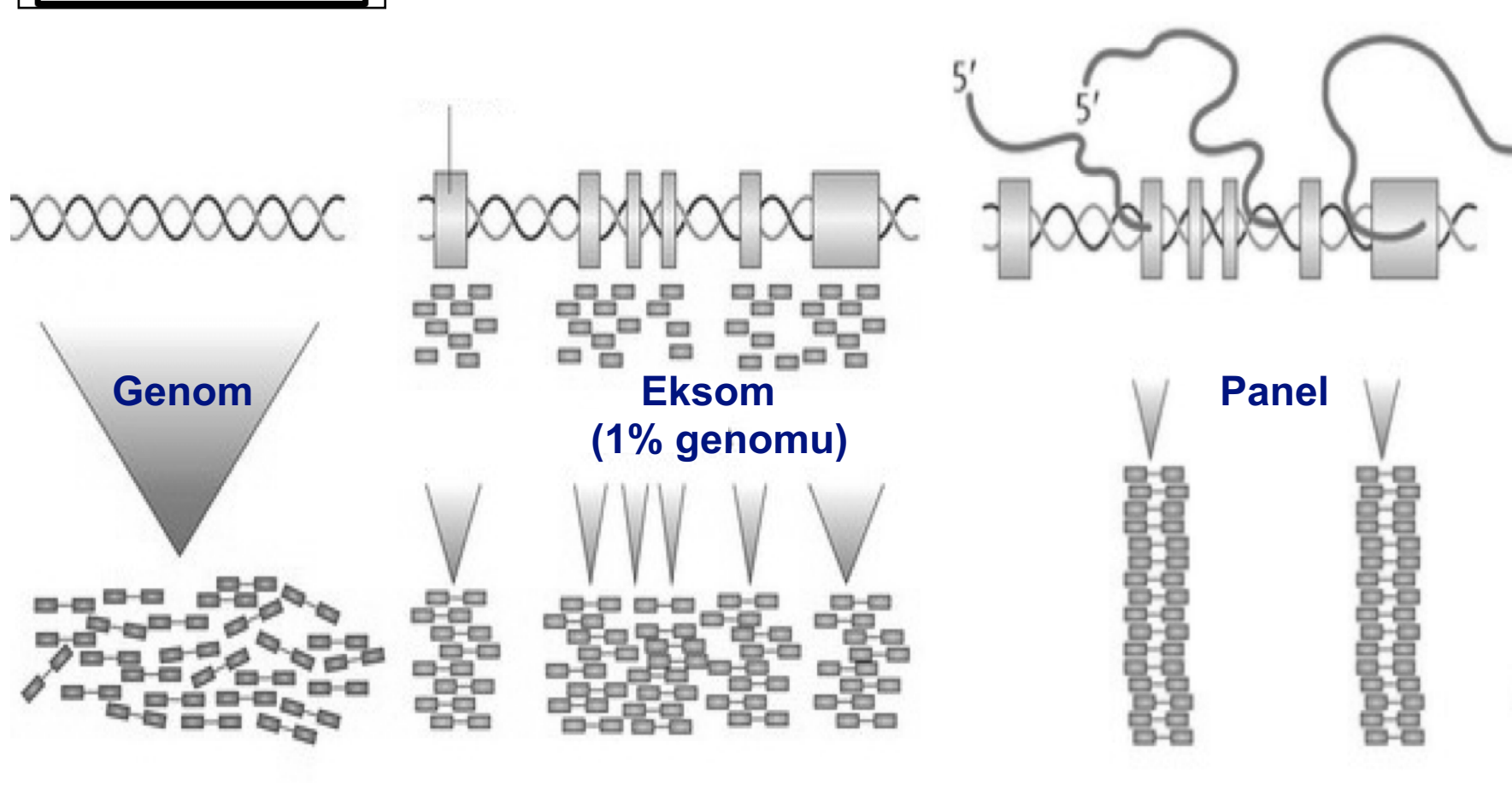
Analiza wyników badań NGS w praktyce

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Zakład Genetyki Medycznej; Instytut Matki i Dziecka w Warszawie
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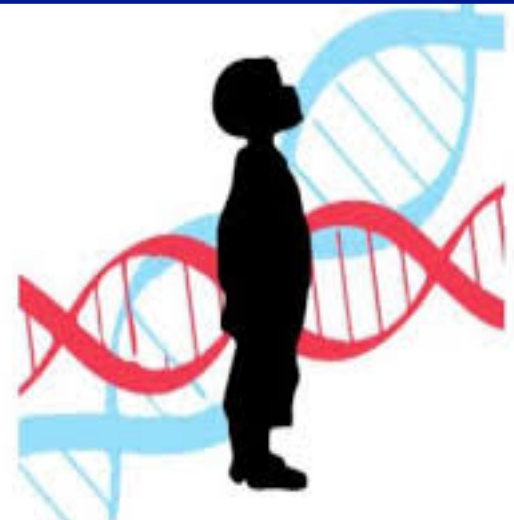
Sekwencjonowanie Następnej Generacji (Next Generation Sequencing – NGS)



Diagnostyka a badania naukowe..

Badania naukowe – poszukiwanie nowego gen powiązanego z daną chorobą w grupie pacjentów o podobnym fenotypie

Badanie diagnostyczne – analiza w celu identyfikacji defektu genetycznego stanowiącego podłoże fenotypu



POTOK ANALIZY DANYCH (*pipeline*)

1. Odczyt nukleotydu
(*base calling*)

przypisanie sygnału do nukleotydu,
plik wynikowy: FASTQ

2. Przyrównanie / uliniowanie
(*alignment, mapping*)

przyrównanie fragmentów do
sekwencji referencyjnej,
plik wynikowy: SAM/BAM

3. Odczyt wariantu
(*variant calling*)

różnice między sekwencją badaną
a referencyjną
plik wynikowy: VCF

4. Adnotacja wariantów i
filtrowanie

scharakteryzowanie wariantów na
podstawie różnorodnych biologicznych
baz danych, odrzucenie części
wariantów

5. Wybór wariantu patogennego

wybór wariantu patogennego
lub wariantów kandydujących



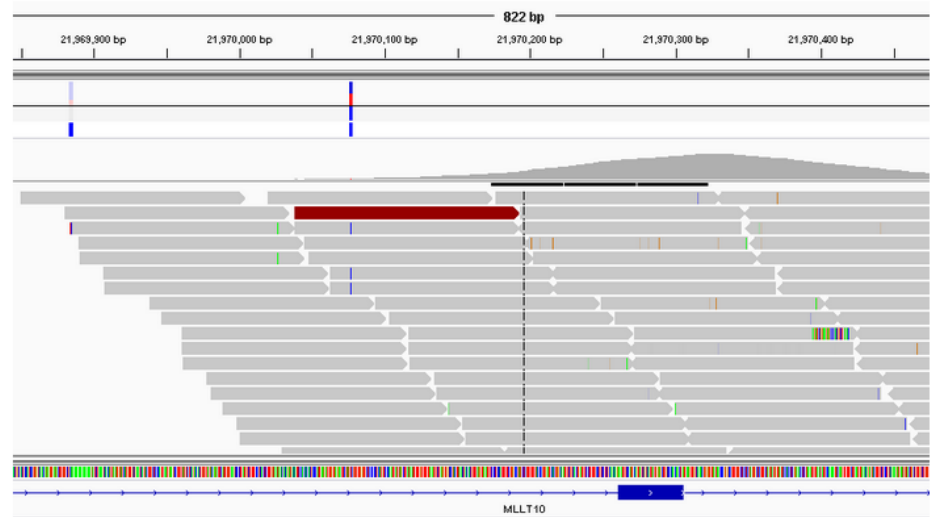
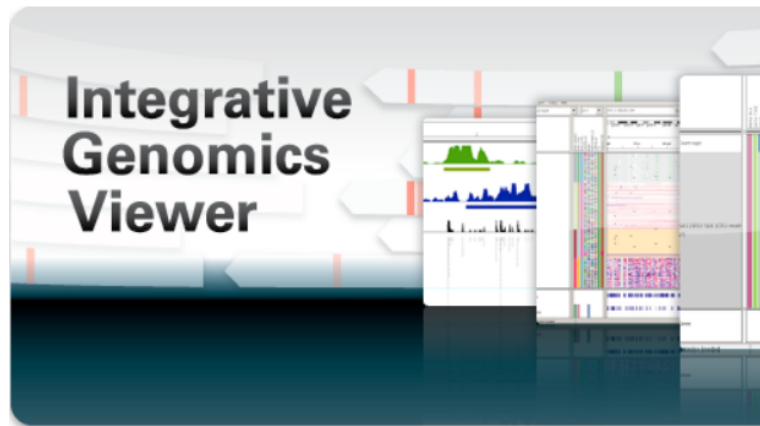
Bioinformatyk



Diagnosta + Klinicysta

Pliki BAM

– wizualizacja zidentyfikowanych wariantów



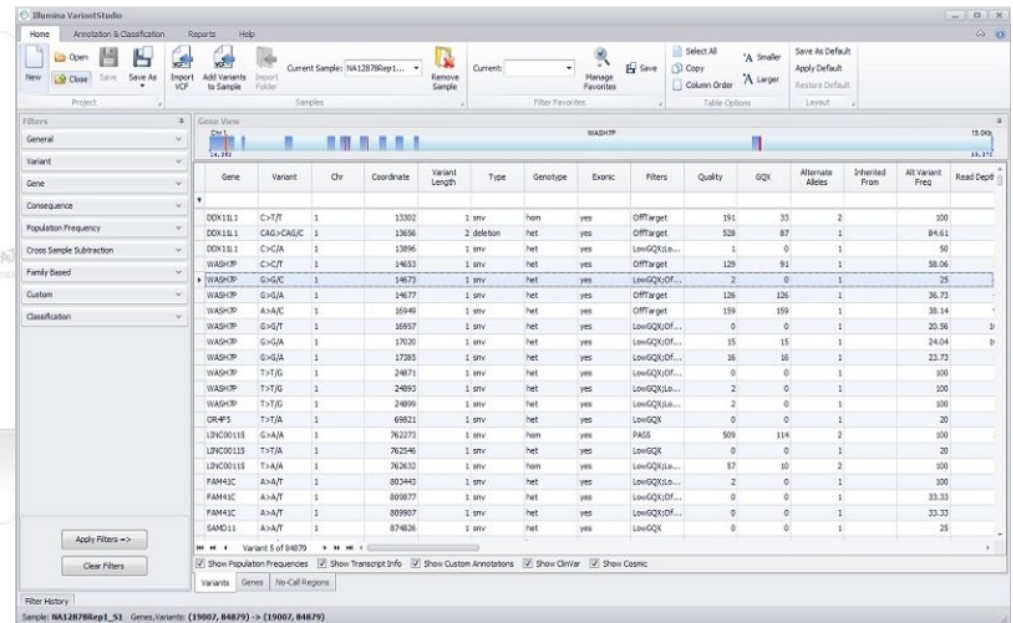
Pliki vcf

Annotation and Filtering Tool



VariantStudio Software v3.0

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The image shows the Illumina VariantStudio interface. The top part of the interface contains a menu bar with options like Home, Annotation & Classification, Reports, and Help. Below the menu bar is a toolbar with various icons for file operations and data management. The main area of the interface is a table of variants. The table has columns for Gene, Variant, Chr, Coordinate, Variant Length, Type, Genotype, Exonic, Filters, Quality, GQ, Alternate, Inherited From, All Variant Freq, and Read Depth. The table contains several rows of variant data, including variants from the DDX13L1, WASH3P, and FAM43C genes. The bottom part of the interface shows a filter history and a sample selection area.

Gene	Variant	Chr	Coordinate	Variant Length	Type	Genotype	Exonic	Filters	Quality	GQ	Alternate	Inherited From	All Variant Freq	Read Depth
DDX13L1	C>T	1	13302	1	snv	het	yes	OffTarget	191	33	2		100	
DDX13L1	CAG>CAGC	1	13656	2	deletion	het	yes	OffTarget	528	87	1		84.61	
DDX13L1	C>C/A	1	13896	1	snv	het	yes	LowGQ,LowQ	1	0	1		50	
WASH3P	C>C/T	1	14653	1	snv	het	yes	OffTarget	129	91	1		58.06	
WASH3P	G>G/C	1	14673	1	snv	het	yes	LowGQ,LowQ	2	0	1		25	
WASH3P	G>G/A	1	14677	1	snv	het	yes	OffTarget	126	126	1		36.73	
WASH3P	A>A/C	1	16949	1	snv	het	yes	OffTarget	159	159	1		38.14	
WASH3P	G>G/T	1	16957	1	snv	het	yes	LowGQ,LowQ	0	0	1		20.56	
WASH3P	G>G/A	1	17020	1	snv	het	yes	LowGQ,LowQ	15	15	1		24.04	
WASH3P	G>G/A	1	17285	1	snv	het	yes	LowGQ,LowQ	16	16	1		23.73	
WASH3P	T>T/G	1	24871	1	snv	het	yes	LowGQ,LowQ	0	0	1		100	
WASH3P	T>T/G	1	24893	1	snv	het	yes	LowGQ,LowQ	2	0	1		100	
WASH3P	T>T/G	1	24899	1	snv	het	yes	LowGQ,LowQ	2	0	1		100	
OR4F5	T>T/A	1	69821	1	snv	het	yes	LowGQ	0	0	1		20	
UNC00115	G>A/A	1	762273	1	snv	het	yes	PASS	509	114	2		100	
UNC00115	T>T/A	1	762546	1	snv	het	yes	LowGQ	0	0	1		20	
UNC00115	A>A/T	1	762632	1	snv	het	yes	LowGQ,LowQ	57	10	2		100	
FAM43C	A>A/T	1	802443	1	snv	het	yes	LowGQ,LowQ	2	0	1		100	
FAM43C	A>A/T	1	809877	1	snv	het	yes	LowGQ,LowQ	0	0	1		33.33	
FAM43C	A>A/T	1	809907	1	snv	het	yes	LowGQ,LowQ	0	0	1		33.33	
SAMD11	A>A/T	1	874826	1	snv	het	yes	LowGQ	0	0	1		25	

END-TO-END BIOINFORMATICS SOLUTION FOR NEXT-GENERATION SEQUENCING



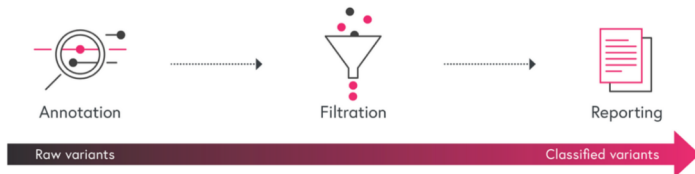
VarSome Clinical is a clinically-certified interpretation of NGS data for whole-genome and exome sequencing, helping geneticists and clinicians reach faster and more accurate diagnoses.

Alissa Interpret
The next evolution of Cartagenia Bench

Make your variant assessment flow



Interactive Biosoftware develops Alamut® software to help clinical researchers in the complex tasks of genomic variants annotation, filtration, and exploration.



HIGH-THROUGHPUT VARIANT ANNOTATION

Alamut® Batch enriches raw NGS variants with a wealth of attributes including effects on human genes, protein structure, and conservation.



INTERACTIVE VARIANT FILTRATION

Starting from annotated variant collections, Alamut® Focus selects candidate variants based on user-defined filters.



ADVANCED VARIANT EXPLORATION

Alamut® Visual is a comprehensive gene browser, helping scientific assess the pathogenic status of human variants.

SOFTGENETICS®
Software PowerTools for Genetic Analysis

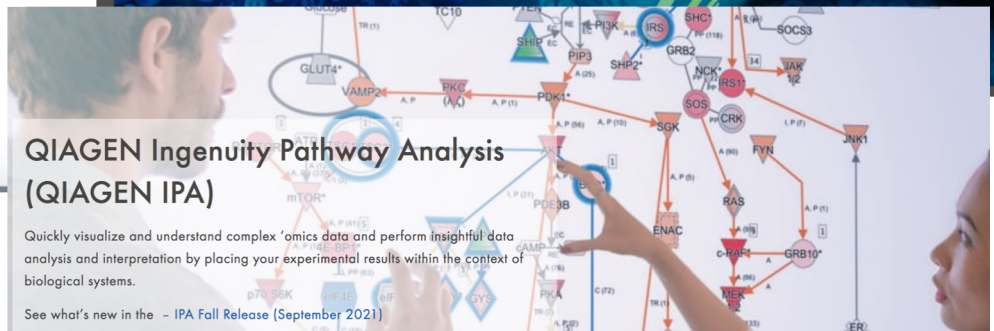
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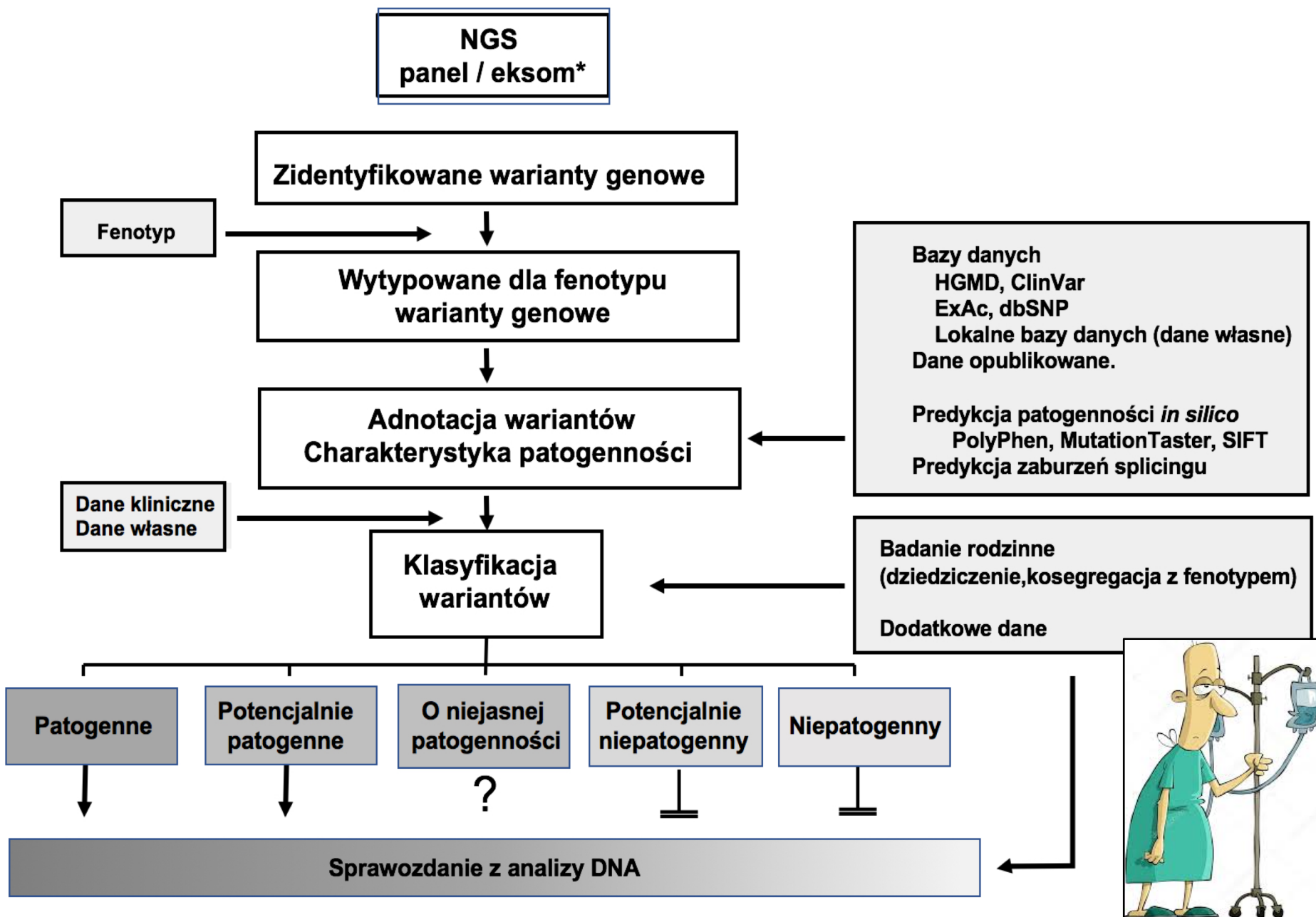
Quickly visualize and understand complex 'omics data and perform insightful data analysis and interpretation by placing your experimental results within the context of biological systems.

See what's new in the - IPA Fall Release (September 2021)



IMiD „home made pipieline” (VEP 2.7; Variant Effect Predictor)

#	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN							
1	Identifier	Sex	Chr	Start	End	Ref	Alt	UCSC	FILTER	QUAL	AD	DP	Zyg	zygNum	Gene.refG	GeneDetail	Func.refG	OMIM_dis	OMIM	dis OMIM	OMIM	gei	hAnyPanc	ExonicFun	AAChange	dbscSNV	J/dbscSNV	I/Mult	het	CLN	CLN	CLN	CLN	CLN	Allel	ZGM	AF	ZGM	AF	Fesp6500s	ExAC	ALL	ExAC	AFR	ExAC	AI	
2	22930_S1	female	chr10	1.03E+08	1.03E+08	T	G	http://gen PASS		358.04	15	44	het	1	P0DZT7		exonic	Usher syn	http://www	http://www	TRUE	nonsynonym NM_00115					TRUE	Benign	53297	not_specif	MedGen:C.criteri	pr	1129	0.830147	1125	0.827206		0	0.8122	0.8038	0.871						
3	22930_S1	female	chr10	1.03E+08	1.03E+08	A	T	http://gen PASS		523.39	16	32	het	1	P0DZT7		exonic	Usher syn	http://www	http://www	TRUE	nonsynonym NM_00115				TRUE	Benign	53292	not_specif	MedGen:C.criteri	pr	1127	0.828267	1118	0.822059		0	0.8109	0.8074	0.8							
4	22930_S1	female	chr10	1.03E+08	1.03E+08	T	C	http://gen PASS		468.65	15	35	het	1	P0DZT7		intronic	Usher syn	http://www	http://www	TRUE	nonsynonym NM_00115				0	0	FALSE	Benign	55376	not_specif	MedGen:C.criteri	pr	775	0.569853	773	0.568382	0.661464	0.5777	0.7943	0.464						
5	22930_S1	female	chr10	26355906	26355906	G	A	http://gen PASS		2723.18	73	74	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54988	not_specif	MedGen:C.criteri	pr	786	0.577941	785	0.577206	0.48839	0.485	0.3601	0.30							
6	22930_S1	female	chr10	26355992	26355992	A	G	http://gen PASS		2857.45	76	76	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54957	not_specif	MedGen:C.criteri	pr	960	0.705882	960	0.705882	0.682531	0.6786	0.6801	0.611							
7	22930_S1	female	chr10	26356014	26356014	C	T	http://gen PASS		2379.41	61	61	hom	2	MYO3A		intronic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54958	not_specif	MedGen:C.criteri	pr	786	0.577941	783	0.575735	0.464478	0.4816	0.3597	0.30							
8	22930_S1	female	chr10	26357747	26357747	C	T	http://gen PASS		2518.64	64	64	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54961	not_specif	MedGen:C.criteri	pr	786	0.577941	784	0.576471	0.453867	0.4834	0.3595	0.3							
9	22930_S1	female	chr10	26357748	26357748	G	A	http://gen PASS		2462.12	63	63	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54962	not_specif	MedGen:C.criteri	pr	960	0.705882	958	0.704412	0.666769	0.6794	0.7016	0.61							
10	22930_S1	female	chr10	26357820	26357820	C	T	http://gen PASS		2878.57	78	79	hom	2	MYO3A		intronic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174				0	0	FALSE	Benign/Lik	54963	not_specif	MedGen:C.criteri	pr	786	0.577941	786	0.577941	0.488006	0.4844	0.3596	0.30						
11	22930_S1	female	chr10	26446312	26446312	G	A	http://gen PASS		3309.11	84	84	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54969	not_specif	MedGen:C.criteri	pr	785	0.577206	785	0.577206	0.521067	0.5064	0.466	0.38							
12	22930_S1	female	chr10	26462790	26462790	G	A	http://gen PASS		4944.74	127	127	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54973	not_specif	MedGen:C.criteri	pr	498	0.366176	498	0.366176	0.306705	0.3445	0.2573	0.29							
13	22930_S1	female	chr10	26463043	26463043	A	T	http://gen PASS		5058.34	127	127	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54974	not_specif	MedGen:C.criteri	pr	615	0.452206	614	0.451471	0.39551	0.4145	0.3354	0.34							
14	22930_S1	female	chr10	26463130	26463130	C	A	http://gen PASS		3636.89	96	96	hom	2	MYO3A		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174					FALSE	Benign/Lik	54976	not_specif	MedGen:C.criteri	pr	797	0.586209	796	0.585294	0.56274	0.5987	0.5536	0.65							
15	22930_S1	female	chr10	55566406	55566406	T	G	http://gen PASS		2913.52	75	75	hom	2	PCDH15		exonic	Deafness	http://www	http://www	TRUE	unknown UNKNOWN					FALSE	Benign	229793	not_specif	MedGen:C.criteri	pr	327	0.240441	326	0.239706	0.223786	0.2127	0.0514	0.10							
16	22930_S1	female	chr10	56077209	56077209	G	A	http://gen PASS		1465.09	46	89	het	1	CDH15		intronic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0174				0	0	FALSE	Benign/Lik	55676	Retinitis	p	MedGen:C.criteri	pr	1021	0.750735	1021	0.750735	0.740197	0.6604	0.7451	0.58					
17	22930_S1	female	chr10	73270906	73270906	T	C	http://gen PASS		2341.7	62	63	hom	2	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55093	Retinitis	p	MedGen:C.criteri	pr	885	0.650735	881	0.647794	0.749597	0.6721	0.9361	0.44						
18	22930_S1	female	chr10	73406504	73406504	T	C	http://gen PASS		1610.41	51	104	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0528					FALSE	Benign	55035	not_specif	MedGen:C.criteri	pr	194	0.142647	194	0.142647	0.149792	0.1521	0.1244	0.08							
19	22930_S1	female	chr10	73434906	73434906	G	A	http://gen PASS		583.46	19	40	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55040	Retinitis	p	MedGen:C.criteri	pr	378	0.277941	378	0.277941	0.249881	0.2724	0.2539	0.30						
20	22930_S1	female	chr10	73455201	73455201	T	C	http://gen PASS		3372.05	87	87	hom	2	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55058	Retinitis	p	MedGen:C.criteri	pr	966	0.710294	964	0.708824	0.668785	0.6362	0.5272	0.44						
21	22930_S1	female	chr10	73455273	73455273	T	C	http://gen PASS		2099.92	54	54	hom	2	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55061	Retinitis	p	MedGen:C.criteri	pr	966	0.710294	962	0.707353	0.669401	0.6363	0.5276	0.44						
22	22930_S1	female	chr10	73492079	73492079	A	G	http://gen PASS		4416.73	115	115	hom	2	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55102	Retinitis	p	MedGen:C.criteri	pr	1122	0.825	1122	0.825	0.812899	0.8159	0.7809	0.80						
23	22930_S1	female	chr10	73501556	73501556	G	A	http://gen PASS		1947.72	50	50	hom	2	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0221					FALSE	Benign/Lik	55120	Retinitis	p	MedGen:C.criteri	pr	1082	0.795588	1078	0.792647	0.741081	0.7752	0.6276	0.78						
24	22930_S1	female	chr10	73544638	73544638	A	G	http://gen PASS		531.51	18	42	het	1	CDH23		intronic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0221				0	0.002	FALSE	Benign/Lik	55147	Retinitis	p	MedGen:C.criteri	pr	264	0.194118	264	0.194118	0.129017	0.1915	0.0695	0.35					
25	22930_S1	female	chr10	73550117	73550117	C	G	http://gen PASS		471.5	16	37	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0221					FALSE	Benign/Lik	55162	Retinitis	p	MedGen:C.criteri	pr	675	0.496324	672	0.494118	0.414431	0.4291	0.2895	0.27						
26	22930_S1	female	chr10	73550969	73550969	G	A	http://gen PASS		457.16	16	43	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55167	Retinitis	p	MedGen:C.criteri	pr	273	0.200735	272	0.2	0.265481	0.3111	0.2832	0.45						
27	22930_S1	female	chr10	73558886	73558886	G	A	http://gen PASS		1211.65	37	70	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55191	Retinitis	p	MedGen:C.criteri	pr	275	0.202206	273	0.200735	0.262008	0.3081	0.27	0.44						
28	22930_S1	female	chr10	7358952	7358952	C	T	http://gen PASS		1423.65	45	87	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55193	Retinitis	p	MedGen:C.criteri	pr	273	0.200735	271	0.199265	0.254335	0.2997	0.2481	0.44						
29	22930_S1	female	chr10	73562744	73562744	G	A	http://gen PASS		1006.27	32	64	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55199	Retinitis	p	MedGen:C.criteri	pr	274	0.201471	273	0.200735	0.24883	0.3019	0.2269	0.44						
30	22930_S1	female	chr10	73571765	73571765	T	C	http://gen PASS		799.6	27	65	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55237	Galactosyl	p	MedGen:C.criteri	pr	44	0.032353	44	0.032353	0.025518	0.0697	0.0091	0.1						
31	22930_S1	female	chr10	73574843	73574843	G	A	http://gen PASS		650.81	20	42	het	1	CDH23		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0011					FALSE	Benign/Lik	55245	Galactosyl	p	MedGen:C.criteri	pr	84	0.061765	84	0.061765	0.069327	0.1317	0.055	0.34						
32	22930_S1	female	chr11	1.21E+08	1.21E+08	A	G	http://gen PASS		1422.43	43	85	het	1	TECTA		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0054					FALSE	Benign	54481	not_specif	MedGen:C.criteri	pr	569	0.418382	567	0.416912	0.497309	0.403	0.6792	0.32							
33	22930_S1	female	chr11	1.21E+08	1.21E+08	A	G	http://gen PASS		1740.96	52	89	het	1	TECTA		exonic	Deafness	http://www	http://www	TRUE	nonsynonym NM_0054					FALSE	Benign	54482	not_specif	MedGen:C.criteri	pr	944	0.694118	940	0.691176	0.770686	0.7117	0.9343	0.61							
34	22930_S1	female	chr11	1.21E+08	1.21E+08	T	C	http://gen PASS		1306.74	41	80	het	1	TECTA		exonic	Deafness	http://www	http://www	TRUE																										



Czy zidentyfikowana mutacja w konkretnym genie odpowiada za chorobę pacjenta ?

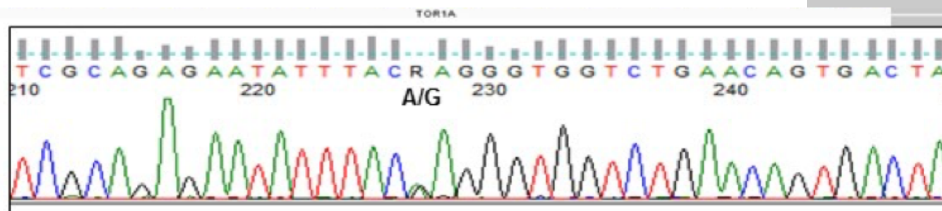
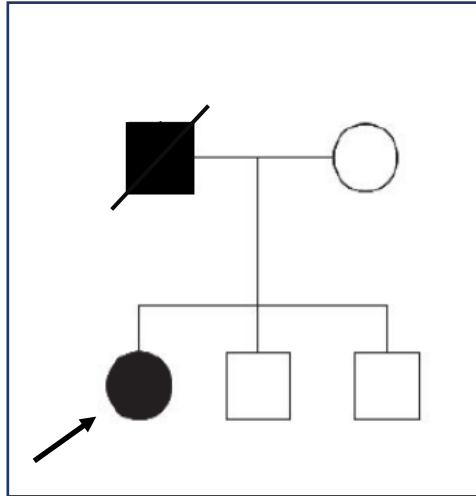
Który ze zidentyfikowanych wariantów jest istotny ?

Czy zidentyfikowany wariant jest mutacją patogenną ?

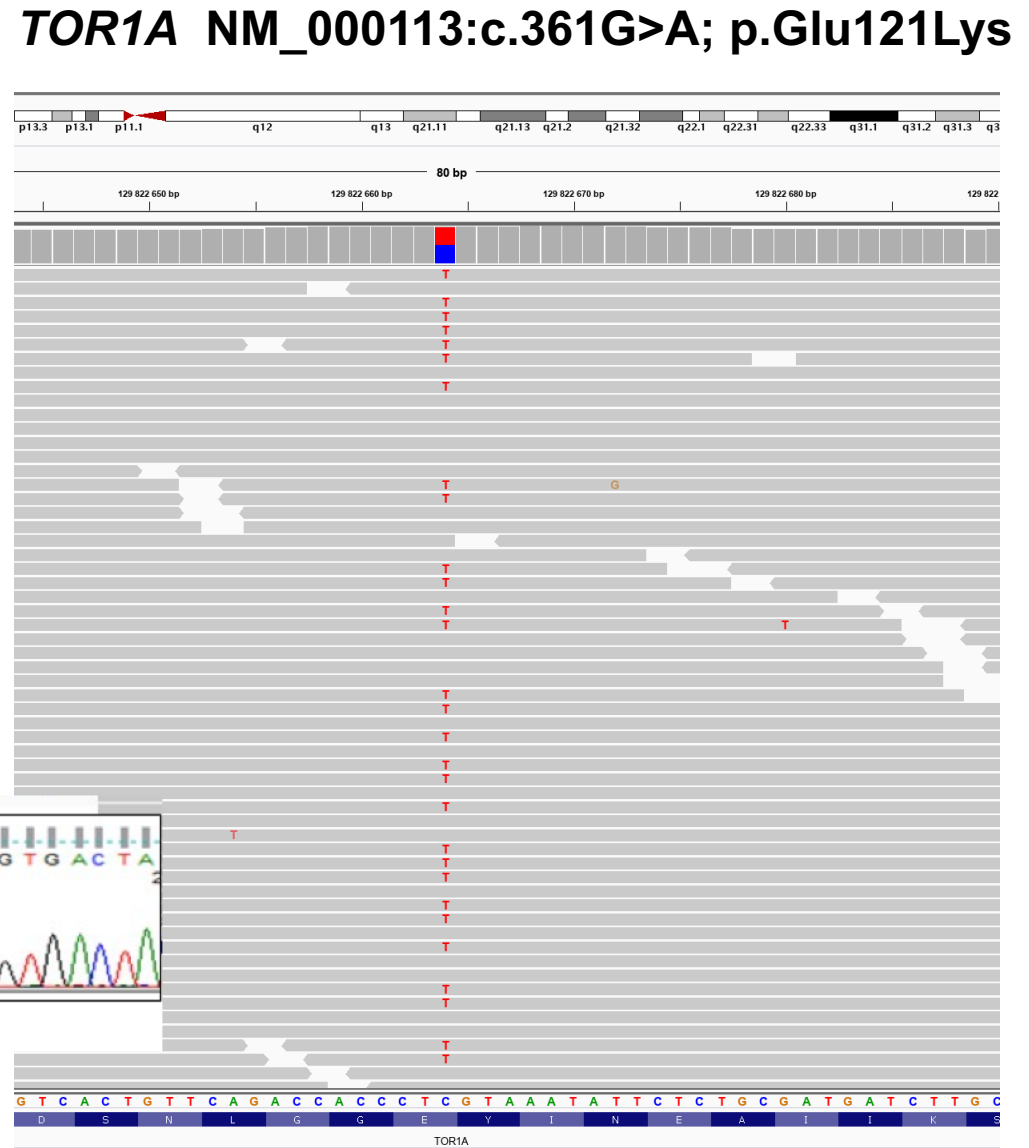
Czy zidentyfikowana mutacja jest istotna biorąc pod uwagę fenotyp pacjenta – gen ?



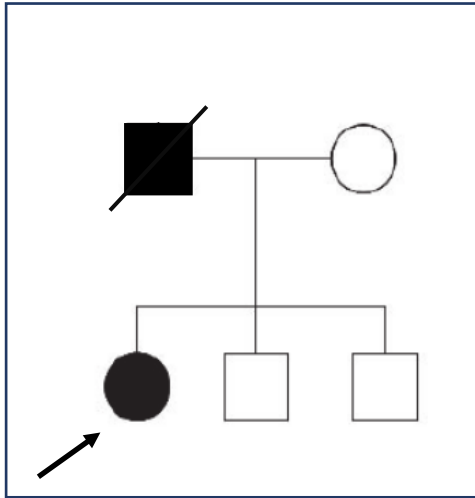
LO-PD (AD)
WES_ DNA probanta



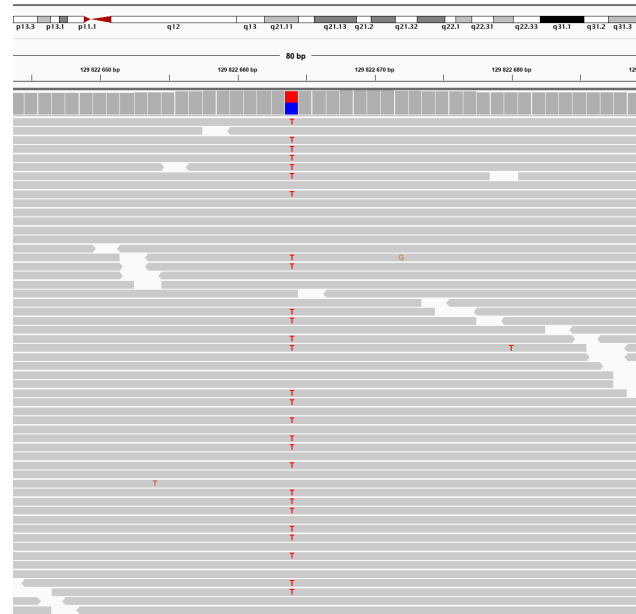
TOR1A c.[G361A];[=] ; p.[(Glu121Lys)];[=]



LO-PD (AD)
WES_ DNA probanda



TOR1A NM_000113:c.G361A; p.Glu121Lys





HGMD® Professional 2019.3



Gene Mutation Phenotype Reference Batch Advanced | Statistics Information Support | Home Logout

NM_000113.2

Gene symbol: [TOR1A](#)

Print friendly

Extended cDNA not available

Include 1 dbSNP entries

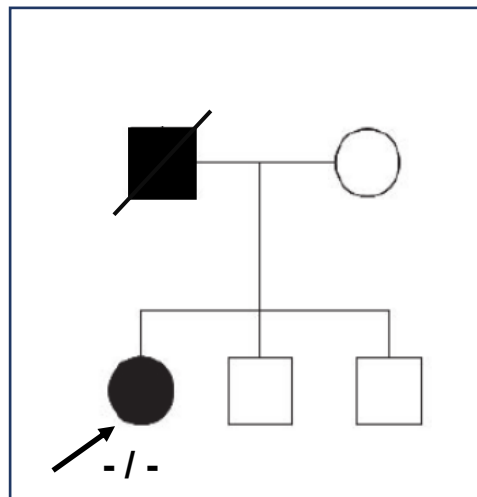
Database: [Missense/nonsense](#) - Single base-pair substitutions in coding regions are represented as a triplet codon change. There are currently 9 mutations available in this category. These data are sorted by location.

Missense/nonsense	Splicing	Regulatory	Small deletions	Small insertions	Small indels	Gross deletions	Gross insertions	Complex	Repeats
9 mutations	No mutations	2 mutations	4 mutations	1 mutation	No mutations	2 mutations	No mutations	No mutations	No mutations

HGMD accession	HGMD codon change	HGMD amino acid change	HGVS (nucleotide)	HGVS (protein)	Variant class	Reported phenotype	Reference	Extra information
CM1310069	GAG-AAG	Glu121Lys	c.361G>A	p.E121K	DM	Dystonia, segmental	Vulinovic (2013) Mov Disord 28S1 S3 Vulinovic (2014) Hum Mutat 35: 1114 [Functional characterisation]	hg38 hg19 CpG dbSNP gnomAD



LO-PD (AD)
WES_ DNA probanta



TOR1A NM_000113:c. 361G>A; p.Glu121Lys



Journal of Clinical Neuroscience

Volume 72, February 2020, Pages 501-503



Short communication

The matter of significance – Has the p.(Glu121Lys) variant of *TOR1A* gene a pathogenic role in dystonia or Parkinson disease?

Łukasz Milanowski ^{a,1} ✉, Dorota Hoffman-Zacharska ^{b,1}, Maciej Geremek ^b, Andrzej Friedman ^a, Monika Figura ^a, Dariusz Koziorowski ^a

HGMD® Professional 2021.3

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NM_000113.3

Gene symbol: **TOR1A**

Print friendly

Extended cDNA

TOR1A in gnomAD

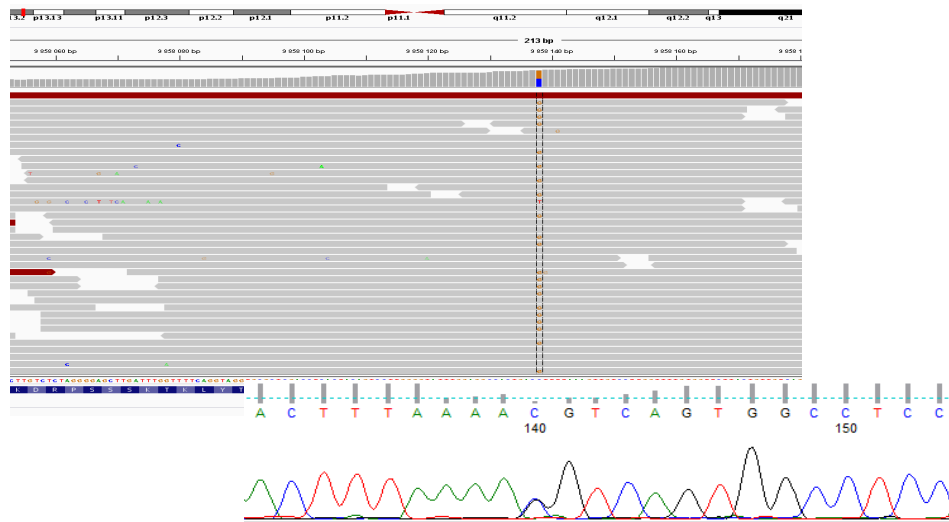
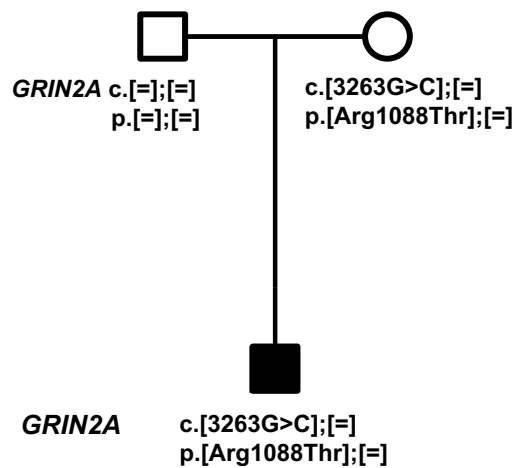
TOR1A in dbSNP

Database: Missense/nonsense - Single base-pair substitutions in coding regions are represented as a triplet codon change. There are currently 12 mutations available in this category. These data are sorted by location.

Missense/nonsense	Splicing	Regulatory	Small deletions	Small insertions	Small indels	Gross deletions	Gross insertions	Complex	Repeats
12 mutations	No mutations	2 mutations	6 mutations	1 mutation	No mutations	2 mutations	No mutations	No mutations	No mutations
HGMD accession	HGMD codon change	HGMD amino acid change	HGVS (nucleotide)	HGVS (protein)	Variant class	Reported phenotype	Reference	Extra information	
CM1310069	GAG-AAG	Glu121Lys	c.361G>A	p.E121K	DM?	Dystonia, segmental	Vulinovic (2013) <i>Mov Disord</i> 28S1 S3 Vulinovic (2014) <i>Hum Mutat</i> 35: 1114 [Functional characterisation] Milanowski (2019) <i>J Clin Neurosci</i> 72: 501 [Additional report]	hg38 hg19 CpG dbSNP	
CM158788	GTC-ATC	Val129Ile	c.385G>A	p.V129I	DM?	Dystonia	Dobričić (2015) <i>Parkinsonism Relat Disord</i> 21: 1256	hg38 hg19 COM dbSNP	

Encefalopatia padaczkowa z afazją

GRIN2A c.3263G>C, p.Arg1088Thr (?)



Welcome to the GRIN Portal

An interactive website for families, clinicians and researchers
dedicated to comprehend GRIN-related disorders



GRIN genes, function and associated disorders

[Basic Information](#)



Foundations, family groups, links to resources and more

[Families](#)



Comprehensive information on variant interpretation

[Variant Analysis](#)



Filter and select a subset of variants for research

[Research](#)



Information on the GRIN Registry and how to register

[GRIN Registry](#)

Single Variant

Multiple Variants

Enter variant

Variant Analysis lets you analyze single or multiple single-nucleotide variants (SNVs) in GRIN genes.

You may also download a report on the clinical significance of the variant (no medical advice).

GRIN gene

GRIN2A

cDNA Position

3263

Ref

G

Alt

C

SEARCH

Amino Acid Position

1088

Ref

ARG

Alt

THR

SEARCH

Variant Information

Gene: GRIN2A

Transcript: NM_001134407.3

Exon: 14/14



Domain: CTD

Amino Acid Position: 1088

Amino Acid Change: Arg (R) - Thr (T)



Control variants: 0

gnomAD Allele Count for this Position

gnomAD Allele Frequency: 0



Clinical Significance (Preliminary Use)

Origin

- ☐ de novo (confirmed)
- ☐ de novo (assumed)
- ☐ Inherited
- ☒ Unknown/Untested

Phenotype

- ☐ Neurodevelopmental Disorder (NDD) + Cortical Malformation
- ☐ NDD + Epilepsy or Cerebral Visual Impairment
- ☐ Unspecified NDD
- ☒ Other

Uncertain

NM_001134407.3: c.3263G>C p.(Arg1088Thr)

Explanation

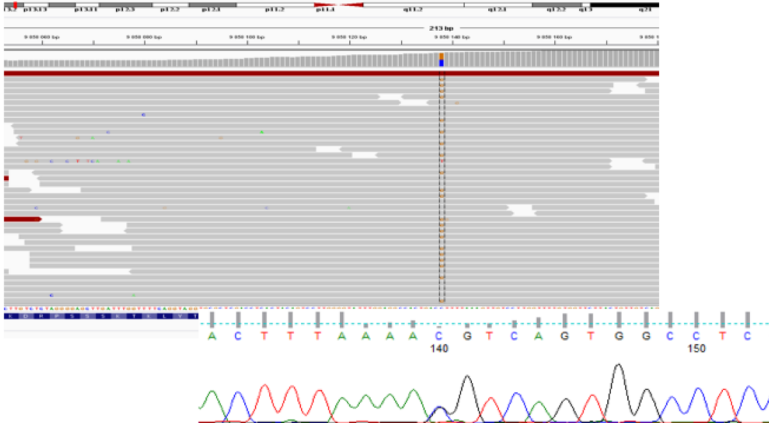
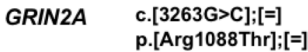
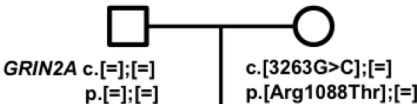
+

GENERATE REPORT

Preliminary/incomplete use. Criteria for GRIN Registry variants were automatically annotated according to standard [ACMG Variant Interpretation Guidelines](#) (GRIN1, GRIN2A, GRIN2D) or the ClinGen GRIN Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines (GRIN2B, unpublished). They are yet incomplete and not to be used in a medical context.

Encefalopatia padaczkowa z afazją

GRIN2A c.3263G>C, p.Arg1088Thr (?)



Filtered Subset
Number of individuals: 479

Genotype Interface

Phenotype Interface

Functional Interface

Animal Models

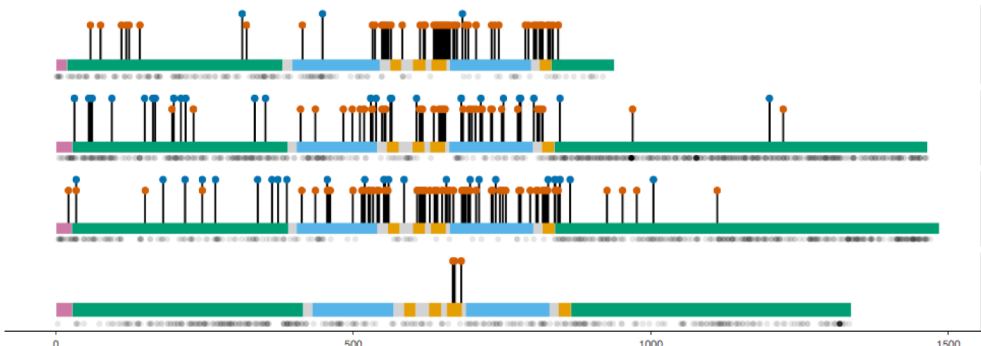
Selected variants are displayed in 2D (lollipop) and 3D (protein structure).

☒ Reference population missense variants (gnomAD)

☐ PERs

☐ iMDs ?

● Missense ● Truncating ● Control



The following transcripts were used: GRIN1: NM_007327.4, GRIN2A: NM_001134407.3, GRIN2B: NM_000834.4, GRIN2D: NM_000836.2

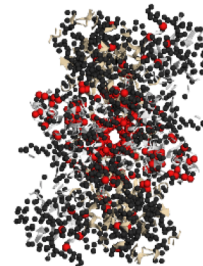
GRIN1

GRIN2A

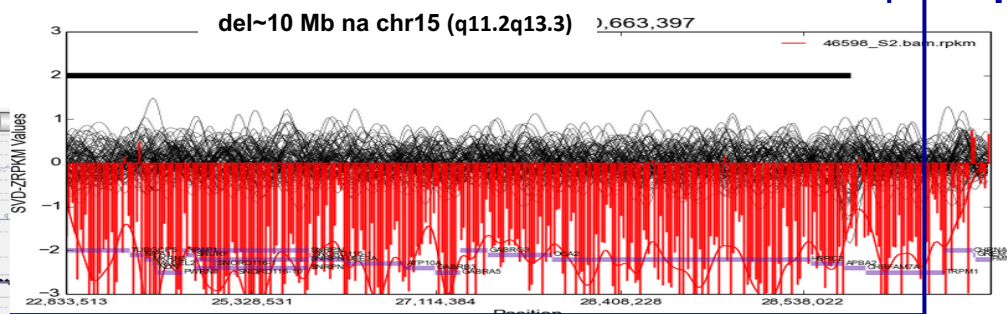
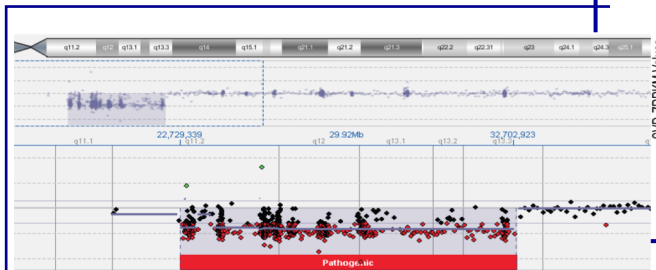
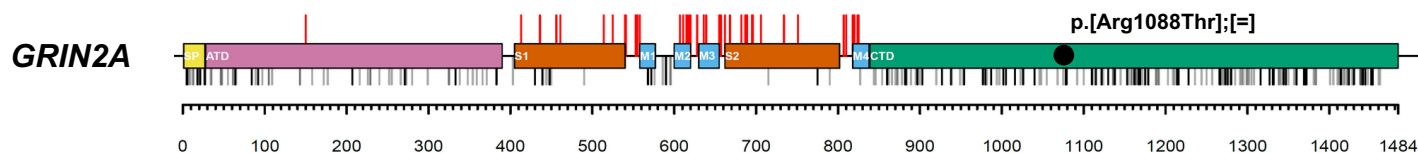
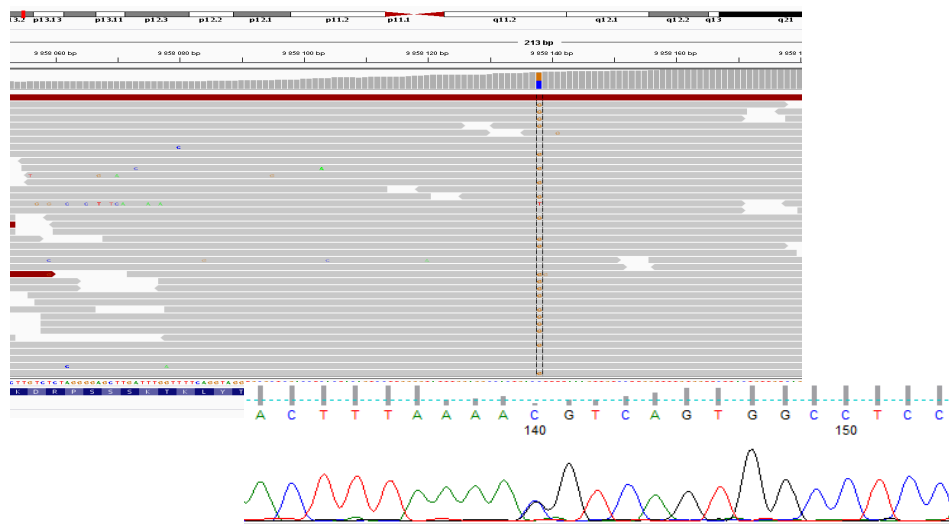
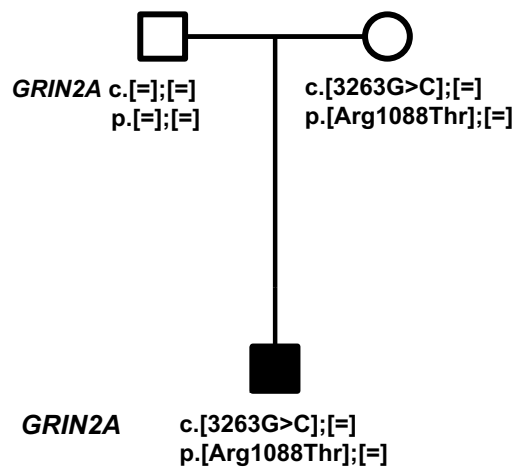
GRIN2B

GRIN2D

GRIN1 and GRIN2A Complex Structure

UniProt GRIN2A: [Q12879](#)

Encefalopatia padaczkowa z afazją



Zespół Angelmana

Information on GRIN2A

History of GRIN2A Research

2010

First Description of *de novo* Variants

Endele et al.

in individuals with intellectual disability

2013

Delineation of the Phenotype

multiple

Carvill et al. Lemke et al. Lesca et al.

2014

First Report on Treatment with Memantine

Pierson et al.

in a Gain-of-Function case

2015

Delineation of the Speech Phenotype

Turner et al.

2019

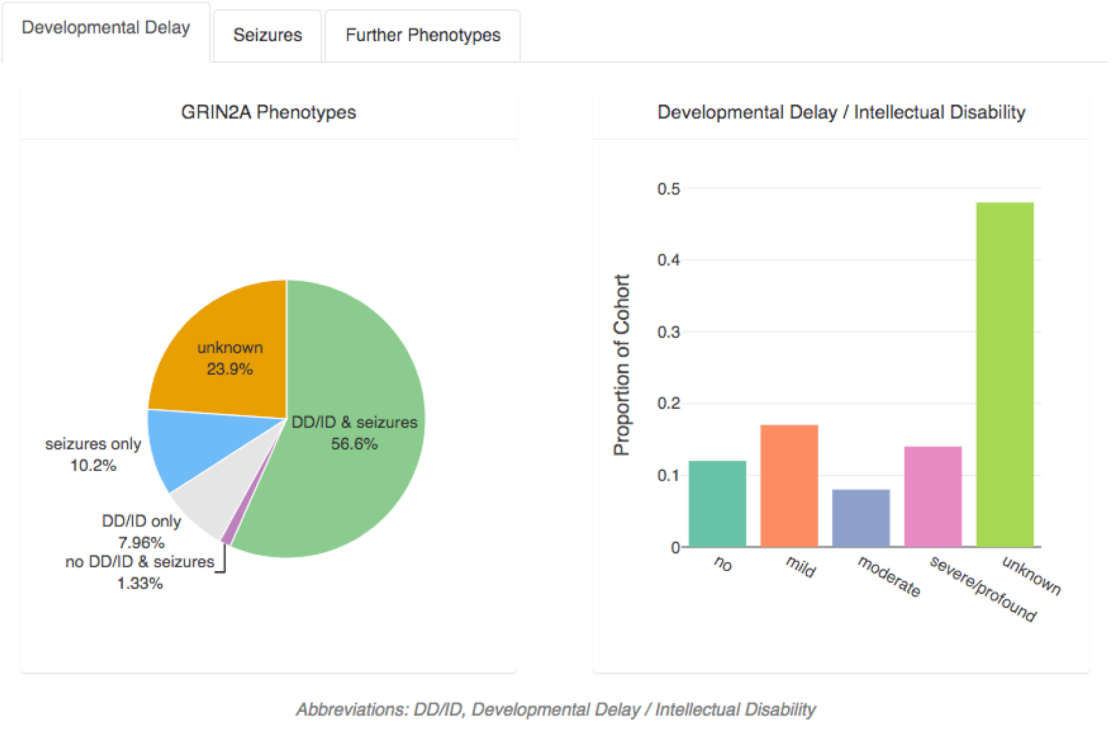
Comprehensive Genotype-Phenotype Correlation

Strehlow et al.

GRIN2A-related Disorder

GRIN2A-related disorder is characterized by either mild-to-profound developmental delay / intellectual disability in two thirds of affected individuals. Other common manifestations are speech disorders, epilepsy, muscular hypotonia, movement disorders, spasticity, feeding difficulties, and behavior problems. More details can be found on [GeneReviews](#).

Clinical Information from the GRIN Registry (226 individuals)



GRIN1

GRIN2A

GRIN2B

GRIN2D

Information on GRIN2A

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2010



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Turner et al.

2019



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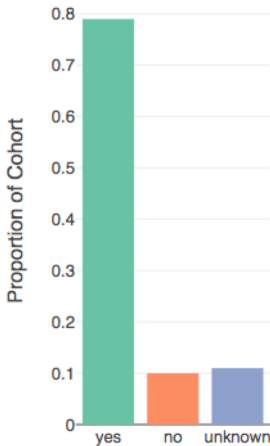
Clinical Information from the GRIN Registry (226 individuals)

Developmental Delay

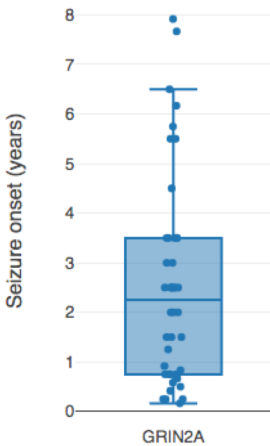
Seizures

Further Phenotypes

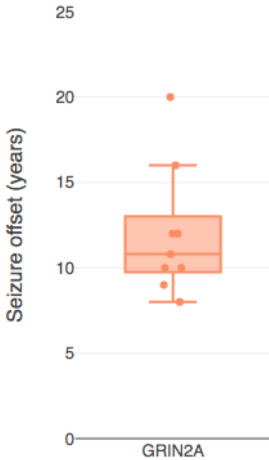
Seizures



Age at Seizure Onset



Age at Seizure Offset



GRIN1

GRIN2A

GRIN2B

GRIN2D

Information on GRIN2A

History of GRIN2A Research

2010

First Description of *de novo* Variants [Endele et al.](#)

in individuals with intellectual disability

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Delineation of the Phenotype [multiple](#)[Carvill et al.](#) [Lemke et al.](#) [Lesca et al.](#)

2014

First Report on Treatment with Memantine [Pierson et al.](#)

in a Gain-of-Function case

2015

Delineation of the Speech Phenotype [Turner et al.](#)

2019

Comprehensive Genotype-Phenotype Correlation [Strehlow et al.](#)

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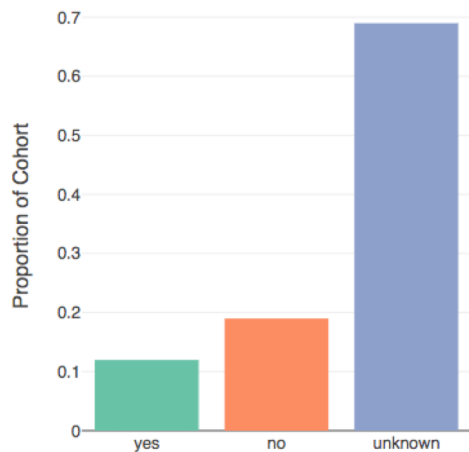
Clinical Information from the GRIN Registry (226 individuals)

Developmental Delay

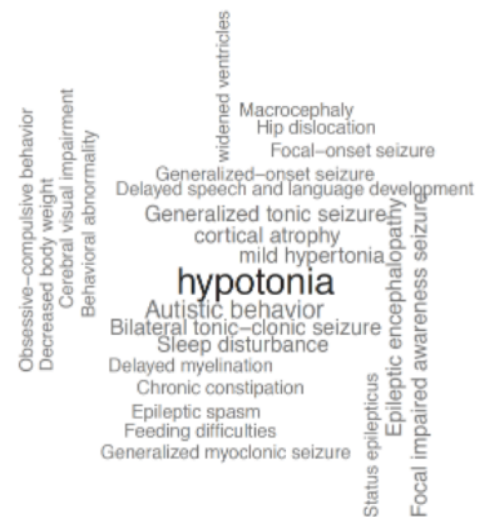
Seizures

Further Phenotypes

Movement Disorder



Further Phenotypes



Frequently described phenotypes in the GRIN Registry.
Further detailed phenotypes will be added soon.



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Clinical Characteristics

Genetically Related (Allelic) Disorders

Differential Diagnosis

Management

Genetic Counseling

Resources

Molecular Genetics

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GRIN2A-Related Speech Disorders and Epilepsy

Kenneth A Myers, MD, PhD, FRCP, and Ingrid E Scheffer, FAA, FAHMS, FRACP, MBBS, PhD.

[Author Information](#)

Initial Posting: September 29, 2016.

Estimated reading time: 22 minutes

Summary

Go to:

Clinical characteristics. *GRIN2A*-related speech disorders and epilepsy are characterized by speech disorders in all affected individuals and a range of epilepsy syndromes present in about 90%. Severe speech disorders observed can include dysarthria and speech dyspraxia, and both receptive and expressive language delay/regression; more mildly affected individuals may display subtly impaired intelligibility of conversational speech. Epilepsy features include seizure onset usually between ages three and six years, focal epilepsy with language and/or global developmental regression, and electroencephalogram (EEG) showing continuous spike-and-wave discharges in sleep or very active centrotemporal discharges. Seizure types include seizures associated with aura of perioral paresthesia, focal or focal motor seizures (often evolving to generalized tonic-clonic), and atypical absence seizures. Epilepsy syndromes can include: Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS), childhood epilepsy with centrotemporal spikes (CECTS), atypical childhood epilepsy with centrotemporal spikes (ACECTS), [autosomal dominant](#) rolandic epilepsy with speech dyspraxia (ADRES), and infantile-onset epileptic encephalopathy.

Diagnosis/testing. The diagnosis of a *GRIN2A*-related speech disorder and epilepsy is established in a [proband](#) by the identification of a *GRIN2A* [heterozygous pathogenic variant](#) on [molecular genetic testing](#).

Management. *Treatment of manifestations:* Significant speech/language deficits require therapy from a speech pathologist. Seizures should be treated with antiepileptic drugs (AEDs). Many different AEDs may be effective, and no one medication has been demonstrated to be effective specifically for these disorders.

Prevention of secondary complications: Monitoring for possible adverse effects of AEDs.

Surveillance: Developmental surveillance in all affected children; routine monitoring of speech and language by a speech pathologist should be considered for all children, particularly those diagnosed before reaching school age.

Agents/circumstances to avoid: In individuals with ECSWS, phenytoin, barbiturates and carbamazepine should be avoided as they are rarely effective, may worsen the EEG, and have negative effects on neuropsychological outcomes.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives in order to identify as early as possible those who would benefit from prompt evaluation for speech disorders and/or seizures and institution of treatment.

<https://per.broadinstitute.org/>

PER viewer

Home

PER identification

About

Video-Tutorials

PER viewer

Explore pathogenic variant enriched regions (PERs) across genes and gene families

Gene search

Submit

PER viewer is a tool for missense variant interpretation. Conserved amino acids among gene-family members are enriched with patient variants and constrained from variants in the general population, here we provide a statistical framework that is able to identify PERs across genes and gene families.

Family

● 1333

Choose Plot

Whole Family

GRIN2B

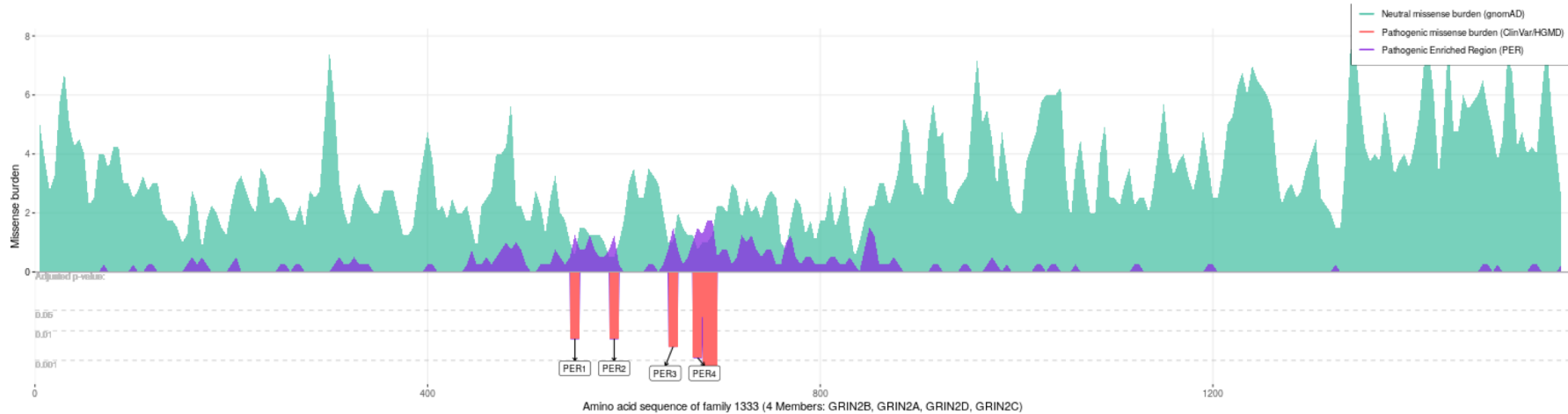
GRIN2A

GRIN2D

GRIN2C

Missense burden analysis

Paralog Conservation



PERs main Features

Browse sequence

Index	GRIN2B	GRIN2A	GRIN2D	GRIN2C	Gene:Disease	per.tag
All	All	1088	All	All	All	All
1156	R_1092	R_1088	A_1089	R_1020	N/A	

Family

● 1333

Choose Plot

Whole Family

GRIN2B

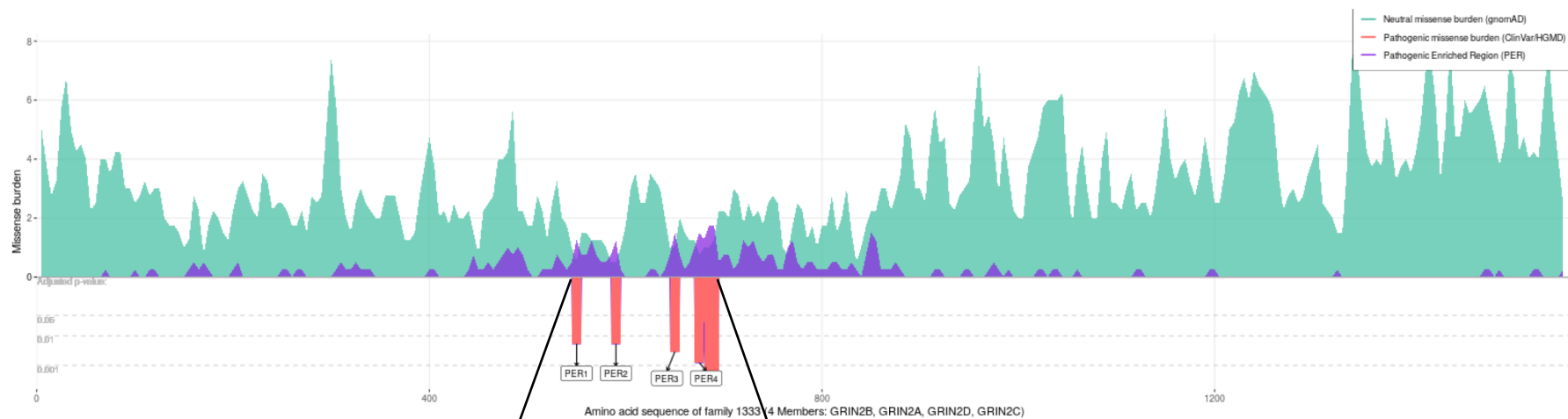
GRIN2A

GRIN2D

GRIN2C

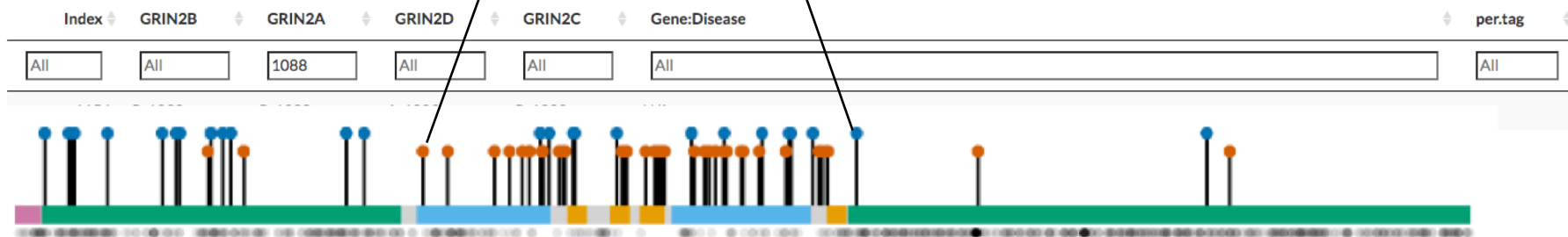
Missense burden analysis

Paralog Conservation



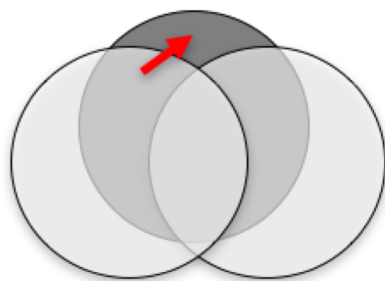
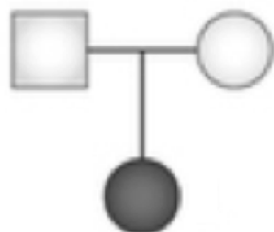
PERs main Features

Browse sequence

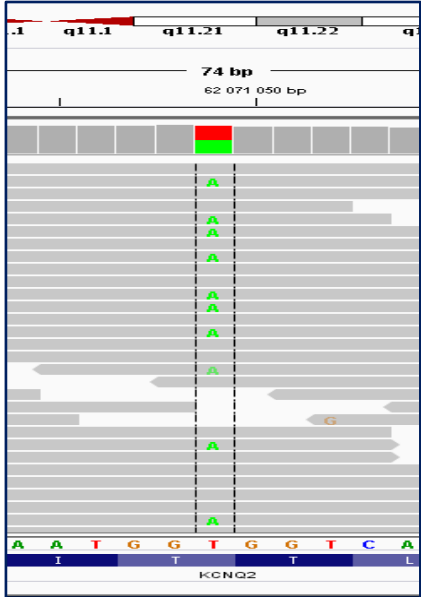
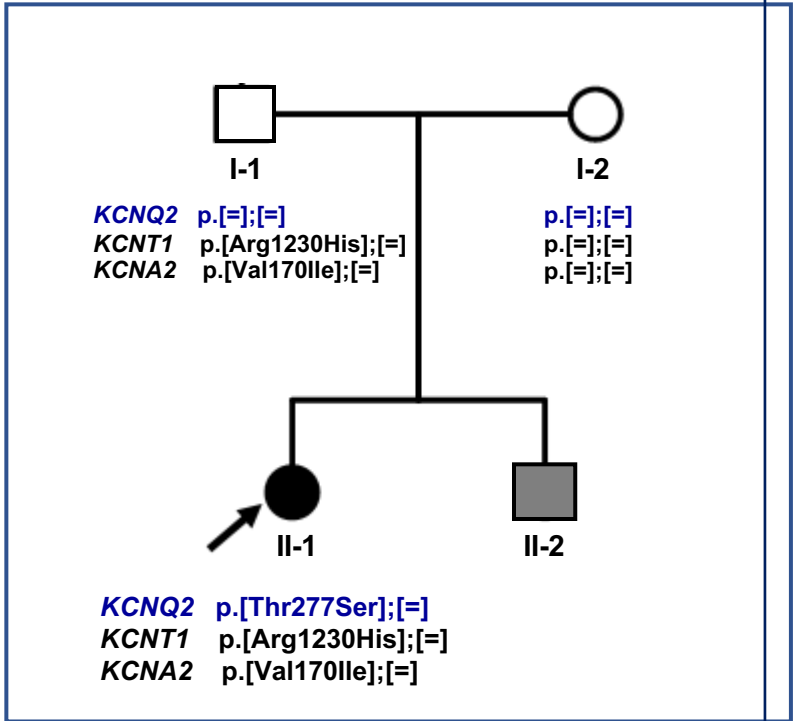


Mutacje *de novo*

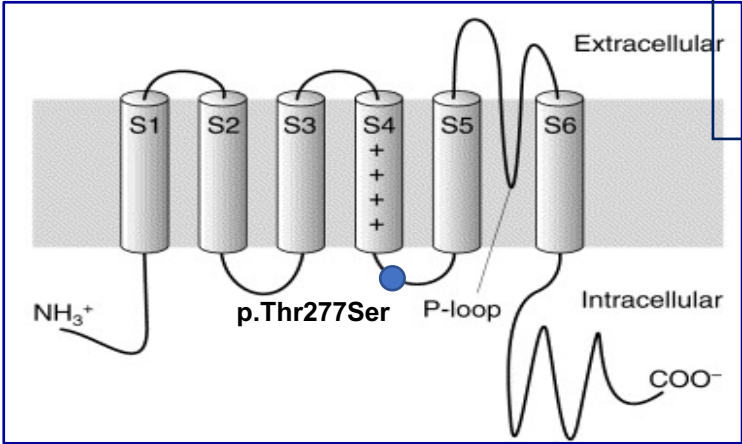
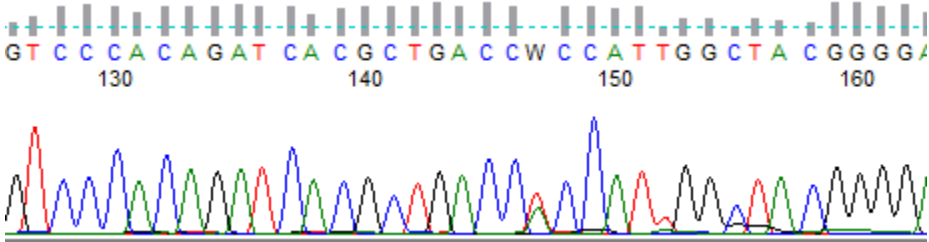
analiza *triosów*



warianty
heterozygotyczne
nie występując u rodziców

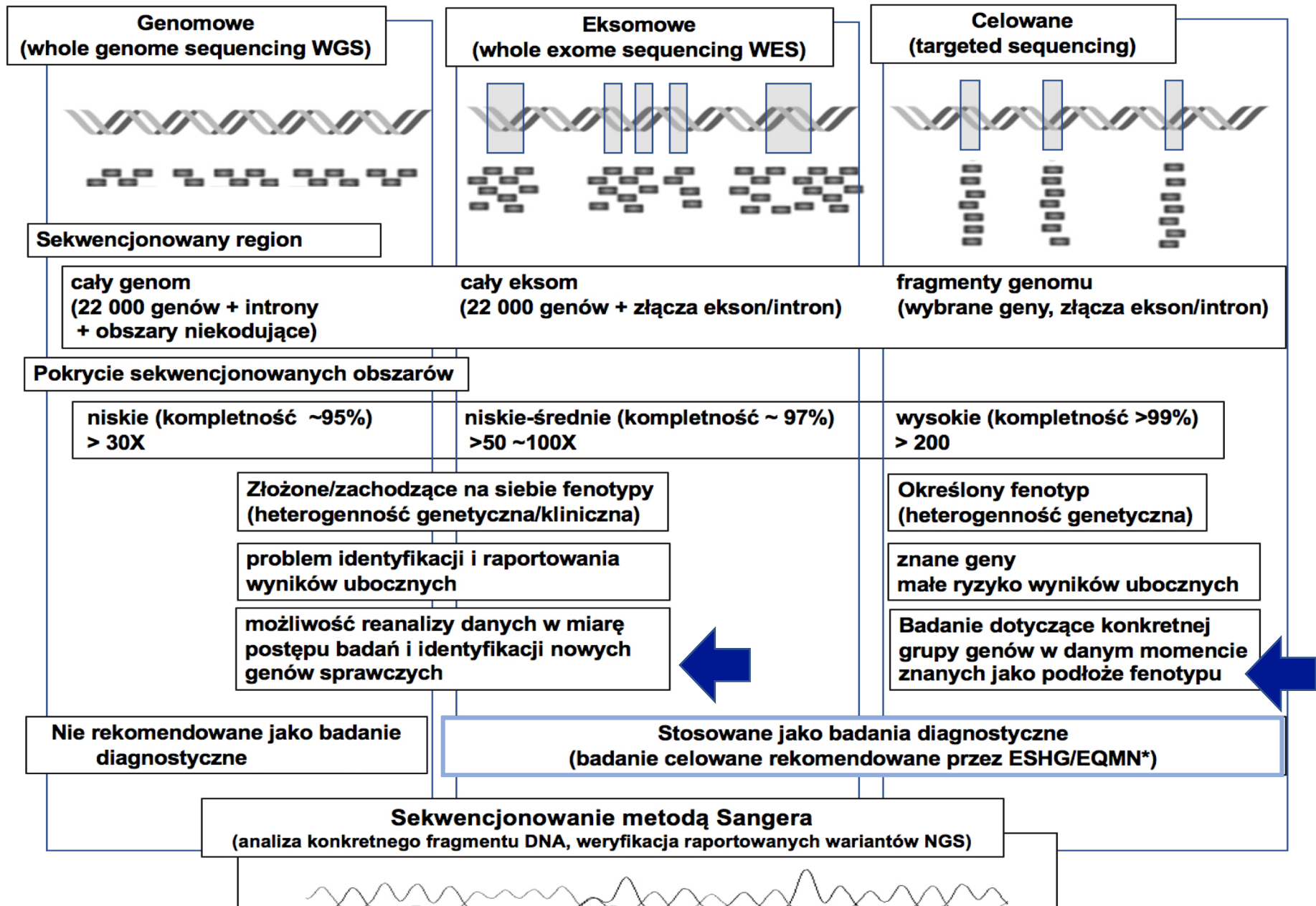


c.829A>T
 p.Thr277Ser



KCNQ2 zależna wczesnodziecięca encefalopatia padaczkowa

Sekwencjonowanie następnej generacji (NGS)



Dane kliniczne

**wydajność
diagnostyczna**

EEG

Niska

4%

Metabolism

5%

<16%

MRI

Niska

Niska

Karyotyp

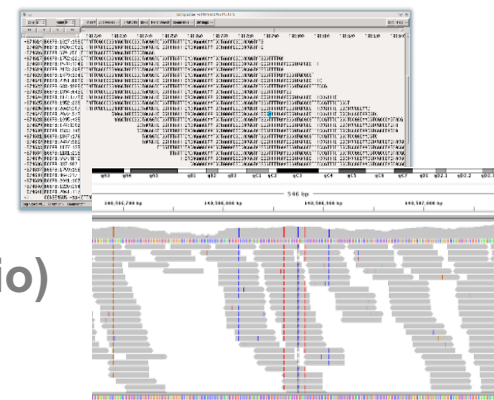
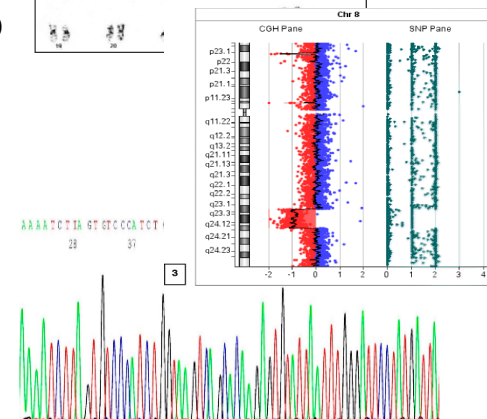
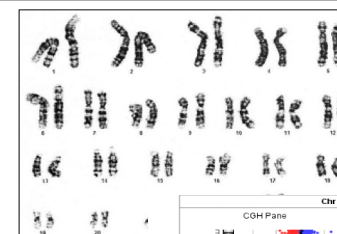
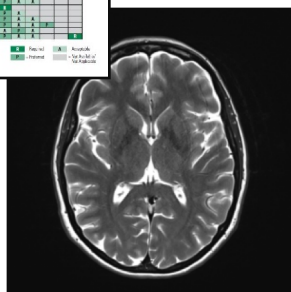
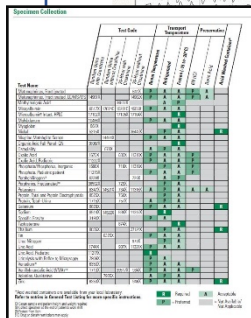
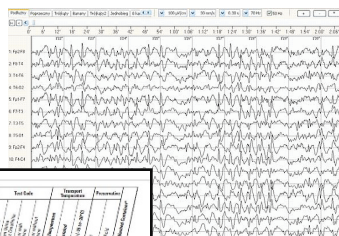
Array

Sanger

Panel

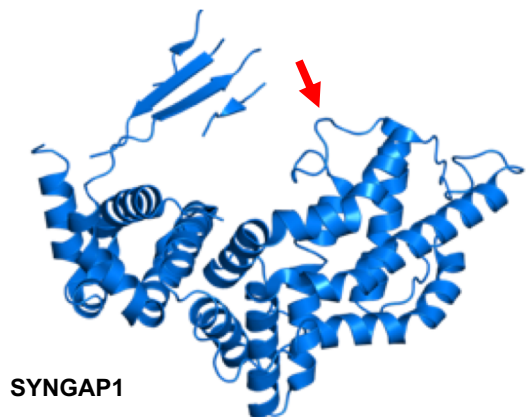
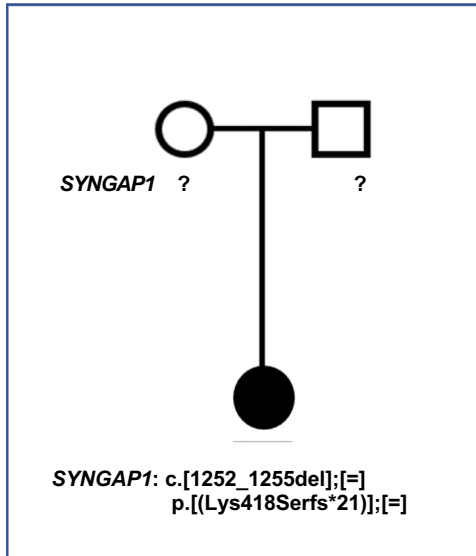
WES

(WES Trio)

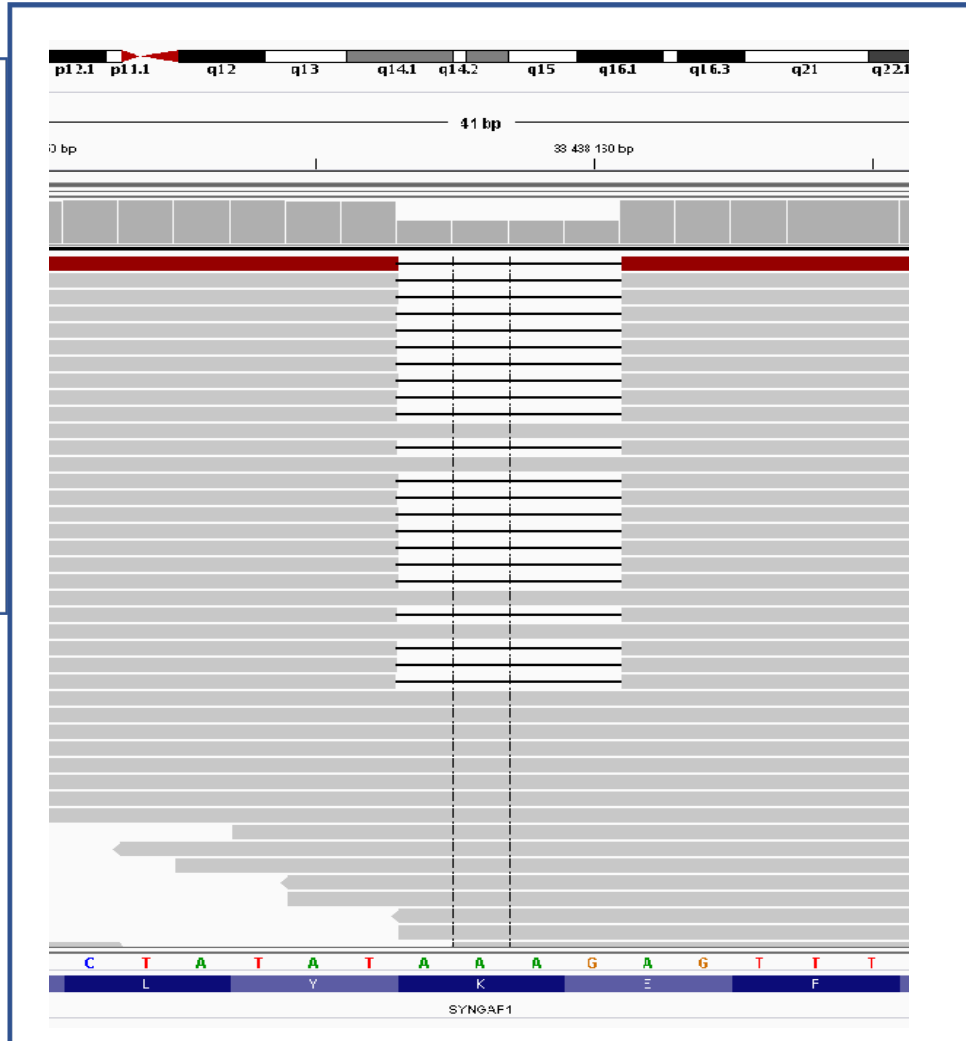


Encefalopatia padaczkowa

padaczka z napadami nieświadomości i miokloniczno-atonicznymi
opóźniony rozwój psychoruchowy



SYNGAP1



SYNGAP1: c.[1252_1255del];[=]
p.[(Lys418Serfs*21)];[=]

SYNGAP1

(Mental retardation, autosomal dominant 5; OMIM 612621)

MENTAL RETARDATION, AUTOSOMAL DOMINANT 5; MRD5

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
6p21.32	Mental retardation, autosomal dominant 5	612621	AD	3	SYNGAP1	603384

Clinical Synopsis

Phenotypic Series

PheneGene Graphics



INHERITANCE

- Autosomal dominant

HEAD & NECK

Head

- Microcephaly (in some patients) ⓘ

Neck

- Torticollis (in some patients)

NEUROLOGIC

Central Nervous System

- Hypotonia
- Delayed development
- Mental retardation, mild to severe
- Developmental regression
- Seizures
- EEG abnormalities
- Developmental regression
- Epileptic encephalopathy (in some patients)
- Normal brain MRI or CT scan

Behavioral/Psychiatric Manifestations

- Autism spectrum disorder
- Behavioral abnormalities

MISCELLANEOUS

- Onset in first years of life
- Most mutations occur de novo

MOLECULAR BASIS

- Caused by mutation in the synaptic Ras GTPase activating protein 1 gene (SYNGAP1, [603384.0001](#))

▲ Close

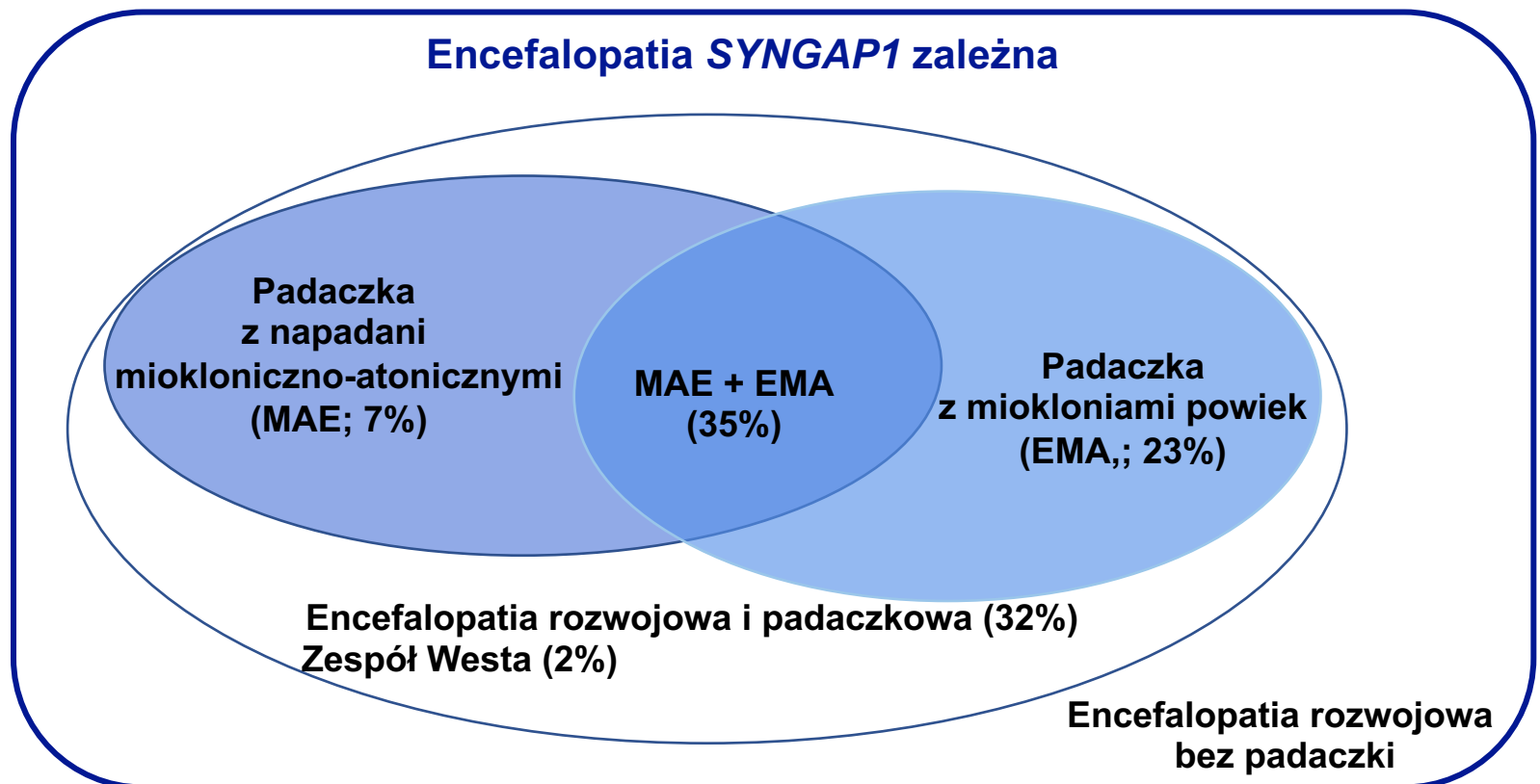
Contributors:
Cassandra L. Kniffin - updated :
09/22/2016
Creation Date:
Cassandra L. Kniffin : 2/11/2009
Edit History:
carol : 08/23/2017

SYNGAP1

- 2009; identyfikacja mutacji patogennych
niezespółowa niepełnosprawność intelektualna,
zaburzenia ze spektrum autyzmu

(Mental retardation, autosomal dominant 5; OMIM 612621)

- 2013; podłoże encefalopatii padaczkowej i rozwojowej



Klinicysta (decyzja o badaniu)

NGS
panel / eksom*

Zidentyfikowane warianty genowe

Fenotyp

!

Klinicysta

Wytypowane dla fenotypu
warianty genowe

Adnotacja wariantów
Charakterystyka patogenności

Bazy danych
HGMD, ClinVar
ExAc, dbSNP
Lokalne bazy danych (dane własne)
Dane opublikowane.

Predykcja patogenności *in silico*
PolyPhen, MutationTaster, SIFT
Predykcja zaburzeń splicingu

Dane kliniczne
Dane własne

Klasyfikacja
wariantów

Badanie rodzinne
(dziedziczenie, kosegregacja z fenotypem)

Dodatkowe dane

!

Klinicysta

Patogenne

Potencjalnie
patogenne

O niejasnej
patogenności

?

Potencjalnie
niepatogenne

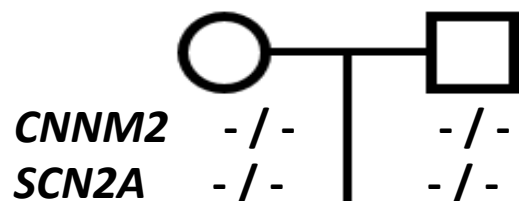
Niepatogenne

Sprawozdanie z analizy DNA

Klinicyści
(lek. kierujący
genetyk klin.)
+
Diagnosta

Diagnoza na podstawie wyników badań genetycznych

- 15 mż
- opóźniony rozwój psychoruchowy
- **brak napadów po osiągnięciu prawidłowego poziomu Mg**
- pacjent chodzi, sprawny ruchowo, ale cechy autystyczne, brak prawidłowego rozwoju mowy



CNNM2 - / -
SCN2A - / -

- / -
- / -

Hypomagnesemia, seizures, and mental retardation
(HOMGSMR)
[MIM:616418]



Early infantile epileptic encephalopathy 11 (EIEE 11)
[MIM MIM:613721]

-

raczej

SCN2A- zależna choroba neurorozwojowa
(autyzm, NI)



CNNM2 p.ILe514Phe / -

SCN2A. p.Arg1235Ter / -

* 182390

SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 2; SCN2A

Alternative titles; symbols

SODIUM CHANNEL, VOLTAGE-GATED, TYPE II, ALPHA SUBUNIT

SODIUM CHANNEL, BRAIN TYPE II, ALPHA SUBUNIT; NAC2

NAV1.2

SODIUM CHANNEL, NEURONAL TYPE II, ALPHA SUBUNIT-1, FORMERLY; SCN2A1,
FORMERLY

HGNC Approved Gene Symbol: [SCN2A](#)

Cytogenetic location: [2q24.3](#) *Genomic coordinates (GRCh38):* [2:165,239,413-165,392,303](#) (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
2q24.3	Developmental and epileptic encephalopathy 11	613721	AD	3
	Episodic ataxia, type 9	618924	AD	3
	Seizures, benign familial infantile, 3	607745	AD	3

PheneGene Graphics 

TEXT

▼ Description

The [SCN2A](#) gene encodes the voltage-gated sodium channel Na(v)1.2, which plays an important role in the initiation and conduction of action potentials. [SCN2A](#) is expressed in axon initiation segments and at nodes of Ranvier in myelinated nerve fibers during early development, and is later expressed in unmyelinated axons (summary by [Wolff et al., 2017](#)). 

In many cell types the sodium channel is responsible for generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large glycosylated alpha subunit (approximately 260 kD) and 2 smaller beta subunits (33-39 kD). See SCN1A ([182389](#)).

* 182390

SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 2;
SCN2A

Alternative titles; symbols

SODIUM CHANNEL, VOLTAGE-GATED, TYPE II, ALPHA SUBUNIT
SODIUM CHANNEL, BRAIN TYPE II, ALPHA SUBUNIT; NAC2
NAV1.2
SODIUM CHANNEL, NEURONAL TYPE II, ALPHA SUBUNIT-1, FORMERLY; SCN2A1,
FORMERLY

HGNC Approved Gene Symbol: [SCN2A](#)

Cytogenetic location: [2q24.3](#) Genomic coordinates (GRCh38): [2:165,239,413-165,392,303](#) (from NCBI)

Gene-Phenotype Relationships

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	Episodic ataxia, type 9	618924	AD	3
	Seizures, benign familial infantile, 3	607745	AD	3

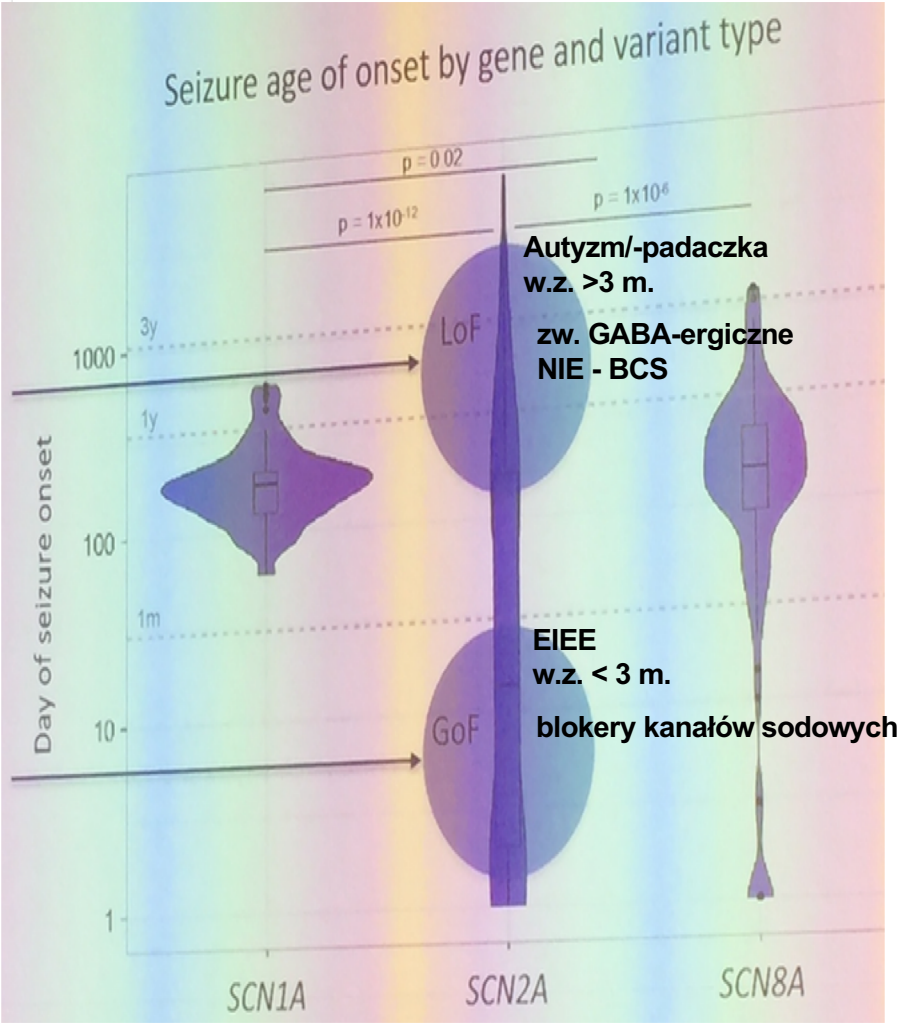
PheneGene Graphics 

TEXT

▼ Description

The [SCN2A](#) gene encodes the voltage-gated sodium channel Na(v)1.2, which plays an important role in the initiation and conduction of action potentials. [SCN2A](#) is expressed in axon initiation segments and at nodes of Ranvier in myelinated nerve fibers during early development, and is later expressed in unmyelinated axons (summary by [Wolff et al., 2017](#)). 

In many cell types the sodium channel is responsible for generation and propagation of action potentials, chiefly in nerve and muscle. Voltage-sensitive sodium channels are heteromeric complexes consisting of a large glycosylated alpha subunit (approximately 260 kD) and 2 smaller beta subunits (33-39 kD). See [SCN1A](#) ([182389](#)).



* 300005

METHYL-CpG-BINDING PROTEIN 2; **MECP2**

HGNC Approved Gene Symbol: **MECP2**

Cytogenetic location: **Xq28** Genomic coordinates (GRCh38): **X:154,021,572-154,097,716** (from NCBI)

Gene-Phenotype Relationships

Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
Xq28	Encephalopathy, neonatal severe	300673	XLR	3
	Intellectual developmental disorder, X-linked syndromic, Lubs type	300260	XLR	3
	Intellectual developmental disorder, X-linked, syndromic 13	300055	XLR	3
	Rett syndrome	312750	XLD	3
	Rett syndrome, atypical	312750	XLD	3
	Rett syndrome, preserved speech variant	312750	XLD	3
	{Autism susceptibility, X-linked 3	300496	XL	3

PheneGene Graphics ▾



TEXT

▼ Description

MECP2, which binds methylated CpGs, is a chromatin-associated protein that can both activate and repress transcription. It is required for maturation of neurons and is developmentally regulated (summary by [Swanberg et al., 2009](#)). [+](#)

[Home Page](#)[MECP2 database](#)[CDKL5 database](#)[FOXG1 database](#)[Useful information](#)[Submit mutations](#)[Contact us](#)

Note : We are revamping website of RettBASE for better access and display of mutation data. Although maximum care is taken to prevent disruption of data some links may be broken during this process. we apologize for any inconvenience caused.

Welcome

Welcome to the [RettSyndrome.org](#) (formerly the International Rett Syndrome Foundation, IRSF) *MECP2* Variation Database (RettBASE), hosted by the [Children's Hospital Westmead](#). Our goal is to gather and curate mutation data related to Rett syndrome, allowing the development of accurate prevalence data for disease-causing mutations, providing a catalog of polymorphisms, and potentially allowing more accurate phenotype-genotype correlations to be drawn. RettBASE encourages input from researchers, clinicians, families of individuals living with Rett syndrome and the general public, in order to enhance our knowledge and understanding of mutations causing Rett syndrome.

Quick navigation

[Mutation databases](#)[General Information](#)[How to cite RettBASE](#)[Submit mutations to RettBASE](#)[The people behind RettBASE](#)[Acknowledgements](#)

RettBASE is a freely-available resource for mutation and polymorphism data pertaining to Rett syndrome and other related clinical disorders. Mutation information is collected from published literature and from our collaborators who submit data directly to [us](#). All variant information is manually curated before inclusion in the database. Please see [links below](#) on how you can contribute to this database. We also welcome queries regarding mutation nomenclature on any variants listed in our databases or for any unpublished *MECP2*, *CDKL5* or *FOXG1* variants.

Please use the current page or <http://mecp2.chw.edu.au/> as your bookmark. We appreciate any feedback or suggestions regarding the databases, as well as any changes for the *MECP2* search engine. Please inform [us](#) of any bugs/broken links encountered.

Mutation databases

Please choose the gene and type of search required from the list below.

In the early years after the identification of *CDKL5* as a disease gene, patients were often classified as having a more severe form of Rett syndrome, the so-called Hanefeld variant. However, as more individuals with pathogenic *CDKL5* variants were identified, it was recognised that individuals with *CDKL5* mutations have a clinical picture that is very distinct from Rett syndrome, and most agree that it should be considered to be a distinct clinical entity, widely recognised as the CDKL5 Deficiency Disorder (see: PMID [22872100](#), [27528505](#) and [30928302](#))

Note regarding nomenclature of *MECP2* variants: variants are traditionally called from the e2 isoform (translation starting in exon 2). Unless otherwise specified in the nomenclature, all variants in RettBASE are named according to this convention (reference sequence [NM_004992](#)). RettBASE has since updated the *MECP2* database to include variants in e1 isoform (NM_001110792.1). Users can now change the transcript of interest in [list of all variants](#) to view variants in each transcript. The variant and proband pages have also been updated to reflect variant nomenclature in both transcripts. For information regarding reference sequence for *MECP2*, please visit our [reference sequence](#) page. Also please see our [nomenclature](#) section for general guidelines for mutation nomenclature. Nomenclature of mutations in exon 3 and exon 4 will differ by 12 amino acids between the two isoforms (e.g. p.R306C or p.Arg306Cys in isoform e2 is equivalent to p.R318C or p.Arg318Cys in isoform e1). cDNA nomenclature will differ by 36 nucleotides.

[Home Page](#)
[MECP2 database](#)
[CDKL5 database](#)
[FOXP1 database](#)
[Useful information](#)
[Submit mutations](#)
[Contact us](#)

MECP2 Variant List

Transcript selected : NM_001110792.1

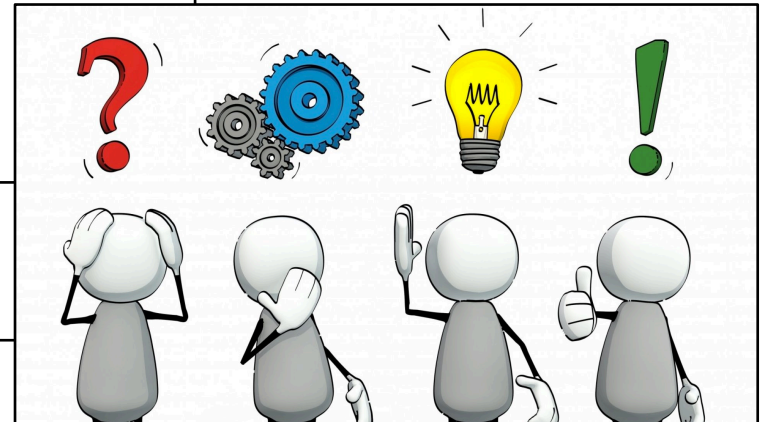
Change Transcript :

[Update](#)

Nucleotide change NM_001110792.1	Genomic name NC_000023.10:	Protein change NP_001104262	Type of sequence change	Domain change	Pathogenicity	Phenotype	Frequency	View record
c.-235G>T	g.153363357C>A		Missense	5'UTR	Polymorphism not causing disease	Not Rett synd.	1	View details
c.-46_-45delGC	g.153363167_153363168delGC	p.(=)	5'UTR variation	5'UTR	Unknown	Not Rett synd.	1	View details
c.-27_-26delAG	g.153363148_153363149delICT	p.(=)	5'UTR variation	5'UTR	Unknown	Not Rett synd.	1	View details
c.-27_-26delinsTT	g.153363148_153363149delinsAA	p.(=)	5'UTR variation	5'UTR	Unknown	Not Rett synd.	1	View details
c.-8_62+5419del	g.153357642_153363130del		exon deletions	N-term	Mutation associated with disease	Rett syndrome-Not certain	14	View details
c.-7_62del	g.153363061_153363129del	intronic variant	frameshift insertion or deletion	N-term	Unknown	Rett syndrome-Not certain	2	View details
c.-7_62del	g.153363061_153363129del	p.?	large deletion	N-term	Mutation associated with disease	Rett syndrome-classical	4	View details
c.*487G>C	g.153295331C>G		3'UTR variation	3'UTR	Polymorphism not causing disease	Not Rett synd.	1	View details
c.[1001C>T;1035G>T]	g.[153296314G>A;153296280C>A]	p.?	Missense, silent	C-term	Unknown	Rett syndrome-Not certain	1	View details
c.[626C>T;710C>T]	g.[153296689G>A;153296605G>A]	p.?	Missense	Inter-domain region, TRD	Mutation associated with disease	Rett syndrome-Atypical	1	View details
c.*93G>A	g.153295725C>T	p.(=)	3'UTR variation	3'UTR	Polymorphism not causing disease	Not Rett synd.	4	View details
c.[1193_1233del41;1268_1276del9]	g.[153296082_153296122del41;153296039_153296047del9]	p.?	Frameshift insertion or deletion	C-term	Mutation associated with disease	Rett syndrome-Classical	1	View details

1. gen, wariant - obraz fenotypowy pacjenta
2. dziedziczenie
3. szczegółowy obraz kliniczny pacjenta
4. ewolucja objawów obserwowanych u pacjenta
5. dane rodowodowe

Pacjent



1. bazy danych
2. dane analiz bioinformatycznych
3. dane badań funkcjonalnych

Dane



**NGS
panel / eksom***

Zidentyfikowane warianty genowe

Fenotyp

**Wytypowane dla fenotypu
warianty genowe**

**Adnotacja wariantów
Charakterystyka patogenności**

Bazy danych
HGMD, ClinVar
ExAc, dbSNP
Lokalne bazy danych (dane własne)
Dane opublikowane.

Predykcja patogenności *in silico*
PolyPhen, MutationTaster, SIFT
Predykcja zaburzeń splicingu

**Dane kliniczne
Dane własne**

**Klasyfikacja
wariantów**

**Badanie rodzinne
(dziedziczenie, kosegregacja z fenotypem)**

Dodatkowe dane

Patogenne

**Potencjalnie
patogenne**

**O niejasnej
patogenności**

**Potencjalnie
niepatogenne**

Niepatogenne

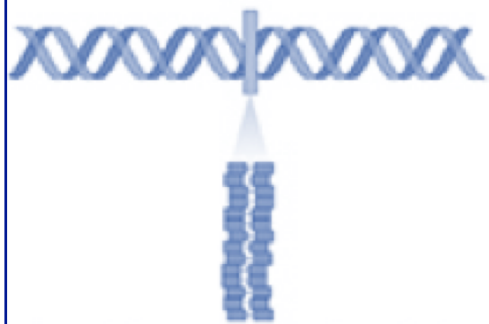
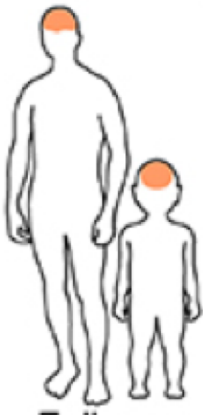
?

Sprawozdanie z analizy DNA



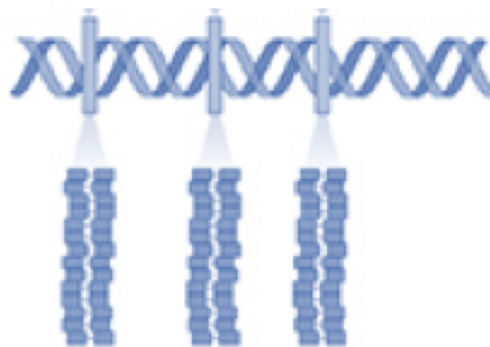
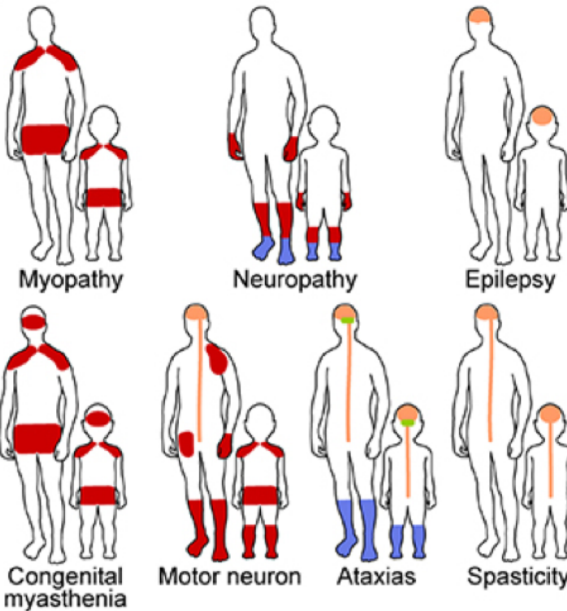
Choroby neurologiczne

choroby
o specyficznym obrazie klinicznym
(podejrzenie mutacji
w konkretnym genie)



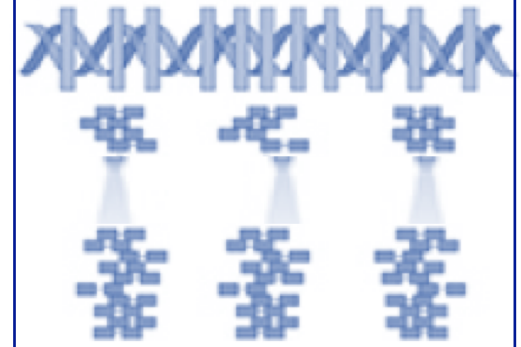
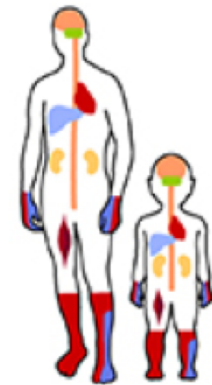
Gen

choroby o heterogennym
podłożu genetycznym



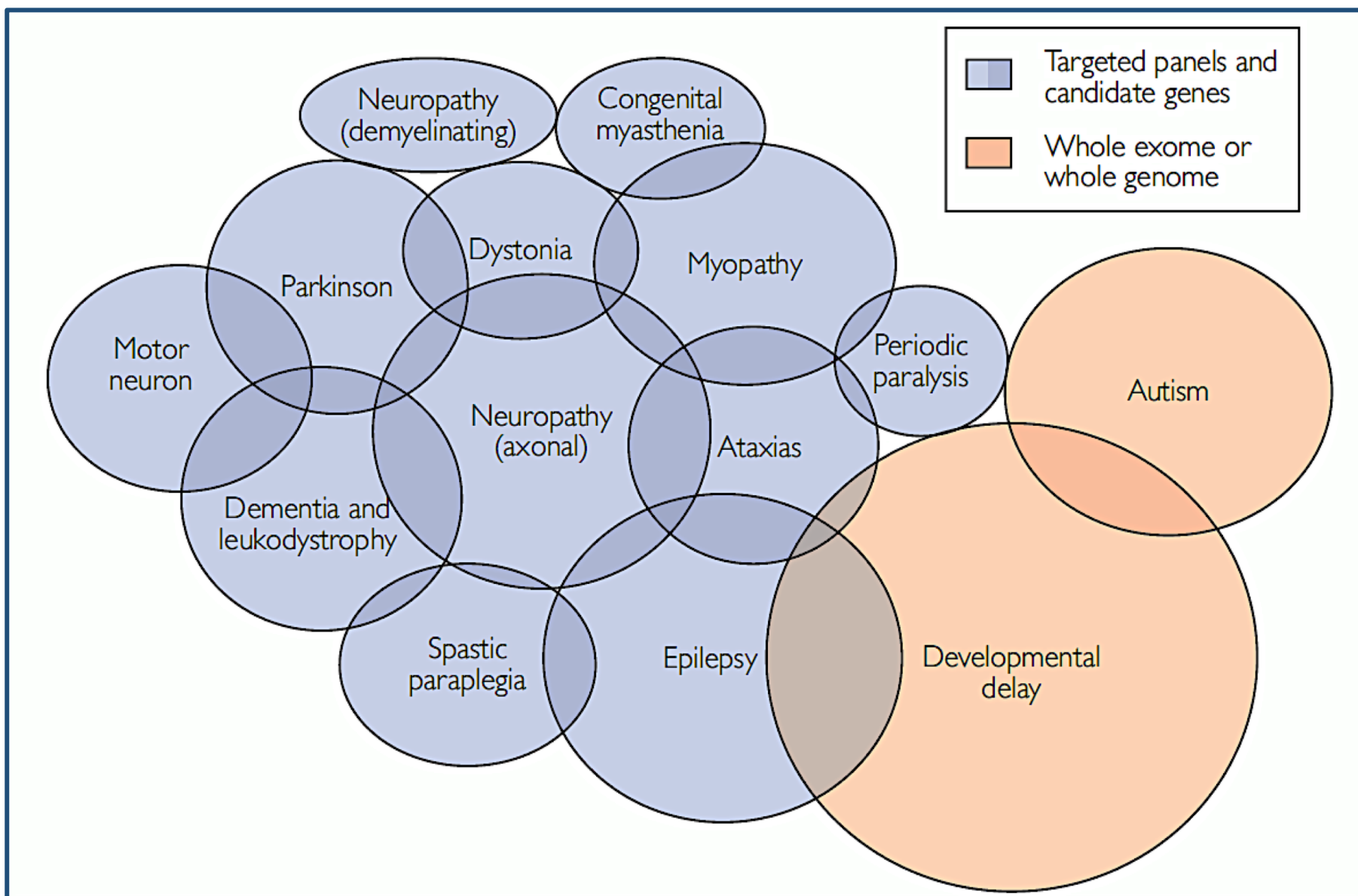
Panel genów

choroby o niespecyficznym
obrazie klinicznym



WES

Genetic testing in diverse mendelian neurologic disorders



NEXT GENERATION SEQUENCING

WGS

Whole genome sequencing



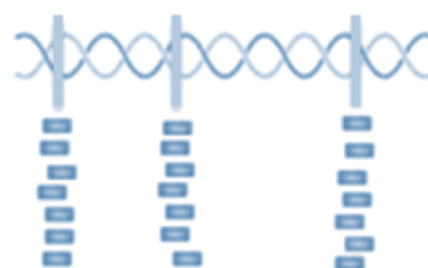
WES

Whole exome sequencing



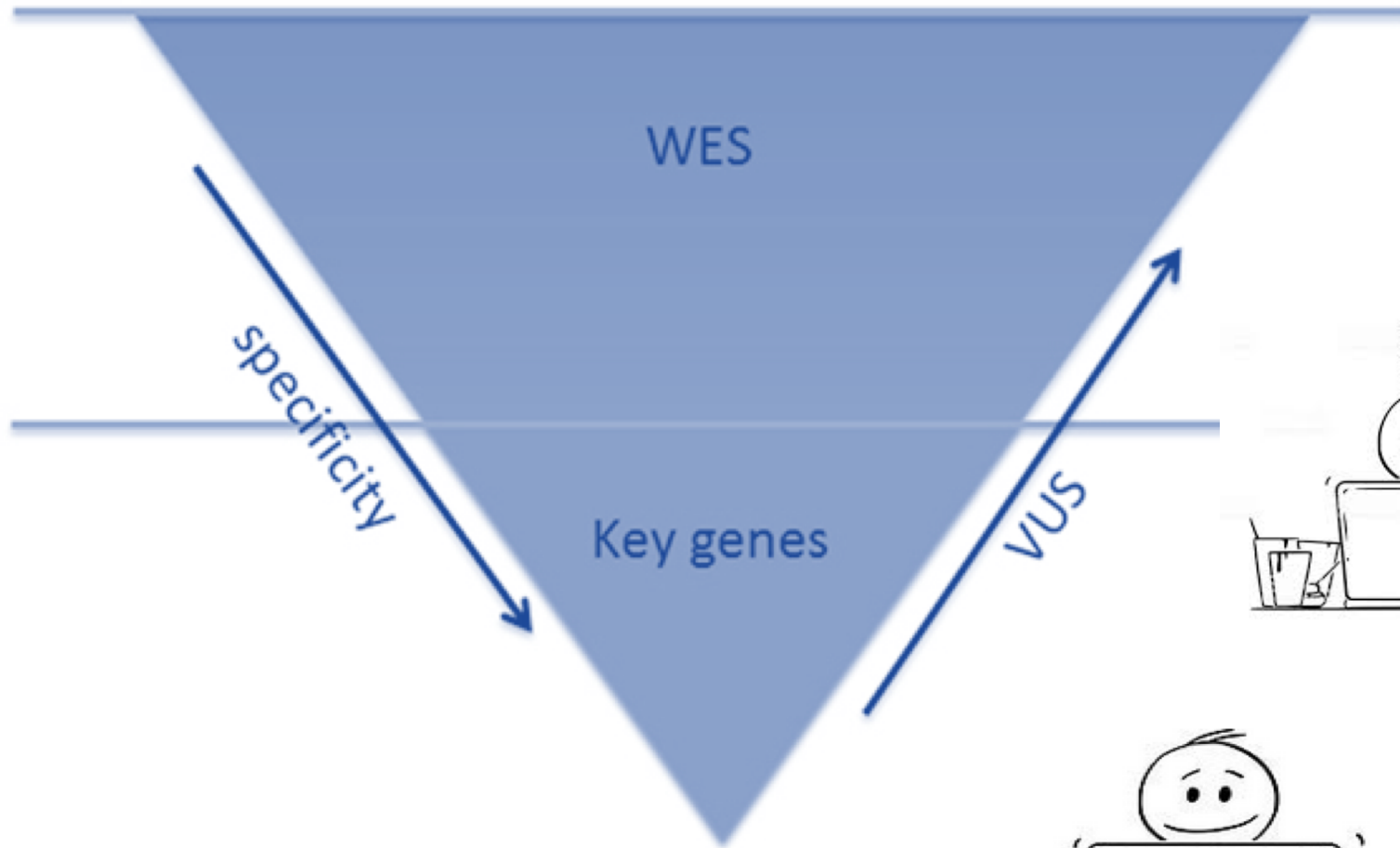
Panel

Targeted sequencing



Jesteśmy w takim momencie, gdy przeprowadzanie testów genomowych (panelowego, cało eksomowe czy nawet całogenomowego), biorąc pod uwagę względy techniczne, może okazać się tańsze niż sekwencjonowanie pojedynczego genu

Cechą tych podejść jest to, że uzyskiwane informacje często mają niepewne znaczenie.



„wyniki uboczne” – [„incidental finding”]

unsolicited findings



**w genach powiązanych
z diagnozowaną chorobą
ale nie fenotypem pacjenta**

secondary findings



**w genach niezwiązanych
z diagnozowaną chorobą**

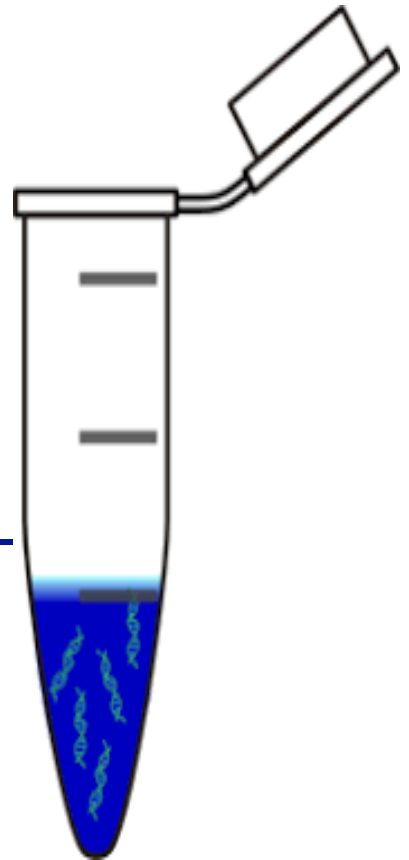
**Analiza panelu kluczowych genów minimalizuje
ryzyko wykrycia *secondary findings*.**

**Diagnostyka – analiza w celu identyfikacji defektu genetycznego
i wyjaśnienia podłoża określonego fenotypu (choroby) pacjenta**

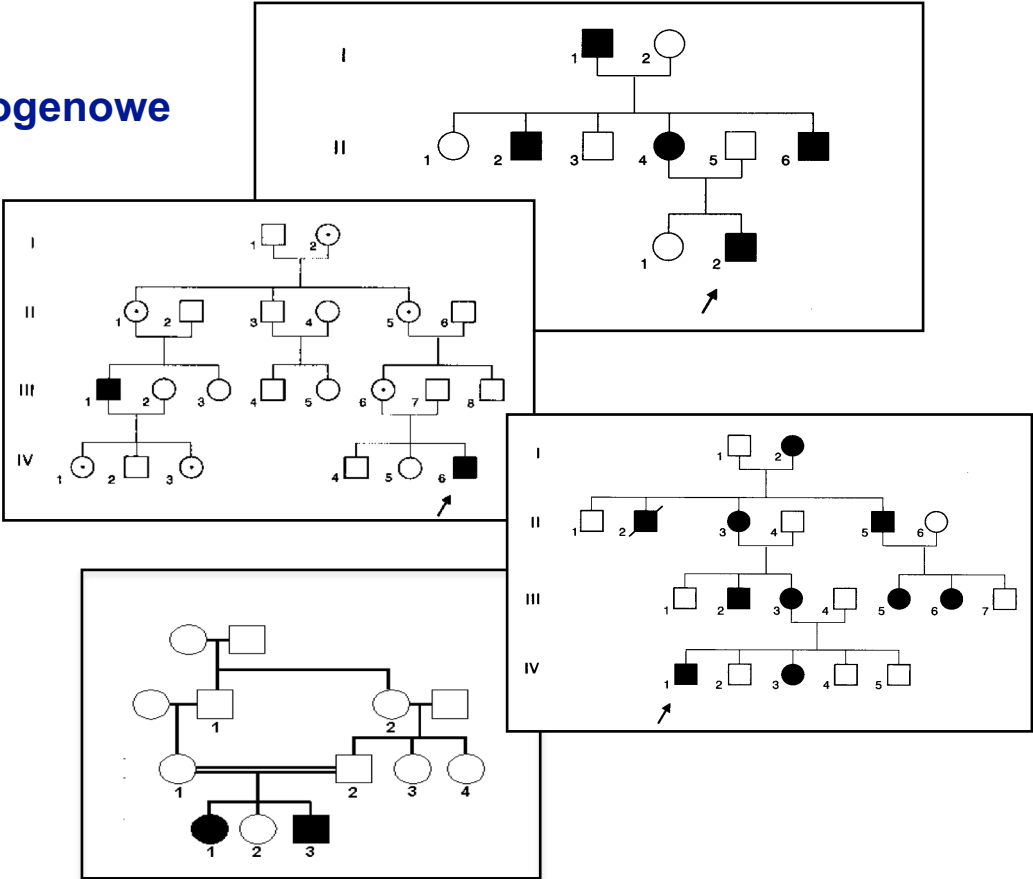
Genetyka medyczna

Diagnostyka a badania naukowe..

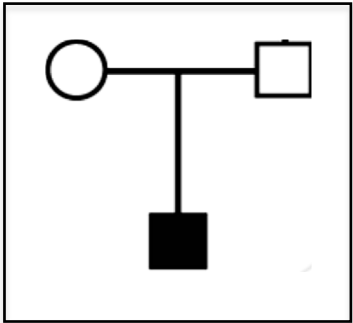
- **Badania naukowe** – poszukiwanie nowego gen powiązanego z daną chorobą w grupie pacjentów o podobnym fenotypie
- **Badanie diagnostyczne** – analiza w celu identyfikacji defektu genetycznego stanowiącego podłoże fenotypu



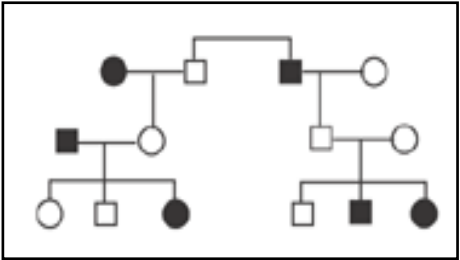
Choroby monogenowe



Mutacje dominujące *de novo*

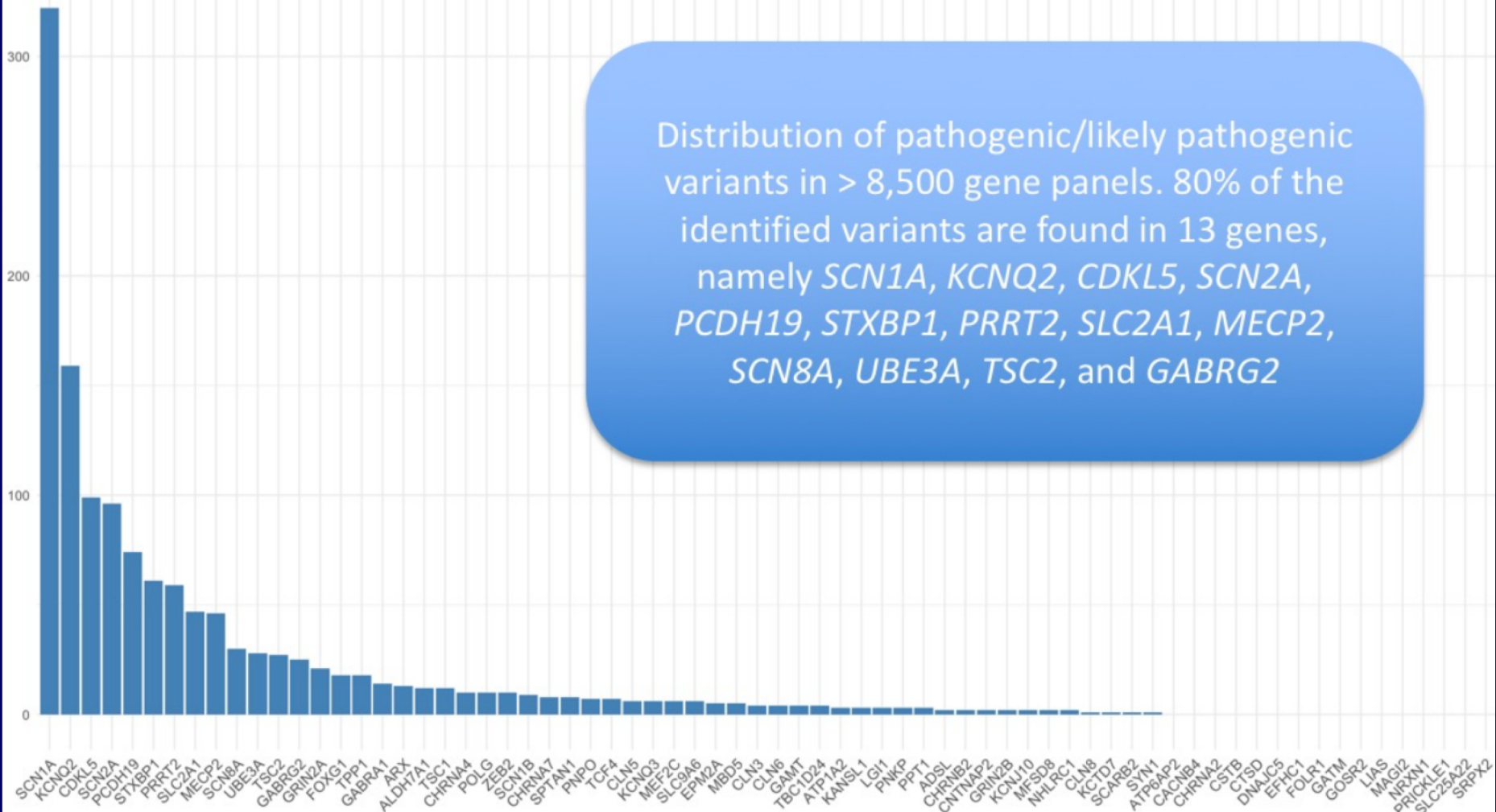


Choroby poligenowe / wieloczynnikowe

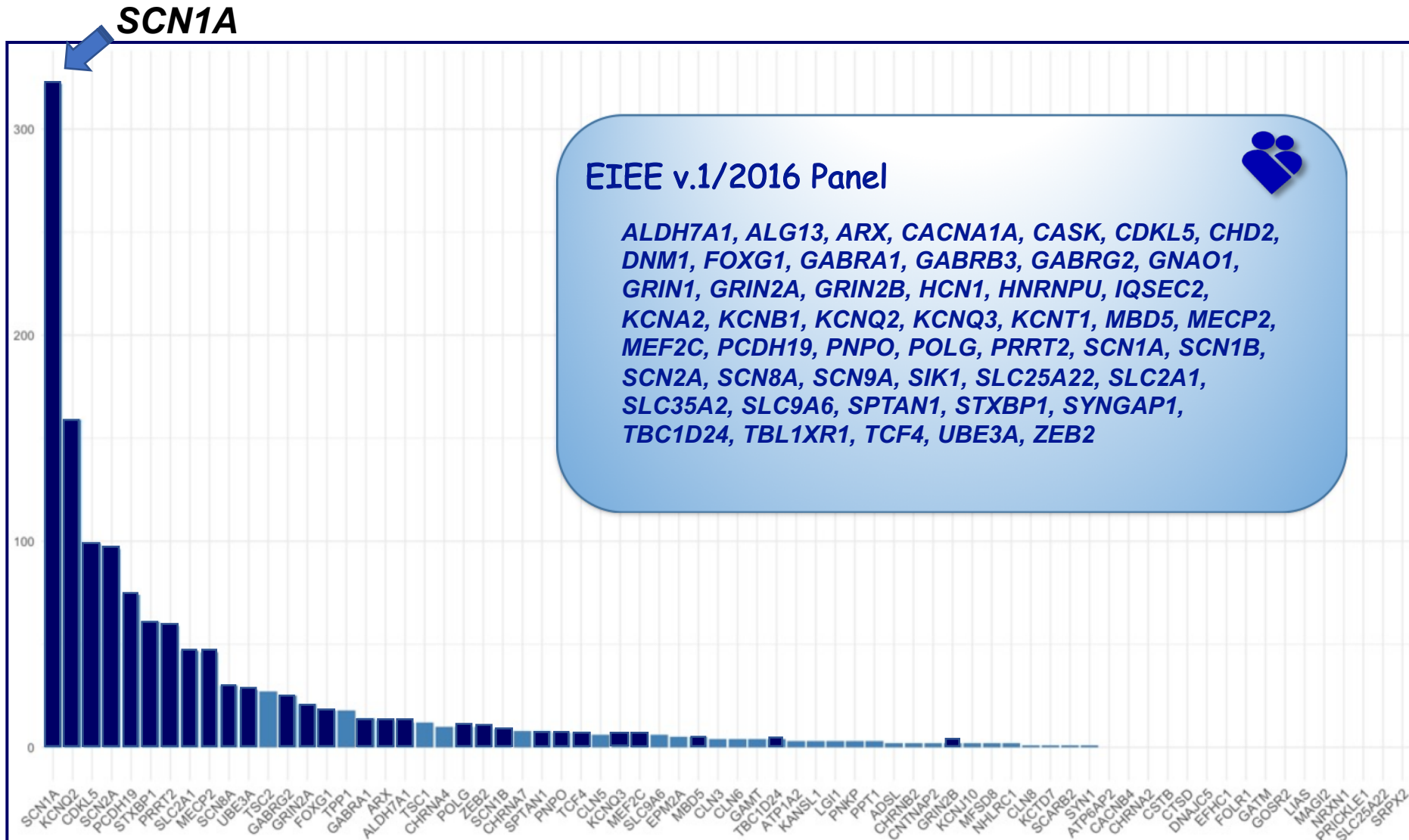


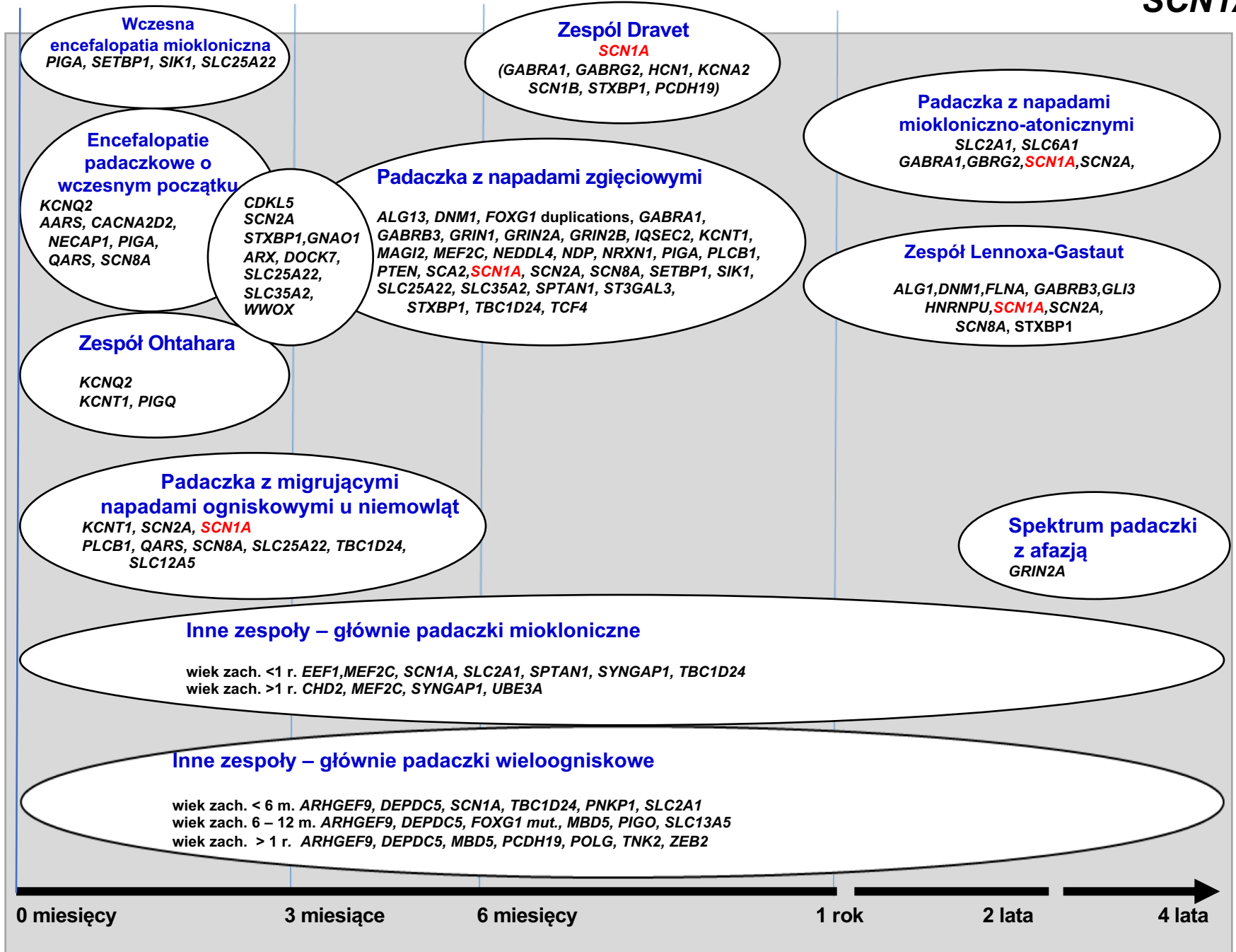
Encefalopatie padaczkowe

Wyniki analizy panelowej (70 genów) dla 8 565 pacjentów (Lindy i wsp. 2018)



Wyniki analizy panelowej (70 genów) dla 8 565 pacjentów (Lindy i wsp. 2018)





* 182389

SODIUM VOLTAGE-GATED CHANNEL, ALPHA SUBUNIT 1; SCN1A

Alternative titles; symbols

SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT
SODIUM CHANNEL, BRAIN TYPE I, ALPHA SUBUNIT; NAC1
NAV1.1

HGNC Approved Gene Symbol: **SCN1A**

Cytogenetic location: **2q24.3** *Genomic coordinates (GRCh38):* **2:165,984,640-166,149,160** (from NCBI)

Gene-Phenotype Relationships

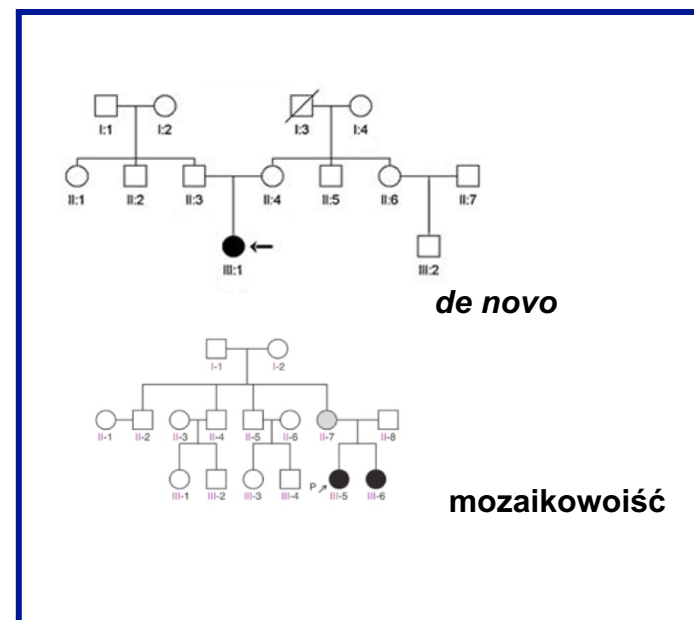
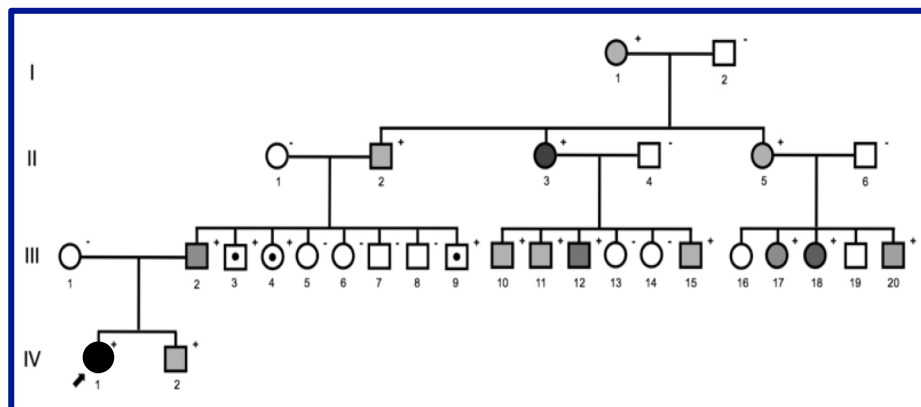
Location	Phenotype Clinical Synopses	Phenotype MIM number	Inheritance	Phenotype mapping key
2q24.3	Developmental and epileptic encephalopathy 6B, non-Dravet	619317	AD	3
	Dravet syndrome	607208	AD	3
	Febrile seizures, familial, 3A	604403	AD	3
	Generalized epilepsy with febrile seizures plus, type 2	604403	AD	3
	Migraine, familial hemiplegic, 3	609634	AD	3

Spektrum chorób związanych z mutacjami genu *SCN1A*

GEFSP2

DRVT

DEE 6B



Generalized epilepsy with febrile seizures plus, type 2; GEFSP2

Dravet Syndrome ; DRVT

Developmental and epileptic encephalopathy 6B, non-Dravet; DEE6B

Generalized epilepsy with febrile seizures plus, type 2; GEFSP2

Dravet Syndrome; DRVT

Developmental and epileptic encephalopathy 6B, non-Dravet; DEE6B

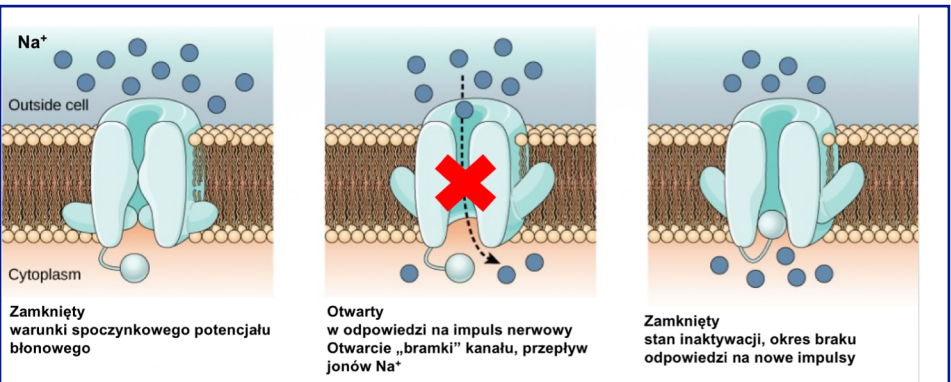
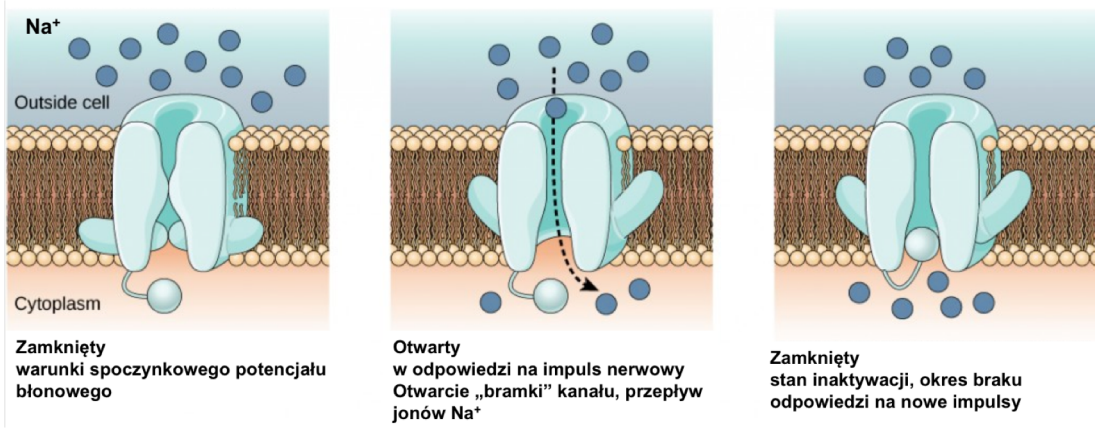
Neonatal developmental and epileptic encephalopathy with movement disorder and arthrogryposis (NDEEMA)

Developmental and epileptic encephalopathy (DEE) with MD (EIDEE/MD)

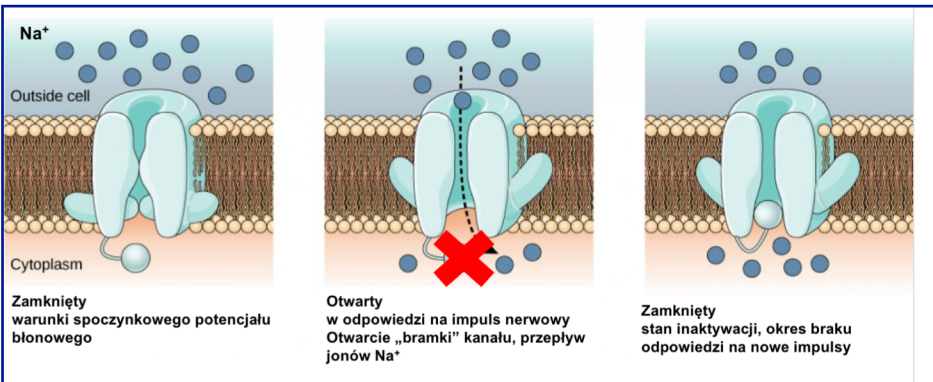
Developmental and epileptic encephalopathy (DEE) without MD

Familial Hemiplegic migraine (FHM3)

zależny od napięcia kanał sodowy (Na⁺)



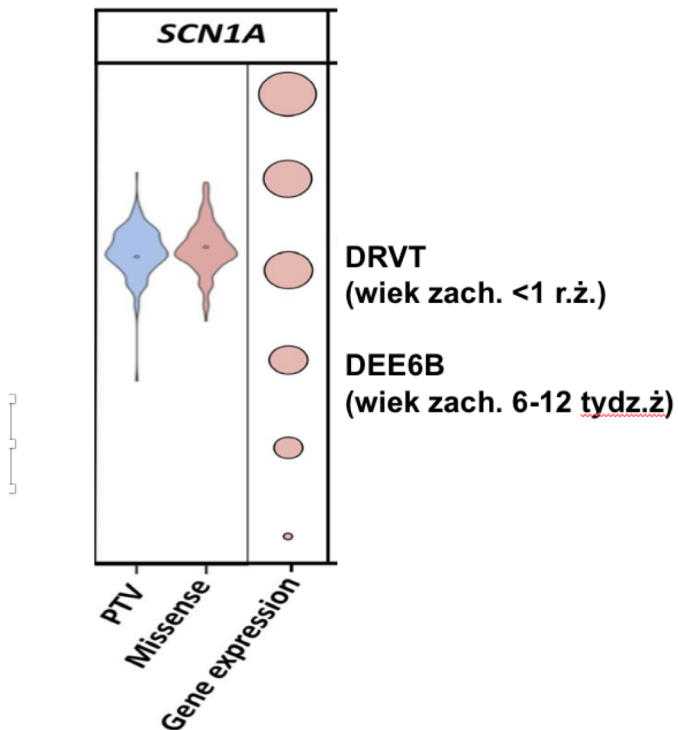
brak lub obniżony prąd sodowy
- utrata funkcji białak (LOF)
- zespół Dravet/GEFS+



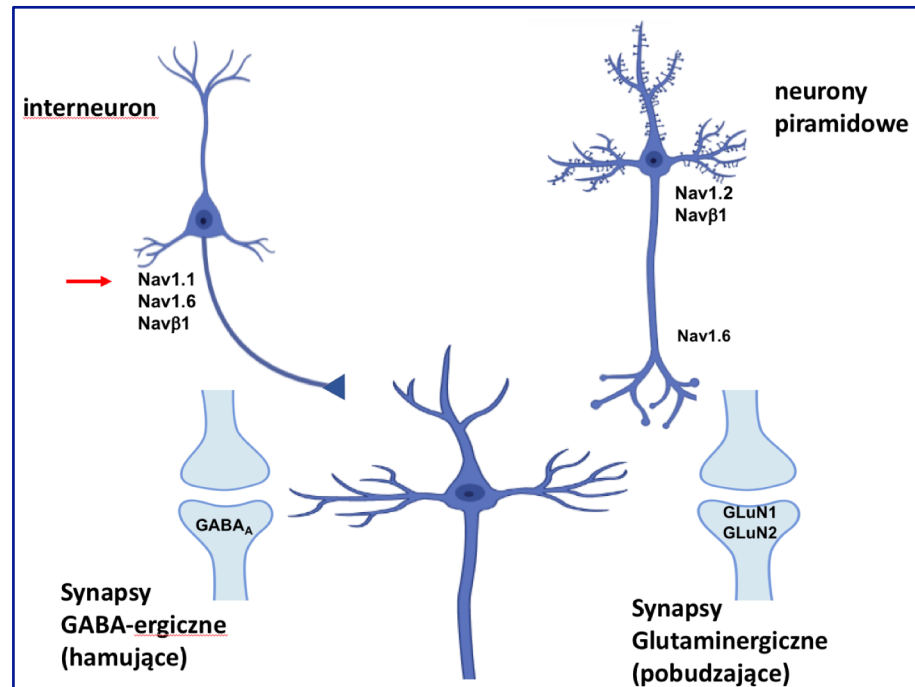
zaburzenie inaktywacji kanału;
podwyższony/przetrwały prąd sodowy
- zmiana/nabycie funkcji białka (GOF)
- FHM3, NDEEMA, EIDEE/MD, EIDEE

SCN1A – ZESPÓŁ DRAVET; DRVT

DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 6B, non-Dravet; DEE6B



SCN1A- zależne choroby, warianty GOF
SCN1A- zależne choroby, warianty LOF



Rozróżnienie wariantów GOF i LOF może być różnicowaniem sposobu terapii
Terapia zorientowana na warianty LOF jest przeciwwskazana dla GOF

* NDEEMA, EIDEE/MD – lekooporny zespół, pacjenci odpowiadają na leczenie SCB (sodium channel blockers), SCBs nie powodują pogorszenia

liczba pacjentów – NDEEMA 8+5 pub., EIDEE/MD 11+10 pub.; SCBs 8/9;4/6]

DEE – 1 pacjent karbamazepina/zmiana leczenia ident. mut *SCN1A*/powrót do SCBs

po pogorszeniu – kontrola napadów, NI w stopniu znacznym

Narzędzia on-line do predykcji GOF/LOF:

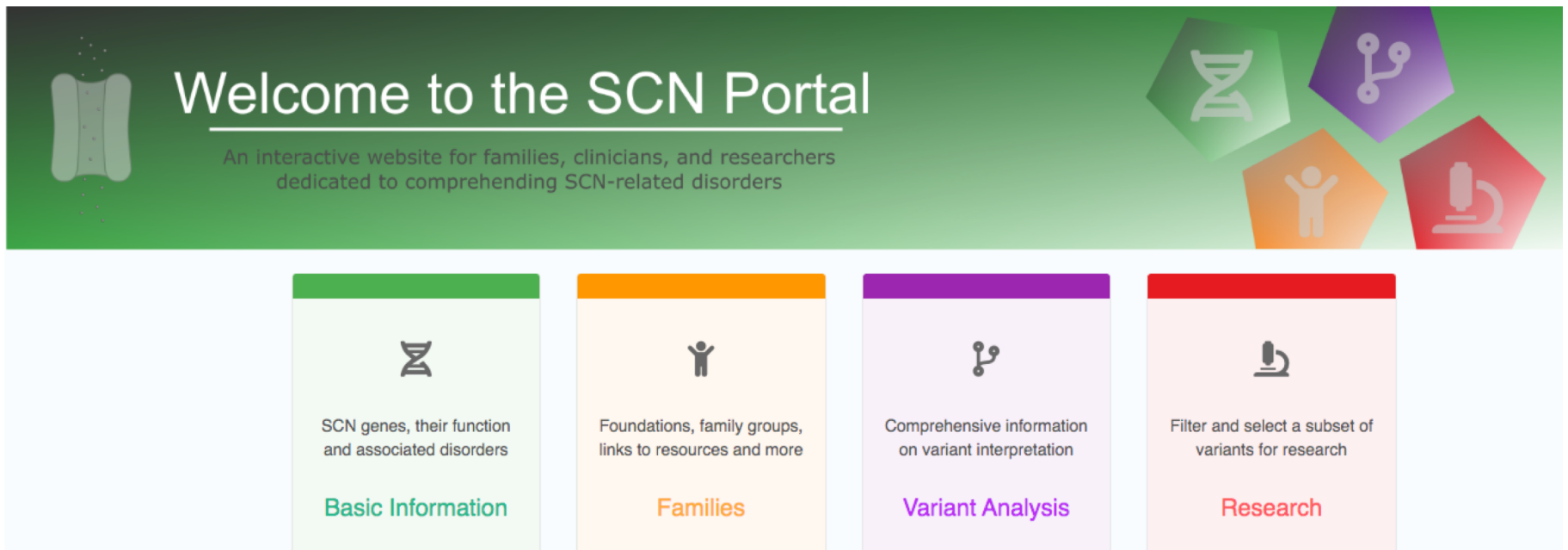
funNCion - Functional variant prediction in Na_vs and Ca_vs ion channels
analiza wariantów patogenne vs. Neutralne, LOF vs. GOF
(<https://funnc.shinyapps.io/shinyappweb/>)

The SCN1A-Epilepsy Prediction Model
(<https://scn1a-prediction-model.broadinstitute.org>)

(wymagany wiek zachorowania pacjenta !!!)

PER viewer

(<https://per.broadinstitute.org/>)



Welcome to the SCN Portal

An interactive website for families, clinicians, and researchers dedicated to comprehending SCN-related disorders

Basic Information	Families	Variant Analysis	Research
SCN genes, their function and associated disorders	Foundations, family groups, links to resources and more	Comprehensive information on variant interpretation	Filter and select a subset of variants for research

Analyse your variants

Enter variant

Select gene

SCN1A

cDNA Position

716

Ref

C

Alt

A

SEARCH

Amino Acid Position

239

Ref

ALA

Alt

ASP

SEARCH

Variant Consequence

MISSENSE

Variant Information

Gene: SCN1A

Transcript: ENST00000303395



Domain: D1: S4-S5-Linker

Amino Acid Position: 239

Amino Acid Change: Ala (A) - Asp (D)



Control variants: 0

gnomAD Allele Count at this aminoacid position: 0

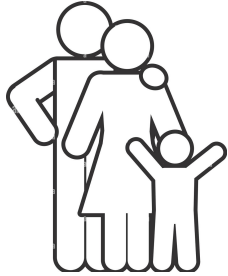
gnomAD Allele Frequency for this aminoacid exchange: 0



Clinical significance according to ClinVar 

No ClinVar variants available

To access variant click [here](#)



HGMD – **variant opisany**

(Na i wsp., 2020) – pacjent Early Inf-onset DEE (1 month < seizures onset < 3 months)

Dravet Syndrome (Likely Path.), seizure onset 90 day

GnomAD – **brak w próbie kontrolnej**

ACMG Classification – **Likely Pathogenic / Pathogenic**

Analiza Bioinformatyczna - **Patogenic (12 algorytmów)**

funNCion - Functional variant prediction in Na_vs and Ca_vs ion channels

analiza wariantów patogene vs. Neutralne, LOF vs. GOF

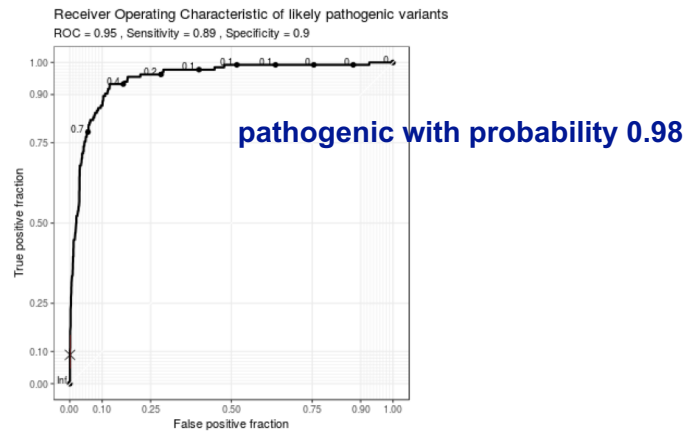
(<https://funnc.shinyapps.io/shinyappweb/>)

Pathogenicity prediction

You chose variant A239D in gene *SCN1A* in transcript(s) ENST00000303395;ENST00000423058;NM_001165963.1;NM_001202435.1 .

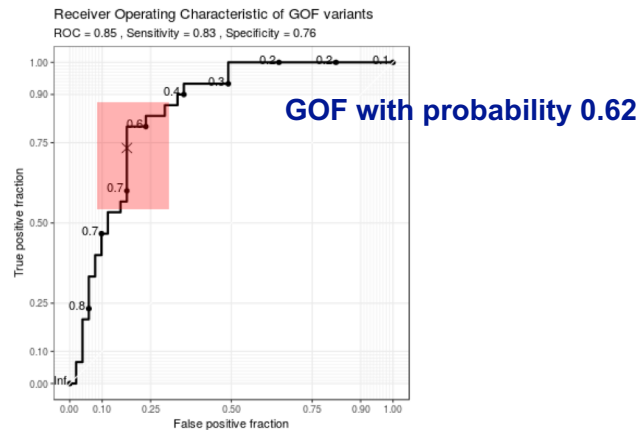
This variant is predicted to be pathogenic with a probability of 0.98 .

Other pathogenicity scores are CADD = 31 , MPC= 2.1 and PolyPhen= 1 . On the figure, you can see where your variant falls on the Receiver Operating Characteristic curve along with 95%-confidence intervals (red area).



Functional prediction

The variant you selected is predicted to be gain-of-function with a probability of 0.62 .

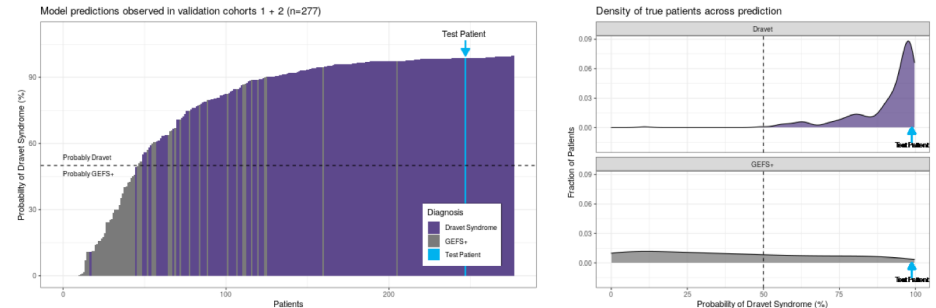


The SCN1A-Epilepsy Prediction Model

(<https://scn1a-prediction-model.broadinstitute.org>)

Test patient has 98.78 % probability of developing Dravet syndrome. However, this individual had a seizure onset at less than 4 months of age. Atypical phenotypes have been described in infants presenting at less than 4 months of age and alternative diagnoses including a profound phenotype with movement disorder (Sadleir et al. 2017) should be considered.

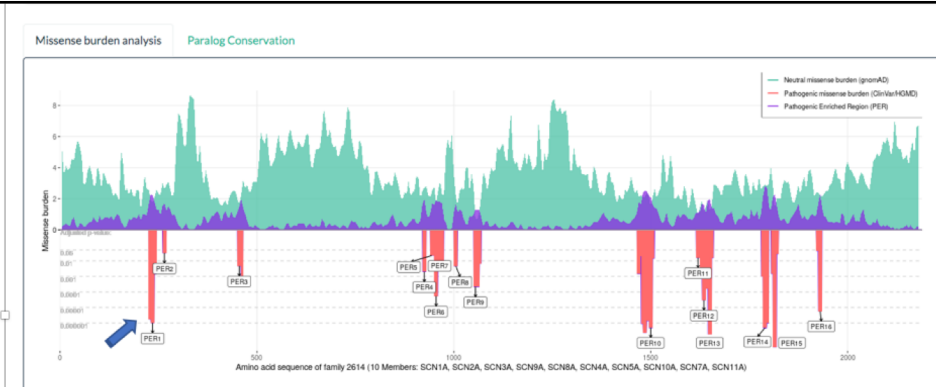
New prediction

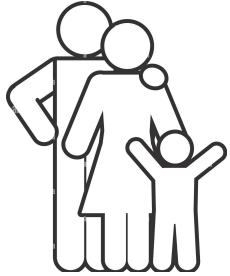


Test patient has 98.78 % probability of developing Dravet syndrome. However, this individual had a seizure onset at less than 4 months of age. Atypical phenotypes have been described in infants presenting at less than 4 months of age and alternative diagnoses including a profound phenotype with movement disorder (Sadleir et al. 2017) should be considered.

PER viewer

(<https://per.broadinstitute.org/>)





HGMD – **wariant opisany**

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ACMG Classification – **Likely Pathogenic / Pathogenic**

Analiza Bioinformatyczna - **Patogenic** (12 algorytmów)

funNCion - Functional variant prediction in Navs and Cavs ion channels

wariant patogenny (praw. – 0.98), **GOF** (prawd. 0.62)

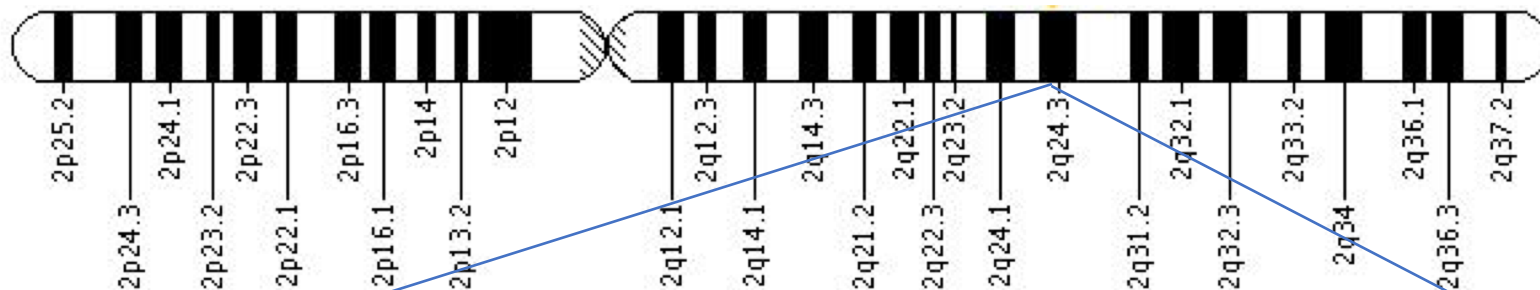
The SCN1A-Epilepsy Prediction Model

98,78% wystąpienia zespołu Dravet; ponieważ objawy, **wiek wystąpienia napadów < 4 mies.**, należy rozważyć alternatywną diagnozę cięższego zespołu z zaburzeniami ruchowymi - NDEEMA, EIDEE/MD, EIDEE

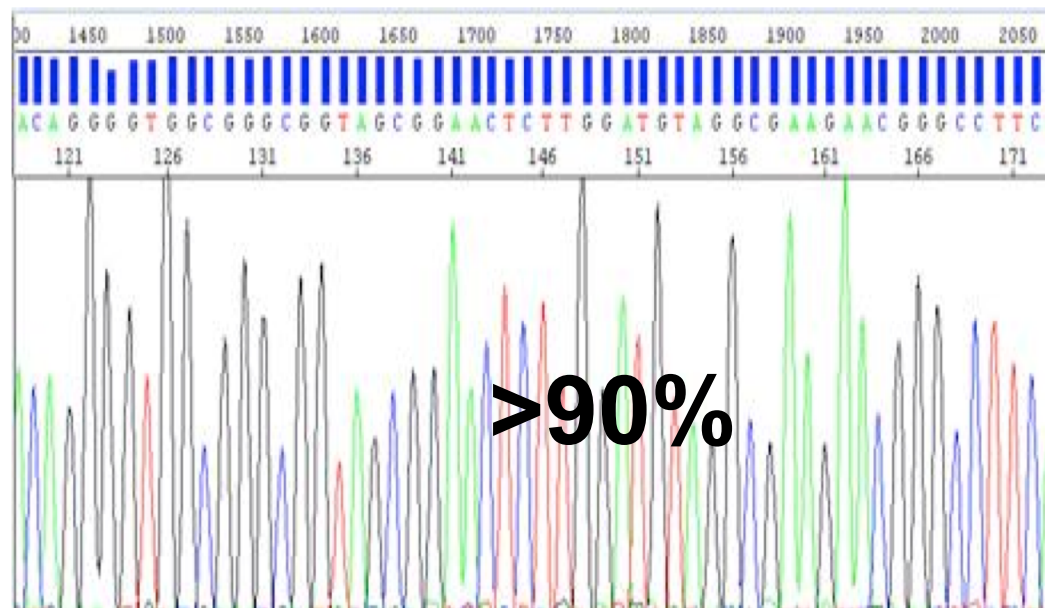
PER viewer

SCN1A – zespół Dravet, brak mutacji patogennych w paralogach (inne geny SCN)

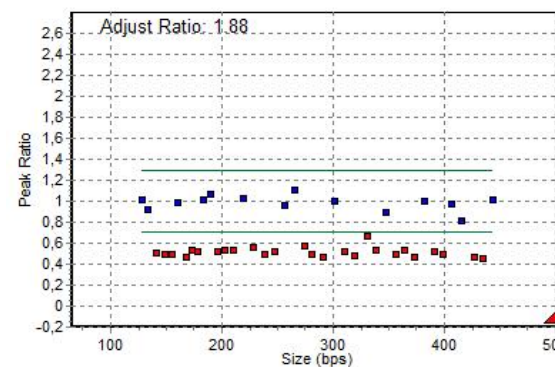
Ostatecznej interpretacji wyniku badania molekularnego, należy dokonać w kontekście szczegółowej analizy danych klinicznych pacjenta.



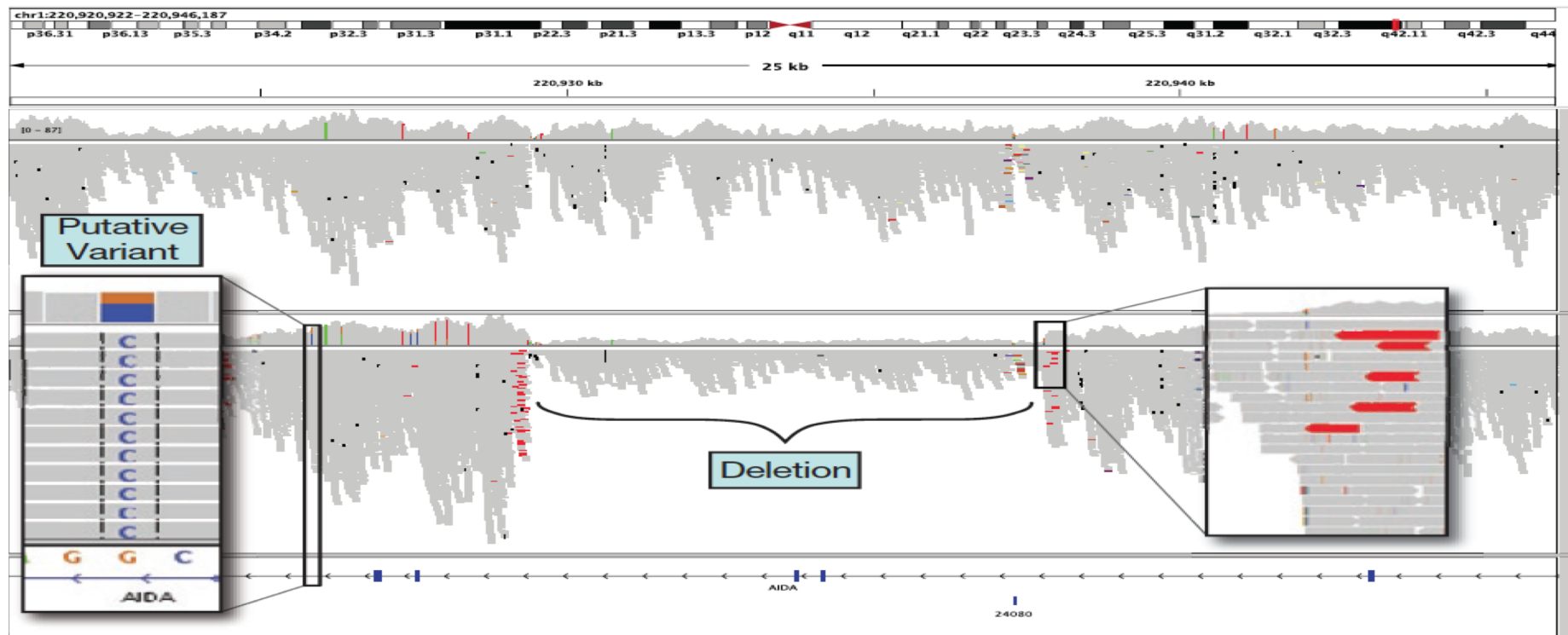
Gen SCN1A (MIM ID *182389); locus 2q24



mutacje punktowe

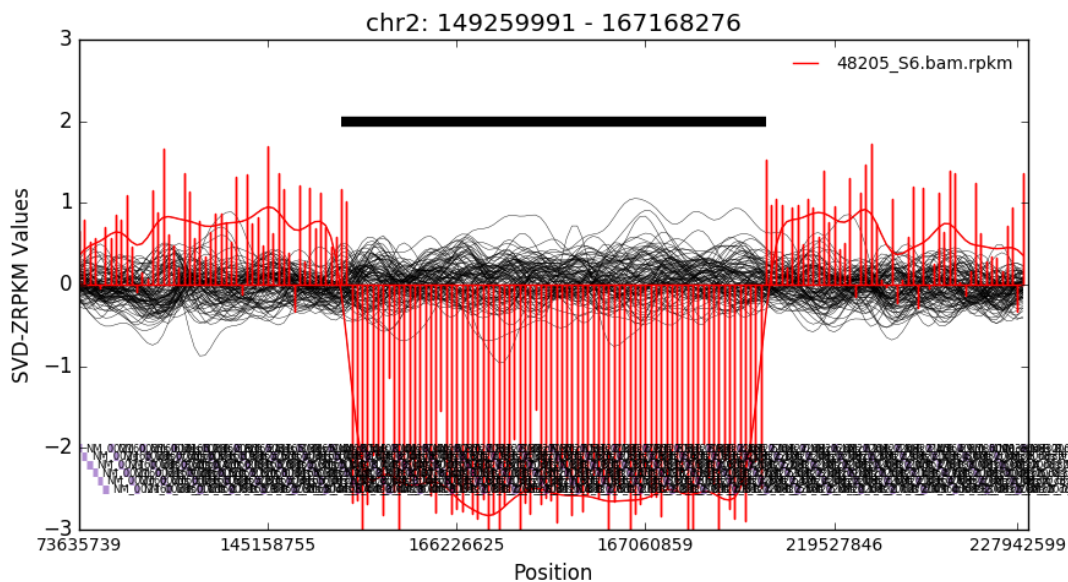


delecje/duplikacje



IMiD „home made pipeline”

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN
1	Identifier	Sex	Chr	Start	End	Ref	Alt	UCSC	Filter	QUAL	AD	DP	Yyg	zygNum	Gene.refG	GeneDetail	Func.refG	OMIM_dis	OMIM_ger	inAry	Pane	ExonicFunc	AACHange	dscSNV_	dscSNV_1	Mult_het	CLN3SG	CLNALLEL	CLNDN	CLNDSDB	CLNREVST	ZGM	Allel_ZGM_AF_	ZGM_Allel_ZGM_AF_	f_exp6500a	ExAC.ALL	ExAC.AFR	ExAC.AM		
2	Z29390.S1	female	chr10	1.03E+08	1.03E+08	T	G	http://gen/PASS		358.04	15	44	22	1	POZD7		exonic	Usher synch	http://www/http://www/TRUE		nonsynNM_NM_00131_		TRUE		TRUE	Benign	53297	not_specif	MedGen:C	criteria_p	1129	0.83047	1125	0.827206	0	0.8122	0.8078	0.878		
3	Z29390.S1	female	chr10	1.03E+08	1.03E+08	T	G	http://gen/PASS		523.39	16	32	het	1	POZD7		exonic	Usher synch	http://www/http://www/TRUE		synonymNM_NM_00131_		TRUE		TRUE	Benign	53292	not_specif	MedGen:C	criteria_p	1127	0.828676	1118	0.82059	0	0.8109	0.8074	0.88		
4	Z29390.S1	female	chr10	1.03E+08	1.03E+08	T	G	http://gen/PASS		468.65	15	35	het	1	POZD7		intronic	Usher synch	http://www/http://www/TRUE				0	0	TRUE	Benign	55376	not_specif	MedGen:C	criteria_p	1127	0.569853	773	0.568382	0.661464	0.5777	0.7943	0.48		
5	Z29390.S1	female	chr10	26355906	26355906	G	A	http://gen/PASS		2723.18	73	74	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54988	not_specif	MedGen:C	criteria_p	786	0.577941	785	0.577920	0.48839	0.485	0.3601	0.30		
6	Z29390.S1	female	chr10	26355992	26355992	A	G	http://gen/PASS		2875.45	76	76	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54957	not_specif	MedGen:C	criteria_p	786	0.705882	780	0.705882	0.682531	0.6786	0.6801	0.611		
7	Z29390.S1	female	chr10	26356014	26356014	T	T	http://gen/PASS		2379.41	61	61	hom	2	MYO3A		intronic	Deafness,	http://www/http://www/TRUE				FALSE		FALSE	Benign/Lik	54958	not_specif	MedGen:C	criteria_p	786	0.577941	785	0.575735	0.464478	0.4816	0.3597	0.30		
8	Z29390.S1	female	chr10	26357747	26357747	C	T	http://gen/PASS		2518.64	64	64	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0174_		FALSE		FALSE	Benign/Lik	54961	not_specif	MedGen:C	criteria_p	786	0.577941	784	0.576471	0.453867	0.4834	0.3595	0.3		
9	Z29390.S1	female	chr10	26357748	26357748	A	T	http://gen/PASS		2462.12	63	63	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54962	not_specif	MedGen:C	criteria_p	786	0.705882	958	0.704412	0.666769	0.6794	0.7016	0.61		
10	Z29390.S1	female	chr10	26357820	26357820	C	T	http://gen/PASS		2878.57	78	79	hom	2	MYO3A		intronic	Deafness,	http://www/http://www/TRUE				0	0	FALSE	Benign/Lik	54963	not_specif	MedGen:C	criteria_p	786	0.577941	786	0.577941	0.488006	0.4844	0.3596	0.30		
11	Z29390.S1	female	chr10	26464632	26464632	G	A	http://gen/PASS		3309.11	84	84	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54969	not_specif	MedGen:C	criteria_p	785	0.577206	521067	0.5364	0.5064	0.466	0.38			
12	Z29390.S1	female	chr10	26467290	26467290	G	A	http://gen/PASS		494.74	127	127	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0174_		FALSE		FALSE	Benign/Lik	54973	not_specif	MedGen:C	criteria_p	786	0.366176	498	0.366176	0.306705	0.3445	0.2573	0.29		
13	Z29390.S1	female	chr10	26469043	26469043	A	T	http://gen/PASS		5058.34	127	127	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54974	not_specif	MedGen:C	criteria_p	786	0.452206	614	0.451471	0.39551	0.4145	0.3354	0.34		
14	Z29390.S1	female	chr10	26463130	26463130	C	G	http://gen/PASS		3636.89	96	96	hom	2	MYO3A		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign/Lik	54976	not_specif	MedGen:C	criteria_p	797	0.586029	796	0.585294	0.56274	0.5987	0.5536	0.65		
15	Z29390.S1	female	chr10	55566406	55566406	T	G	http://gen/PASS		2913.52	75	75	hom	1	PCHD15		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0174_		FALSE		FALSE	Benign	22793	not_specif	MedGen:C	criteria_p	327	0.240441	326	0.239706	0.223786	0.2127	0.0514	0.10		
16	Z29390.S1	female	chr10	57752209	56077209	G	A	http://gen/PASS		1465.90	46				PCHD15		intronic	Deafness,	http://www/http://www/TRUE				0	0	FALSE	Benign/Lik	55676	Retinitis_p	MedGen:C	criteria_p	1021	0.750735	1021	0.750735	0.740197	0.6604	0.7451	0.58		
17	Z29390.S1	female	chr10	73270906	73270906	T	C	http://gen/PASS		2341.7	63	62			CHD23		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_01001_		FALSE		FALSE	Benign/Lik	55093	Retinitis_p	MedGen:C	criteria_p	885	0.650735	881	0.647794	0.749597	0.6721	0.9361	0.44		
18	Z29390.S1	female	chr10	73406504	73406504	T	T	http://gen/PASS		1610.41	51	104	het	1	CHD23		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0528_		FALSE		FALSE	Benign	55035	not_specif	MedGen:C	criteria_p	194	0.142647	194	0.142647	0.149792	0.1521	0.1244	0.08		
19	Z29390.S1	female	chr10	73434906	73434906	G	A	http://gen/PASS		583.46	19	40	het	1	CHD23		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0111_		FALSE		FALSE	Benign	55040	Retinitis_p	MedGen:C	criteria_p	378	0.277941	378	0.277941	0.249881	0.2724	0.2539	0.30		
20	Z29390.S1	female	chr10	73455201	73455201	C	T	http://gen/PASS		337.05	87	87	hom	1	CHD23		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0111_		FALSE		FALSE	Benign/Lik	55058	Retinitis_p	MedGen:C	criteria_p	966	0.710294	964	0.708804	0.668785	0.6362	0.5272	0.44		
21	Z29390.S1	female	chr10	73455273	73455273	T	C	http://gen/PASS		2099.02	54	54	hom	1	CHD23		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0111_		FALSE		FALSE	Benign/Lik	55061	Retinitis_p	MedGen:C	criteria_p	966	0.710294	964	0.707353	0.669401	0.6363	0.5276	0.44		
22	Z29390.S1	female	chr10	73492079	73492079	A	G	http://gen/PASS		4416.73	115	115	hom	2	CHD23		exonic	Deafness,	http://www/http://www/TRUE		synonymNM_NM_0111_		FALSE		FALSE	Benign/Lik	55102	Retinitis_p	MedGen:C	criteria_p	1122	0.825	1122	0.825	0.812899	0.8159	0.7809	0.80		
23	Z29390.S1	female	chr10	73501556	73501556	G	A	http://gen/PASS		1947.72	50	50	hom	2	CHD23		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0221_		FALSE		FALSE	Benign/Lik	55120	Retinitis_p	MedGen:C	criteria_p	1082	0.795588	1078	0.792647	0.741081	0.7521	0.6726	0.78		
24	Z29390.S1	female	chr10	73544638	73544638	A	G	http://gen/PASS		531.51	18	42	het	1	CHD23		intronic	Deafness,	http://www/http://www/TRUE				0	0.002	FALSE	Benign/Lik	55147	Retinitis_p	MedGen:C	criteria_p	264	0.194118	264	0.194118	0.129017	0.1915	0.0695	0.35		
25	Z29390.S1	female	chr10	73550117	73550117	C	G	http://gen/PASS		47.15	16	37	het	1	CHD23		exonic	Deafness,	http://www/http://www/TRUE		nonsynNM_NM_0221_		FALSE		FALSE	Benign/Lik	55162	Retinitis_p	MedGen:C	criteria_p	675	0.496324	672	0.494118	0.414431	0.4291	0.2895	0.27		
26	Z29390.S1	female	chr10	73550969	73550969	G	A	http://gen/PASS		457.16	16	43	het	1																										
27	Z29390.S1	female	chr10	73558886	73558886	G	A	http://gen/PASS		1211.65	37	70	het	1																										
28	Z29390.S1	female	chr10	73558952	73558952	C	T	http://gen/PASS		1423.65	45	87	het	1																										
29	Z29390.S1	female	chr10	7362744	7362744	G	A	http://gen/PASS		1006.27	32	64	het	1																										
30	Z29390.S1	female	chr10	73571765	73571765	T	C	http://gen/PASS		799.6	27	65	het	1																										
31	Z29390.S1	female	chr10	73574843	73574843	G	A	http://gen/PASS		650.81	20	42	het	1																										
32	Z29390.S1	female	chr11	1.21E+08	1.21E+08	A	G	http://gen/PASS		1422.43	43	85	het	1																										
33	Z29390.S1	female	chr11	1.21E+08	1.21E+08	A	G	http://gen/PASS		1740.96	52	89	het	1																										
34	Z29390.S1	female	chr11	1.21E+08	1.21E+08	T	C	http://gen/PASS		1306.74	41	80	het	1																										
35	Z29390.S1	female	chr11	1.21E+08	1.21E+08	T	C	http://gen/PASS		1450.66	44	85	het	1																										
36	Z29390.S1	female	chr11	1.21E+08	1.21E+08	G	A	http://gen/PASS		1947.54	50	50	hom	2																										
37	Z29390.S1	female	chr11	17517235	17517235	A	G	http://gen/PASS		509.06	17	40	het	1																										
38	Z29390.S1	female	chr11	17519742	17519742	C	G	http://gen/PASS		678.31	23	53	het	1																										
39	Z29390.S1	female	chr11	17522638	17522638	G	A	http://gen/PASS		1054.62	33	69	het	1																										
40	Z29390.S1	female	chr11	17542439	17542439	T	C	http://gen/PASS		1190.82	37	78	het	1																										
41	Z29390.S1	female	chr11	17569527	17569527	C	G	http://gen/PASS		681.55	21	41	het	1																										
42	Z29390.S1	female	chr11	17573632	17573632	A	T	http://gen/PASS		800.56	24	48	het	1																										
43	Z29390.S1	female	chr11	17579783	17579783	C	A</																																	





Podejrzenie EIEE analiza genu *STXBP1* (? Panel / WES)

- identyfikacja mutacji punktowych
(sekwencjonowanie – wszystkie eksony !!!!!)
- w przypadku braku identyfikacji mutacji punktowych
rozszerzenie analizy o rearanżacje genu (delecje /duplikacje)

Ostatecznym zakończenie analizy genu *STXBP1* jest przeprowadzenie sekwencjonowania i analizy reranżacji

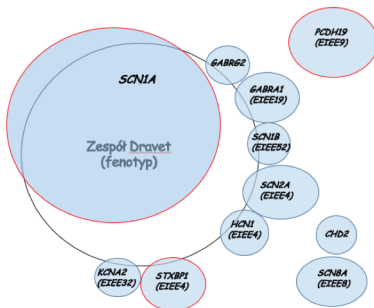
- reanaliza fenotypu – rozszerzenie badania o inne geny związane EIEE



Podejrzenie zespołu Dravet analiza genu *SCN1A* (? Panel / WES)

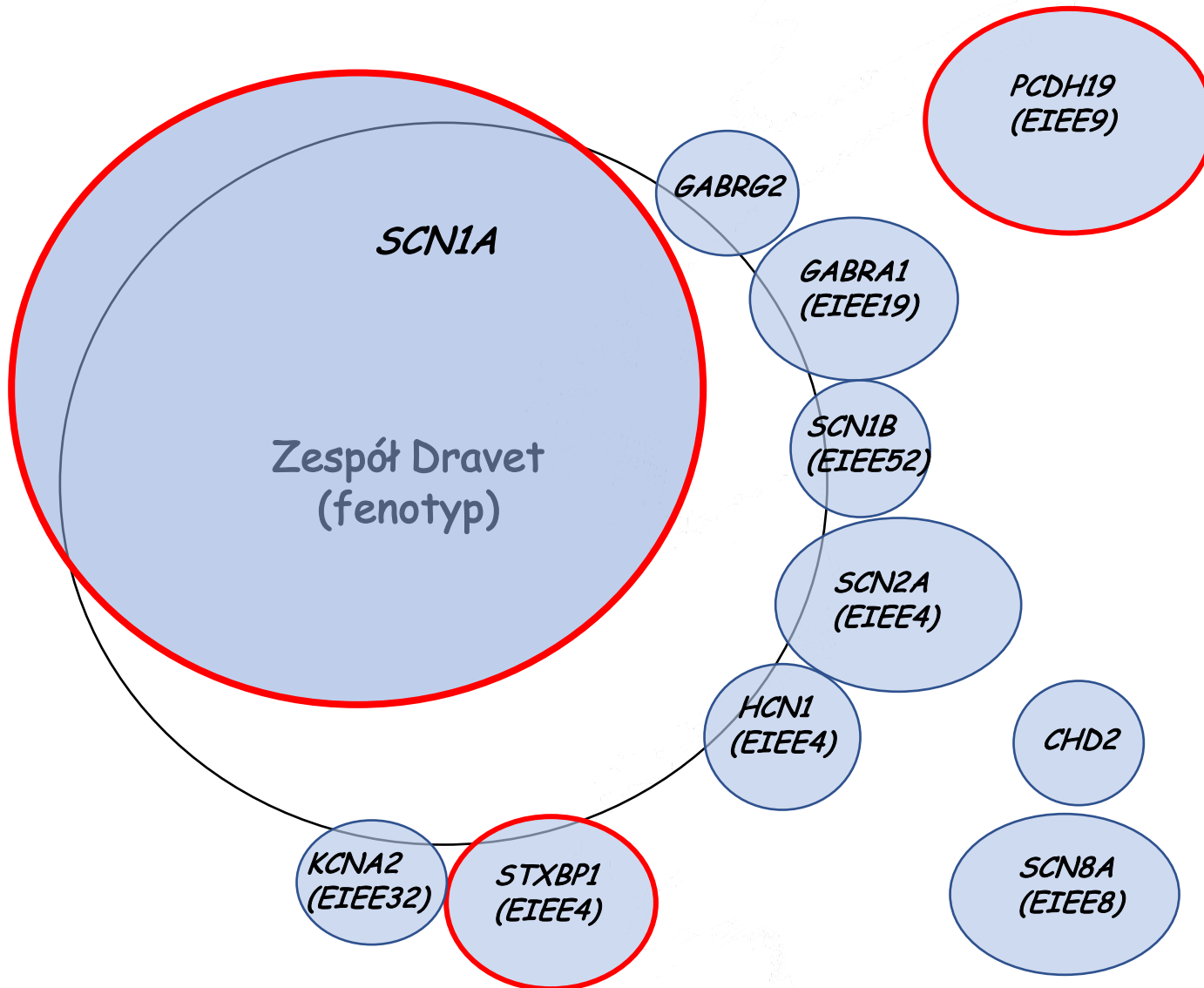
- identyfikacja mutacji punktowych
(sekwencjonowanie – wszystkie eksony !!!!!)
- w przypadku braku identyfikacji mutacji punktowych
rozszerzenie analizy o rearanżacje genu (delecje /duplikacje)

Ostatecznym zakończenie analizy genu *SCN1A* jest przeprowadzenie sekwencjonowania i analizy reranżacji

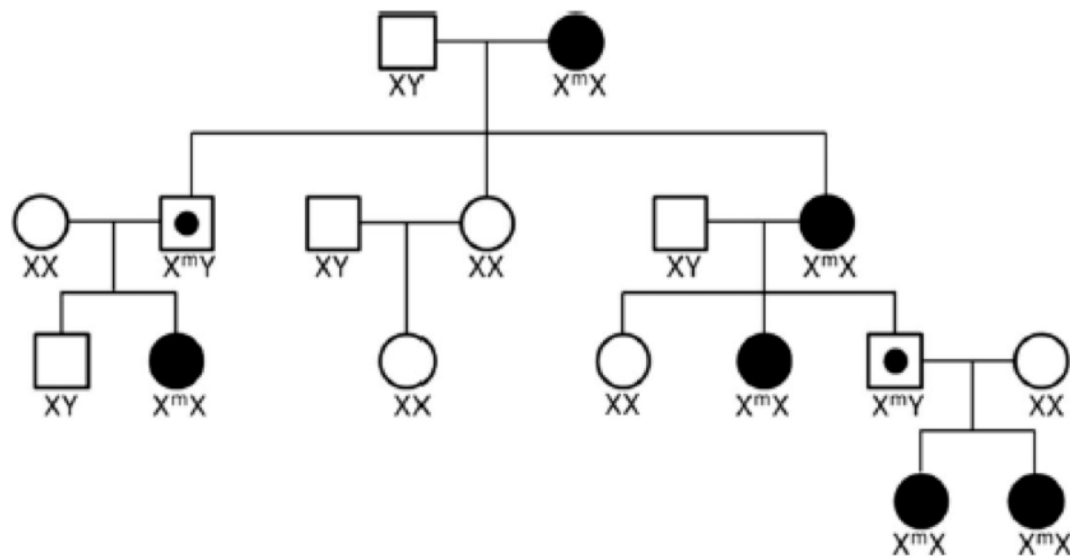


- reanaliza fenotypu – rozszerzenie badania o inne geny związane z chorobami Dravet-like
(w przypadku niektórych z nich nie wystarczy analiza sekwencji)

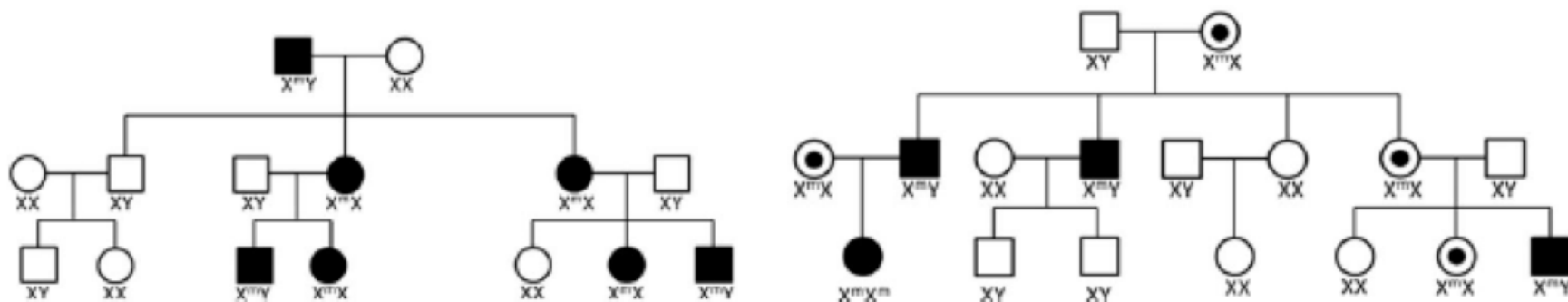
„Geny zespołu Dravet”

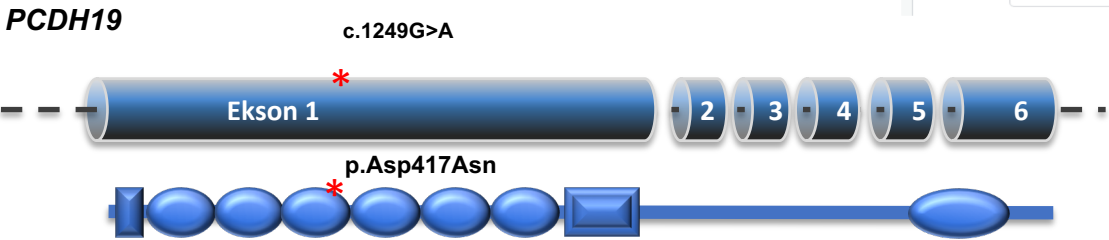
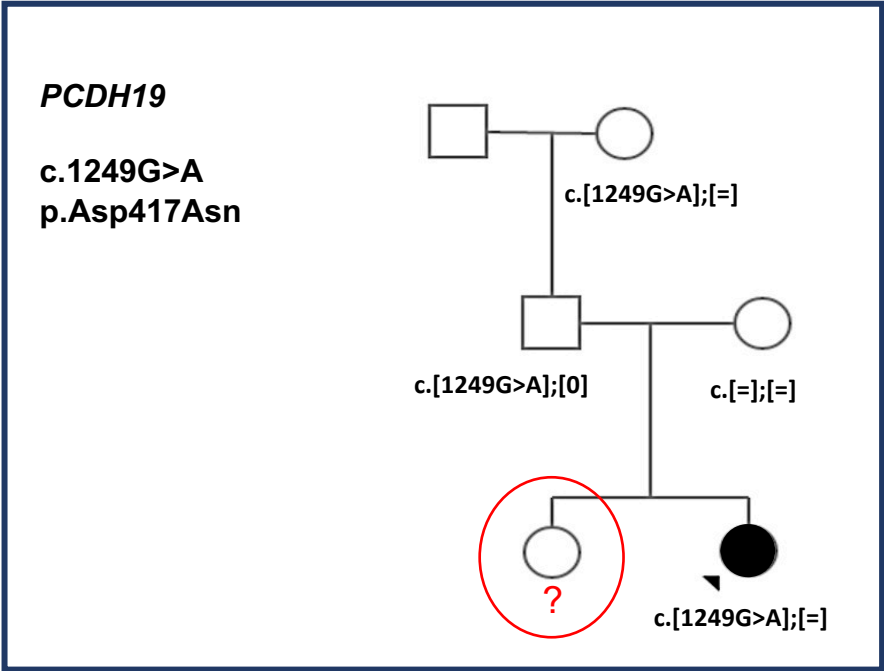


**Ograniczone do kobiet dziedziczenie
dominujące sprzężone z chromosomem X**



Zespół upośledzenia umysłowego i padaczki ograniczony do kobiet





Search Page PCDH19:c.1249G>A

chrX-100407349 C>T | p.Asp417Asn | NM_001184880.2 | UCSC | gnomAD

Franklin ACMG Classification Variant Assessment Publications Gene A

Suggested Classification
VUS

Benign Likely Benign VUS Likely Pathogenic Pathogenic

EVIDENCE
Aggregated from public databases using ACMG Guidelines

Functional Data

PM1 Pathogenic Moderate:
Non-truncating non-synonymous variant is located in a mutational hot spot and/or critical and well-established functional domain
[See Details](#)

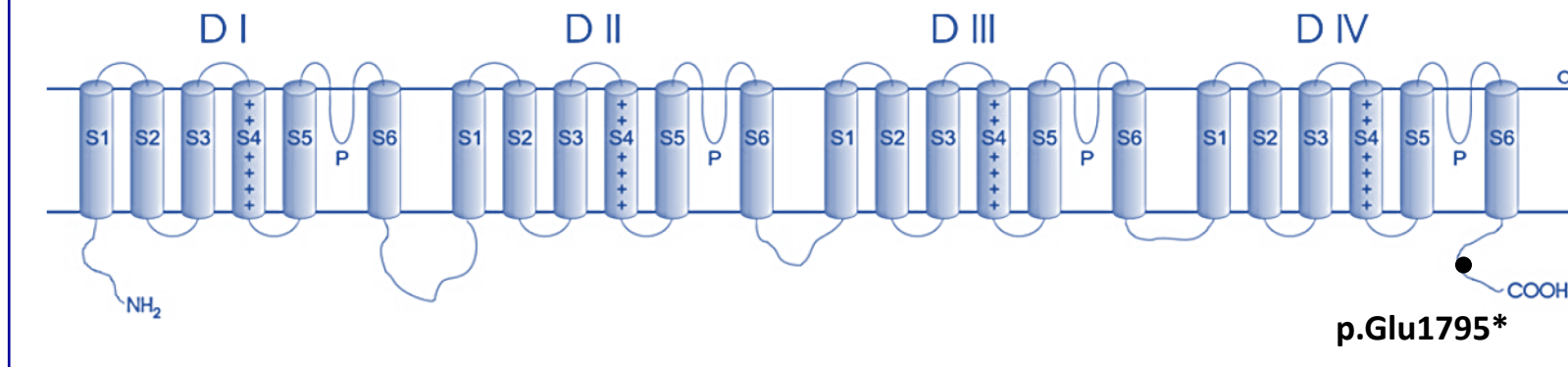
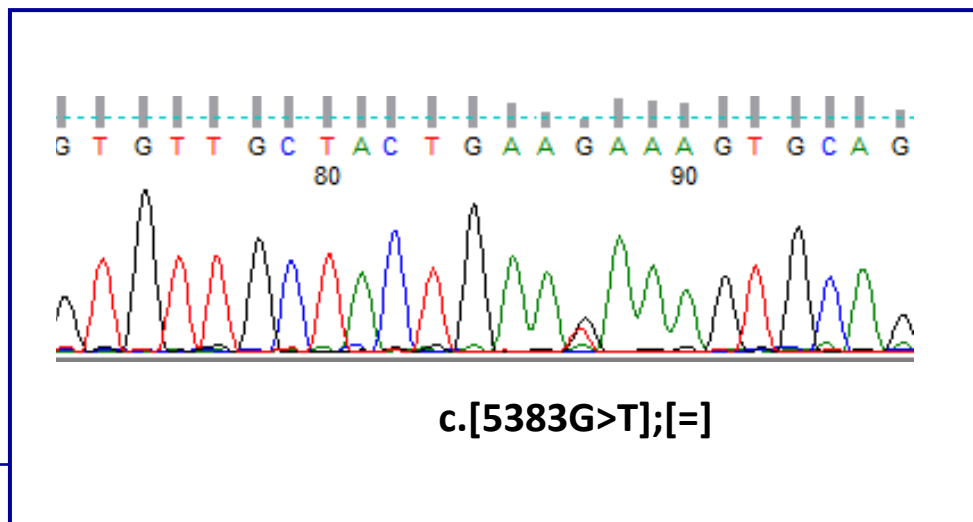
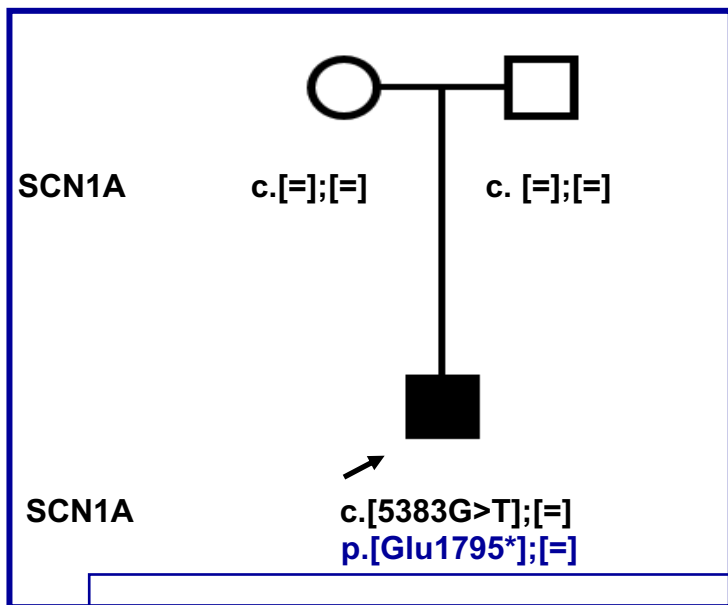
PP2 Pathogenic Supporting:
Missense variant in a gene with low rate of benign missense mutations and for which missense mutation is a common mechanism of a disease
[See Details](#)

Population Data

PM2 Pathogenic Moderate:
Extremely low frequency in gnomad population databases
[See Details](#)

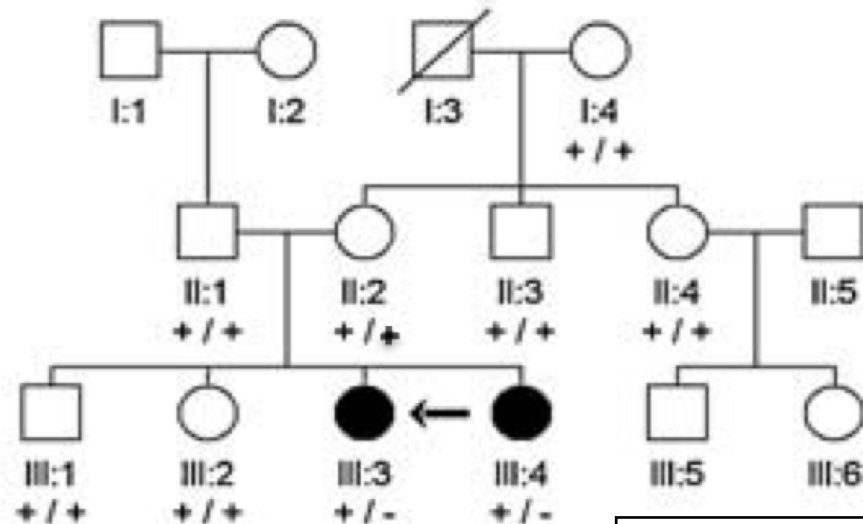
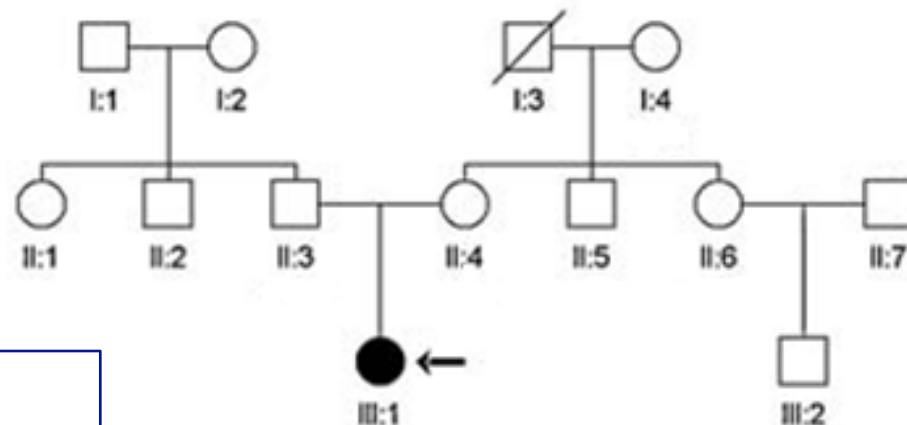
UNMET: BA1 | BS1 | BS2 [See Details](#)

Encefalopatia padaczkowa – zespół Dravet



p.[Glu1795*];[=]

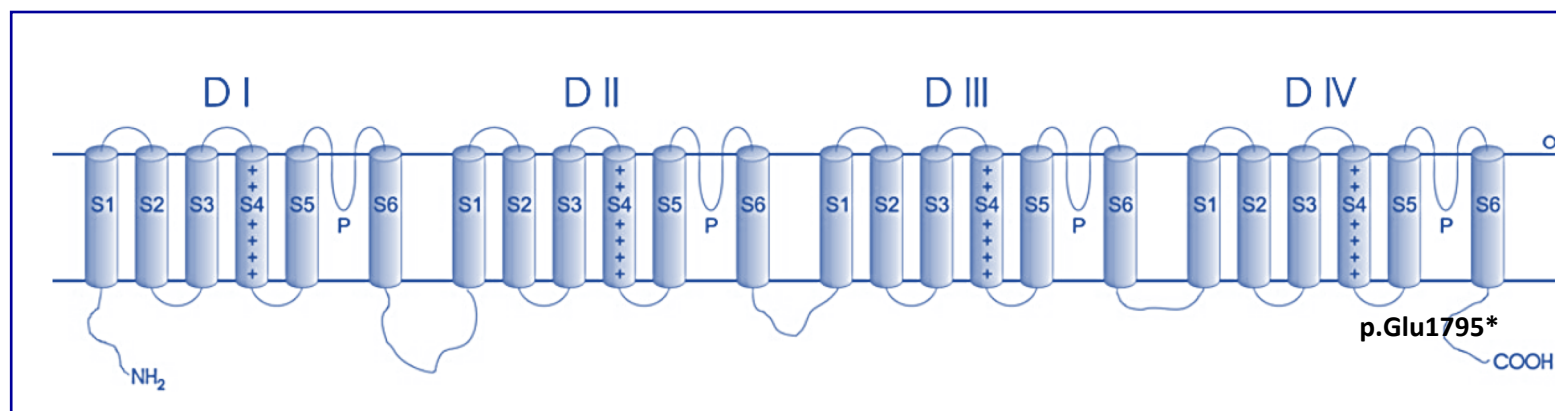
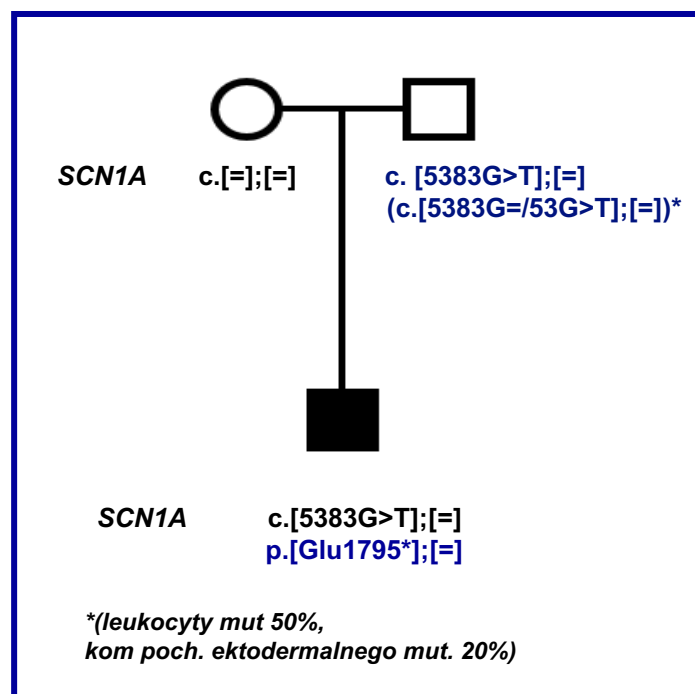
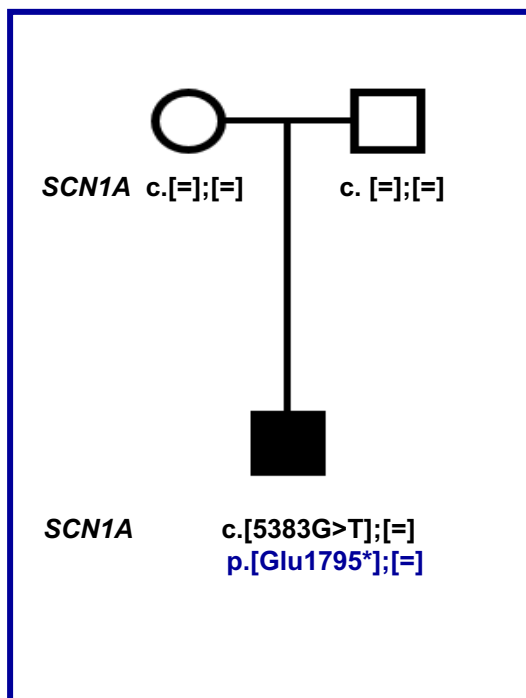
AD; mutacje *de novo* w rodowodzie „przypadek sporadyczny”



Mozaikowość

- obecność dwóch (lub więcej) genetycznie różnych linii komórkowych powstałych postzygotycznie
- mozaikowość germinalna (dotycząca komórek rozrodczych) (mutacja zaszła na wczesnym etapie rozwoju embrionalnego, dotycząc progentitorowych komórek rozrodczych (grupa komórek rozrodczych jest klonem zmutowanej kom. pierwotnej))

Encefalopatia padaczkowa – zespół Dravet



p.[Glu1795*];[=]

Heterogenność obrazu klinicznego

Czy zidentyfikowana mutacja odpowiada z fenotyp zespołu Dravet ?



CM034964
Generalized epilepsy with febrile seizures plus

p.R1657H
CM072002
Cryptogenic focal epilepsy

NM_001165963.4(SCN1A):c.4786C>T (p.Arg1596Cys)

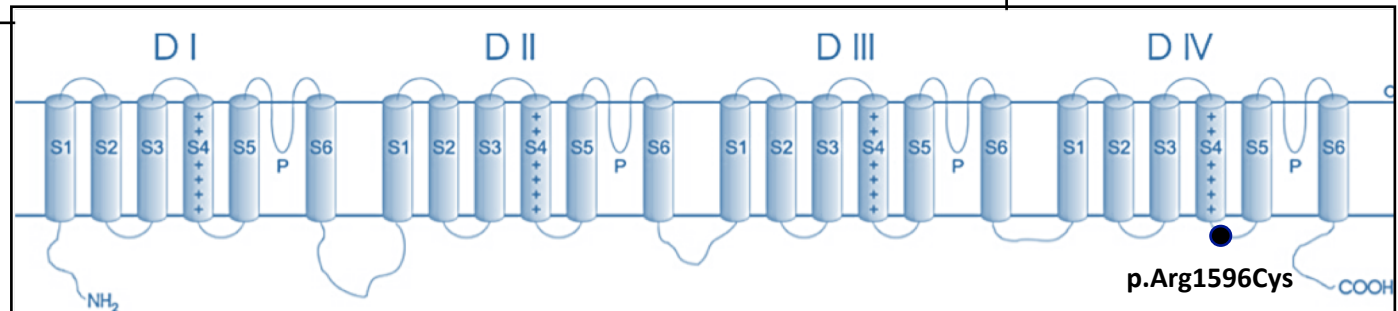
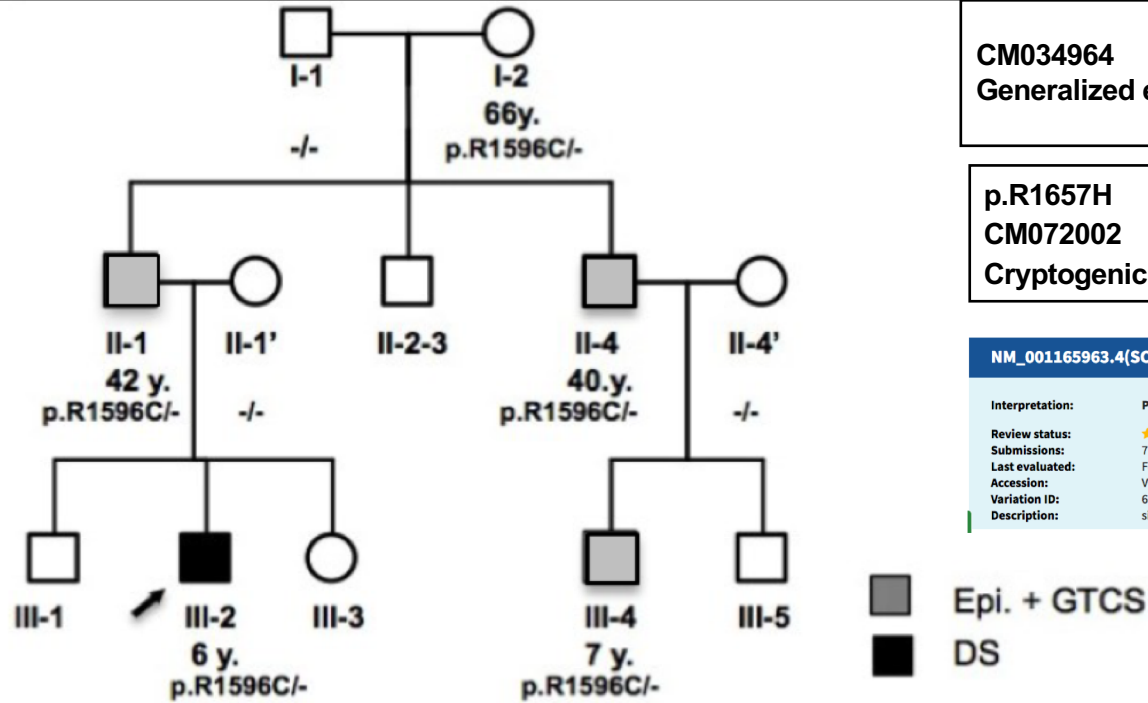
ClinVar

Interpretation:	Pathogenic/Likely pathogenic
Review status:	★☆☆ criteria provided, multiple submitters, no conflicts
Submissions:	7 (Most recent: Jul 6, 2020)
Last evaluated:	Feb 26, 2020
Accession:	VCV000068553.9
Variation ID:	68553
Description:	single nucleotide variant

SCN1A

SCN1A

SCN1A



mutacja odziedziczona

Pathogenicity Scores				
DANN ⓘ <i>version 2014</i>	Score			
	0.9994			
MutationTaster ⓘ <i>dbNSFP version 4.0</i>	Prediction ⓘ Disease causing	Accuracy ⓘ 1	converted rankscore 0.81	
Mutation assessor ⓘ <i>dbNSFP version 4.0</i>	prediction Medium	score 3	rankscore 0.8587	
FATHMM ⓘ <i>dbNSFP version 4.0</i>	prediction Damaging	score -4.51	converted rankscore 0.9767	
FATHMM-MKL ⓘ <i>dbNSFP version 4.0</i>	coding prediction Damaging	coding score 0.9734	coding rankscore 0.7411	
FATHMM-XF ⓘ <i>dbNSFP version 4.0</i>	coding prediction Damaging	coding score 0.8653	coding rankscore 0.7844	
LRT ⓘ <i>dbNSFP version 4.0</i>	prediction Deleterious	score 0	converted rankscore 0.8433	Omeg 0
DEOGEN2 ⓘ <i>dbNSFP version 4.0</i>	prediction Damaging	score 0.9894	rankscore 0.9995	
EIGEN ⓘ <i>dbNSFP version 4.0</i>	prediction Pathogenic	raw coding 0.9069	raw coding rankscore 0.9209	pred coding score 11.231
EIGEN PC ⓘ <i>dbNSFP version 4.0</i>	prediction Pathogenic	PC raw coding score 0.8686	PC raw coding rankscore 0.9405	PC phred coding score 12.4706
SIFT ⓘ <i>dbNSFP version 4.0</i>	prediction Damaging	score 0	converted rankscore 0.9125	
SIFT4G ⓘ <i>dbNSFP version 4.0</i>	prediction Damaging	score 0.032	converted rankscore 0.5343	
PROVEAN ⓘ <i>dbNSFP version 4.0</i>	prediction Damaging	score -4.29	converted rankscore 0.7641	

Verdict
Pathogenic

Transcript NM_006920.6, canonical, protein length 1999, gene SCN1A, missense variant

Rules

☒ PVS1 ⓘ	☒ PS1 ⓘ	☐ PS2 ⓘ	☒ PS3 ⓘ	☐ PS4 ⓘ	☒ PM1 ⓘ Strong	☒ PM2 ⓘ Moderate	☐ PM3 ⓘ
☒ PM4 ⓘ	☒ PM5 ⓘ Moderate	☐ PM6 ⓘ	☐ PP1 ⓘ	☒ PP2 ⓘ Supporting	☒ PP3 ⓘ Supporting	☐ PP4 ⓘ	☒ PP5 ⓘ Very Strong
☒ BA1 ⓘ	☒ BS1 ⓘ	☒ BS2 ⓘ	☒ BS3 ⓘ	☒ BS4 ⓘ			
☒ BP1 ⓘ	☐ BP2 ⓘ	☒ BP3 ⓘ	☒ BP4 ⓘ	☐ BP5 ⓘ	☒ BP6 ⓘ	☒ BP7 ⓘ	

The verdict will update automatically if you enable or disable rules or change their strength. The blue question marks displays details about the rule, including why it was not triggered.

▲ Users of VarSome Premium benefit from additional data sources included in the automated classification.

Automated criteria

Rule	Explanation
PP5 Very Strong	ClinVar classifies this variant as Pathogenic, rated 2 stars, with 6 submissions, 10 publications () and no conflicts. UniProt classifies this variant as Pathogenic, associated with Epileptic encephalopathy, early infantile, 6Focal epilepsy, related publications: 17347258, 18930999, 22156295 and 23917401. Using strength Very Strong because of the evidence presented by ClinVar and UniProt.
PM1 Strong	Using strength Strong because Hot-spot of length 61 base-pairs has 25 non-VUS coding variants (25 pathogenic and 0 benign), pathogenicity = 100.0%, qualifies as a dense hot-spot.
PM2 Moderate	GnomAD exomes allele count = 0 is less than 5 threshold for gene SCN1A (good gnomAD exomes coverage = 58.6). Variant not found in gnomAD genomes (good gnomAD genomes coverage = 31.6).
PMS Moderate	Alternative variant chr2:166850721 C→A (Arg1585Leu) is classified Pathogenic by UniProt Variants (and confirmed using ACMG). Alternative variant chr2:166850721 C→T (Arg1585His) is classified Pathogenic by UniProt Variants (and confirmed using ACMG).
PP2 Supporting	1,072 out of 1,103 non-VUS missense variants in gene SCN1A are pathogenic = 97.2% which is more than threshold of 51.0%, and 1,642 out of 2,639 clinically reported variants in gene SCN1A are pathogenic = 62.2% which is more than threshold of 12.0%.
PP3 Supporting	Pathogenic computational verdict based on 12 pathogenic predictions from BayesDel_addAF, DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, MutationAssessor, MutationTaster, PrimateAI, REVEL and SIFT vs no benign predictions.

Results

+

Prediction/Confidence

PolyPhen-2

prediction of functional effects of human

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HumDiv

This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)

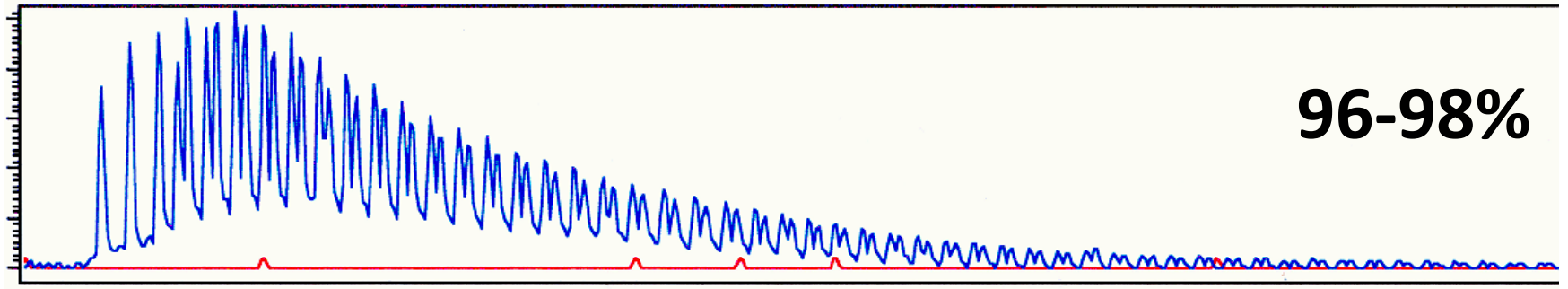
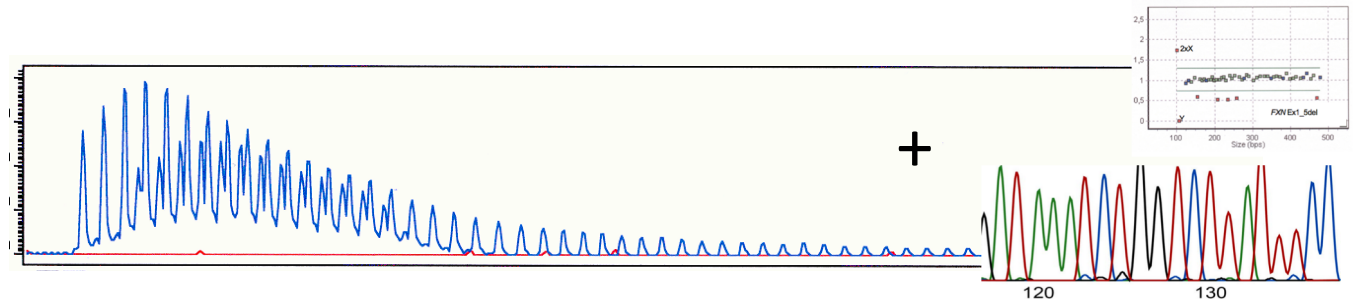
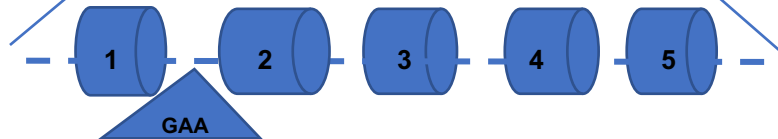
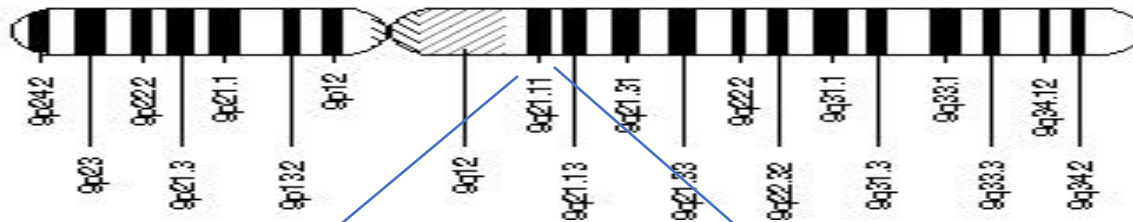
HumVar

This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)

Ataksja Friedreicha – mutacja dynamiczna

AR

Gen FXN; locus 9q21.11





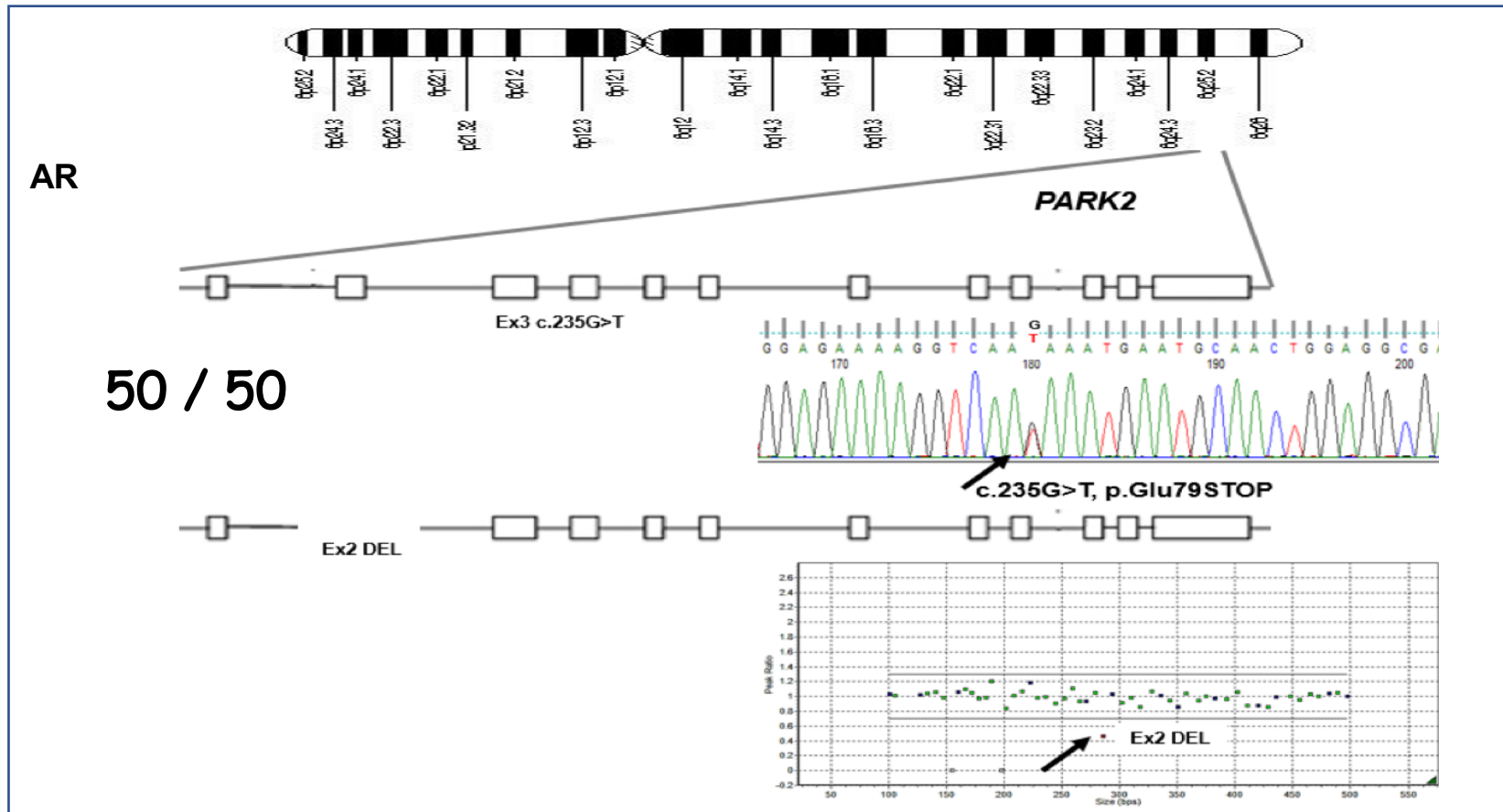
Podejrzenie ataksji - AR (? Panel / WES)

Ataksja Friedreicha

- **identyfikacja mutacji dynamicznej
(sekwencjonowanie – wszystkie eksony !!!!!)**
- **w przypadku braku identyfikacji mutacji dynamicznej
możemy mieć do czynienia z nosicielstwem**

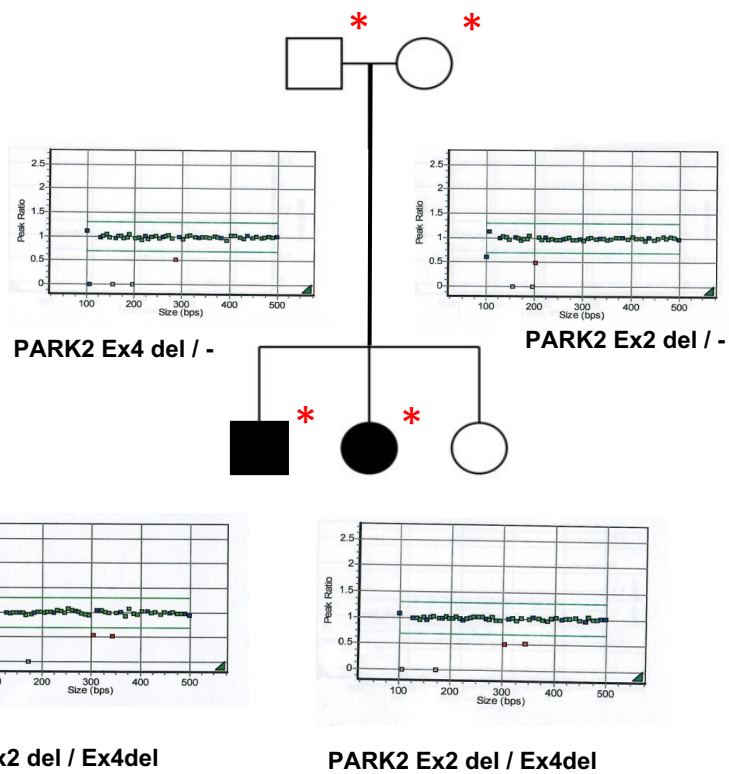
**Ostatecznym zakończenie analizy genu *FXN* jest
przeprowadzenie sekwencjonowania i analizy obecności
mutacji dynamicznej**

Choroba Parkinsona – o wczesnym początku (*PARK2*, *PINK1*, *DJ1*)



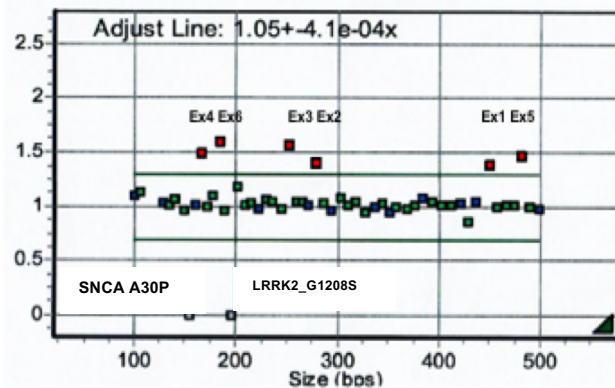
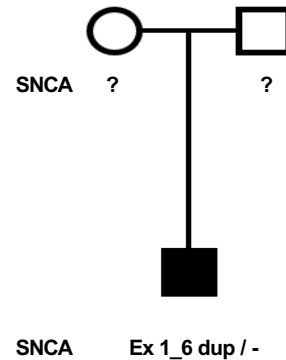
Ostatecznym zakończenie analizy genów *PARK2*, *DJ1*, *PINK1* jest przeprowadzenie sekwencjonowania i analizy reranżacji genów
+ wykazanie bialleliczności mutacji (dziedziczenie AR)

EO-PD PARK2



~~WES~~

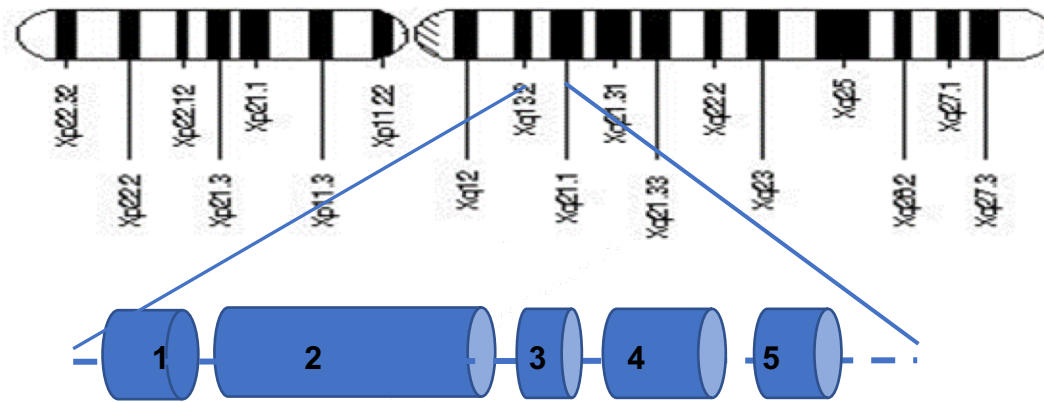
EO-PD SNCA duplikacija genu



	Probe Name	Bin Size	Height Ratio
1	X	100.5	1.102
2	Y	105.0	1.128
3	Ctrl_05q31	127.2	1.023
4	TNFRSF9	133.0	1.011
5	PINK1_ex05	140.2	1.065
6	PINK1_ex01	148.0	0.971
7	SNCA_A30P	153.5	-1
8	Ctrl_15q21	159.3	1.010
9	SNCA_ex04	166.0	1.482
10	PINK1_ex02	171.7	0.998
11	ATP13A2_ex09	177.8	1.094
12	SNCA_ex06	183.8	1.609
13	Ctrl_9p13	189.0	0.965
14	LRRK2_G2019S	196.2	-1
15	PARK2_ex4	201.4	1.182
16	PINK1_ex03	208.4	1.019
17	ATP13A2_ex02	215.2	1.033
18	Ctrl_8q12	221.7	0.975
19	PINK1_ex07	228.5	1.071
20	PARK2_ex1	235.8	1.054
21	PARK7_ex06	244.0	0.978
22	SNCA_ex03	251.5	1.566
23	Ctrl_18q21	258.9	1.044
24	LPA Downstream	264.6	1.052
25	PARK7_ex2	270.5	1.016
26	SNCA_ex2	278.2	1.402
27	PARK2_ex02	285.6	1.028
28	Ctrl_3p22	293.4	0.969
29	PARK2_ex8	302.1	1.082
30	PINK1_ex06	309.8	1.007
31	PARK7_ex4	317.0	1.049
32	PARK2_ex09	326.9	0.951
33	Ctrl_2q36	335.4	0.997
34	PARK2_ex6	343.1	1.028
35	PARK7_ex1	350.5	0.948
36	PARK2_ex10	357.8	0.994
37	PARK7_ex5	368.5	0.981
38	PARK2_ex11	375.0	1.013
39	Ctrl_11p14	383.1	1.076
40	PARK2_ex12	393.1	1.048
41	PINK1_ex4	402.2	1.014
42	PARK7_ex03	410.5	1.015
43	PARK2_ex5	420.3	1.027
44	PARK7_ex01	428.9	0.856
45	Ctrl_6p12	435.8	1.053
46	SNCA_ex1	448.1	1.377
47	PARK7_ex7	455.6	0.991
48	PINK1_ex08	465.0	1.012
49	PARK2_ex3	472.6	1.011
50	SNCA_ex5	481.4	1.463
51	PARK2_ex7	488.9	1.004
52	Ctrl_2p13	497.1	0.983

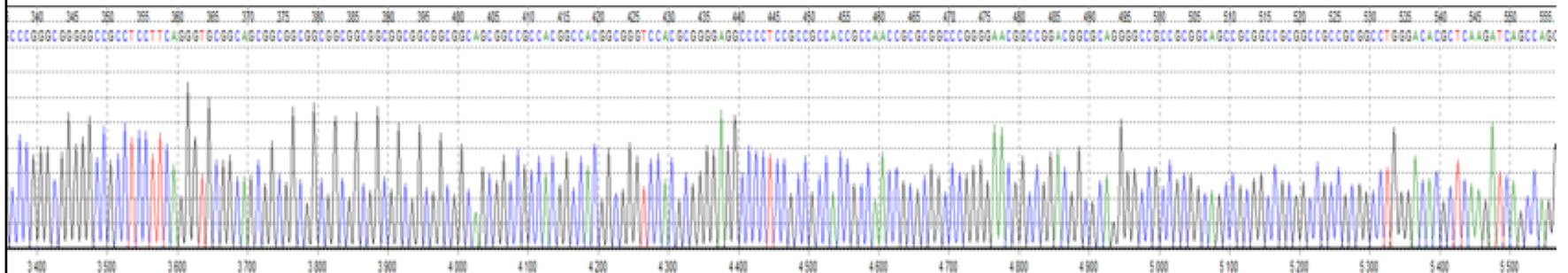
WES

Gen ARX (MIM ID *300382); locus Xq21.3



poliA
 c. [209_345] (GCG)₁₆
 p. Ala₁₆

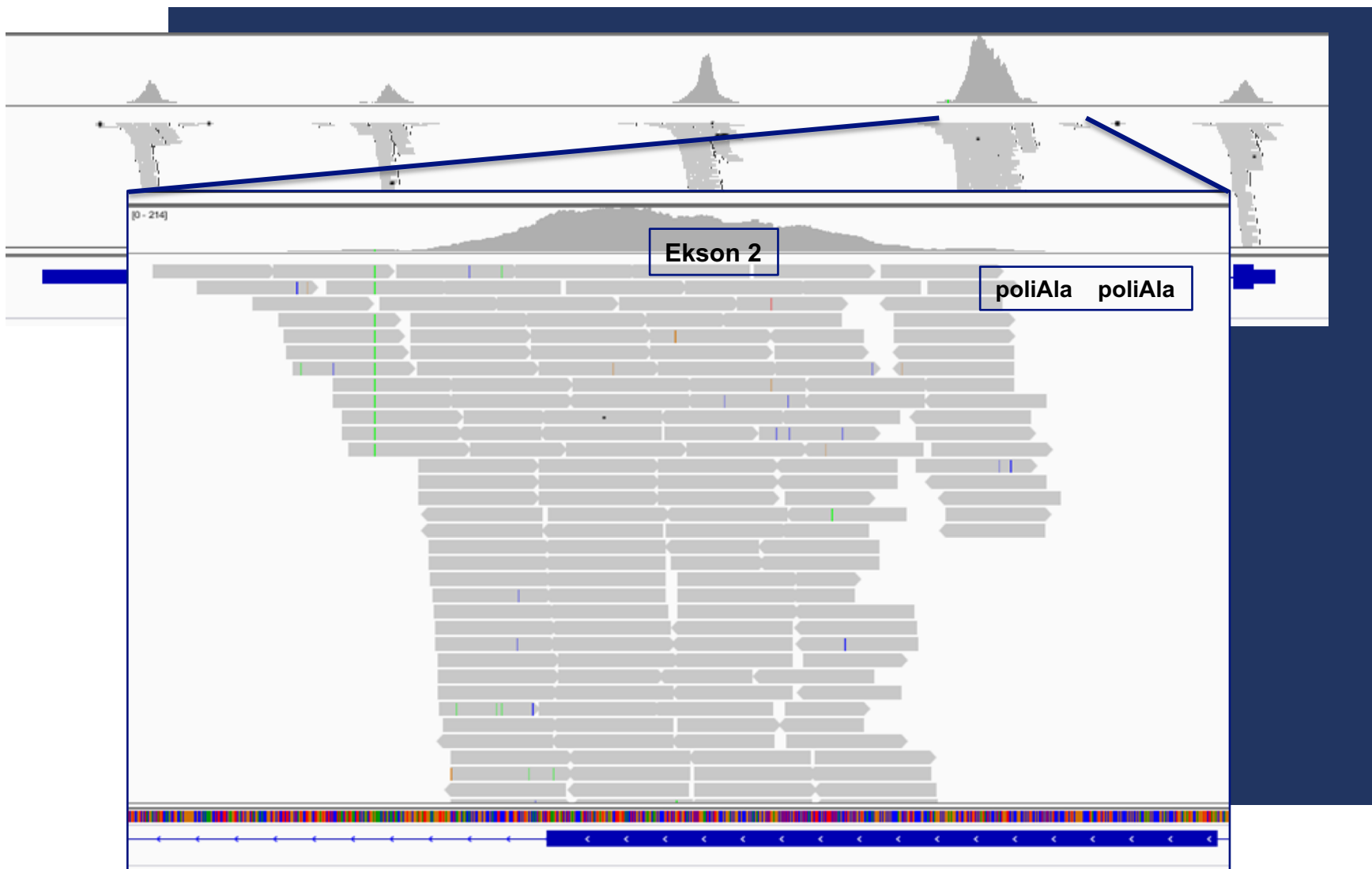
poliA
 c. [430_365] (GCG)₁₂
 p. Ala₁₂



c.304ins(GCG)₇

c.428_451dup

ARX - TruSight One Sequencing Panel (Illumina)



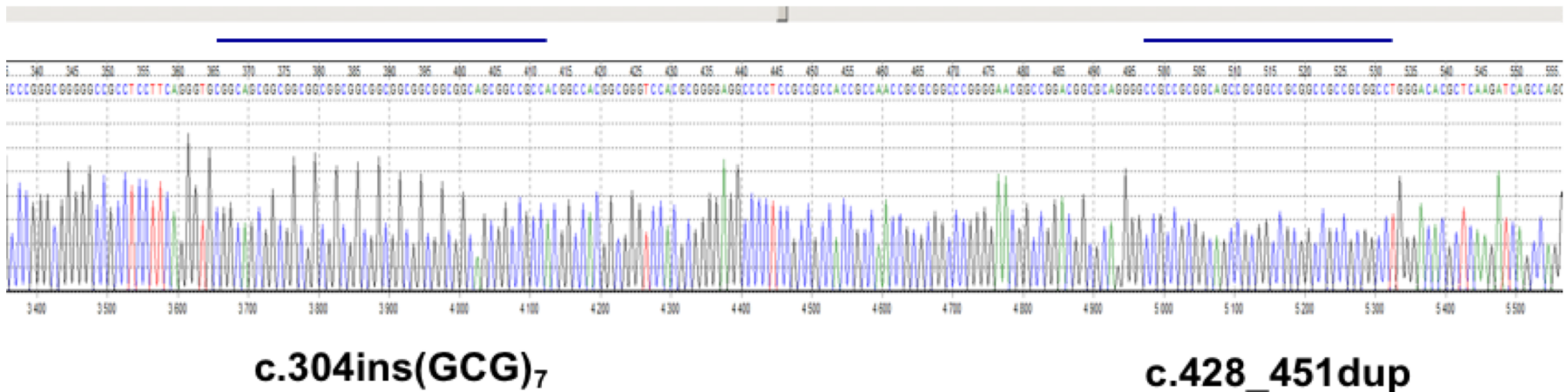
W wyniku przeprowadzenia analizy danych sekwencjonowania całoksomowego (WES) wykonanego u Pacjenta nie zidentyfikowano wariantów mogących stanowić przyczynę zdiagnozowanej u niej choroby.

Uzyskany wynik nie potwierdza ale i nie wyklucza podłoża genetycznego choroby.

Na obecnym etapie konieczna jest konsultacja w Poradni Neurologicznej w celu szczegółowej oceny klinicznej Pacjenta, w przypadku podtrzymania rozpoznania zespołu Westa **w pierwszej kolejności konieczne jest rozszerzenie badania o analizę najczęstszych mutacji w genie ARX - c.428_451dup (24bp) i c.304ins(GCG)₇ w eksonie 2 genu (nie wykrywane metodą NGS).**

poliA
c. [209_345] (GCG)₁₆
p. Ala₁₆

poliA
c. [430_365] (GCG)₁₂
p. Ala₁₂



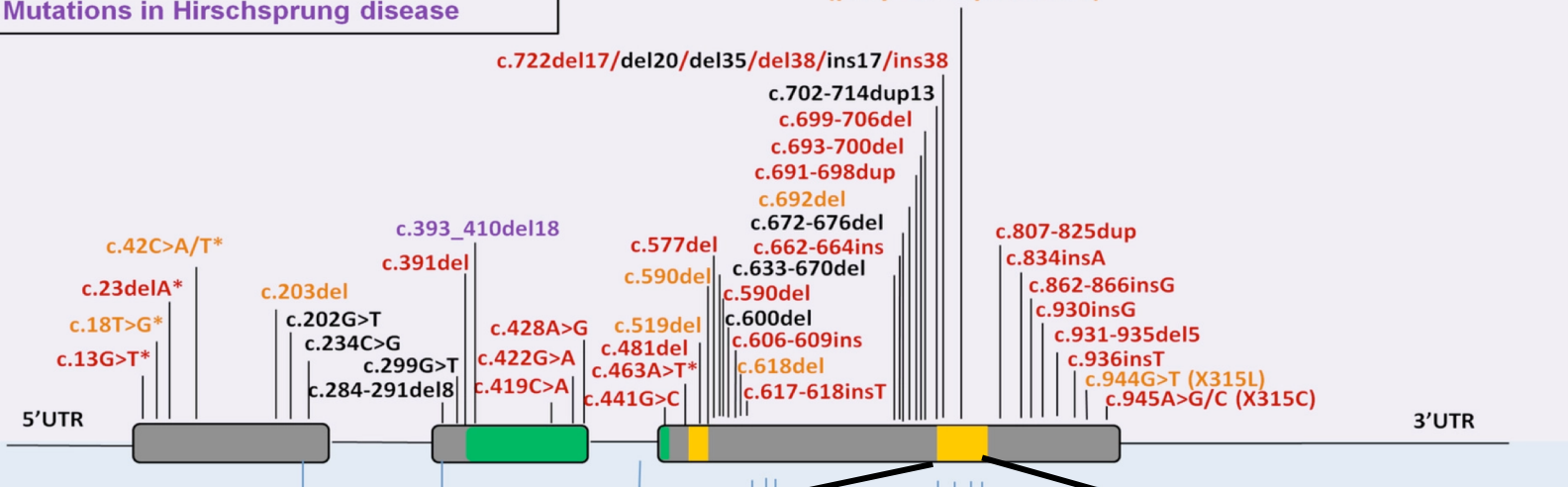
PHOX2B

Zespół ośrodkowej hipowentylacji

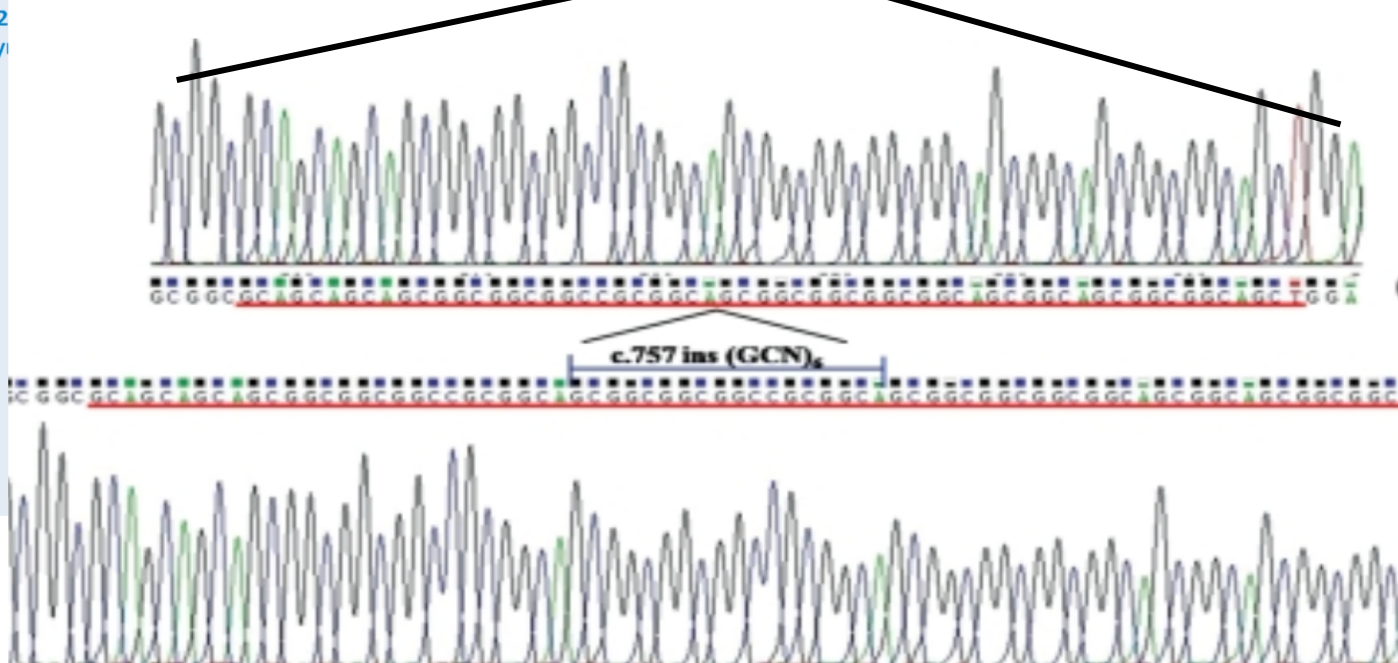
CAUSATIVE MUTATIONS

Mutations in CCHS (isolated - syndromic)
Mutations in neuroblastoma or TSNS
Mutations in Hirschsprung disease

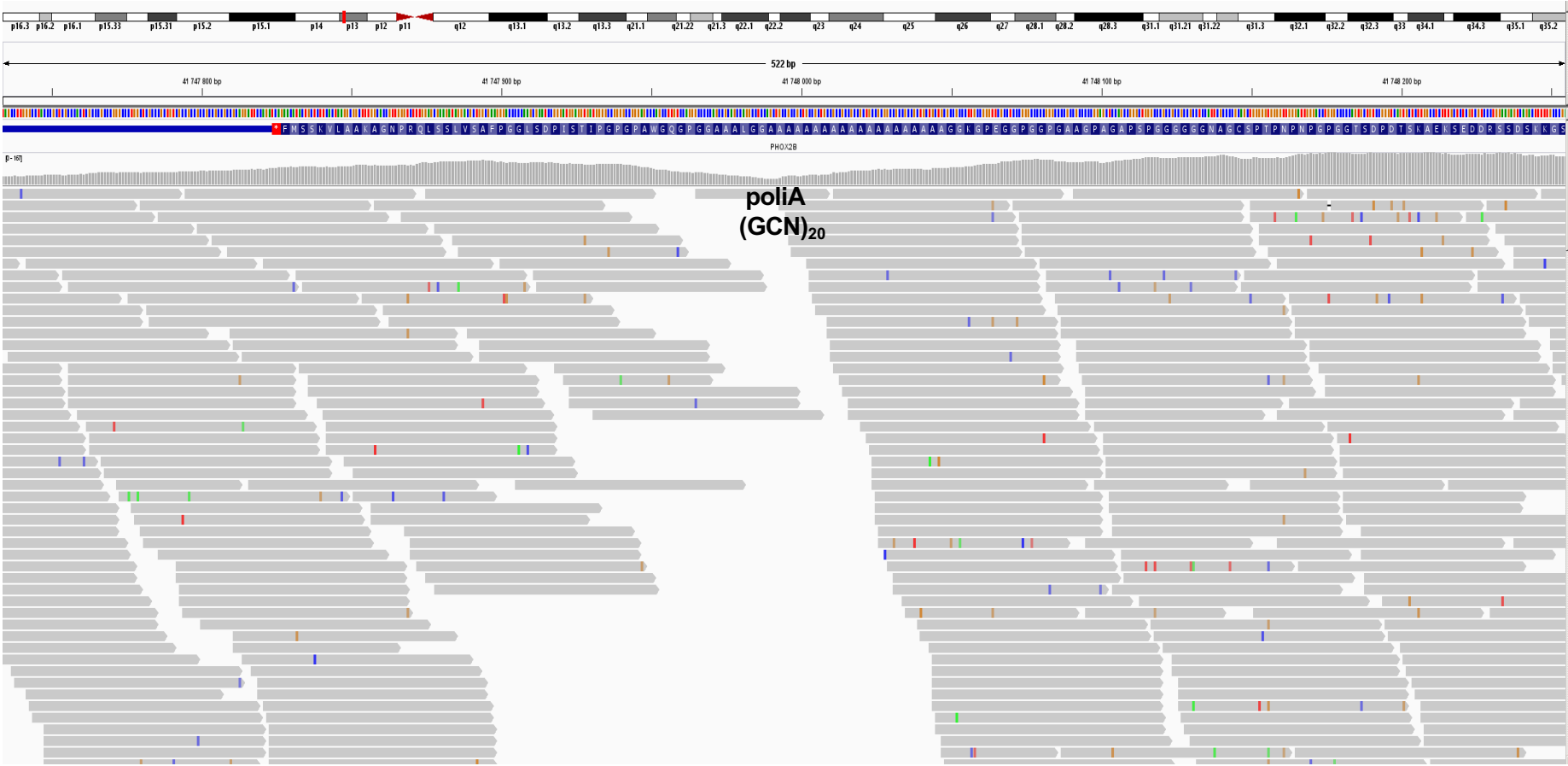
In frame duplications
(polyAa expansions)



COMMON VARIANTS

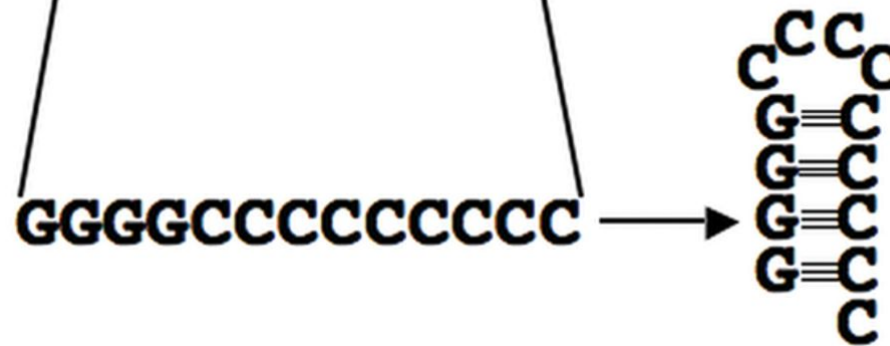
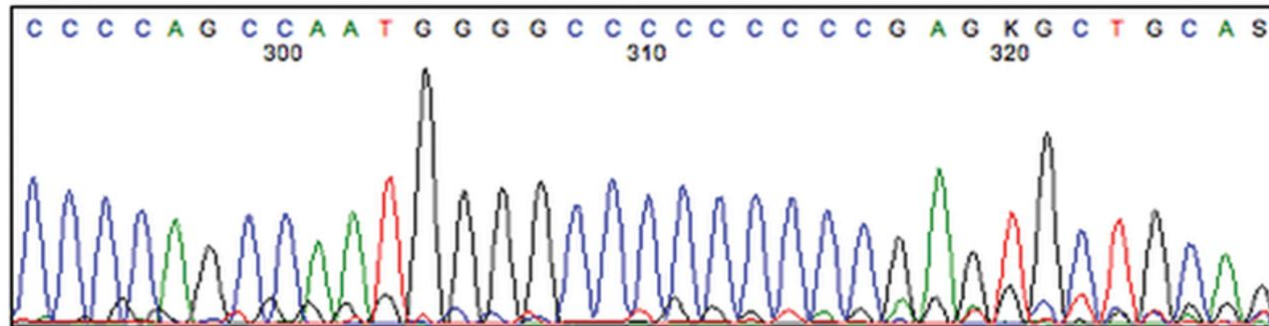


PHOX2B c.756_776dup, p.(Ala254_Ala260dup)

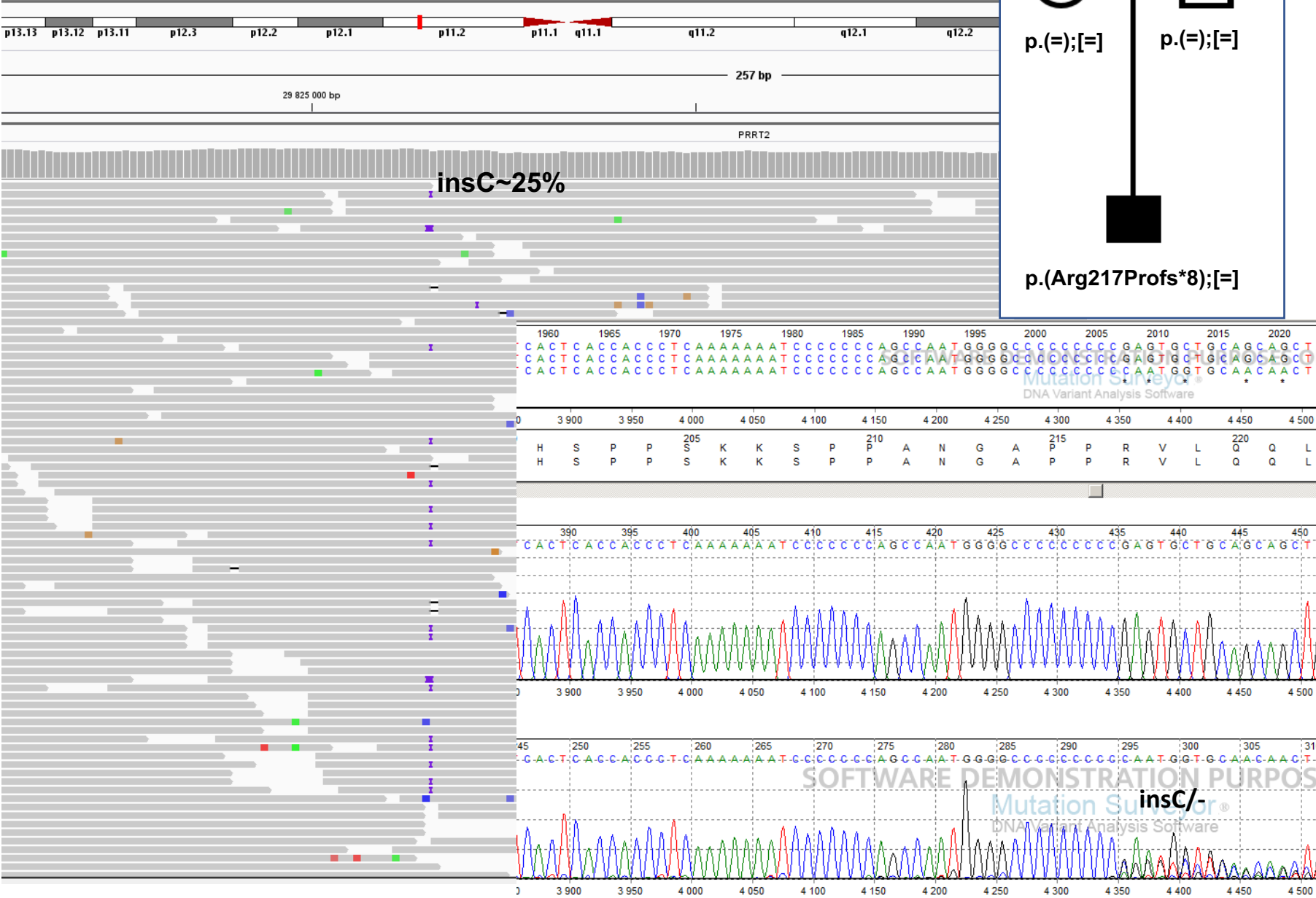


***PRRT2* c.649dupC, p.(Arg217Profs*8)**

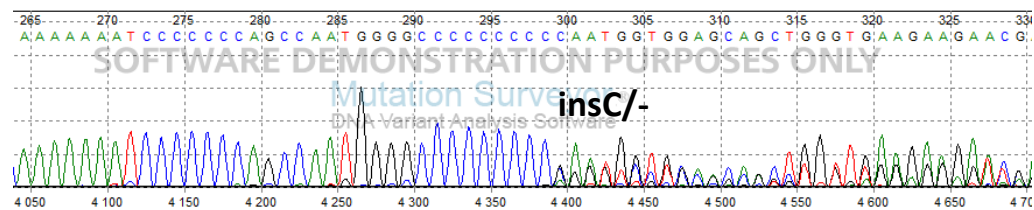
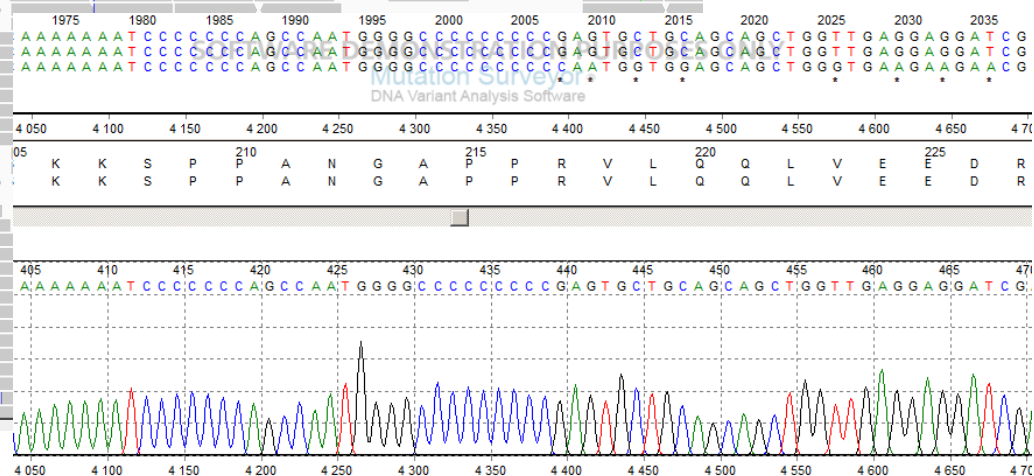
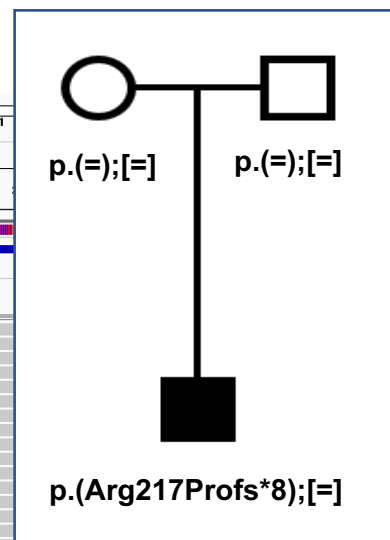
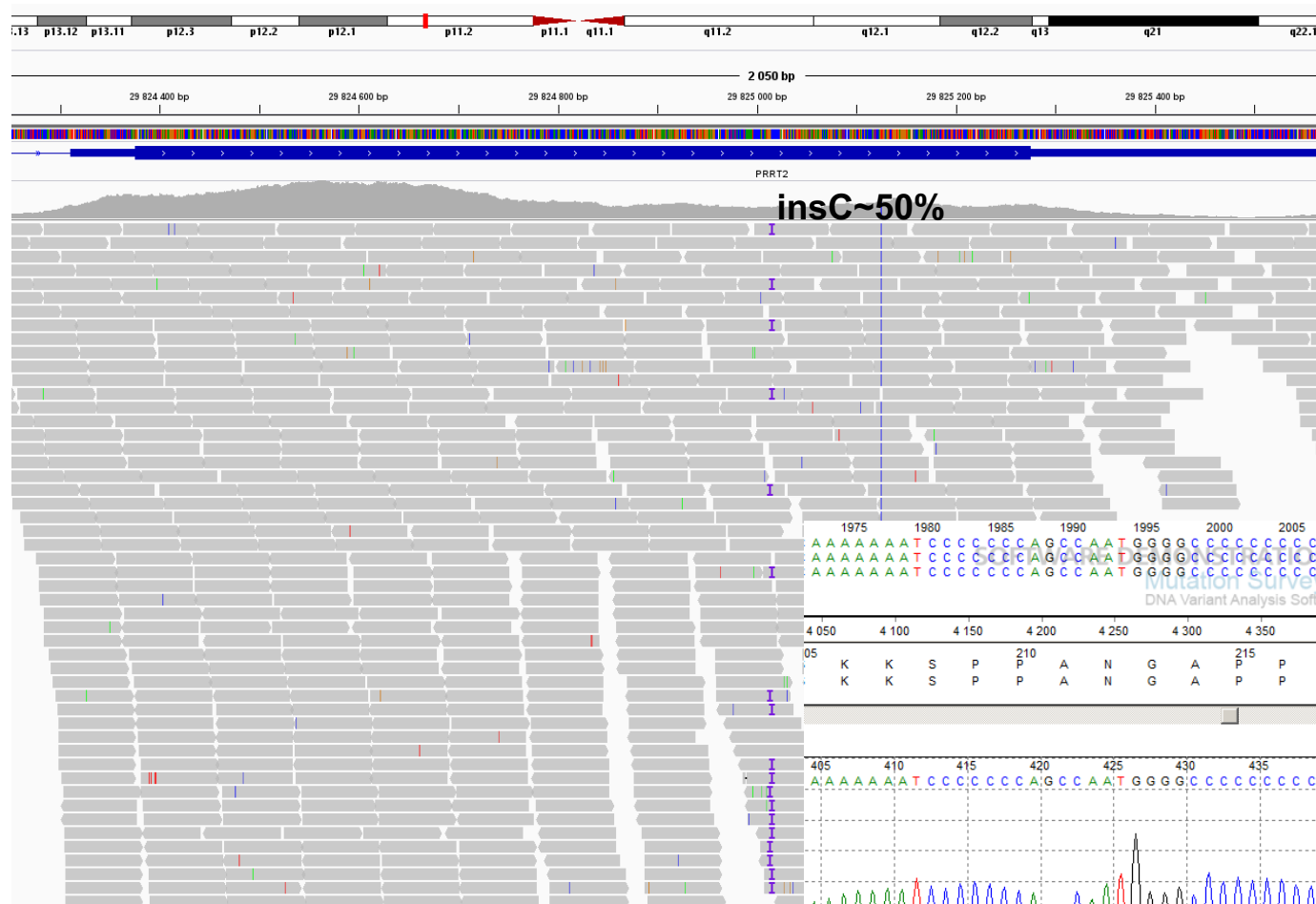
PRRT2



PRRT2 c.649dupC, p.(Arg217Profs*8)

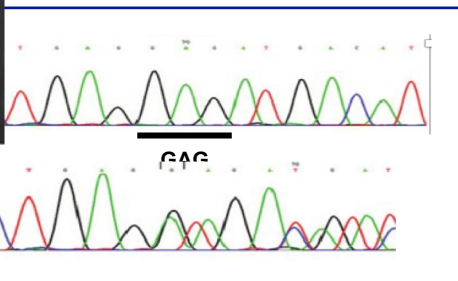
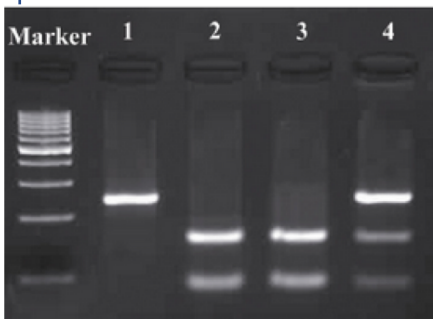


***PRRT2* c.649dupC, p.(Arg217Profs*8)**



DYT1

- podłoże molekularne mutacja w genie *TOR1A*
- najczęstsza mutacja 904-906 del GAG/*TOR1A*

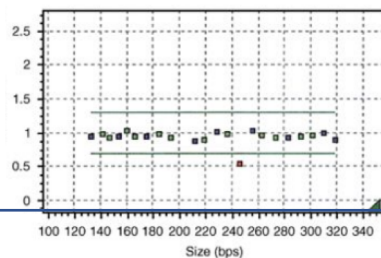
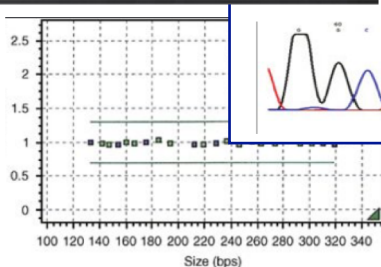


TOR1A

Prawidłowa sekw. ...GTGGCT**GAGGAG**ATGAC.....

Mut. GAGdel

...GTGGCT**GAG**ATGAC.....



Klinicysta (decyzja o badaniu)

NGS
panel / eksom*

Zidentyfikowane warianty genowe

Fenotyp



Klinicysta

Wytypowane dla fenotypu
warianty genowe

Adnotacja wariantów
Charakterystyka patogenności

Bazy danych
HGMD, ClinVar
ExAc, dbSNP
Lokalne bazy danych (dane własne)
Dane opublikowane.

Predykcja patogenności *in silico*
PolyPhen, MutationTaster, SIFT
Predykcja zaburzeń splicingu

Dane kliniczne
Dane własne

Klasyfikacja
wariantów

Badanie rodzinne
(dziedziczenie, kosegregacja z fenotypem)

Dodatkowe dane



Klinicysta

Patogenne

Potencjalnie
patogenne

O niejasnej
patogenności

?

Potencjalnie
niepatogenne

Niepatogenne

Sprawozdanie z analizy DNA

Klinicyści
(lek. kierujący
genetyk klin.)
+
Diagnosta

Analiza wyników badań NGS w praktyce



Jesteśmy w takim momencie, gdy przeprowadzanie testów genomowych (panelowego, cało eksomowe czy nawet całogenomowego), biorąc pod uwagę względy techniczne, może okazać się tańsze niż sekwencjonowanie pojedynczego genu

Cechą tych podejść jest to, że uzyskiwane informacje często mają niepewne znaczenie.

NGS
panel / eksom*

Zidentyfikowane warianty genowe

Fenotyp

Bazy danych

Ostatecznej interpretacji wyniku badania molekularnego, należy dokonać w kontekście szczegółowej analizy danych klinicznych pacjenta.

Dane własne

Klasyfikacja
wariantów

Badanie rodzinne
(dziedziczenie, kosegregacja z fenotypem)

Dodatkowe dane

Patogenne

Potencjalnie
patogenne

O niejasnej
patogenności

?

Potencjalnie
niepatogenne

Niepatogenne

Sprawozdanie z analizy DNA