DRAVET Syndrome UK

Hope for families with life-limiting epilepsy

Parent/Carer & Professional Conference 2019

#DSUKLondon19

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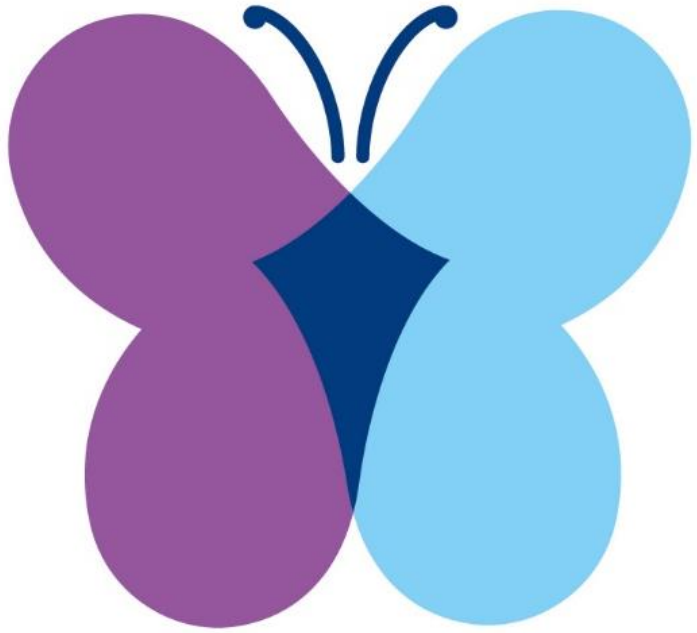


Current Thinking in Genetics, Research Update

Sanjay Sisodiya

What is the point of genetics research in Dravet?

There is a recognisable picture of Dravet syndrome

But there is also significant variation in the clinical picture

Does this matter?

Important because

1. Helps us understand the condition better, and that can only be good
2. Finding the cause of variation may provide clues to better treatment options
3. Even a condition ‘due to’ mutations in one gene is complicated – not just one standard pattern

What is the point of genetics research in Dravet?

Table 1 Characteristics of the study population

	Total, n	%	Non-Dravet (n = 103), n	Dravet (n = 97), n	Missing data, n	p Value (χ^2)
Sex					0	0.596
Male	109	54.5	58	51		
Female	91	45.5	45	46		
Mutation type					0	<0.001
Missense	129	64.5	78	51		
Splicing	19	9.5	13	6		
Nonsense	19	9.5	4	15		
Fs/rearrangements	33	16.5	9	24		
Family history of seizures					1	<0.001
Yes	111	55.8	78	33		
No	88	44.2	25	63		
Age at seizure onset, mo					47	<0.001
0–6	81	52.9	12	69		
6–12	37	24.2	18	19		
>12	35	22.9	35	0		
Mean (SD)	10.80 (14.48)		18.4 (19.51)	5.19 (2.233)		<0.001
Fever at first seizure					33	0.019
Yes	134	80.2	67	67		
No	33	19.8	9	24		
Seizure types					32	0.003
Clonic-tonic/clonic	142	84.5	73	69		
Focal	20	11.9	2	18		
Myoclonic	5	3.0	1	4		
Absence	1	0.6	0	1		
Seizure duration, min					74	0.001
0–5	65	51.6	37	28		
5–30	37	29.4	9	28		
>30	24	19.0	5	19		
EEG abnormalities					112	0.207
Yes	38	43.2	11	27		
No	50	56.8	21	29		

Abbreviation: Fs = frameshift mutations.
Seizure duration was grouped into 3 classes: 0 to 5, 5 to 30, and >30 minutes. Age at seizure onset was grouped into 3 classes: 0 to 6, 6 to 12, and >12 months. Seizure type, fever, seizure duration, age at seizure onset, and EEG discharges were calculated on 182 patients, excluding 18 individuals who did not experience seizures.

Cetica et al. Neurology 2017;88:103

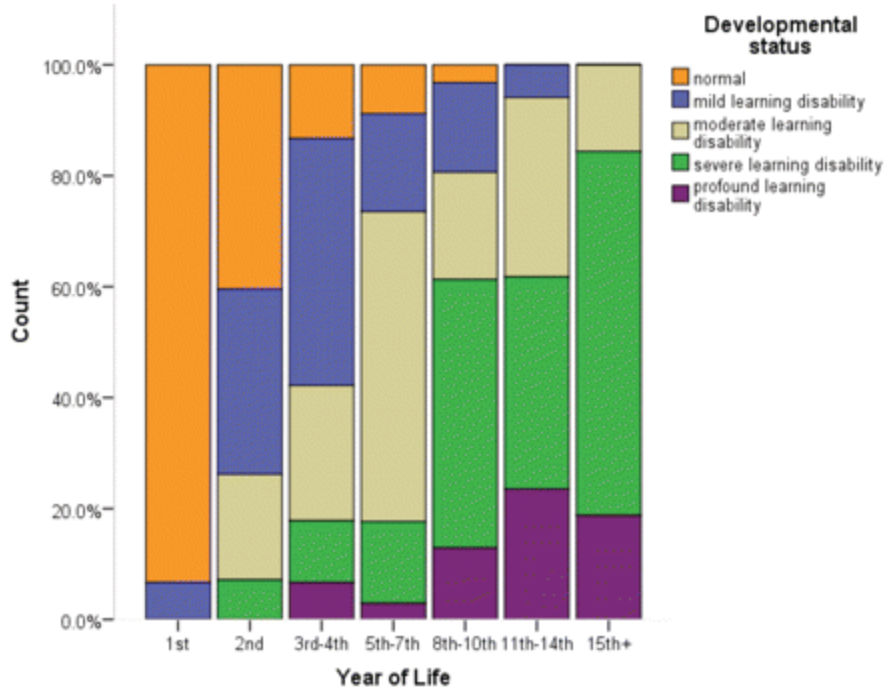


Table 3 Ordinal univariate logistic regression analysis for variables predicting worse developmental outcome (*n* = 157; adjusted for age at assessment)

Predictor variable	B	Wald test χ^2	OR (95% CI)	P
Motor disorder (yes/no)	1.19	12.31	3.28 (1.69–6.38)	<0.001
EEG abnormalities in Year 1 (yes/no)	1.74	9.93	5.70 (1.93–16.8	0.002
Status epilepticus (yes/no)	1.12	9.09	3.07 (1.48–6.35)	0.003
Age at onset of delay (months)	−0.04	6.81	0.96 (0.94–0.99)	0.009
Early focal seizures with impairment of awareness ⩽24 months (yes/no)	1.19	4.24	3.30 (1.06–10.28)	0.039
Age at onset of myoclonic seizures (months)	−0.03	3.65	0.97 (0.94–1.00)	0.056

CI = confidence interval; OR = odds ratio.

Brunklaus et al. 2012;135:2329

What is the point of genetics research in Dravet?

What causes differences between people with Dravet syndrome?

Many possibilities, including:

- mutation in *SCN1A* or another gene?
- if mutation in *SCN1A*, what type of mutation (e.g. missense vs protein-truncating)?
- mutation in *SCN1A* and another mutation(s) elsewhere in the genome?
- other genomic phenomena – mosaicism, poison exons, epigenetic processes, others

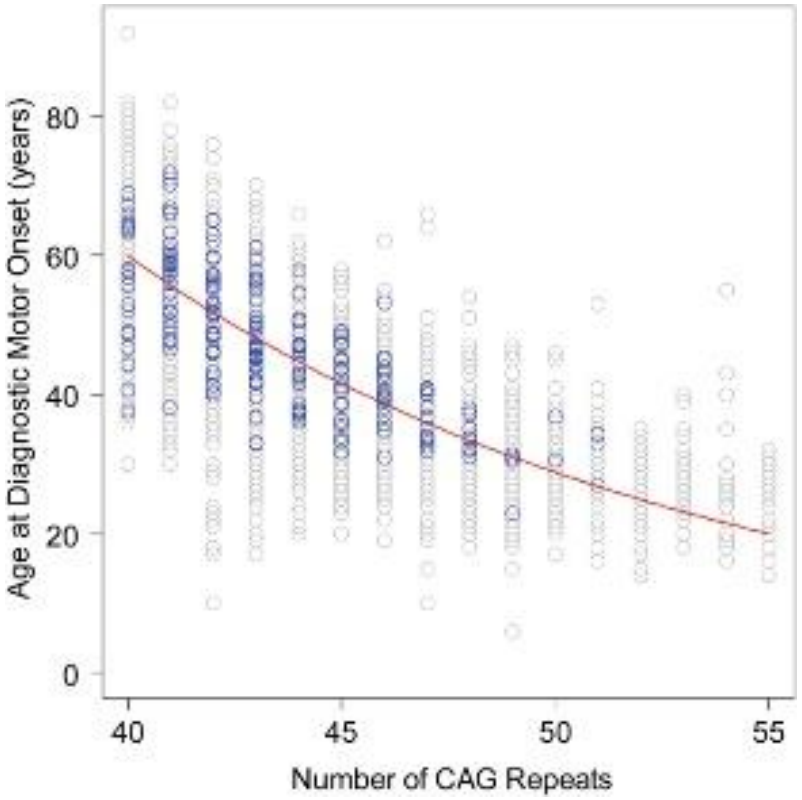
- non-genetic causes – environment, microbiome, many other possibilities
- these are generally less easy to address

So, first step is to address what is happening at the genetic level: this is the purpose of genetic research in Dravet syndrome

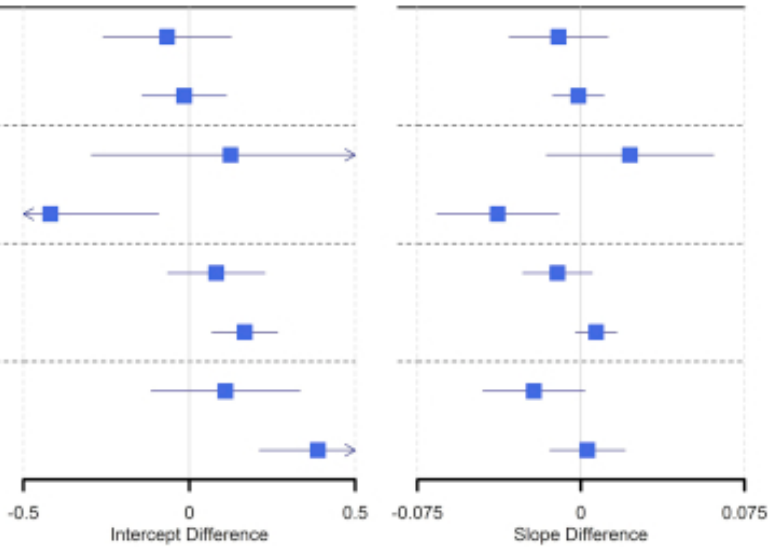
'Modifier variants / variation'

Walking before we run!

Examples of genetic modifiers



Modifier Locus	HD Gene Status	Tag SNP	Comparison of Modifier vs Wild-Type
Chr 8 bad modifier (heterozygous)	Control	rs1037699	AG - GG
	Case	rs1037699	AG - GG
Chr 15 bad modifier (heterozygous)	Control	rs146353869	AC - CC
	Case	rs146353869	AC - CC
Chr 15 good modifier (heterozygous)	Control	rs2140734	GT - TT
	Case	rs2140734	GT - TT
Chr 15 good modifier (homozygous)	Control	rs2140734	GG - TT
	Case	rs2140734	GG - TT



Long et al. Am J Hum Genet. 2018;103(3):349

Examples of environmental (?) modifiers

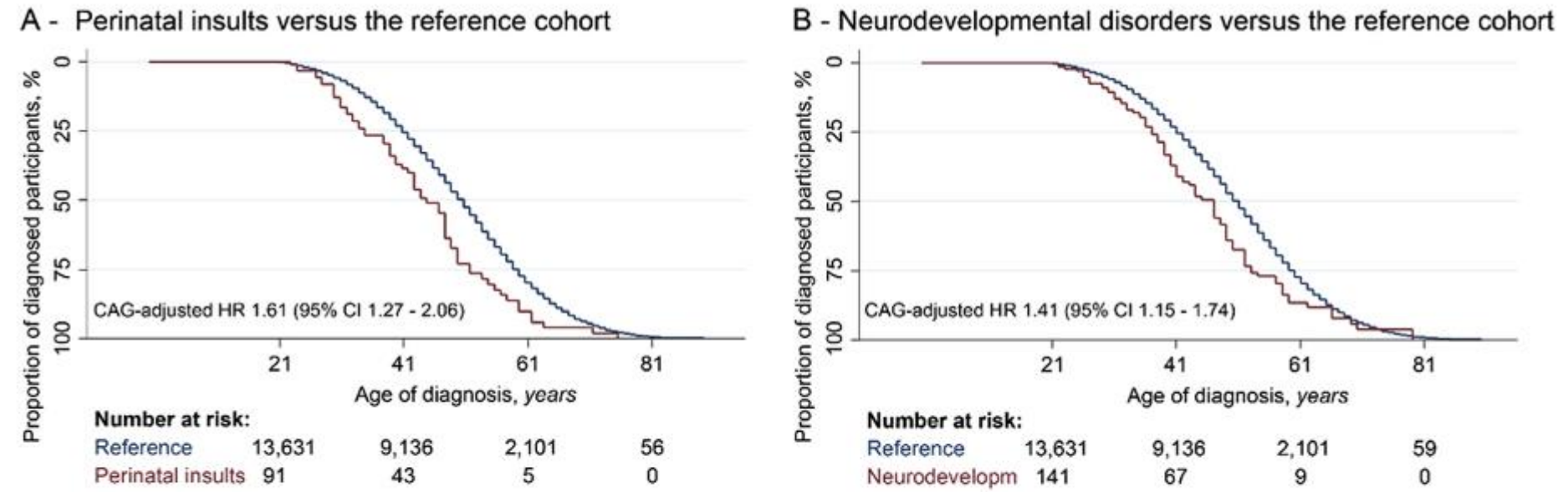
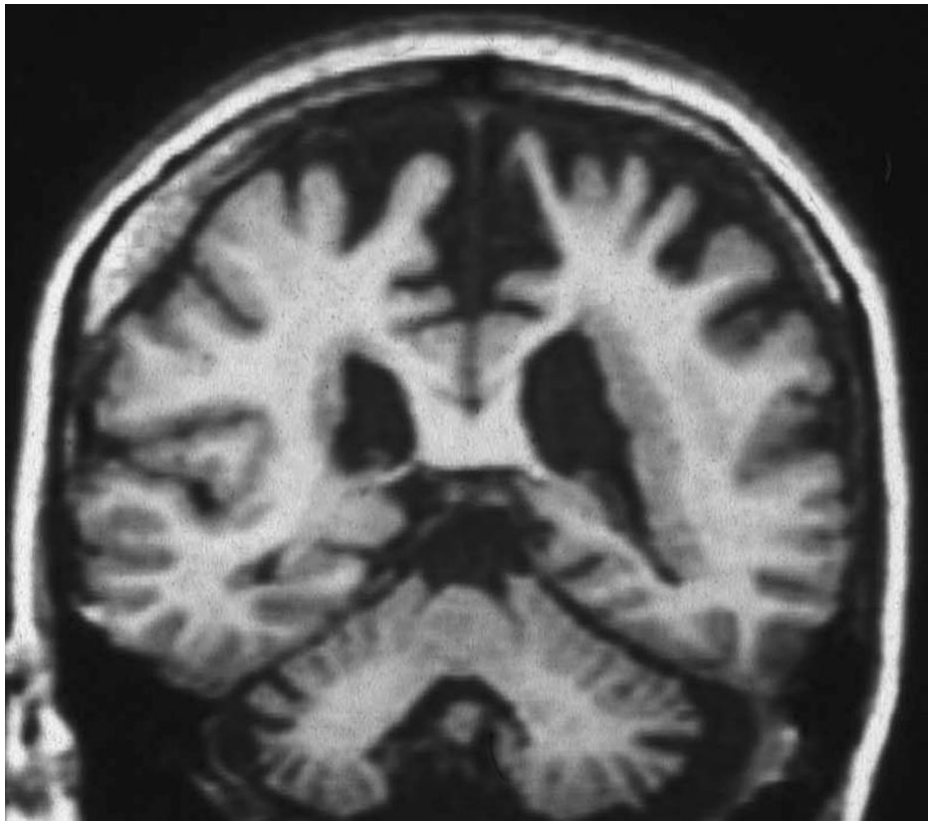


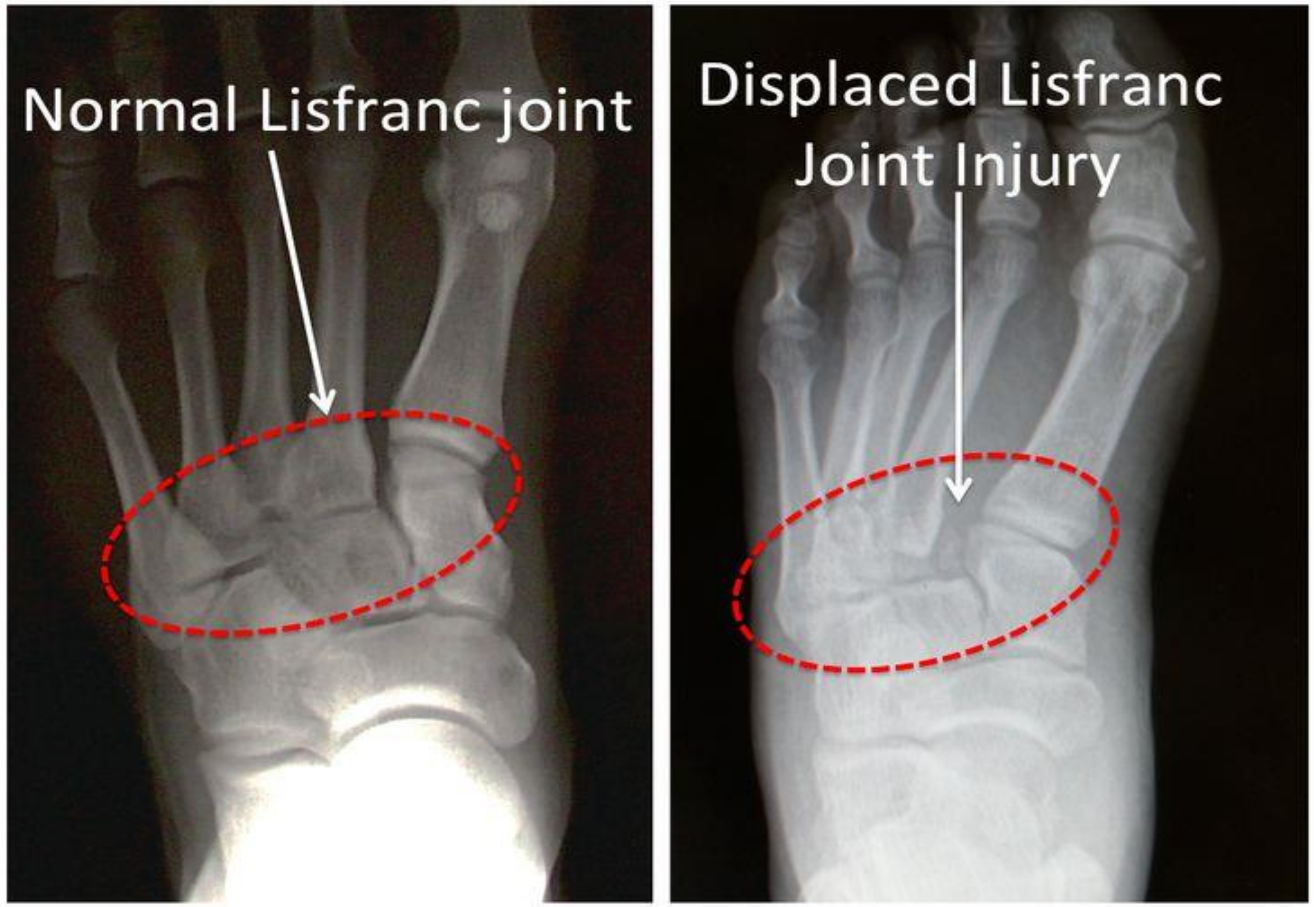
Fig. 1. Kaplan-Meier survival curves of the age of diagnosis for the merged cohort. A Participants with perinatal insults versus the "reference" group; B Participants with neurodevelopmental disorders versus the "reference" group. 95% CI, 95% confidence interval; HR, hazard ratio; Neurodevelopm, neurodevelopmental disorders.

Barkhuizen et al. Parkinsonism Relat Disord. 2018 ;55:55

Examples of more than one gene & disease

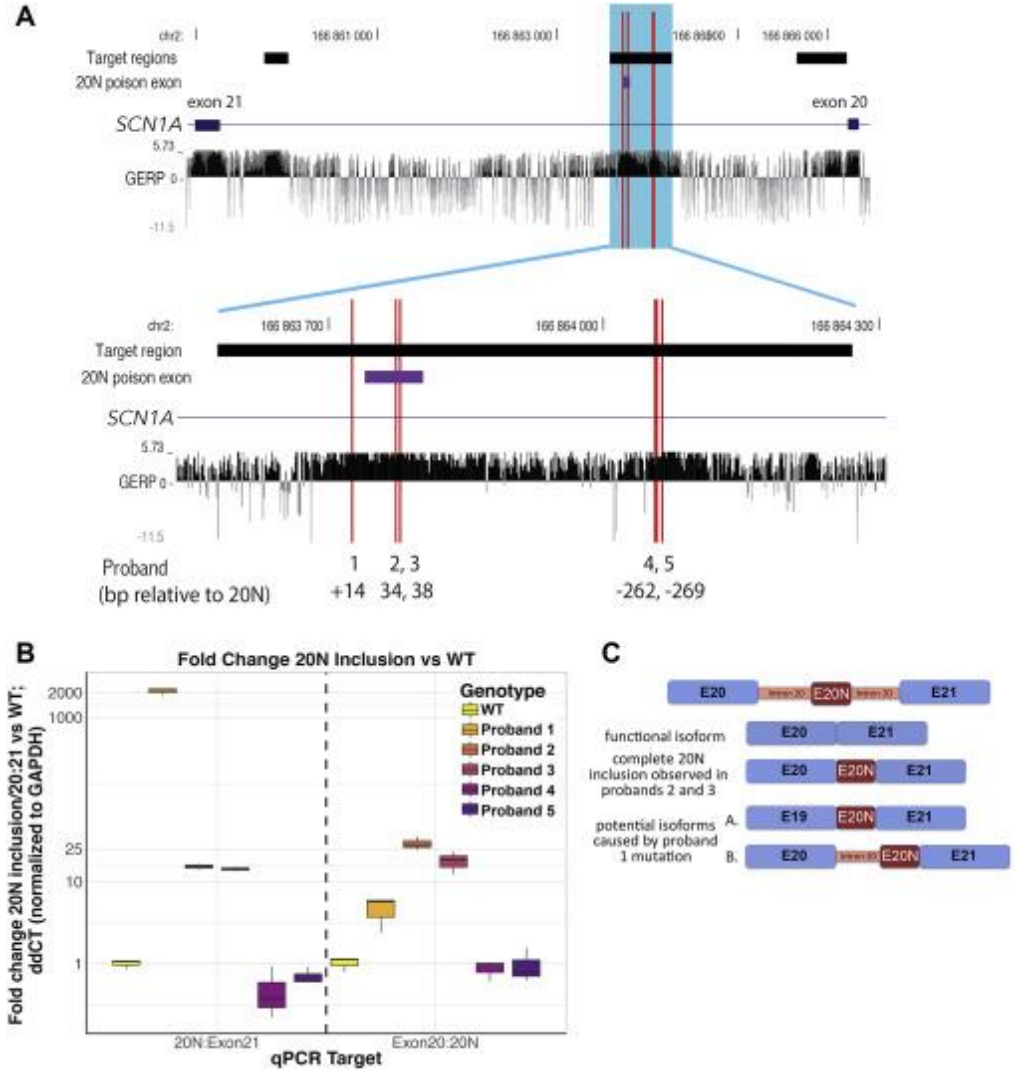


Examples of more than one gene & disease



Zouwail et al. Ann Clin Biochem. 2019;56:515

And more evidence of modifier variants



Carvill et al. Am J Hum Genet. 2018;103:1022

What about Dravet syndrome?

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Focussing on genetics

How do we do this?

How can we ‘measure’ Dravet syndrome?

There could be a number of ways e.g. phenotype scoring, gait measures, seizure frequency

Hardly ever is the effect of the *SCN1A* change causing the Dravet syndrome measured

What about Dravet syndrome?

Focussing on genetics

How do we do this?

Looking at the rest of the genome

Whole genome sequencing

~1200 DNA samples submitted

Findings in ~20% of individuals so far

Many more diagnoses to come

Iterative analysis