The odyssey continues:

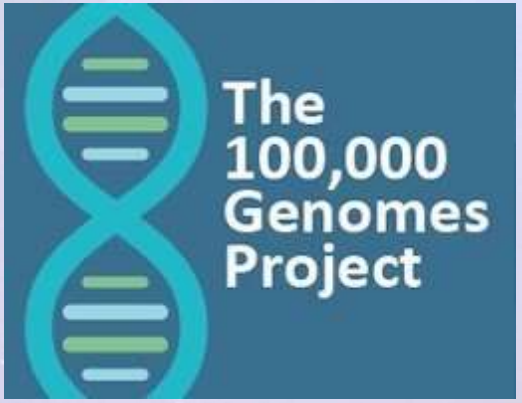
A ‘deep dive’ into NI’s 100k Genomes Project undiagnosed.

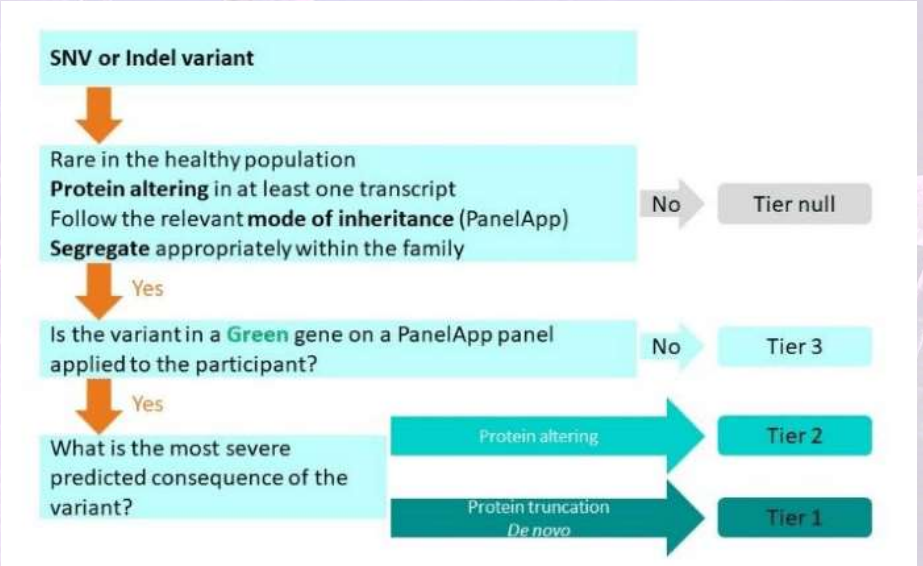
C McKenna[1], K Kerr[2], D Thomas[2], S Heggarty[1], W Wright[1], R Martin[1], P Hart[1], G Rea[1], L Soeters[1], C Flanagan[2], S McKee[1], AJ McKnight[2]
1. Northern Ireland Regional Molecular Diagnostics Service, Belfast Health & Social Care Trust, 2. Queen's University Belfast

Artist: Dr Shane McKee

The back story…

- 100,000 genomes project
- NIRMDS recruited 442 probands
- GEL tiering system
  - Clinician review of tier 1 & 2
  - Formal classification by local clinical scientists
- Diagnostic yield 18.5% (n=82)

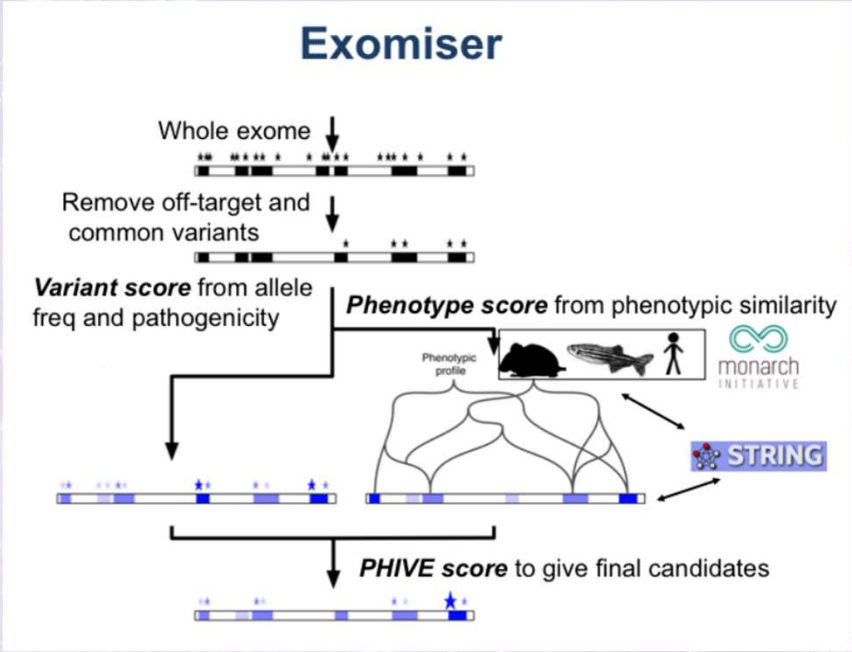




What we are doing…

- 360 probands remained undiagnosed…

- 100KGP top 5 exomiser variants
- Relevant data collated
  - Inheritance, OMIM morbidity, gnomAD prevalence, REVEL score, missense constraint and pLI.
- Clinician review, of variants & phenotype
- Formal classification by clinical scientists & discussion at Genomics MDT



EXOMISER TOP 5 (SNVs)

Exomiser	Variant co-ordinates[1] Type	Gene (transcript) (HGVS)	Zygosity	Inheritance (if known)	Omim Morbid Y/N	GnomAD exome+genome AC[2]	No. of gnomAD exome/genome homozygotes[3]	Missense variants only		Null variants only[4]
								REVEL score[5]	GnomAD Z-score[7]	GnomAD pLI[6]
1	4:968279:C:T SNV splice_region_variant	DGKQ(NM_001347.4):c.663+3G>A	Het	De novo	N	2199	0	n/a	n/a	0
2	X:48560533:C:T SNV missense_variant	TBC1D25(ENST00000376771.9):c.1625C>T (p.Pro542Leu)	Hemi	Mat	N	9	0	0.05999	3.1	n/a
3	22:31267899:C:T SNV missense_variant Compound Heterozygous	LIMK2(ENST00000331728.9):c.1252C>T (p.Arg418Cys)	Het	Mat	N	67	0	0.6179	1.4	n/a
3	22:31266023:G:A SNV missense_variant Compound Heterozygous:	LIMK2(ENST00000331728.9):c.932G>A (p.Arg311His)	Het	Pat	N	1	0	0.6679	1.4	n/a
4	17:18278287:C:T SNV missense_variant Compound Heterozygous	TOP3A(NM_004618.5):c.2215G>A (p.Gly739Arg)	Het	Mat	Y	211	0	0.4399	1.31	n/a
4	17:18278232:G:A SNV missense_variant Compound Heterozygous	TOP3A(NM_004618.5):c.2270C>T (p.Pro757Leu)	Het	Pat	Y	700	1	0.03599	1.31	n/a
5	20:62326876:C:T SNV missense_variant Compound Heterozygous	LAMA5(NM_005560.6):c.5203G>A (p.Val1735Met)	Het	Mat	N	2140	9	0.4219	-0.27	n/a
5	20:62324168:G:A SNV missense_variant Compound Heterozygous	LAMA5(NM_005560.6):c.5680C>T (p.Arg1894Cys)	Het	Pat	N	285	Not reported	0.286	-0.27	n/a

1 Build Hg38

What we have found so far…

- 200/360 probands top 5 exomiser variants reviewed
  - >1,000 variants
- Potential causative variants in 42 patients (21%)
  - 13 formal classification
    - 6 likely pathogenic / pathogenic
    - 7 hot VUS

Why were they “missed” in tier 1/2…

- HPO terms ‘incomplete’ / too narrow
- New gene disease association has emerged / is emerging
- X-linked variants in females
- Variants dismissed by clinician
- Variant inherited from “unaffected” parent / not shared with “affected sibling”

5 key lessons learned…

1. Comprehensive phenotyping is key
2. Variant 1st, phenotype 2nd
3. One eye on the patient, one eye on the data
4. Filtering by inheritance is dead, prioritisation is King
5. Access to functional work is imperative