Precision medicine in NTUH
Rapid diagnosis for genetic conditions by next-generation sequencing

Wuh-Liang Hwu
Department of Pediatrics and Medical Genetics
National Taiwan University Children's Hospital

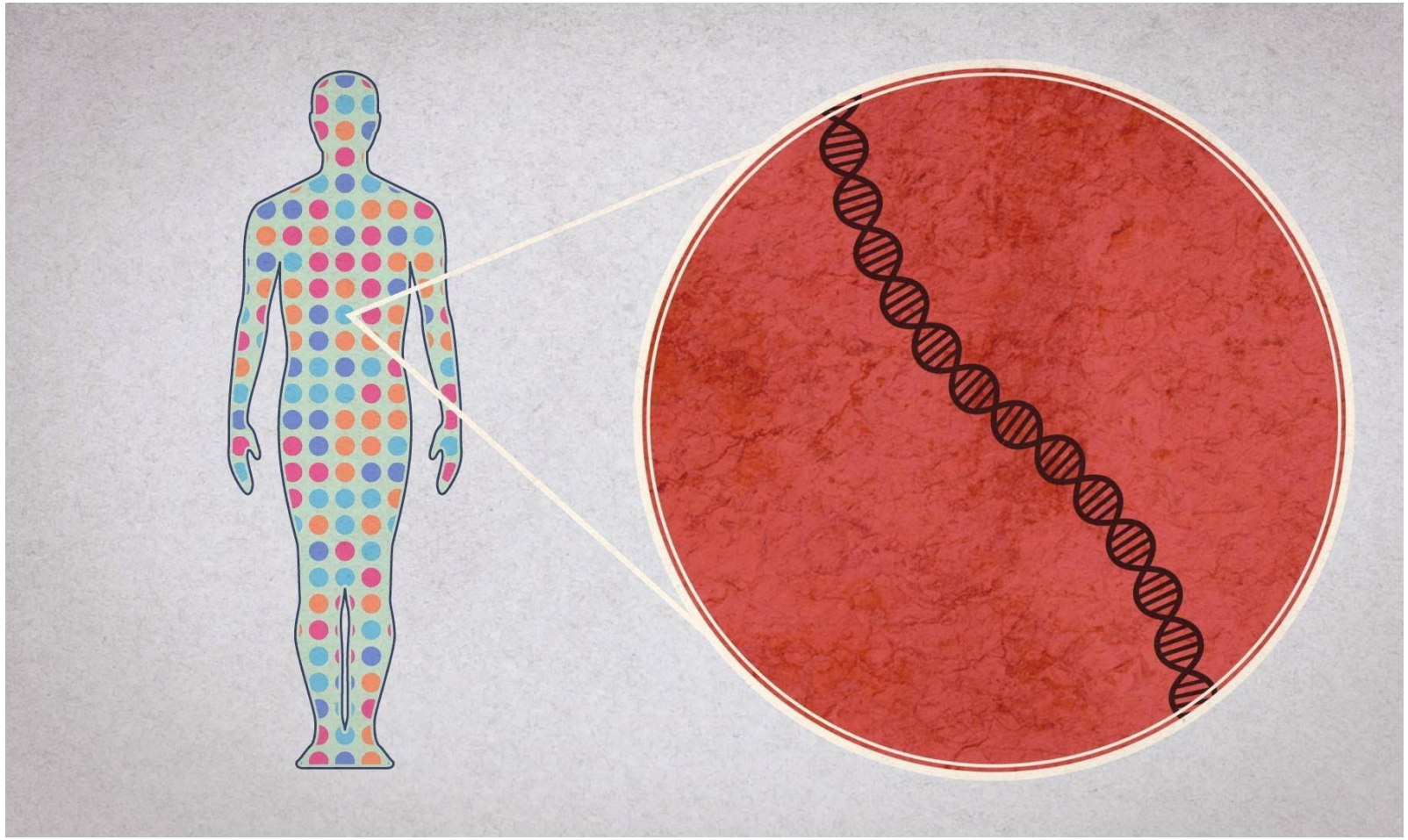
Quality

Quality Control (QC)

Quality in medicine can’t be achieved without a correct diagnosis

The Burden of Genetic Disease on Inpatient Care in Children’s Hospitals is high

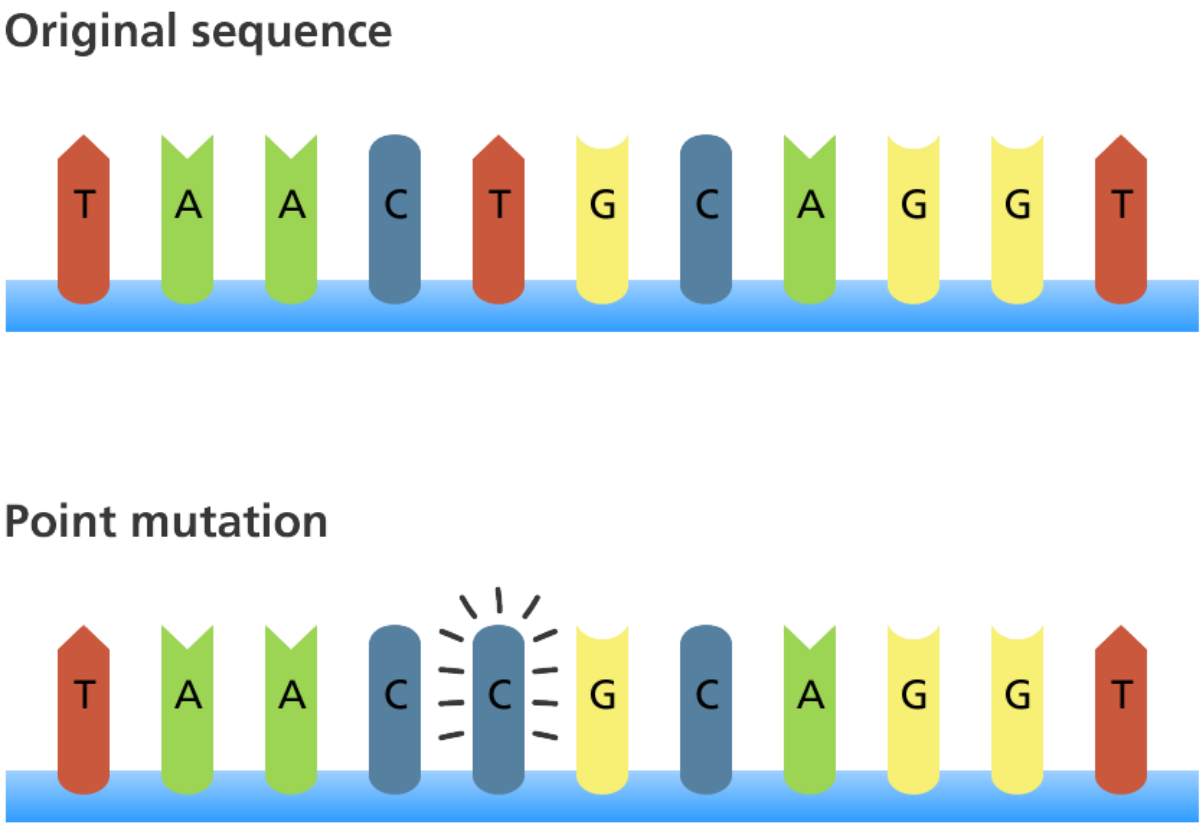
The human genome contains over 3 billion base pair of DNA



23 pairs of chromosome
Total length: over 3 billion base pairs
~20,000 protein coding genes

https://www.youtube.com/watch?v=MvuYATh7Y74; https://www.ncbi.nlm.nih.gov/genome/guide/human/

If DNA sequences change, you may got sick



https://www.yourgenome.org/facts/what-types-of-mutation-are-there

Mutation in DNA sequence causes human diseases

Sam Berns, 17y
Progeria

Queen Victoria
Hemophilia

https://www.newsmax.com/thewire/sam-berns-progeria-aging-disease/2014/01/13/id/546793/

OMIM Gene Map Statistics

OMIM Morbid Map Scorecard (Updated February 8th, 2019)

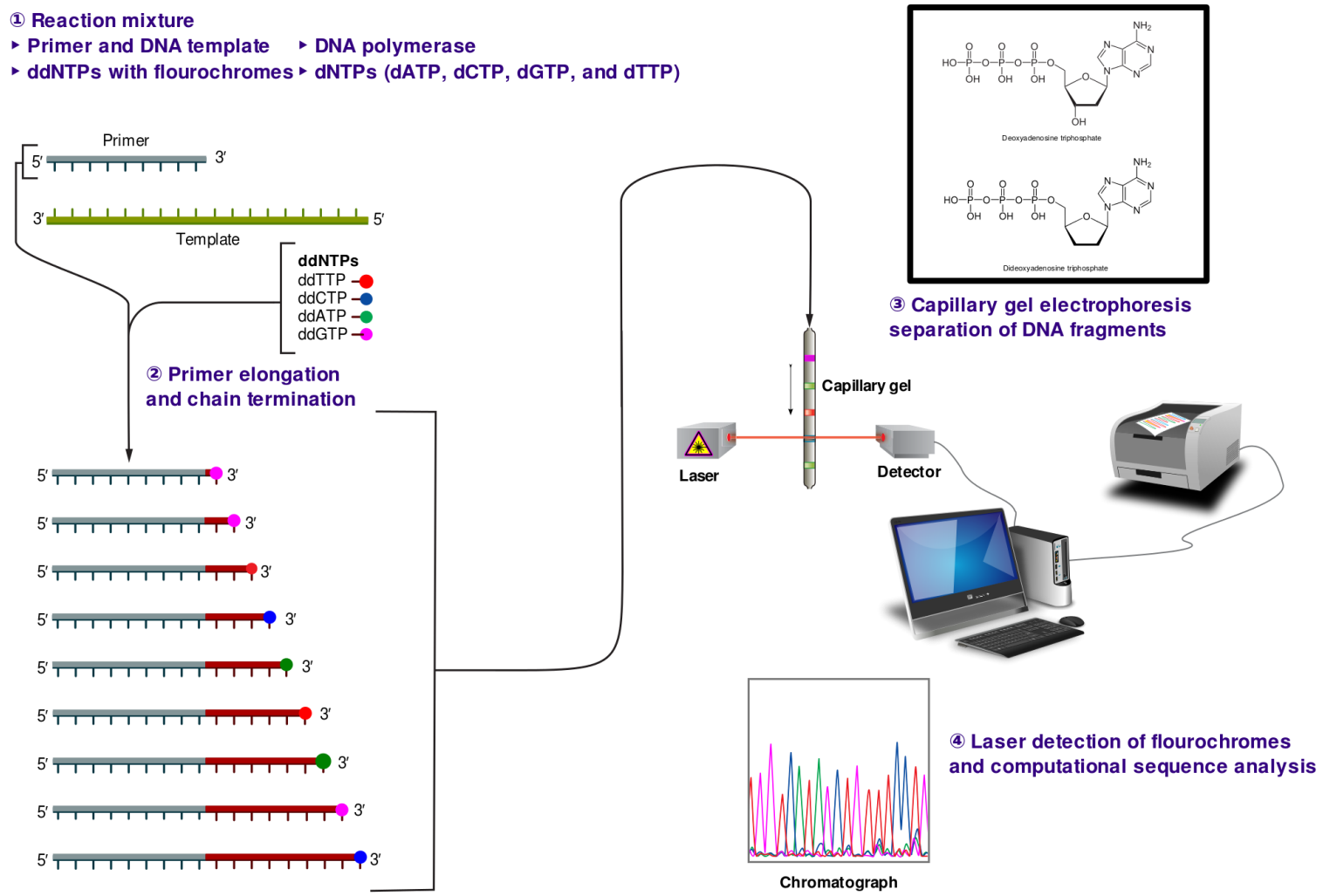
Total number of phenotypes* for which the molecular basis is known	6,357
Total number of genes with phenotype-causing mutation	4,040

Distribution of Phenotypes across Genes (Updated February 8th, 2019)

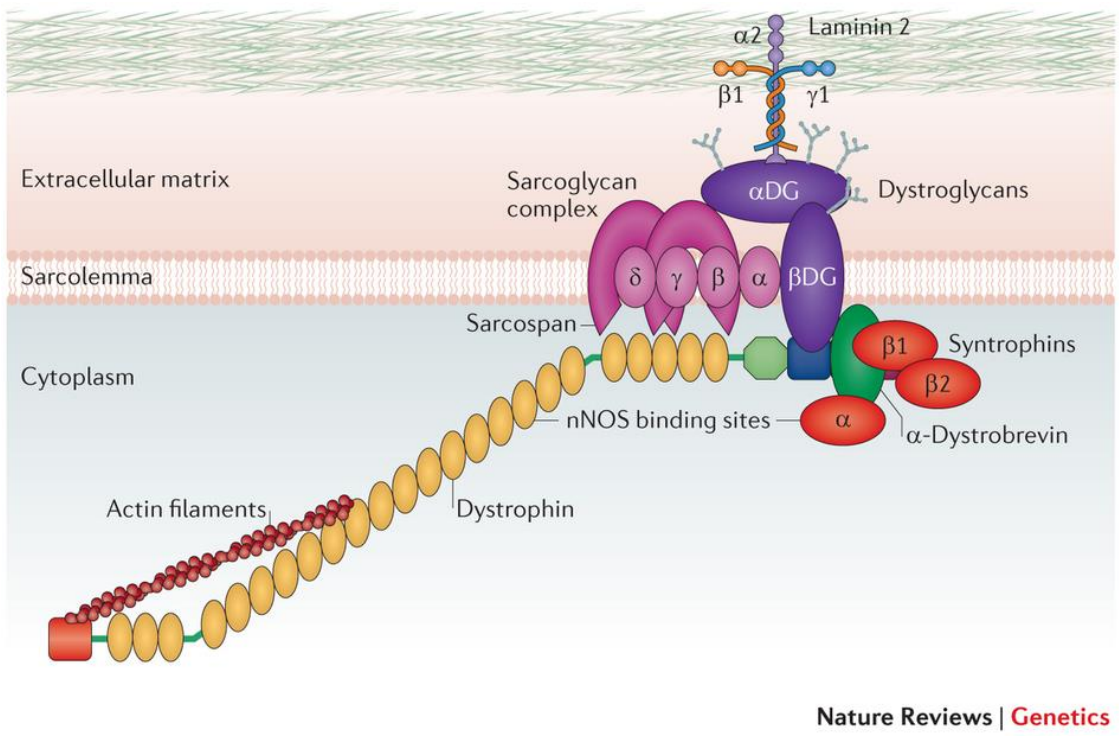
Number of genes with 1 phenotype	2,779
Number of genes with 2 phenotypes	762
Number of genes with 3 phenotypes	265
Number of genes with 4+ phenotypes	234

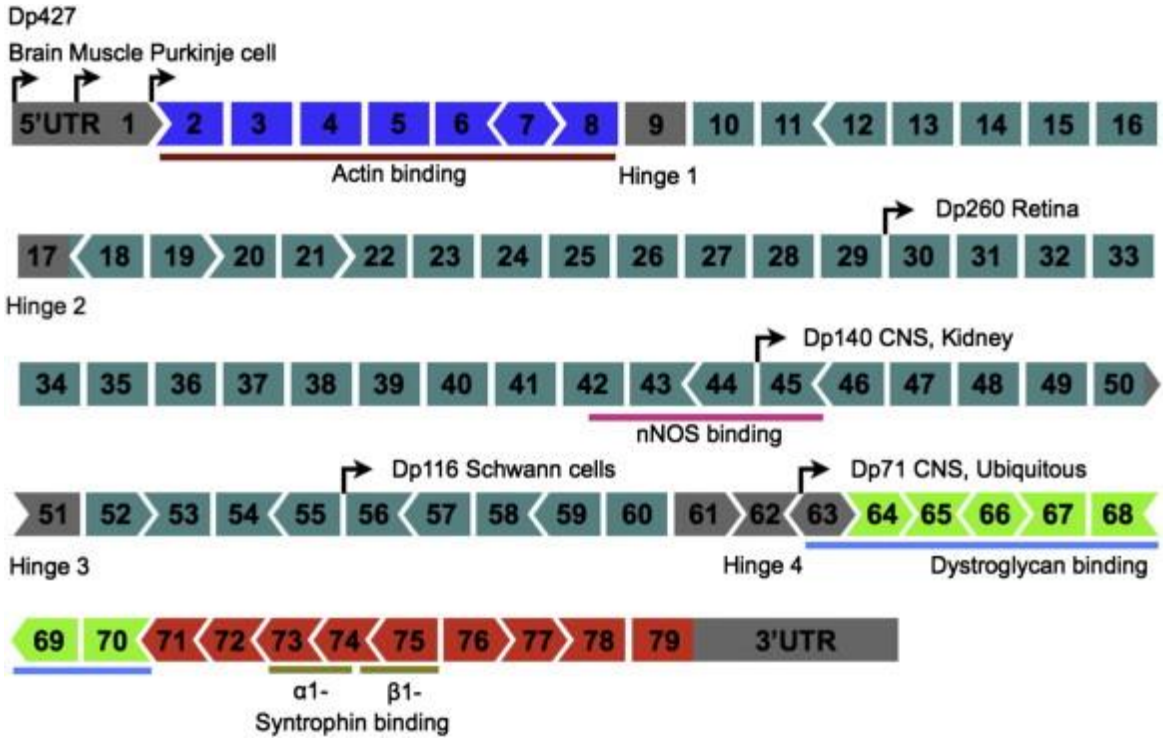
How to find a mutation?

Capillary sequencing (Sanger sequencing)



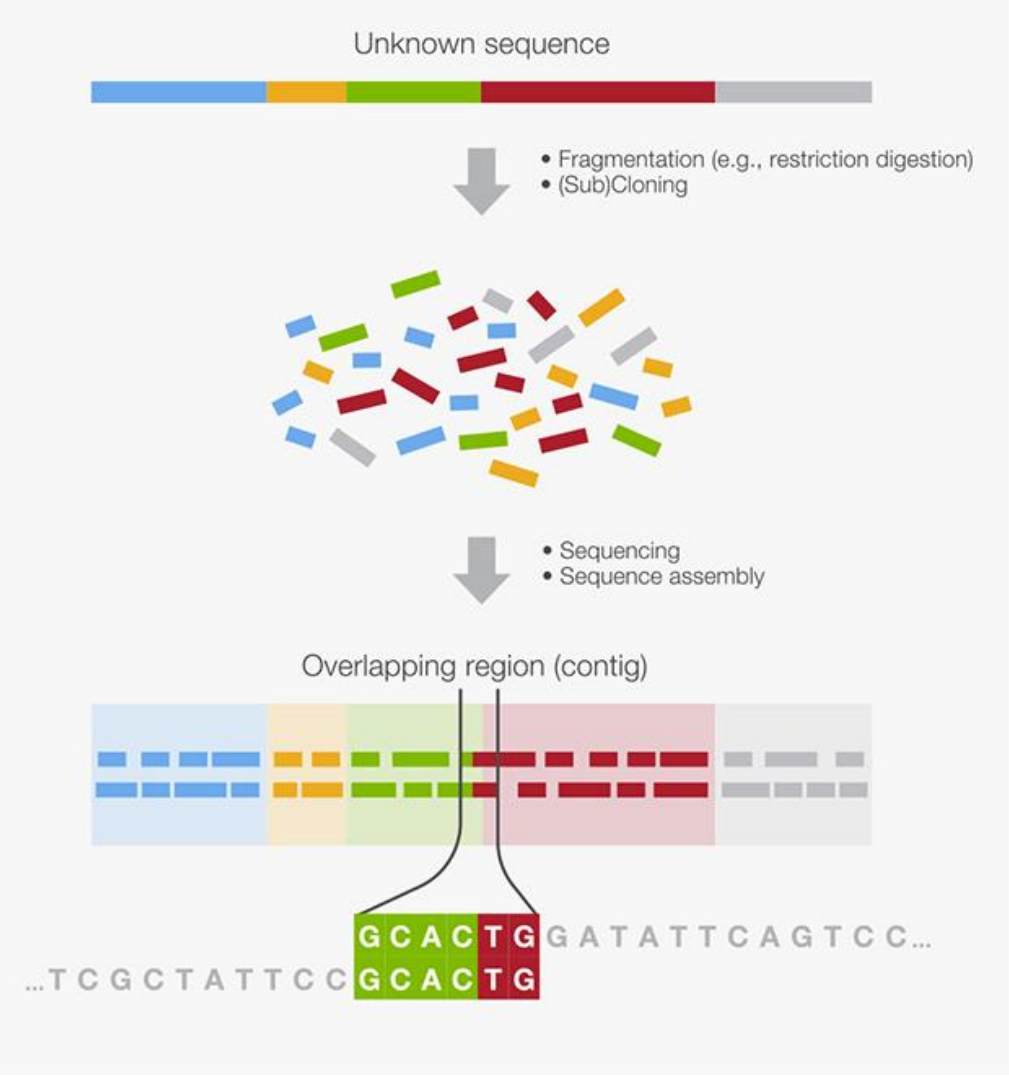
Dystrophin gene

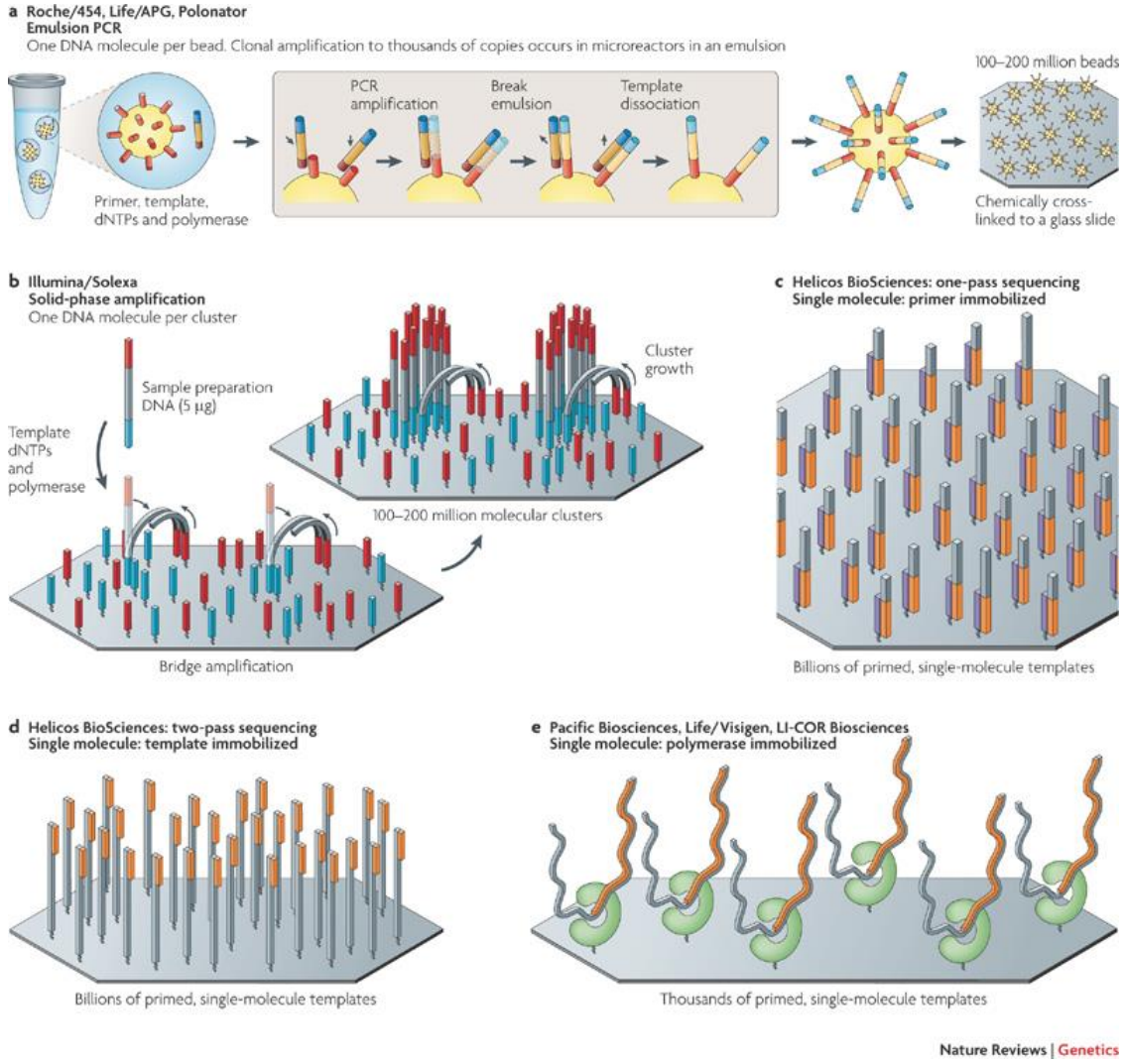




This big gene is quite refractory to Sanger sequencing

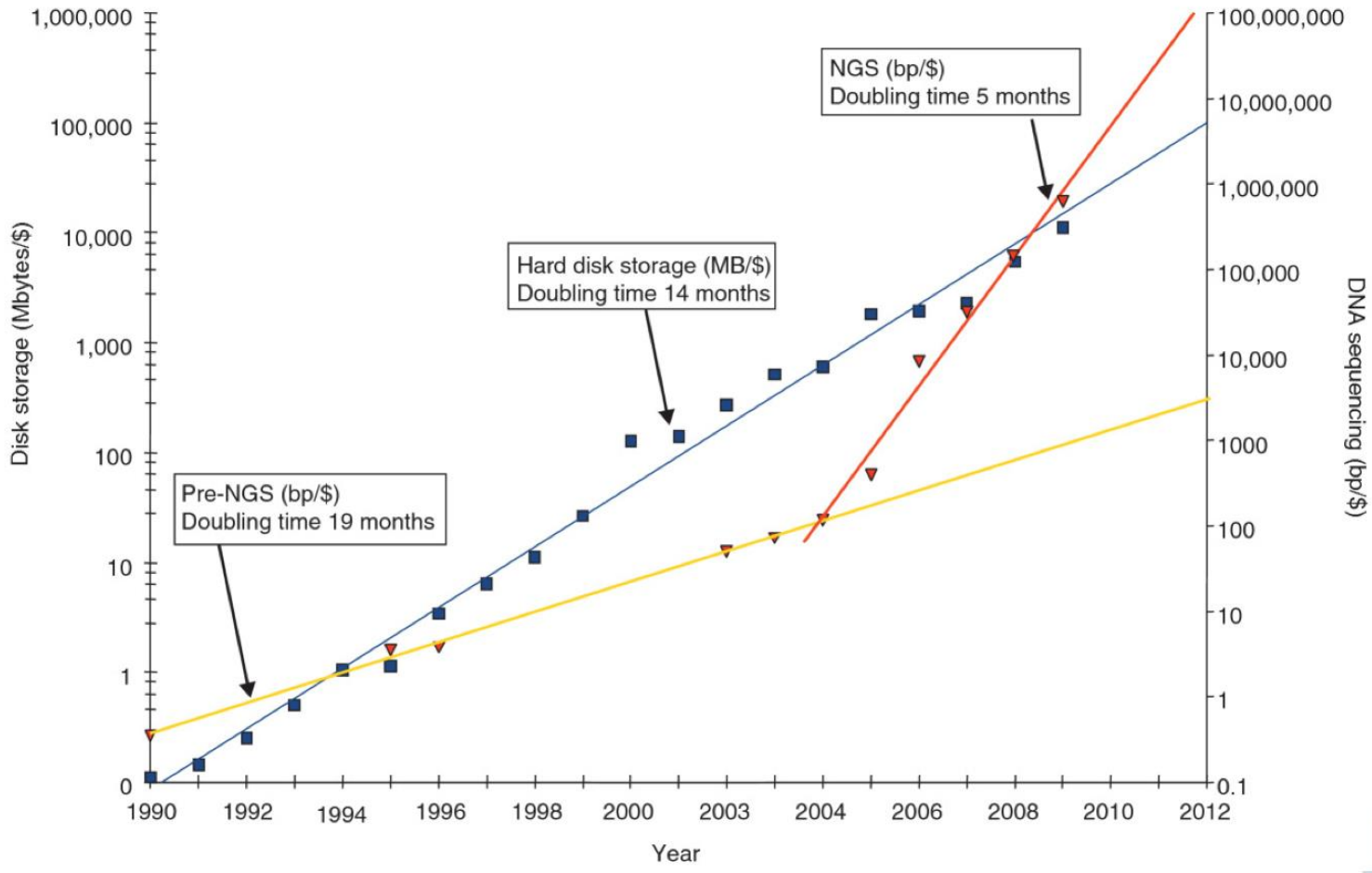
Next generation sequencing





Nature Reviews Genetics 11, 31-46 (January 2010)

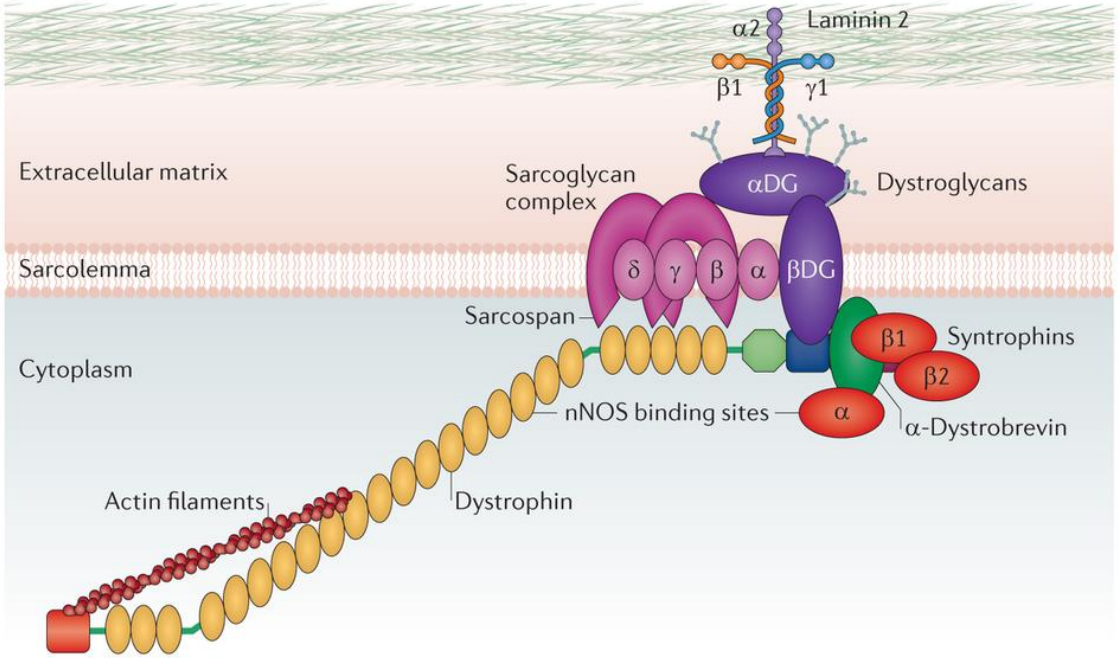
NGS a Game-Changer



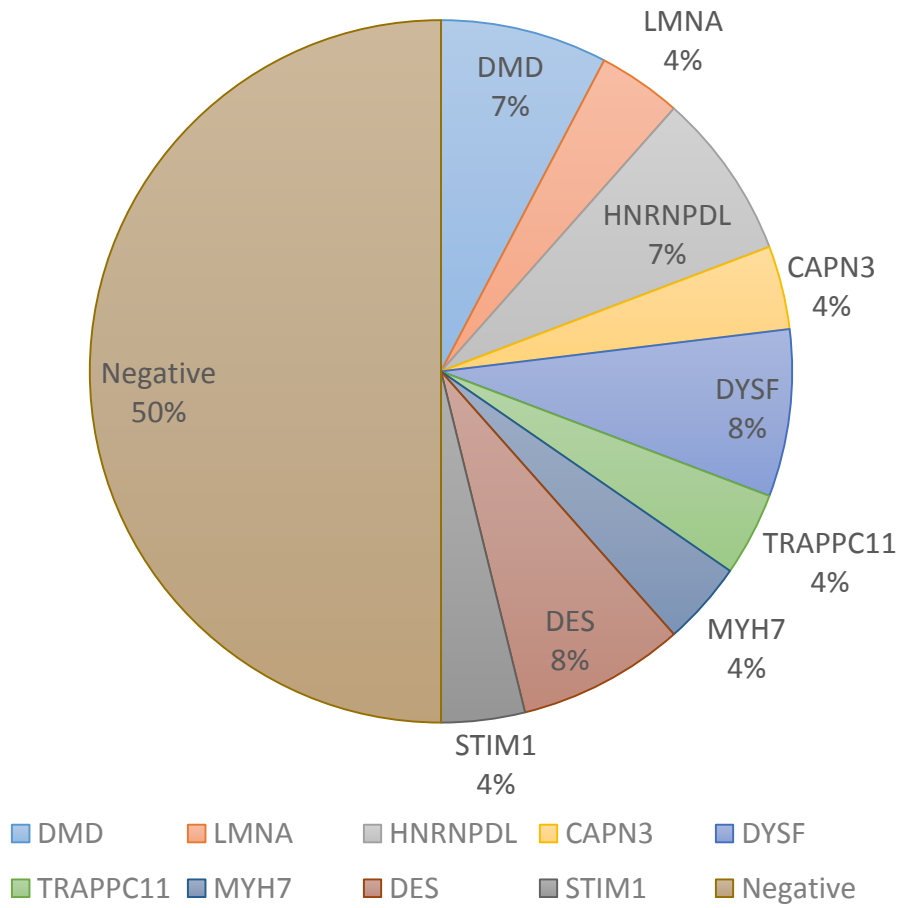
NTUH 400-gene NGS panel

- Neuromuscular diseases
- Skeletal diseases
- Metabolic diseases

NGS diagnosis of 26 cases of Muscular Dystrophy in NTUH 2017

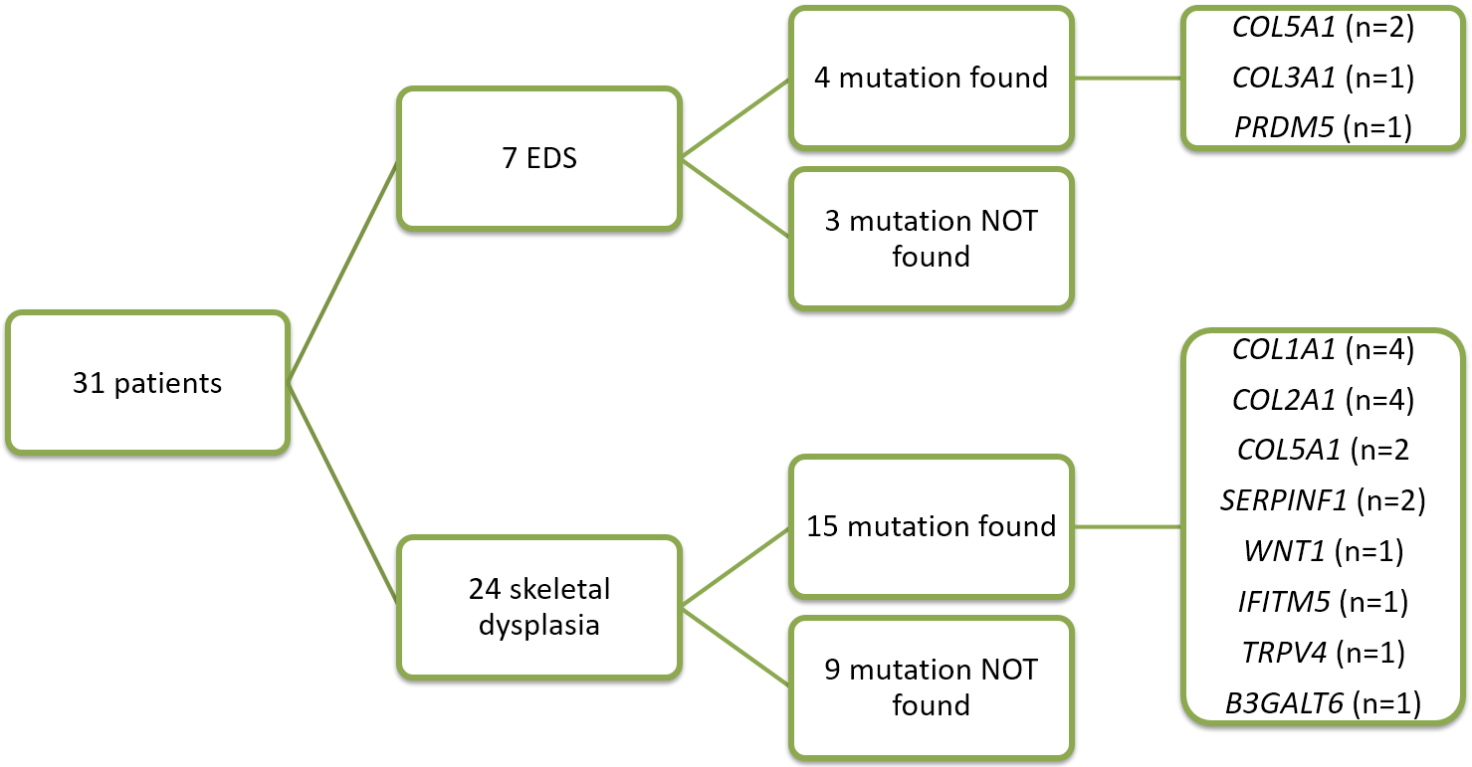


Nature Reviews | Genetics



ASHG poster 2017

Diagnosis of osteogenesis imperfect (OI) and Ehlers-Danlos syndrome (EDS) in NTUH



	EDS subtype	Associated genes
1	Classical (cEDS)	*COL5A1, COL5A2* (rarely *COL1A1)*
2	Classical-like (clEDS)	*TNXB*
3	Cardiac-valvular (cvEDS)	*COL1A2*
4	Vascular (vEDS)	*COL3A1* (rarely *COL1A1)*
5	Hypermobile (hEDS)	Unknown
6	Arthrochalasia (aEDS)	*COL1A1, COL1A2*
7	Dermatosparaxis (dEDS)	*ADAMTS2*
8	Kyphoscoliotic (kEDS)	*PLOD1, FKBP14*
9	Brittle cornea syndrome (BCS)	*ZNF469, PRDM5*
10	Spondylodysplastic (spEDS)	*B4GALT7, B3GALT6, SLC39A13*
11	Musculocontractural (mcEDS)	*CHST14, DSE*
12	Myopathic (mEDS)	*COL12A1*
13	Periodontal (pEDS)	*C1R, C1S*

Whole exome sequencing (WES)

Sequencing of more than 200,000 exons

(> 37 Mb)

More than 40,000 variants arise from WES

40,000-100,000 variants

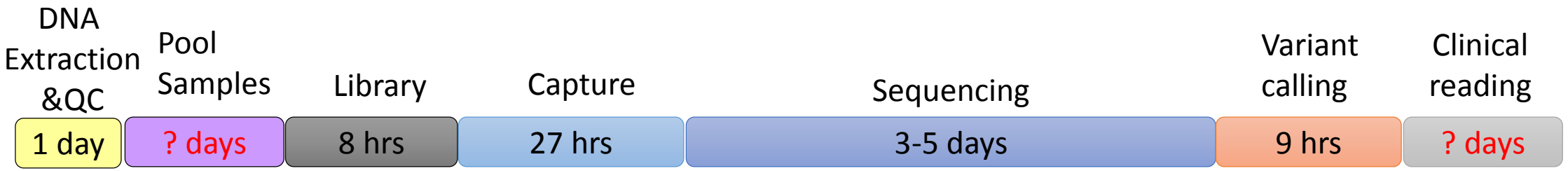
MViewer software and

Variant Prioritizer

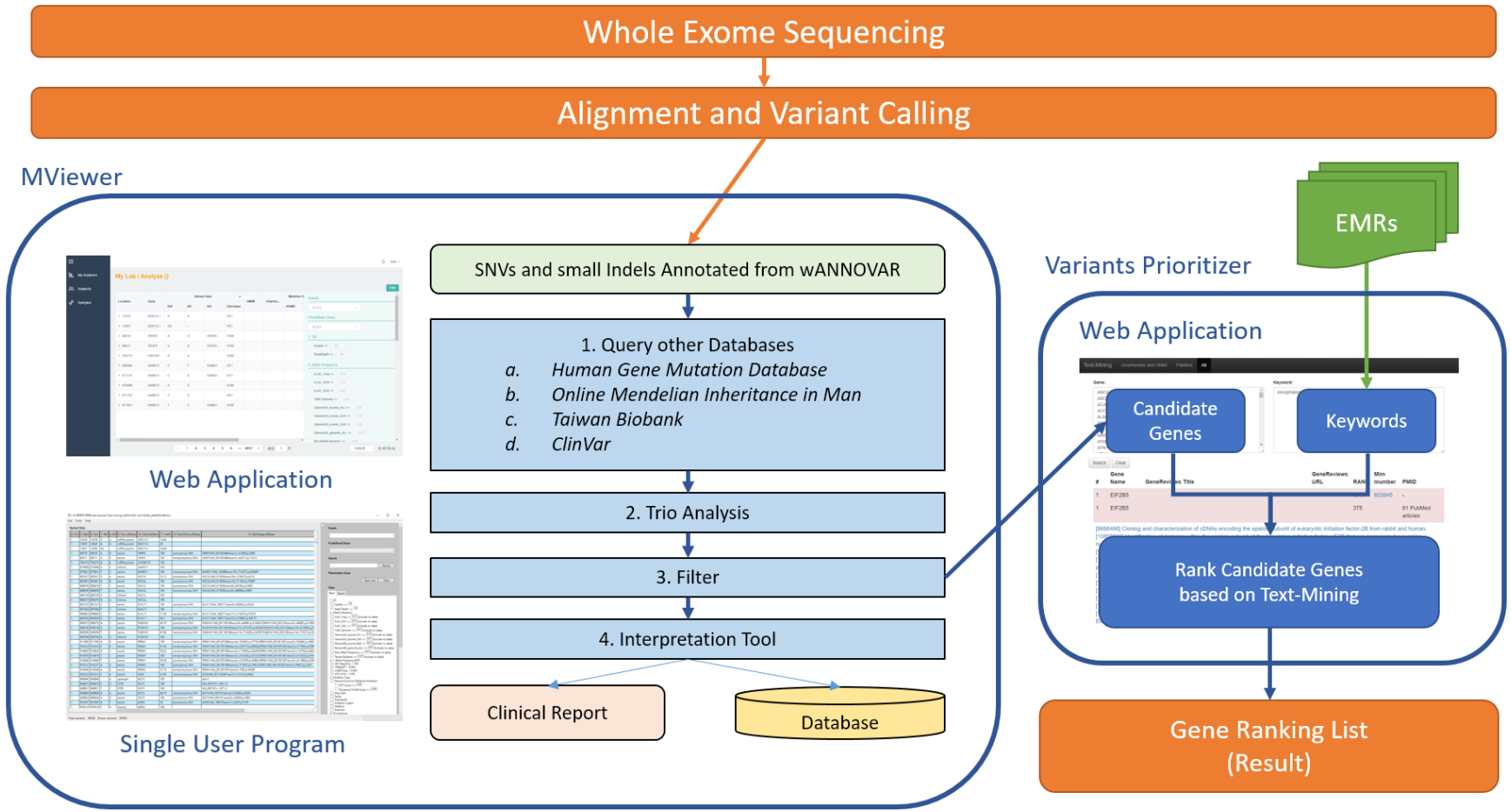
1-2 variants in 1 gene

Previous turnaround time of WES

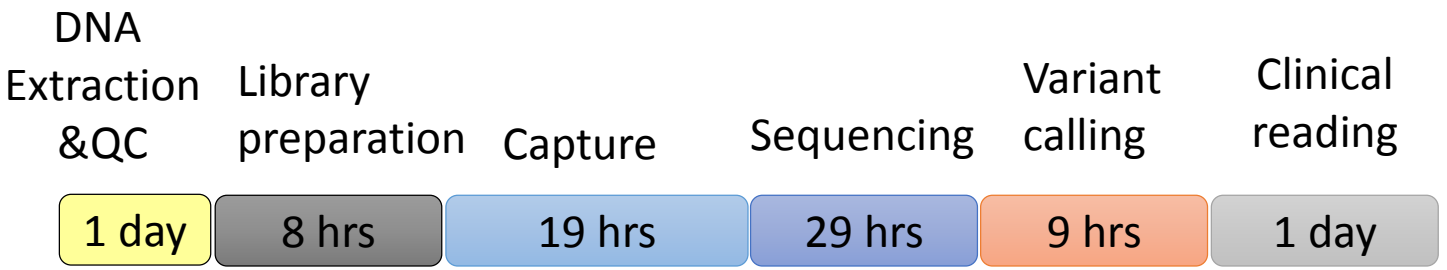
3 months



The MViewer software: Developed by NTU/NTUH



Rapid WES trio analysis for infants and children with acute illness (Funded by MOST)



Turn-around time: 7 days

Diagnostic yield: 52.1% (37/71)

	Total (n=71)	Positive (n=37)
Mean age±SD	15±2.9	18±29.8
Sex (M/F)	40/31	18/18
Turn around time (working days)		
Mean±SD	6.0±1.0	**5.8±0.9**
Median (Range)	4.3-9.9	4.3-8.4

55.6% (20/36) of the cases are first identified in Taiwan

Wu ET, et al. Pediatr Crit Care Med. 2019 Jul 1

Benefits from molecular diagnosis

HPO	Positive cases	Specific treatment (%)		Total cases	Redirection of treatment (%)
Nervous system	11	6 (55%)		22	8 (36%)
Cardiovascular system	3	3 (100%)		13	2 (15%)
Metabolism/homeostasis	10	8 (80%)		16	6 (38%)
Immune system	3	3 (100%)		8	3 (38%)
Liver	3	3 (100%)		5	3 (60%)
Genitourinary system	2	2 (100%)		2	2 (100%)
Musculature	2	0 (0%)		2	2 (100%)
Multiple congenital anomaly	3	0 (0%)		3	1 (33%)

Wu ET, et al. Pediatr Crit Care Med. 2019 Jul 1

Prizes and exhibitions

Thanks

- Ministry of science and technology
- All the team members of NTU Medical Genetics
- Referring physicians
- Patients and families