Solve-RD - Solving the unsolved Rare Diseases

European Commission | Horizon 2020 European Union funding for Research & Innovation

Solve-RD

Solving the unsolved Rare Diseases

How Genomics solves undiagnosed patients

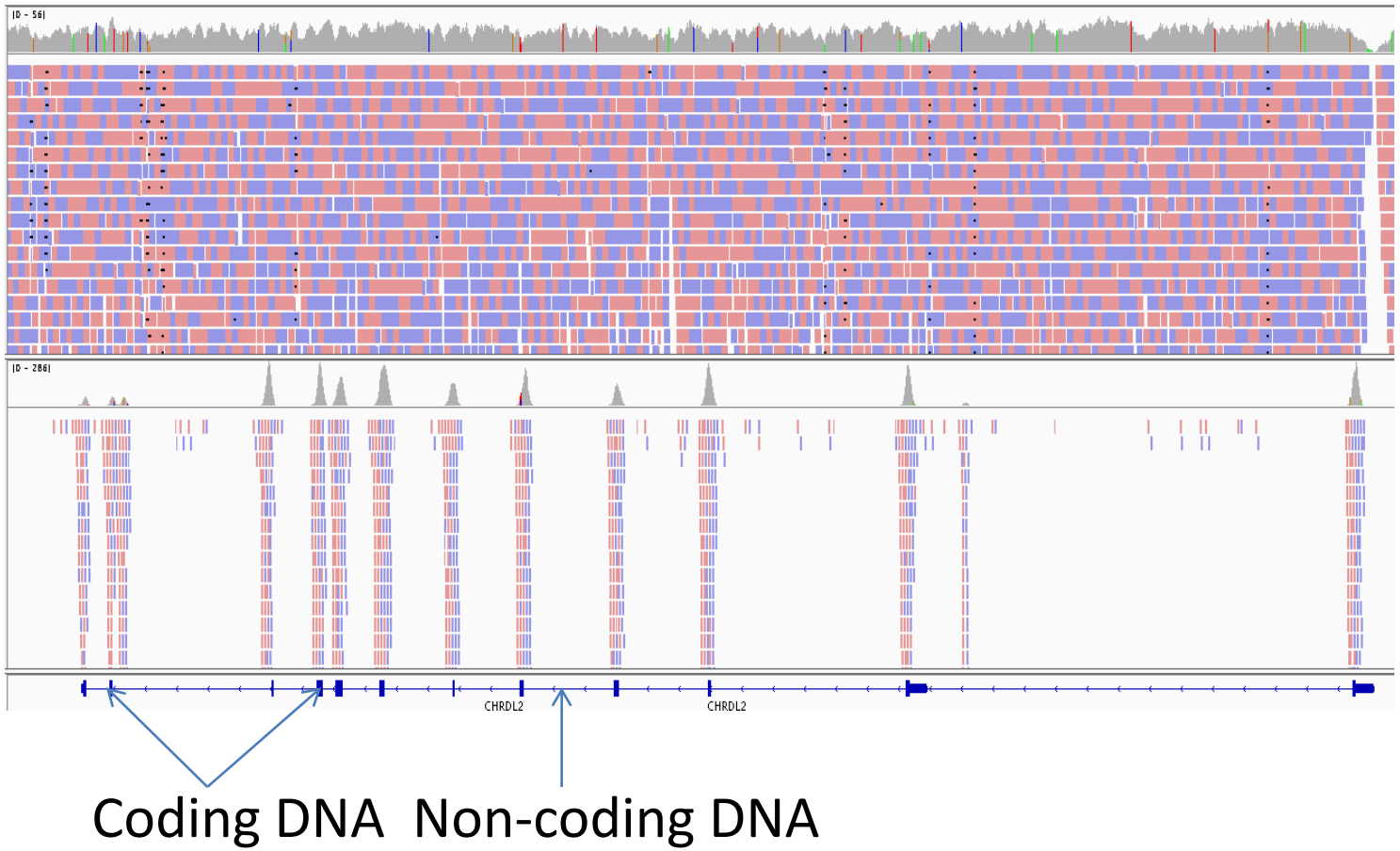
This project receives funding from the European Union's Horizon 2020 research and innovation programme

Start date: January 2018, Duration: 5 years

Conflict of interest:

I declare no potential conflict of interest in relation to this presentation.

SOLVE-RD: Beyond the exome



The exome is only 1-2% of our entire genome!

UNSOLVED after WES:
50% of all patients with a rare disease will not have access to health care without having a clear diagnosis

300 Mio RD patients worldwide
150 Mio patients unsolved

30 Mio patients in Europe
15 Mio unsolved

3-4 Mio RD patients in Germany
1.5 Mio unsolved after WES

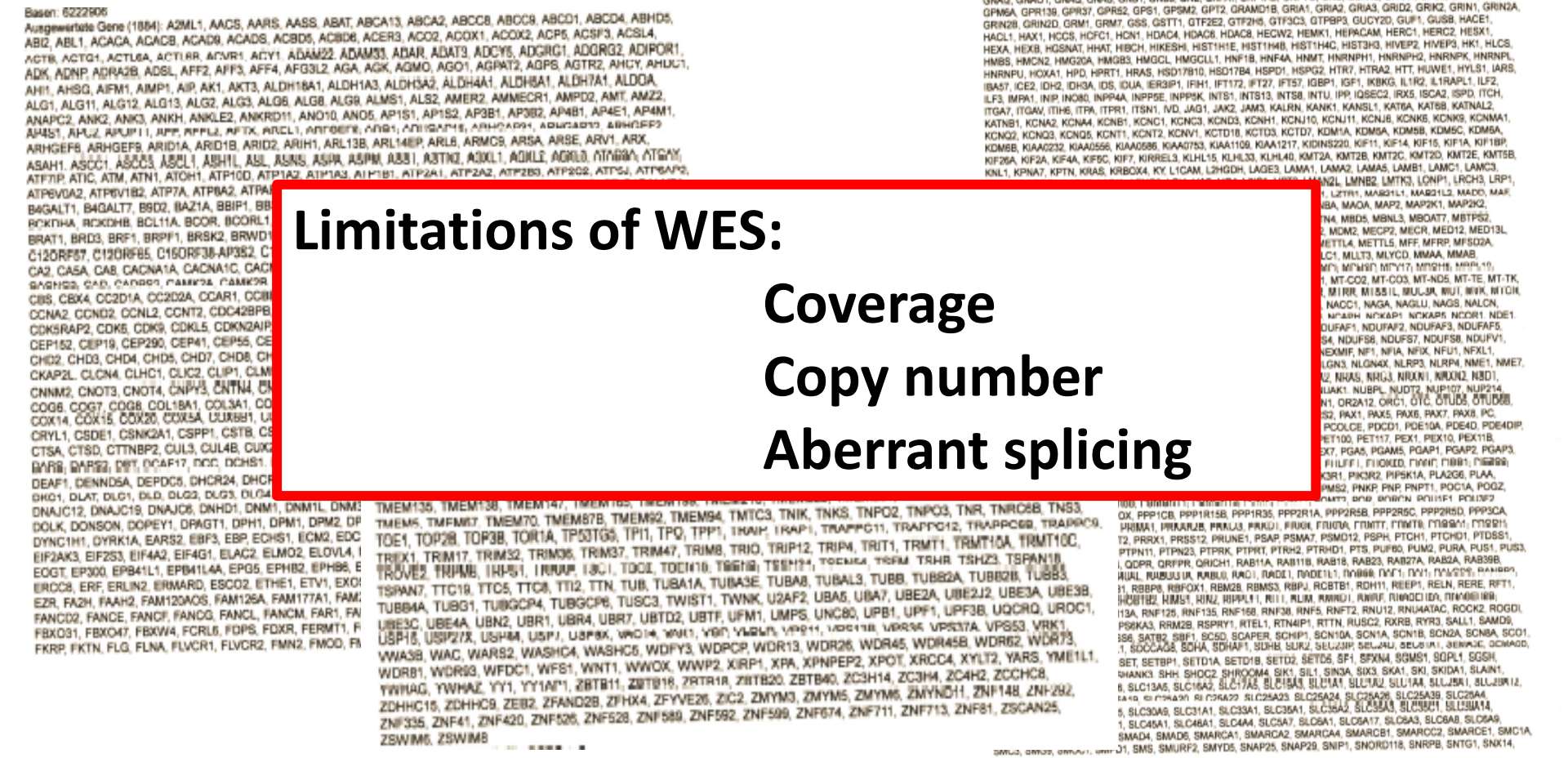
Limitations of Whole Exome Sequencing (WES)

Important: Type of enrichment system: SureSelectXT Human All Exon v6

Statistics of coverage: complete coding sequence +/-5bp intronic region

depth of sequencing (at least 20 fold)

coverage: 98.99%



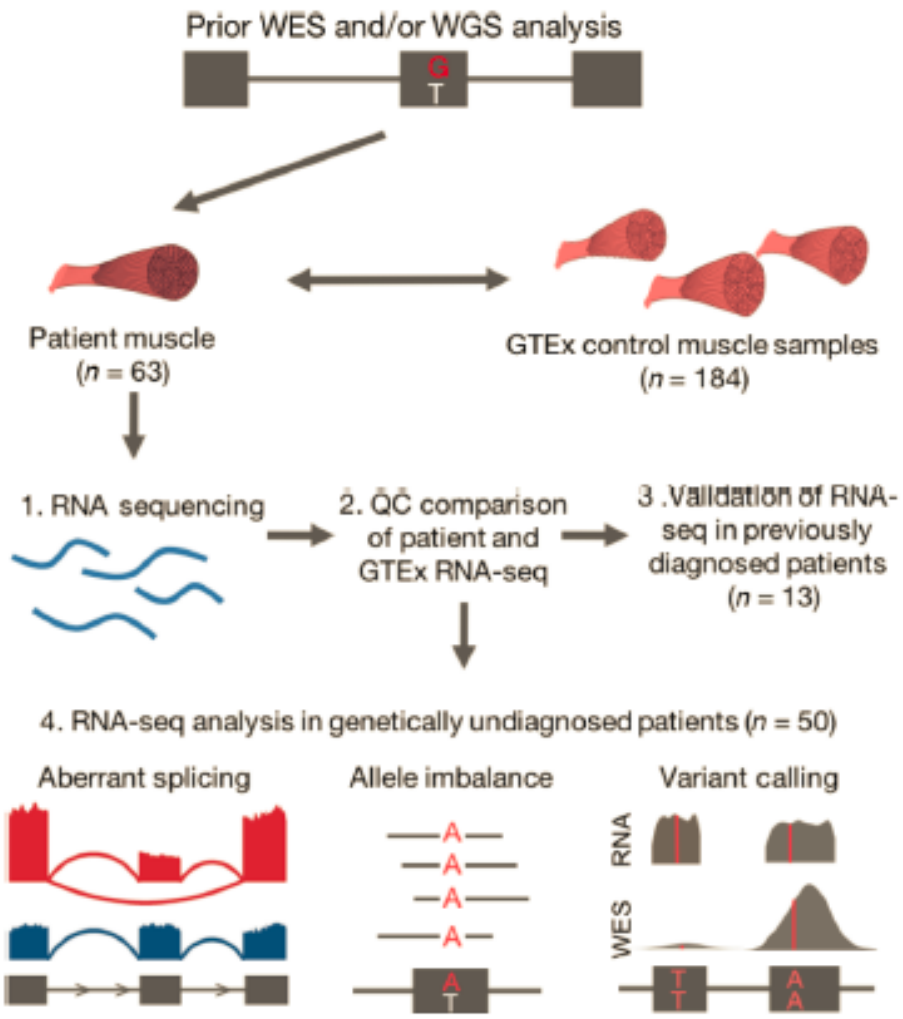
Limitations of WES:

Coverage

Copy number

Aberrant splicing

RNAseq in diagnostics

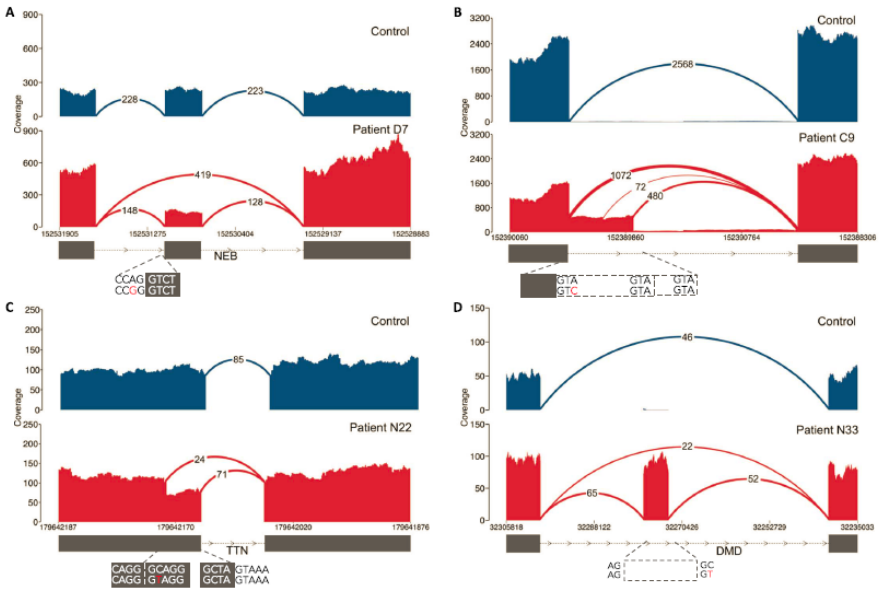


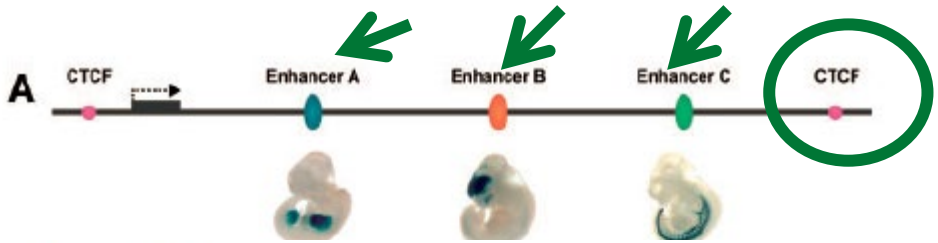
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

GENETIC DIAGNOSIS

Improving genetic diagnosis in Mendelian disease with transcriptome sequencing

Beryl B. Cummings,[1,2,3] Jamie L. Marshall,[1,2] Taru Tukiainen,[1,2] Monkol Lek,[1,2,4,5] Sandra Donkervoort,[6] A. Reghan Foley,[6] Veronique Bolduc,[6] Leigh B. Waddell,[4,5] Sarah A. Sandaradura,[4,5] Gina L. O'Grady,[4,5] Elicia Estrella,[7] Hemakumar M. Reddy,[8] Fengmei Zhao,[1,2] Ben Weisburd,[1,2] Konrad J. Karczewski,[1,2] Anne H. O'Donnell-Luria,[1,2] Daniel Birnbaum,[1,2] Anna Sarkozy,[9] Ying Hu,[6] Hernan Gonorazky,[10] Kristl Claeys,[11] Himanshu Joshi,[5] Adam Bournazos,[4,5] Emily C. Oates,[4,5] Roula Ghaoui,[4,5] Mark R. Davis,[12] Nigel G. Laing,[12,13] Ana Topf,[14] Genotype-Tissue Expression Consortium, Peter B. Kang,[7,8] Alan H. Beggs,[7] Kathryn N. North,[15] Volker Straub,[14] James J. Dowling,[10] Francesco Muntoni,[9] Nigel F. Clarke,[4,5]* Sandra T. Cooper,[4,5] Carsten G. Bönnemann,[6] Daniel G. MacArthur[1,2†]





Neural Tube

Eye

Heart

hs157

hs222

hs229

Ear

hs110

hs579

hs543

hs692

hs840

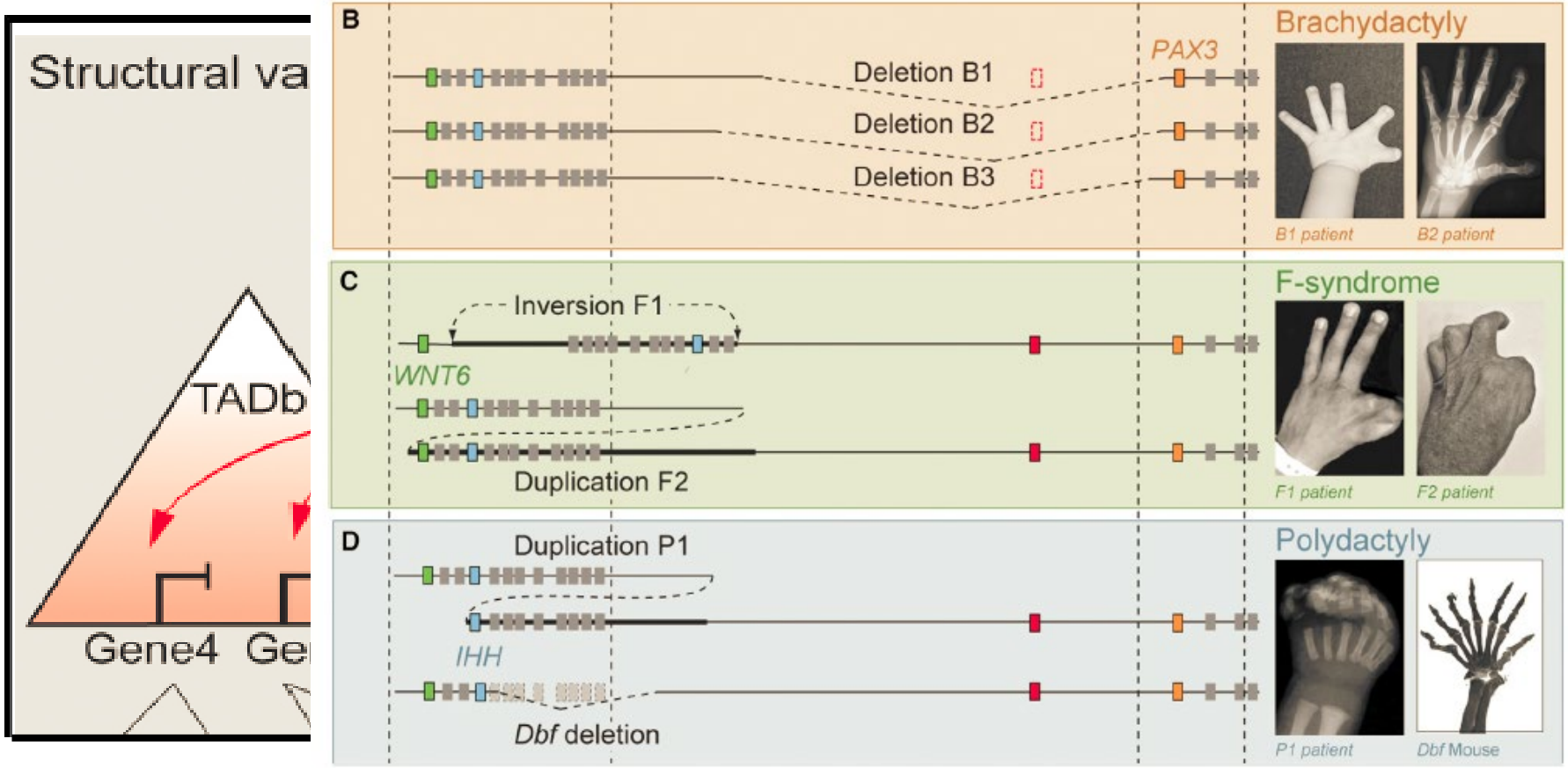
hs742

hs798

https://enhancer.lbl.gov/gallery_n.html

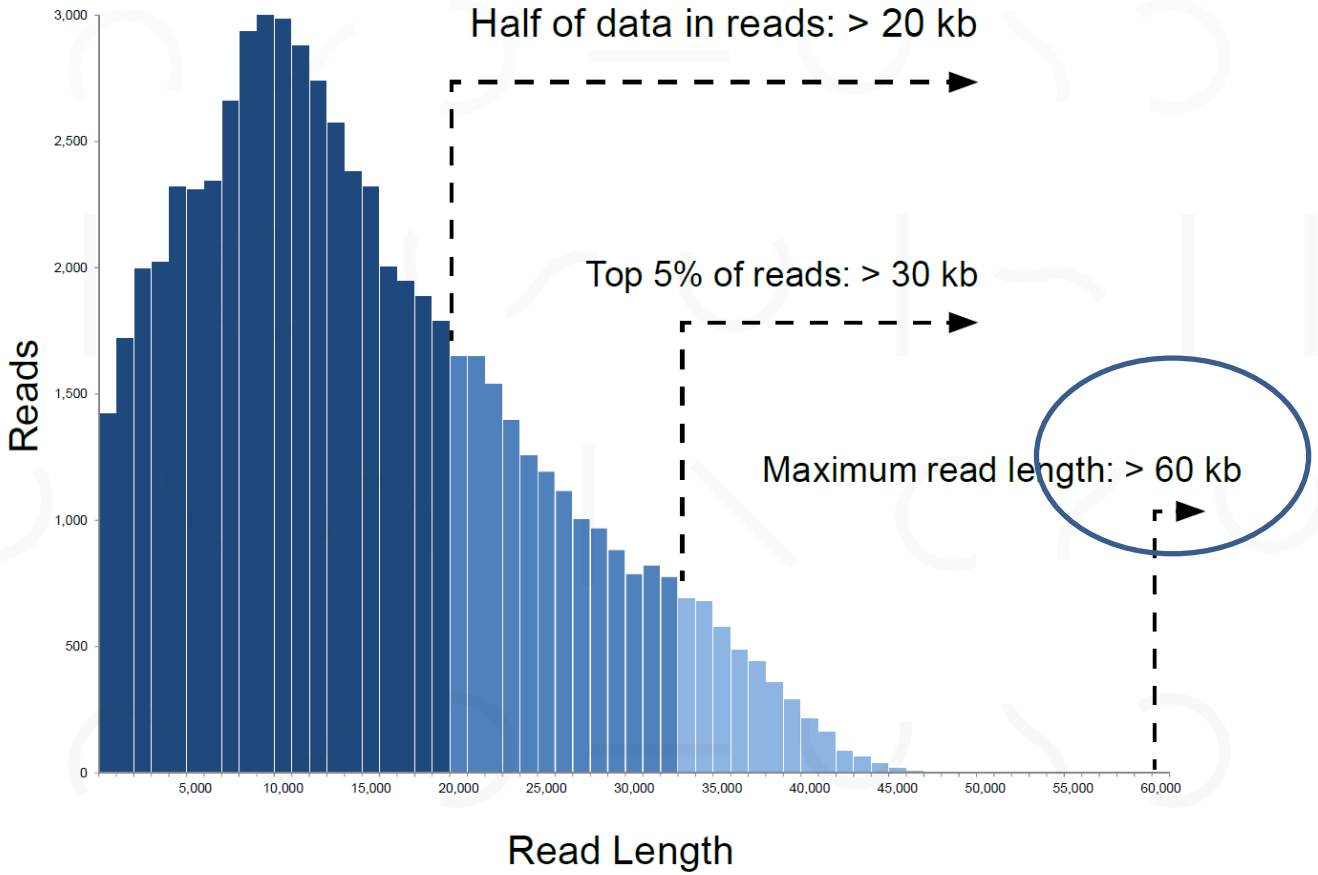
Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions

Darío G. Lupiáñez,[1,2] Katerina Kraft,[1,2] Verena Heinrich,[2] Peter Krawitz,[1,2] Francesco Brancati,[3] Eva Klopocki,[4] Denise Horn,[2] Hülya Kayserili,[5] John M. Opitz,[6] Renata Laxova,[6] Fernando Santos-Simarro,[7,8] Brigitte Gilbert-Dussardier,[9] Lars Wittler,[10] Marina Borschiwer,[1] Stefan A. Haas,[11] Marco Osterwalder,[12] Martin Franke,[1,2] Bernd Timmermann,[13] Jochen Hecht,[1,14] Malte Spielmann,[1,2,14] Axel Visel,[12,15,16] and Stefan Mundlos[1,2,14,*]



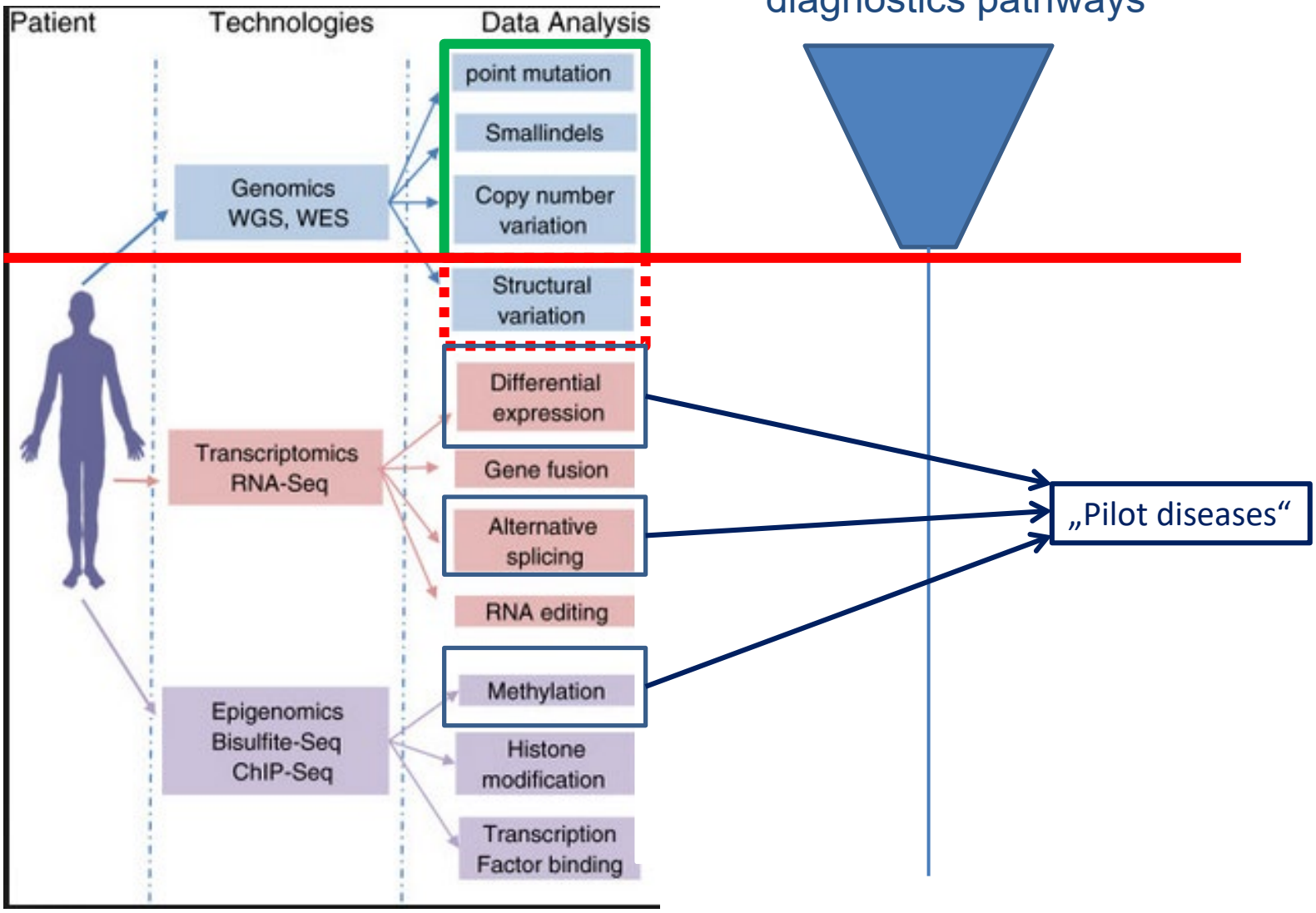
PacBio sequencing reads

Read lengths > 20 kb
Data per SMRT Cell: 750 Mb – 1.25 Gb



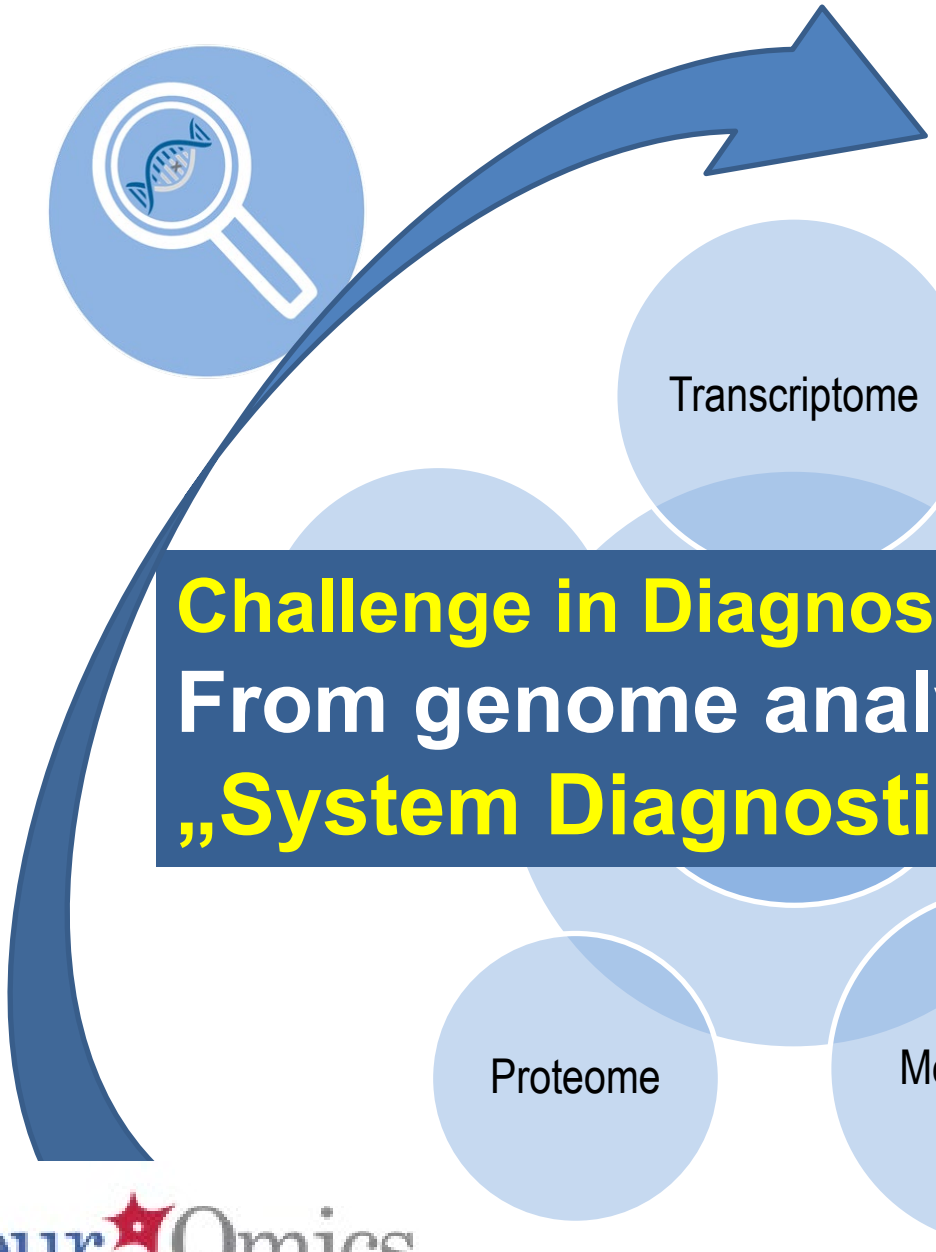
From: http://www.pacificbiosciences.com

Technical hurdles in diagnostics



Modified from Shyr and Liu 2013

Technological hurdles in diagnostics



Solve-RD - Solving the unsolved Rare Diseases

European Commission | Horizon 2020 European Union funding for Research & Innovation

SolveRD

Solving the unsolved Rare Diseases

Challenge in Diagnostic Transition:
From genome analysis towards „System Diagnostics“

NeuroOmics

„in numbers“

- Re-analysis of **19.000** exomes of unsolved cases
- **800 ultra-rare** RD patients presenting new phenotypes that will undergo WES/WGS
- **WGS for 2.000 cases** to achieve a more complete coding sequence
- **Long-read genomes for 500 cases** with smartly chosen phenotypes such as anticipated repeat expansion disorders (SBMA; DM1 and DM2)
- **Novel omics approaches** (transcriptome, epigenome, proteome, metabolome, deep WES, deep molecular phenotyping) for more than **2.000 cases**
- **Multi-Omics approaches for 120 „unsolvable syndromes“**

Main implementation steps

Challenge 2: New and improved approaches for the discovery of novel molecular causes		
3	Reanalyse exomes / genomes	➔ Data mining on the variants and regions detected with Solve-RD standard analysis pipelines ➔ Approaches: (i) a data driven approach, (ii) an expert driven approach.
4	Novel molecular strategies	➔ Solve unsolved diseases from unique RD cohorts provided by 4 ERNs with unique phenotypes applying novel (multi-) omics tools ➔ Solve ultra-rare diseases presenting with novel phenotypes by holding phenotype-jamborees‘ ➔ ‚Solve the unsolvable syndromes‘ with joined power of clinical ERN and genomics experts applying all available latest -omics tools
5	Functional analysis	➔ Validate up to 50 novel candidate genes identified by a re-sequencing those in even larger cohorts of relevant clinical samples (n=5,000) ➔ Implement an innovative brokerage system which allows gene/model/pathway experts to verify pathogenicity of new genes or new disease mechanisms quickly

Resources and infrastructures

Core group of 4 European Reference Networks: ERN-RND, ERN-EURO-NMD, ERN-ITHACA, ERN-GENTURIS

Associated networks: 6 additional ERNs and 2 Undiagnosed Patient Programmes (Italy, Spain)

Existing RD infrastructures: RD-Connect/ELIXIR, Orphanet, HPO, EuroGentest, Canadian Models and Mechanisms Network

Patient organisations: EURORDIS, Genetic Alliance UK

Solving the unsolved Rare Diseases

Coordinators: Olaf Riess, Holm Graessner (Tübingen)

Co-coordinators: Han Brunner (Nijmegen), Anthony Brookes (Leicester)

Partic-ipant N°	Participant Organisation Name	Short Name	Country
1	Eberhard Karls Universitaet Tuebingen	EKUT	Germany
2	Stichting Katholieke Universiteit Nijmegen	RUMC	Netherland
3	University of Leicester	ULEIC	U.K.
4	University of Newcastle upon Tyne	UNEW	U.K.
5	Central Manchester University Hospitals NHS Foundation Trust	MUH	U.K.
6	Centre Hospitalier Reg Universitaire Dijon	DIJON	France
7	Fundacio Centre de Regulacio Genomica	CRG-CNAG	Spain
8	EURORDIS – European Organisation for Rare Diseases Association	EURORDIS	France
9	Institut National de la Sante et de la Recherche Medicale	INSERM	France
10	Univerzita Karlova	CUP	Czech Republic
11	European Molecular Biology Laboratory	EMBL-EBI	U.K.
12	The Jackson Laboratory Non Profit Corporation	JAX	USA
13	King's College London	KCL	U.K.
14	University College London	UCL	U.K.
15	Universiteit Antwerpen	UA	Belgium
16	Universita degli Studi della Campania Luigi Vanvitelli	Uni Naples	Italy
17	Universita degli Studi di Ferrara	UNIFE	Italy
18	Universitaetsklinikum Bonn	UHB	Germany
19	IPATIMUP – Instituto de Patologia Eimunologia Molecular da Universidade do Porto PCUP	UoP	Portugal
20	Academisch Ziekenhuis Groningen	UMCG	Netherlands
21	Charite – Universitaetsmedizin Berlin	Charité	Germany