Human Genetics Nijmegen

UMC St Radboud

Next generation sequencing: Paradigm shift in genetic testing

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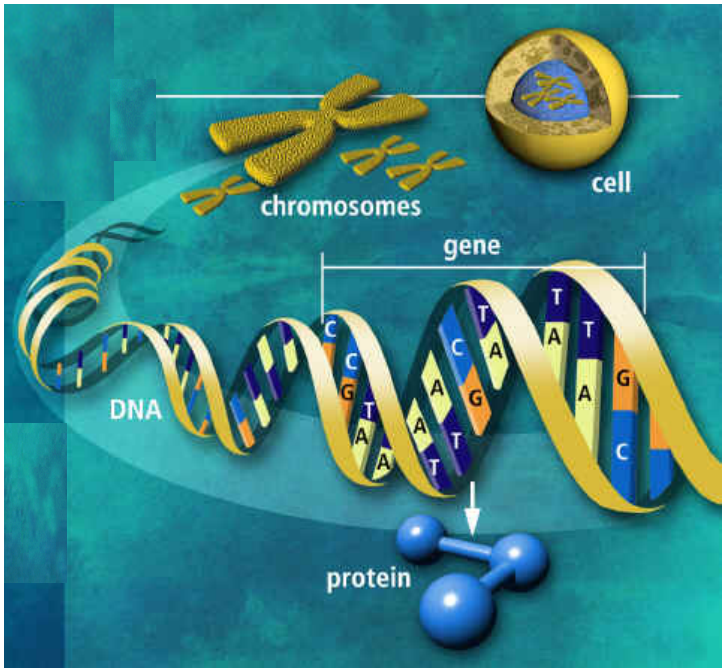
& diagnostics!

"Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order."

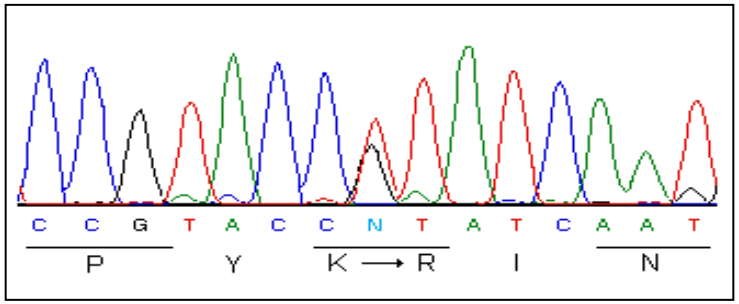
- Sydney Brenner, 2002 Nobel Prize Winner

Finding the genetic causes of disease

- Diploid human genome consists of ~6 billion nucleotides
- A mutation at 1 position can result in disease
- Two individuals differ at ~3 million nucleotide positions



*How can we reliably **identify** and **interpret** these variants in individual patients?*



Challenges in genetic diagnostics

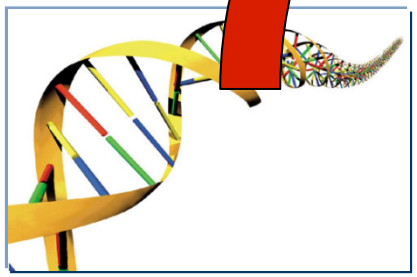
- Clinically diagnosing genetic disease is an art, ordering the right genetic test is difficult
- Single gene tests are laborious to set-up & expensive
- Diseases can be caused by different types of genetic variation, requiring different tests
- The genetic cause of 1000s of rare diseases is unknown
- Common diseases are genetically heterogeneous & their genetic causes are largely unknown

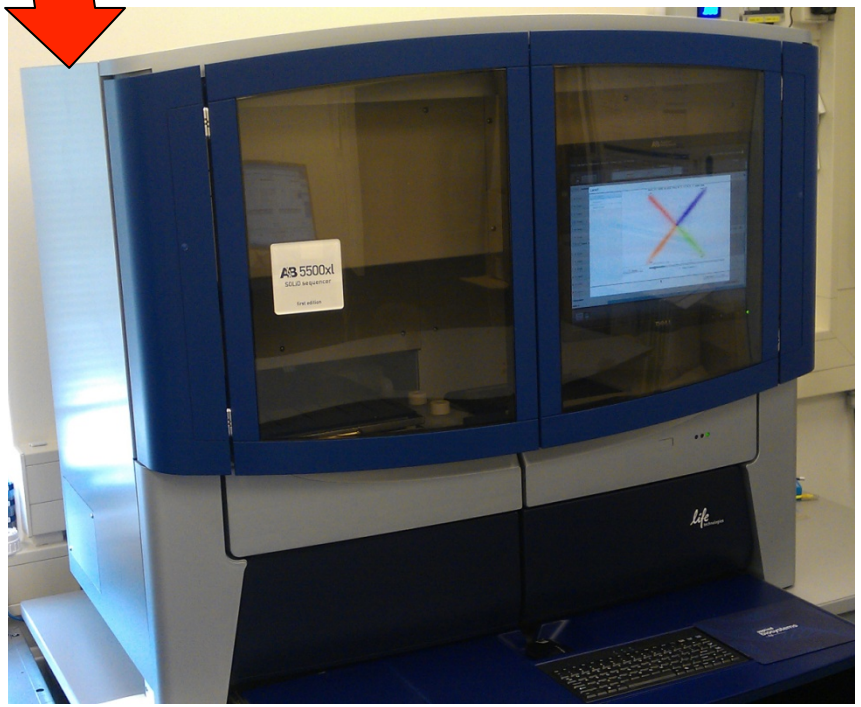
No genetic diagnosis for majority of diseases
Role of genetics in medicine is limited

Need for simple, cheap & effective genetic diagnosis

Next generation sequencing: Simple, cheap & effective?

DNA from blood





Genome sequence with all variation

Important:
- Accuracy
- Speed
- Price

Lessons learned from exome sequencing in disease gene identification

- Exome sequencing is a robust approach that can be highly automated
- It is not difficult to interpret the data if you ask the right question and have bioinformatic expertise
- Success rate of exome sequencing 70-80%, determined largely by the quality of clinical collection & sequencing
- Sporadic diseases have become amenable to genetic disease research, no need for families!
- *De novo* mutations; Important cause of sporadic disease

Gilissen et al. EJHG 2012

Diagnostic next generation sequencing

- Where can NGS make the most difference now?

  Monogenic diseases with locus heterogeneity!

  ID, blindness, deafness, movement disorders, mitochondrial disease, heriditary cancers etc.

- What approach: target genesets, exome or genome?

  Set of disease genes is rapidly expanding

  Exome sequencing is a generic test, allows most flexibility
  Genome sequencing not high-throughput & affordable yet

Which NGS-test to choose: Targeted assays *vs.* Exome

Targeted

- Develop per (group of) diseases
- Can be optimized for "perfect" disease gene screening
- Higher throughput
- Needs to be updated regularly
- Interpretation only once
- Only data on selected genes
- No incidental findings
- Cheaper as a single test
- More easy interpretation
- Lower diagnostic yield per test

Exome

- Generic test for all diseases
- May miss causative mutations in known disease genes
- Lower throughput
- Less updating required
- Data interpreted repeatedly
- Normal variation accumulates
- Chance for incidental findings
- More expensive as a single test
- More follow-up required
- Higher diagnostic yield per test

Nelen & Veltman, Pharmacogenomics 2012

NGS in diagnostics: The time is now!

- This ESHG!

- Cockburn (Leeds): targeted BRCA1&2, TP53 etc. >1400 reports
- Matthijs (Leuven): targeted BRCA1&2, 1500 reports
- Dean (Bristol): targeted seq hypercholesterolemia genes, reports?
- Bergmann (Ingelheim): targeted seq cilia-related genes, reports?
- Black (Manchester): targeted RP-genes, validation phase

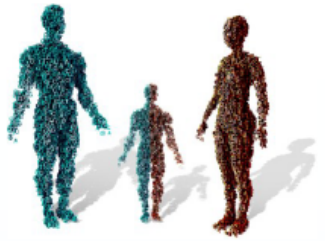
- Biesecker (NIH, Bethesda): diagnostic exome seq, 580 reports
- Nelen (Nijmegen): diagnostic exome seq, 300 reports
- Stray-Petersen (Oslo, Houston): diagnostic exome seq, reports?

Some personal thoughts

- Do not only set-up tests for one or two years, try to look a bit further down the road if possible
- Don't wait for tests to become perfect, optimization will have to happen during the implementation phase
- Europe can lead in this effort because of excellent link between research and diagnostics
- Proceed with care, openly discuss bottlenecks for reaching long-term goals, develop joint strategies
- Involve all stakeholders early in the process
- **Genome sequencing will be the dominant diagnostic test in 5-10 years time**

New Frontiers Symposium 2012

Personal Genomics



Sydney Brenner

James Lupski

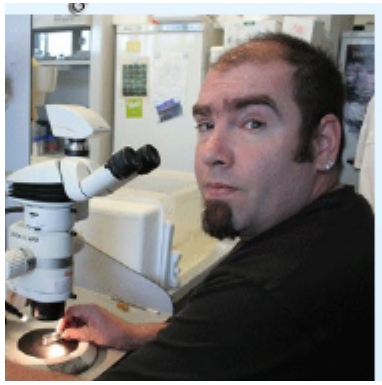
Nicholas Katsanis

John Burn

Stylianos Antonarakis

Richard Durbin

Peter Holland



Jose Luis Gomez-Skarmeta

Nijmegen, NL
December 3&4 2012

Registration now open

www.ncmls.eu/newfrontiers2012

Radboud University Nijmegen Medical Centre

Major challenges for clinical implementation of exomes & genomes

- NGS-sequencing is imperfect, technology needs to improve, costs need to go down
- Affordable & large-scale data storage
- User-friendly software to interpret enormous amounts of data
- International data sharing to improve understanding
- Appropriate counseling with informed consent
- Additional challenge: Dealing with “incidental findings”
- Approach towards re-analysis of negative exomes/genomes
- Education/training of laboratory personnel & clinicians
- Need to evaluate and demonstrate clinical utility
- Need for practical guidelines in a clinical setting