Rare Disease, Primary Care and Genomics

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Overview

• “When you hear hoofbeats, don’t expect to see a Zebra.”\(^1\)

• A rare disease is defined as: a disease which affects fewer than 1 in 2000 people.

• So this includes diseases we are familiar with: CF, Haemochromatosis.

• There are 6000-8000 diseases.\(^2\)

• 1 in 17 people are affected by a rare disease during their lifetime.

• So for a typical surgery of 8,000 patients, this equals 470 patients.

• Collectively RARE DISEASES ARE NOT RARE

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• 80% of rare diseases have a genetic basis.³

• Most are severely disabling, life limiting and affect children, with 30% of patients not reaching their 5th birthday.⁴

• BUT rare diseases affect individuals of all ages.

• Genomic research has led to new diseases being described at a rate of 5 each week.⁴

• NHS England define ultra rare diseases for service provision as affecting fewer than 500 patients.


⁴ Rare Disease UK. About Rare Diseases. Available from: http://www.raredisease.org.uk/about-rare-diseases.htm
Rare disease diagnosis

- “Diagnostic Odyssey”
- Years, or even decades of uncertainty, investigations hospital attendances, misdiagnoses and ineffectual treatments.
- Waste of time, effort and resources\(^2\).
- Improved diagnostic tests. Better molecular understanding of disease.
- But still a long diagnostic odyssey for many.
Rare disease diagnosis

• Benefits - even in the absence of disease specific therapy (upto 95% of rare diseases have no approved therapy\(^5\)).

• End uncertainty and the odyssey.
• Explanation.
• Access expert care, patient support groups. Opportunities for clinical trials and drug development.
• Reproductive choice and family planning.
• Decisions about lifestyle - home/work/etc.
• Access educational and social support.

5) Global Genes. Global Genes Factsheet on Rare Diseases Available at: https://globalgenes.org/rare-diseases-facts-statistics/
Rare disease what’s the relevance to primary care?

- Collectively not rare, and significant unmet need.
- May be no local expertise or knowledge. GP can know the patient, family and disease.
- GPs’ unique position. Generalists with over view of whole patient.
- Ability to identify patterns frequently missed by secondary care.
- Continuity of record.
- Knowledge of the broader family. Are they at risk? Are there reproductive issues they need to be aware of?
- Skills in managing uncertainty and excluding the rare amongst the common. Diagnosing conditions we may see only a few times in our career (e.g., meningococcal sepsis amongst the thousands of self-limiting viral illness).
Rare disease diagnosis in primary care.

- Linking the dots, information and the bigger picture is lost between different specialties.
- Revisiting inadequate historical diagnoses. ‘Is there a more plausible explanation?’
- No one can know 7000 diseases
- Make use of their ‘gut feeling’ doesn’t fit with normal pattern recognition.
- Three-generation family history.
- Problem-based search for differential diagnoses using web based resources:
  - www.omim.org
  - phenomizer-orphanet: http://compbio.charite.de/phenomizer_orphanet/.

8) Svenstrup D, Jørgensen HL, Winther O. Rare disease diagnosis: A review of web search, social media and large-scale data-mining approaches. Rare Dis [Internet]. 2015;3(1):e1083145.
Is this a rare disease?

• *Family history: 3 generation FHx. Multiple affected siblings or individuals in multiple generations. NB No Fhx does NOT rule out genetic causes.*

• **G:** group of congenital anomalies. Common anatomic variations are common; but two or more anomalies are much more likely to indicate the presence of a syndrome.

• **E:** extreme or exceptional presentation of common conditions. Early onset CV disease, cancer, or renal failure. Unusually severe reaction to infectious or metabolic stress. Recurrent miscarriage.

• **N:** neurodevelopmental delay or degeneration. Developmental delay in the paediatric age group carries a very high risk for genetic disorders. Developmental regression in children or early onset dementia in adults should similarly raise suspicion for genetic etiologies.

• **E:** extreme or exceptional pathology.

• **S:** surprising laboratory values. Markedly abnormal pathology results.

Joyce is a 20 year old girl who moved with her parents from Sudan when she was 14. She has mild learning difficulties attributed to a head injury when she was an infant. Well controlled epilepsy on epilim seen and discharged by adult neurology when she was 18. After an acute episode of hypocalcaemia when a teenager she was diagnosed with hypoparathyroidism managed with calcium and vitamin D supplemenation.
Identifying previously missed patterns

- She attends with her mother and younger sister with a hx of menorrhagia.
- The GP noted incidently mild dysmorphic features, prominent forehead broader nose, not previously commented upon but more apparent when seen with 2 members of the family.
- The history of hypoparathyroidism, epilepsy and learning difficulties seemed an unusual combination.
- The history of being dropped as a baby seemed an unlikely cause of learning difficulty.
After the surgery the GP reviewed her limited notes. The neurology letter made no reference to the previous head injury and commented that a CT performed was normal. Neither the endocrinologist nor neurologist commented on dysmorphism. The GP performed a search on web based phenotype search engines, using the terms hypocalcaemia/ learning difficulties/ epilepsy. This produced a list of differential diagnoses. At the top of list was 22q11.2 deletion syndrome. This seemed a plausible explanation.
Identifying previously missed patterns

- The GP gained consent for further investigation and referral.
- The GP liaised with the local genetics department, who advised referral for deeper phenotyping and investigation.
- An array CGH confirmed the diagnosis of 22q11.2 deletion syndrome. Also known as velocardiofacial syndrome (VCFS) or DiGeorge syndrome.
- Significant variation in features and severity of disease. The patient had neither cardiac nor palate issues.
- Explanation for Joyce and Family. Suitable surveillance for ongoing issues and problems.

Evolving diagnostics

- When to revisit diagnoses?
- New advanced diagnostics.
  - New phenotypical gene panels/ exome/ genome sequencing.
  - 100,000 genome – Rare diseases.
  - Computer learning/ Diagnostic algorithms. But how to incorporate into practice.
  - The phenotype of many rare diseases is broadening. Later presentation milder variants, frequently missed.
  - Common diseases with better molecular understanding will be broken into multiple molecularly defined subtypes. Will these be rare diseases?
Summary

- Rare diseases are common
- Getting a diagnosis is important
- Follow ‘gut feelings’. Is it plausible?
- Use diagnostic search engines.
- Revisit diagnoses and consider referral for new diagnostics.
Thank you

• For more information on genomics in primary care, please visit:

• For questions or comments please contact us at genomics@rcgp.org.uk

• For more information on genomics education, please visit:
  https://www.genomicseducation.hee.nhs.uk/