The Minutes of the Derby Medical Society Wednesday 8th March 2017
Derby Medical School, Lecture Theatre

Speaker:
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Genomics in Practice

Genomics is the study of entires gemones - see photos

Genomics technologies available - see photo
Both technologies underpinned by bioinformatics

Why Use Genomic Technology?

Standard chromosome tests only pick up 2.5% of abnormalities
BAC arrays picked up 20% of abnormalities
Oligo + SAP arrays pick up 30% of abnormalities

Arrays work by using probes to pick up signals in genes.
The reflection intensity of a laser beam is compared against controls and any deletions are picked up.

Case history of a hypotonic baby with developmental delay, dysmorphic features and scoliosis.
Standard chromosome and genetic tests normal.
BAC array showed a micro deletion on Ch19 with a loss of 35 protein coding genes.
This included deletion of NFIX which causes Malan syndrome.
He also had a calcium channel gene deletion (CACNA1A) that causes Episodic Ataxia type 2.
Although the child has not had symptoms of ataxia yet. Awareness means some treatments can be used early.
THe other microdeletions are not yet known about.

International database is used (DECIPHER) to compile data and phenotypes of children with microdeletions

Case 2
Exomphalos, developmental delay and severe LD, facial dysmorphism and premature pu
Array testing showed a duplication in part of chromosome 7 (7p22.1)

Case 3
9 year old boy. Global developmental delay, limited speech age 9 years,, hypotonia with macrocephaly, short palpebral fissures, long feet.
Newer technology used to repeat the array and this showed a micro deletion in Ch10 (Ohdo syndrome)

Modern Genome analysers ternate 1.8 trillion base pairs of data in one run!
Explained how analysers work - DNA broken into fragments and made into an emulsion.
PCR done from one fragment of DNA
The reads are subject to quality control
If variants are picked up it has to be compared against expected variants in the population.
It then needs to be determined if the variant is pathological or an incidental variant.
Costs of next generation are not prohibitive - see photo.

Clinical Applications of Next generation sequencing - see photo

GEMINI
Diagnostic Clinical Exome Sequencing
Store gene sequence data on a computer but only run panels for specific pathologies
E.g. Gene areas for skeletal dyspplasia, developmental delay, renal disorders, orofacial clefting

Case 4
Adult man diagnosed with Treacher-Collins
Partner was pregnant and they wanted to have pre-natal testing
Differential diagnosis changed on clinical examination as thumbs were hypoplastic.
His genome was tested with a panel screen to determine if this was Treacher-Collins.

Clinical Exome Sequencing Study
See photo for inclusion and exclusion criteria

Now available as a diagnostic whole Exome sequencing - see photos
Used for families with multiple pregnancy loss, TOP through abnormality or where children have problems.

100 000 Genome Project
NHS project to see if feasible to use for therapy
Recruiting rare disorders and some cancers - see photos

But is you don't get an answer from the whole exome, it is unlikely the answer will come from the whole genome.

Challenges of Genomic tests
See photo
Coincidental but significant findings

Went through some cases of diagnoses and dilemmas of picking up multiple abnormalities

How is this changing how we practice?
See photo of flowchart

Mainstreaming genetic testing:
Epithelial Ovarian Cancer
Certain breast cancers
Autosomal dominant polycystic kidneys disease
Retinal dystrophy and congenital cataracts
Phaeochromocytoma

Conclusions
See photo

There were many questions on the subjects of:

Keeping up with the changes in genetics - tend to subspecialise
Genetics of Parkinson's
Gemomic diagnosis of Mental Health disorders - felt to be multifactorial
Ethics of whole genomic screening
Who "owns" the genomic data especially if the sequencing is performed in a child
Screening with FH of cancers
Penetrance of BRACA in non-Ashkanzi 80%, Ashkenazic penetrance is 50% but incidence of BRACA is much higher.
Implications for insurance - moratorium until 2019 with caveats
Non-disclosure of consanguinity in clinical setting