Lessons from the Deciphering Developmental Disorders (DDD) Project

Dom McMullan
Consultant Clinical Scientist
West Midlands Regional Genetics Laboratory
Background

• 1:100 children born in UK with severe Developmental Disorder

• > 50% remain without a genetic diagnosis
  – Phenotype-driven detection of monogenic disorders
  – Whole Genome microarray

• Need for large scale translational research studies utilising advances in sequencing and bioinformatics
Deciphering Developmental Disorders

ddd_help@sanger.ac.uk

Health Innovation Challenge Fund and Sanger Institute
Deciphering Developmental Disorders (DDD)

Objectives:

**RESEARCH**: Delineate the genetic architecture of undiagnosed developmental diseases

**TRANSLATION**: Optimize ethical implementation of genomic technologies for clinical diagnosis

**UK-wide collaboration**: Patients, their families, all 24 UK & Eire Regional Genetics Services (RGS) and the Wellcome Trust Sanger Institute (WTSI)

**Plan:**
Recruit **12,000 patients and their families**
Collect saliva and blood-extracted DNA samples
Record clinical phenotypes systematically
Apply microarrays and sequencing
**Identify and feedback likely causal variants to RGS for clinical and technical validation**
Share data through DECIPHER
Lead and facilitate research
Inclusion criteria – severe and extreme phenotypes

- Neurodevelopmental disorder
- Congenital anomalies
- Abnormal growth parameters
- Dysmorphic features
- Unusual behavioral phenotype
- Genetic disorder of significant impact for which the molecular basis is currently unknown

EXCLUSION:

- Terminations and stillbirths
- Adopted children
- Children who are a product of an incestuous relationship
- Children with a known molecular diagnosis
DECIPHER: online database of genomic variation with patient phenotypes
DDD cohort: phenotypic characteristics

- Intellectual disability or developmental delay (87%)
- Autism spectrum disorder (10%)
- Hearing impairment (7%)
- Oral cleft (6%)
- Congenital heart defects (11%)
- Polydactyly (1%)

- Seizures (24%)
- Visual impairment (3%)
- Scoliosis (5%)
Assay Designs

• Exon-arrayCGH (probands)
  - Agilent custom 2x1 million array
    • 5 probes per exon, conserved regions, linc RNAs
    • CNV genotyping probes
    • Genome backbone probes – every ~3 kb
    • Originally complemented by 800K SNP-chip

• Whole Exome sequence (trios)
  - Illumina HiSeq NGS + Agilent SureSelect
    • Multiplexed
    • **Approx 50x coverage**
    • Sanger Exome (~60 MB: exons + ultraconserved regions, regulatory regions, ncRNAs, enhancers, etc)
Bioinformatics workflow

Flowchart:
- **BAM**
  - SNVs/indels
    - GATK + DNG
    - CONVEX + CIFER
  - CNV
  - UPD
    - UPDio
    - MrMosaic
    - INDELible
  - Mosaic SV
  - Complex SV
  - Combined VCF
    - QC
    - Annotation
  - Supplementary File
    - QC
    - Annotation
  - Annotated Combined VCF
    - Annotation
  - Clinical Filtering
    - QC

Software tools:
- GATK
- CONVEX
- CIFER
- UPDio
- MrMosaic
- INDELible
- QC
- Annotation
- DECIPHER
- GRCh37
Gene Content (SNVs, indels, CNVs) - DDG2P

Genotype matches genetic mode
Heterozygotes in monoallelic and X-linked dominant genes
Homozygotes or compound heterozygotes in trans in biallelic genes

Inheritance matches family history
Parents unaffected: de novo, compound het, homozygote, hemizygote in boys
Parent(s) affected: As above, plus heterozygotes inherited from affected parent(s)

Functional consequence (Using Variant Effect Predictor – Ensembl)
MODERATE/SEVERE ONLY
Included: transcript ablation, splice donor variant, splice acceptor variant, stop gained, frameshift variant, stop lost, initiator codon variant/start lost, inframe insertion, inframe deletion, missense variant, transcript amplification, coding sequence variant/protein altering variant
Excluded: synonymous, splice region, missense variants where PolyPhen2 predicts ‘benign’ unless de novo

Allele frequency (Maximum Allele Frequency across internal and external datasets – MAF)
MAF <0.05% AND ExAC heterozygous count <5 in monoallelic and XLD genes
MAF <0.5% in biallelic genes
MAF <0.05% AND ExAC hemizygote count =0 in hemizygous genes
Developmental Disorders Genotype-2-Phenotype @DDG2P Database

https://www.ebi.ac.uk/gene2phenotype/

Aim: link genes to developmental disorders via genetic mechanism and consequence to enable rule based analysis of novel variation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Status</th>
<th>Mode</th>
<th>Consequence</th>
<th>Disease / Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAAS</td>
<td>Confirmed</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>Achalasia-Addisonianism-Alacrima Syndrome</td>
</tr>
<tr>
<td>AARS</td>
<td>Probable</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>Early-Onset Epileptic Encephalopathy with Persistent Myelination Defect</td>
</tr>
<tr>
<td>AASS</td>
<td>Probable</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>Hyperlysinemia</td>
</tr>
<tr>
<td>ABCB11</td>
<td>Confirmed</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>ABCB11-Related Intrahepatic Cholestasis</td>
</tr>
<tr>
<td>ABCB7</td>
<td>Confirmed</td>
<td>Hemizygous</td>
<td>All missense/in frame</td>
<td>Anemia, Sideroblastic, with Ataxia</td>
</tr>
<tr>
<td>ABCC6</td>
<td>Confirmed</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>Arterial Calcification, Generalized, of Infancy, 2</td>
</tr>
<tr>
<td>ABCC9</td>
<td>Confirmed</td>
<td>Monoallelic</td>
<td>Activating</td>
<td>Cantu Syndrome Hypertrichotic Osteochondrodysplasia</td>
</tr>
<tr>
<td>ABCD1</td>
<td>Both DD and IF</td>
<td>Hemizygous</td>
<td>Loss of function</td>
<td>Adrenoleukodystrophy, X-Linked</td>
</tr>
<tr>
<td>ABCD4</td>
<td>Probable</td>
<td>Biallelic</td>
<td>Loss of function</td>
<td>Methylmalonic Aciduria and Homocystinuria, CBLJ Type</td>
</tr>
</tbody>
</table>
Results to Date

• Large batch releases
• Iterative re-analysis including new information
  – New genes (DDG2P list expansion – 1,200 to 1,700)
  – Difficult variants (e.g. mosaic structural imbalance)
• Trios initially
• Duos and singletons later

• FULL INITIAL CLINICAL REPORTING BY (?) END 2018
Prevalence and architecture of *de novo* mutations in developmental disorders

Deciphering Developmental Disorders Study*

The genomes of individuals with severe, undiagnosed developmental disorders are enriched in damaging *de novo* mutations (DNMs) in developmentally important genes. Here we have sequenced the exomes of 4,293 families containing individuals with developmental disorders, and meta–analysed these data with data from another 3,287 individuals with similar disorders. We show that the most important factors influencing the diagnostic yield of DNMs are the sex of the affected individual, the relatedness of their parents, whether close relatives are affected and the parental ages. We identified 94 genes enriched in damaging DNMs, including 14 that previously lacked compelling evidence of involvement in developmental disorders. We have also characterized the phenotypic diversity among these disorders. We estimate that 42% of our cohort carry pathogenic DNMs in coding sequences; approximately half of these DNMs disrupt gene function and the remainder result in altered protein function. We estimate that developmental disorders caused by DNMs have an average prevalence of 1 in 213 to 1 in 448 births, depending on parental age. Given current global demographics, this equates to almost 400,000 children born per year.
Take-home:

- ~42% have a (coding) pathogenic de novo mutation (DNM)
- ~23% DNM in curated/DDG2P genes
  - ~50% LOF
  - ~50% protein altering
- ~10% have recessive or X-linked inherited condition
- ~5% “other” variation (CNV/SV)

**CURRENT DIAGNOSTIC YIELD**

~40%

Figure 2 | Genes exceeding genome-wide significance. Manhattan plot of combined P values across all tested genes. The red dashed line indicates the threshold for genome-wide significance ($P < 7 \times 10^{-7}$). Genes exceeding this threshold have labelled HGNC symbols. De-identified realistic average (‘composite’) faces were generated using previously validated software from clinical photos of individuals with DNM in the same gene, and are shown here for the six most significantly associated genes. Confirmation of de-identification was performed by careful review by two experienced clinical geneticists. Each face was generated from clinical photos of more than ten children.
# Consent # N/Mil. Pop. % Trios % Info % Phenotype Variants % Pathogenicity Completed % Validation Completed

<table>
<thead>
<tr>
<th>Project</th>
<th># Consent</th>
<th># N/Mil. Pop.</th>
<th>% Trios</th>
<th>% Info</th>
<th>% Phenotype</th>
<th>Variants</th>
<th>% Pathogenicity Completed</th>
<th>% Validation Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
<td>1149</td>
<td>221</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>1241</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Sheffield</td>
<td>1057</td>
<td>587</td>
<td>81</td>
<td>100</td>
<td>100</td>
<td>1074</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Manchester</td>
<td>981</td>
<td>178</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>1021</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>GOSH, London</td>
<td>952</td>
<td>238</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>920</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Wessex</td>
<td>718</td>
<td>239</td>
<td>87</td>
<td>99</td>
<td>99</td>
<td>737</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Belfast</td>
<td>705</td>
<td>392</td>
<td>91</td>
<td>100</td>
<td>100</td>
<td>598</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>St George's, London</td>
<td>645</td>
<td>174</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>629</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Leeds</td>
<td>624</td>
<td>156</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>607</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>NW Thames, London</td>
<td>615</td>
<td>176</td>
<td>87</td>
<td>100</td>
<td>99</td>
<td>736</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Newcastle</td>
<td>592</td>
<td>197</td>
<td>90</td>
<td>100</td>
<td>100</td>
<td>484</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Glasgow</td>
<td>547</td>
<td>228</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>451</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>Nottingham</td>
<td>534</td>
<td>243</td>
<td>84</td>
<td>100</td>
<td>100</td>
<td>469</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Guy's, London</td>
<td>532</td>
<td>133</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>644</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Cambridge</td>
<td>527</td>
<td>211</td>
<td>92</td>
<td>100</td>
<td>100</td>
<td>529</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Bristol</td>
<td>493</td>
<td>190</td>
<td>88</td>
<td>100</td>
<td>100</td>
<td>401</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Oxford</td>
<td>478</td>
<td>159</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>423</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Exeter</td>
<td>471</td>
<td>277</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>416</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Wales</td>
<td>370</td>
<td>132</td>
<td>82</td>
<td>100</td>
<td>100</td>
<td>327</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Leicester</td>
<td>339</td>
<td>339</td>
<td>84</td>
<td>100</td>
<td>100</td>
<td>358</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

13,620 families
Case 1

16 years
Severe learning difficulties
ADHD
Dysmorphic features
    Broad forehead
    deep set eyes
    short philtrum, thin upper lip
    simple ears,
    long thumbs
    mild 5\textsuperscript{th} finger clinodactyly
Pregnancy was normal
Birth weight was 3.4 kg, 2ell as a baby
Developmental delay
Absence seizures on medication
Poor sleep – did not improve with melatonin

Prior Genetic Testing:
Angelman syndrome
Rett syndrome
Microarray CGH
Case 1

De novo frameshift variant in TCF4 – premature truncation of protein

C.820_823del

Pitt-Hopkins Syndrome
Pitt Hopkins syndrome

- Global developmental delay
- Severe to moderate learning difficulties
- Significant speech delay
- Hypotonia - slows down motor development, but most learn to walk - often with an unsteady gait.
- Some will develop epilepsy
- Abnormal breathing pattern of hyperventilation and/or apnoea.
- Brain scans often show agenesis of the corpus callosum.
- Common gastrointestinal problems: chronic constipation and reflux.
- Dysmorphism: a wide mouth with cupid bow upper lip and full lower lip with widely spaced teeth.
- Very happy and affectionate, but can become frustrated due to the lack of communication skills.
- Short and microcephaly
- Tendency to smile frequently and this characteristic, together with some unsteadiness on walking leads to the diagnosis often being confused with Angelman Syndrome
# WM-DDD TCF4 patients

<table>
<thead>
<tr>
<th>DECIPHER ID</th>
<th>Variant</th>
<th>Sex</th>
<th>Size</th>
<th>Pathogenicity / Contribution</th>
<th>Inheritance</th>
<th>Phenotype(s)</th>
<th>Patient Open-Access Variants</th>
<th>Consent</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD-BWH260601</td>
<td>18</td>
<td>46XY</td>
<td>SNV</td>
<td>Uncertain None</td>
<td>Unknown</td>
<td>Abnormal heart morphology, Abnormality of the kidney, Asymmetry of the thorax, Atrial septal defect, Hypertelorism, Hypoplastic nipples, Patient ductus arteriosus, Pulmonic stenosis, Single transverse palmar crease, Specific learning disability, Submucous cleft hard palate, Velopharyngeal insufficiency</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>DDD-BWH265788</td>
<td>18</td>
<td>46XX</td>
<td>SNV</td>
<td>Pathogenic</td>
<td>De novo constitutive</td>
<td>Abnormality of the palmar creases, Generalized hypotonia, Global developmental delay, Melanocytic nevus, Wide mouth, Widely spaced teeth</td>
<td>1</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>DDD-BWH270830</td>
<td>18</td>
<td>46XX</td>
<td>SNV</td>
<td>Pathogenic</td>
<td>De novo constitutive</td>
<td>Abnormal emotion/affect behavior, Abnormality of vision, Delayed gross motor development, Delayed speech and language development, Excessive salivation, Global developmental delay, Prenatal movement abnormality, Self-mutilation, Severe global developmental delay, Stereotypy, Strabismus, Tachypnea</td>
<td>1</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>DDD-BWH272019</td>
<td>18</td>
<td>46XX</td>
<td>-4 bp</td>
<td>Pathogenic</td>
<td>De novo constitutive</td>
<td>Abnormal facial shape, Abnormality of the thumb, Apnea, Behavioral abnormality, Clinodactyly of the 5th finger, Cupped ear, Deeply set eye, Delayed speech and language development, Global developmental delay, Hyperactivity, Low anterior hairline, Low posterior hairline, Short philtrum, Thin vermilion border</td>
<td>1</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>DDD-BWH279790</td>
<td>18</td>
<td>46XY</td>
<td>SNV</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Abnormal facial shape, Delayed speech and language development, Global developmental delay, Long fingers, Long toe, Malar flattening, Pes planus, Specific learning disability</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Case 2

- Hoarse voice
- Sleep disturbance
- Stridor
- Large growth parameters, overgrown feet
- Macroglossia
- Aggressive behaviour
- Pes planus (flat feet)
- 16 years

De novo variants
>80% are likely to be diagnostic

<table>
<thead>
<tr>
<th>Variant Location (GRCh37)</th>
<th>Gene</th>
<th>HGVS</th>
<th>Inheritance: Genotype</th>
<th>Mechanism</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:30,723,453 - 30,723,454</td>
<td>SRCAP</td>
<td>ENST00000262518.4:c.1790_1791delAGinsA</td>
<td>De novo; Heterozygous</td>
<td>Monoallelic</td>
<td>Likely LOF</td>
</tr>
</tbody>
</table>

1 This variant and its inheritance has been confirmed using an independent assay
Truncating mutations within 3’ region cause Floating Harbor syndrome via a **dominant negative** mechanism

Hood, et al.  AJHG,2012
### SRCAP in ExAC and DGV

<table>
<thead>
<tr>
<th>Constraint from ExAC</th>
<th>Expected no. variants</th>
<th>Observed no. variants</th>
<th>Constraint Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonymous</td>
<td>470.6</td>
<td>552</td>
<td>$z = -2.33$</td>
</tr>
<tr>
<td>Missense</td>
<td>1225.6</td>
<td>1066</td>
<td>$z = 2.23$</td>
</tr>
<tr>
<td>LoF</td>
<td>89.1</td>
<td>8</td>
<td>$PU = 1.00$</td>
</tr>
</tbody>
</table>

ExAC constraint metric suggests LoF variants are not tolerated.

Lack of population evidence for tolerated CNV.
Array report

16p11.2 de novo microdeletion encompassing SRCAP gene in a patient with speech impairment, global developmental delay and behavioural problems

Francesca Gerundino, Giuseppina Marseglia, Chiara Pescucci, Elisabetta Pelo, Matteo Benelli, Claudia Giachini, Benedetta Fedorghi, Carla Antonelli, Francesca Torricelli

SOD Diagnostica Genetica, Azienda Ospedaliero Universitaria Careggi, Firenze, Italy
Unità Operativa di Neuropsichiatria Infantile, Azienda Ospedaliero Universitaria Careggi, Italy

- Speech delay
- Global dev. delay
- Behavioural problems
- Clinodactyly, delayed bone maturation
- Subtle phenotypic features resembling FHS?
- Haploinsufficiency for SRCAP an alternative mechanism?
<table>
<thead>
<tr>
<th>BWH DDD</th>
<th>Gerundino et al 2014</th>
<th>Floating-Harbor syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>c.1793delG p.(Gly598Valfs*9)</strong> Exon 12</td>
<td>186kb deletion inc. SRCAP</td>
<td>Dominant negative ex 33-34 mutations</td>
</tr>
<tr>
<td>• Sleep disturbance</td>
<td>• Speech impairment</td>
<td>• Distinctive facial features</td>
</tr>
<tr>
<td>• Large growth parameters, overgrown feet</td>
<td>• Global dev delay</td>
<td>• Short stature</td>
</tr>
<tr>
<td>• MacroGLOSSia</td>
<td>• Behavioural problems</td>
<td>• Delayed bone maturation</td>
</tr>
<tr>
<td>• Aggressive behaviour</td>
<td>• Delayed bone maturation</td>
<td>• Speech impairment</td>
</tr>
<tr>
<td>• Hoarse voice</td>
<td>• Clinodactyly</td>
<td>• Intellectual disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinodactyly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• Sleep disturbance</th>
<th>• Speech impairment</th>
<th>• Distinctive facial features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Large growth parameters, overgrown feet</td>
<td>• Global dev delay</td>
<td>• Short stature</td>
</tr>
<tr>
<td>• MacroGLOSSia</td>
<td>• Behavioural problems</td>
<td>• Delayed bone maturation</td>
</tr>
<tr>
<td>• Aggressive behaviour</td>
<td>• Delayed bone maturation</td>
<td>• Speech impairment</td>
</tr>
<tr>
<td>• Hoarse voice</td>
<td>• Clinodactyly</td>
<td>• Intellectual disability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinodactyly</td>
</tr>
</tbody>
</table>

| c.1793delG p.(Gly598Valfs*9) Exon 12 | 186kb deletion inc. SRCAP | Dominant negative ex 33-34 mutations |

**Table**

**Floating-Harbor syndrome**

Image from Nowaczyk et al 2012, GeneReviews®

**References**

Gerundino et al 2014

BWH DDD
Phenotype and mechanism not consistent with FHS

- **PVS1**
  - Null variant where LOF is a known mechanism of disease

- **PS2**
  - De novo (maternity and paternity confirmed)

- **PM2**
  - Absent from controls

Caveat: The phenotype in the patient matches the gene’s disease association with reasonable specificity

- Haploinsufficiency/LOF for SRCAP causes novel phenotype?
  - No population evidence for tolerated LOF/CNV

- Few overlapping path.CNVs reported

- Emerging DDD / 100,000 genomes data may aid reclassification

Uncertain
Consented patients in DECIPHER can be queried via Matchmaker Exchange.

“Follow this variant”
DDD: successes, legacy, lessons

• Ending Diagnostic odysseys
  – Estimated ~5,000 UK families with confirmed genetic diagnosis
  – ~530 West Midlands patients

• Greater delineation of very rare syndromes
• Description of new syndromes / new genes
• Global data-sharing via DECIPHER
New Genes/Syndromes >30 in 3 years

<table>
<thead>
<tr>
<th>Gene</th>
<th>DDD Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNP</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>BCL11A</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>CDK13</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>CHAMP1</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>CHD4</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>CNOT3</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>COL4A3BP</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>CSNK2A1</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>DDX3X</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>DNM1</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>GNAI1</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>HACE1</td>
<td>Nature Genetics 2015</td>
</tr>
<tr>
<td>KCNQ3</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>KIAA0586</td>
<td>Nature Genetics 2015</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>DDD Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP21</td>
<td>Nature Genetics 2015</td>
</tr>
<tr>
<td>MSL3</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>PCGF2</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>POGZ</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>PPM1D</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>PPP2R1A</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>PPP2R5D</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>PRMT7</td>
<td>Nature Genetics 2015</td>
</tr>
<tr>
<td>PUF60</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>PURA</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>QRICH1</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>SET</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>SUV420H1 (KMT5B)</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>TCF20</td>
<td>Nature 2017</td>
</tr>
<tr>
<td>TRIO</td>
<td>Nature 2015</td>
</tr>
<tr>
<td>ZBTB18</td>
<td>Nature 2017</td>
</tr>
</tbody>
</table>

Akawi et al, Nature Genetics, 2016
DDD: successes, legacy, lessons

• Creation of Developmental Disorder MDT
  – Developed further and more formally for 100K genomes
  – Best practice for imminent NHSE Genomic Medicine Service
  – Extensible to other Rare Disease scenarios e.g prenatal – PAGE

• Increased skills in genomic variant interpretation

• Development of bioinformatics pipelines / filtering strategies
  – Algorithms.....de novo, mosaicism, structural variants
  – DDG2P curated gene panel (>1,600 genes)
  – Clinical Decision support software - DECIPHER
New Genomic Medicine Service

• Trio Whole Genome Sequencing (WGS) commissioned for severe developmental disorders
• >1,000 West Midlands patients per year
• Most genomic variation detectable in single assay
• Analysis and interpretation building on lessons from DDD
Acknowledgements:

West Midlands patients and families
DDD core team at Sanger
West Midlands Clinical and Laboratory Genetics