Developing a comprehensive fetal anomalies gene panel for the NHS England Genomic Medicine Service

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Panel publicly available from PanelApp: https://panelapp.genomicsengland.co.uk/panels/478 and the PanelApp API

Background

Virtual gene panels are widely used by clinical diagnostic services to prioritise potentially disease-causing variants identified by next-generation sequencing. Genomics England's PanelApp (https://panelapp.genomicsengland.co.uk) is a publicly available tool originally developed to support the 100,000 Genomes Project analysis pipeline. Subsequent to the 100,000 Genomes Project, the NHS is implementing a Genomic Medicine Service in England that will include rapid exome sequencing for fetuses with multiple abnormalities where a monogenic malformation disorder is considered the likely aetiology. Fetal exome results will be returned within the time frame of a pregnancy and may inform decision-making, thus genes included in this panel must be based on robust gene-disease associations and relevant to the fetus, ie. associated with structural anomalies known to be, or that could potentially be, detected in fetal life.

Objective

To develop and validate **a virtual gene panel of fetally relevant genes** to prioritise potentially disease-causing variants identified by whole exome sequencing as part of the **NHS England Genomic Medicine Service rapid fetal exome service.**

Methods

The PanelApp curation platform was used to develop the virtual panel. Genes rated as 'Confirmed' in the Developmental Disorders Gene2Phenotype database (DDG2P) and additional genes reported in four recent, large scale studies of fetal exome/genome sequencing were systematically reviewed to determine the suitability of each gene for inclusion.

Inclusion criteria:

'A gene with a reported structural phenotype detectable with standard ultrasound screening or other imaging modalities, e.g. MRI, that could present at any stage in fetal life.'

Prenatal presentation was determined by expert review supported by systematic literature search. Where there was doubt and presentation in infancy was reported, these genes were included.

In reviewing genes for inclusion in the panel, the potential for incidental findings was considered. In general, where there was significant potential that a variant in the gene might explain a fetal structural anomaly, it was considered that this outweighed the potential **risk of incidental findings**.

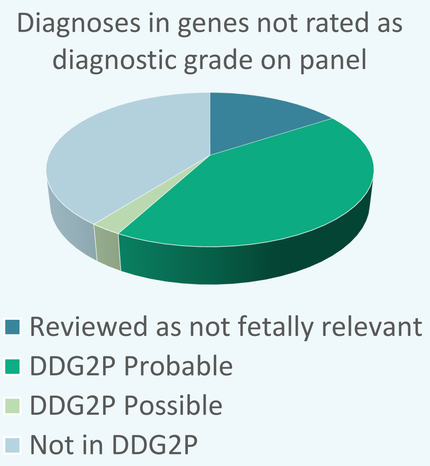
Results and Validation

A total of 964 genes meeting inclusion criteria were identified and included as diagnostic grade in the fetal panel. The panel gene content was validated using a cohort of 197 patients with genetic diagnoses made through the 100,000 Genomes Project, where the clinical phenotype included one or more fetally relevant features.

Diagnoses in genes on panel		Diagnoses in genes not on panel	
Gene(s)	**Diagnoses**	**Gene(s)**	**Diagnoses**
ACY1, ALDH18A1, ALG1, AMER1, ANOS1, BCL11A, BLM, BRAF, BRPF1, C11ORF70, CCDC39, CDK13, CHAMP1, CHD4, COASY, COL1A2, COL2A1, COL6A1, COL6A2, COL6A3, CTNNB1, DNMT3A, DOCK6, DYNC2H1, EFTUD2, EYA1, FGFR2, FLNA, GATA4, GATA6, GBE1, GLI3, GRIN1, GRIN2B, HNF1B, HNRNPK, IDUA, KANSL1, KAT6A, KAT6B, KDM5C, KIAA0586, LARP7, LTBP3, MCOLN1, MRPS22, MYCN, NAA10, NALCN, NANS, NFIX, NIPBL, OBSL1, OFD1, OTX2, PIEZO1, PIEZO2, PTPN11, RAI1, RET, RYR1, SALL1, SCN2A, SEPSECS, SETD5, SIX3, SKI, SMARCA4, SOS1, SOX9, SPG11, TBL1XR1, TCF4, TFAP2A, TMEM67, TRAF7, TSC2, TSEN54, TTN, TUBB, TUBB4A, VPS13B, WT1, ZBTB18, ZBTB20, ZC4H2	1	BICD2, CACNA1A, COL3A1, COL4A4, CTSB, CYB5A, DHX30, FZD2, HSPB1, INF2, INPP5K, KCNQ1, KIF5A, MAP3K7, MFSD8, MORC2, MSTO1, NAA15, NFKB2, NONO, PBX1, PPP1R13L, PSMD12, RPL26, SACS, SHANK3, SIN3A, SOX11, TBC1D32, TBR1, TPP1, TRIO, UMOD, USP9X, ZNF148	1
AHDC1, ANKRD11, ASXL1, CASK, COL1A1, DNAH5, DYRK1A, FOXG1, GJA8, KMT2A, KMT2D, LZTR1, MTOR, PUF60, SATB2, SON, TUBA1A	2	ASXL3, PACS1	2
ARID1B, CREBBP, DDX3X, EHMT1, NF1	3	MED13L	3
ADNP, PKD2	4		
PKD1	11		

Analysis of phenotype in cases where gene reviewed as not fetally relevant		
Gene	**Relevant HPO terms (fetally relevant terms in bold)**	**Comments**
BICD2	Fasciculations, Proximal upper limb amyotrophy, Scoliosis, Flexion contracture, **Equinovarus deformity, Structural foot deformity**, Progressive muscle weakness, Fatigable weakness, Sensory impairment, Dysautonomia, Decreased fetal movement, Respiratory insufficiency, EMG abnormality	Given progressive nature of condition, 'equinovarus deformity' may represent acquired feature
COL4A4	Chronic kidney disease, Hypertension, Gout, **Polycystic kidney dysplasia**	Polycystic kidneys not a recognised feature of Alport syndrome
CSTB	**Cortical gyral simplification**, Severe intellectual disability, Infantile encephalopathy, Microcephaly, Dyskinesia, Limb hypertonia, Abnormal myelination	Not consistent with pathophysiology of condition
KCNQ1	Syncope, **Bicuspid aortic valve**, Arrhythmia	May represent chance association
MFSD8	**Aplasia/Hypoplasia of the cerebellum**, Abnormality of the basal ganglia, Leukodystrophy, Seizures, Sensorineural hearing impairment, Developmental regression, Intellectual disability	May represent a hitherto unrecognised fetal phenotype
TPP1	**Polyhydramnios, Aplasia/Hypoplasia of the maxilla**, Anterior creases of earlobe, **Ventricular septal defect, Atria septal defect, Tetralogy of Fallot, Coarctation of aorta, Cardiomyopathy, Large placenta, Abdominal wall defect, Omphalocele, Umbilical hernia**	HPO terms suggest an additional diagnosis ?Beckwith-Wiedemann syndrome

Validation of the panel using data from the **100,000 Genomes Project** demonstrated that the review process was effective at defining fetally relevant genes. The main reason for the non-inclusion of genes from the panel was that the gene did not have a 'Confirmed' rating in DDG2P, and was therefore not reviewed for inclusion in the panel. A pathogenic variant was found in *MFSD8*, which had been reviewed as not fetally relevant due to the reported age of onset. This gene will be included in future iterations of the panel. This finding also prompted review of other genes associated with neuronal ceroid lipofuscinosis, as it highlighted the possibility of unrecognised fetal phenotypes in this condition.



Conclusions

We have developed a publicly available comprehensive fetal anomalies gene panel covering a wide range of clinically relevant fetal structural anomalies.
Validation of the panel demonstrated that the panel sensitivity is high, but would be improved by

- systematically reviewing all genes currently rated as Probable or Possible in DDG2P for new evidence of disease association
- drawing on additional sources of fetally relevant genes
- ongoing peer review and update

Lack of awareness of fetal phenotypes for known postnatal conditions, and identification of new conditions presenting prenatally mean that this panel will require regular updates.
Future use in the NHS Genomic Medicine Service will permit further validation and refinement of the panel.

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Feedback:

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