Impact of the Deciphering Developmental Disorders Study on Exome Sequencing Yield: an Analysis of 163 Cases

H. Savage[1], R. Dubis[1], A .Haworth[1], L. Ive[1], E. Serra[1], N. Lench[1], J. Short[2], C. Crosby[2], S. Mansour[2], E. Dempsey[2], T. Homfray[2], F. Elmslie[2], A. Saggar[2], P. Ostrowski[2], J. Kenny[2], K. Josephs[2], K. Tatton-Brown[2], M. McEntagart[2], N. Lahiri[2], S. Talukdar[2] and S. Drury[1]

[1]Congenica Ltd, UK; [2]SW Thames Regional Genetics, UK

Introduction

The Deciphering Developmental Disorders (DDD) study was a groundbreaking project established in collaboration with the UK National Health Service (NHS) to investigate the underlying causes of developmental disorders in undiagnosed paediatric patients. Although DDD ended recruitment of new patients in April 2015, analysis and reanalysis of the microarray, SNP array and Exome Sequencing (ES) data of 13,600 patients have resulted in the identification of over 30 new genes associated with developmental disorders.

Congenica was formed in 2014 to facilitate and support the incorporation of genomic services like the DDD study into Clinical Practice, through the design and development of a clinical decision support platform suitable for the analysis of genomic data. In conjunction with the South West Thames Regional Genetics Service (London, UK) (SWTRGS), Congenica has provided ES analysis and interpretation to identify the causes of developmental disorders in a cohort of undiagnosed individuals.

Here we present the results highlighting the diagnoses facilitated by the discoveries of the DDD study.

Methods

All individuals and families referred for testing were consented by the SWTRGS team for clinical research ES and subsequent analysis of phenotypically relevant genes. DNA from a subset of individuals referred with suspected developmental disorder were sequenced on an Illumina platform using either the Agilent Clinical Research Exome V2, or the Nonacus ExomeCG capture kits, for detection of single nucleotide variants and Indels. Data were processed and analysed using the Congenica platform. A DDD-type filtering approach was implemented to narrow down the variants requiring review, in addition to the application of DDG2P and phenotypically-relevant PanelApp (Genomics England) gene panels.

Results

163 families were referred with postnatal phenotypes consistent with that of a developmental disorder between January 2018 and June 2020; 61 singletons, 10 duos, 90 trios and 2 quads (Figure 1). 40/163 cases (25%) had a genetic diagnosis identified by Congenica and confirmed by supplementary testing by SWTRGS. Of the 123 'negative' cases, 29 (24%) had one or more 'hot' variants of uncertain significance (VUS), warranting further testing and investigation.

Of the 40 diagnosed cases, variants were identified in 37 different genes (Table 1); three of which were identified as part of the DDD study (*ADNP, DDX3X* and *PURA)*. Four genes were responsible for more than one diagnosis in our cohort; *DDX3X, DYRK1A, FOXG1* and *PTPN11.* Interestingly two of the diagnosed families were found to have a compound phenotype, with contributing variants identified in two genes (*PTPN11/VPS13B* and *RERE/PHKA2*). Of the hot VUSs reported, a further two DDD genes were linked to the patient phenotypes (*COL4A3BP* and *TRIO*). In the 30 trio families in which it was possible to determine inheritance, 26 (87%) diagnoses resulted from *de novo* variants; this is compared to only 62% of DDD diagnoses. Unsurprisingly, the diagnostic yield was greatest when trio analysis was performed.

Discussion

The DDD study has had a significant impact on routine genomic testing around the world. 4 out of 40 (10%) confirmed diagnoses, and 2 out of 29 (7%) potential diagnoses in our center were detected in genes identified by the DDD project. We observed a much larger proportion of diagnoses caused by *de novo* variants than originally reported in the DDD study; this may be the result of our comparatively small sample size and the lack of consanguinity reported in our sequenced patient population.

Continued research and reanalysis of the DDD data will no doubt continue to uncover new genes and diagnoses to the benefit of international patients with rare developmental disorders.

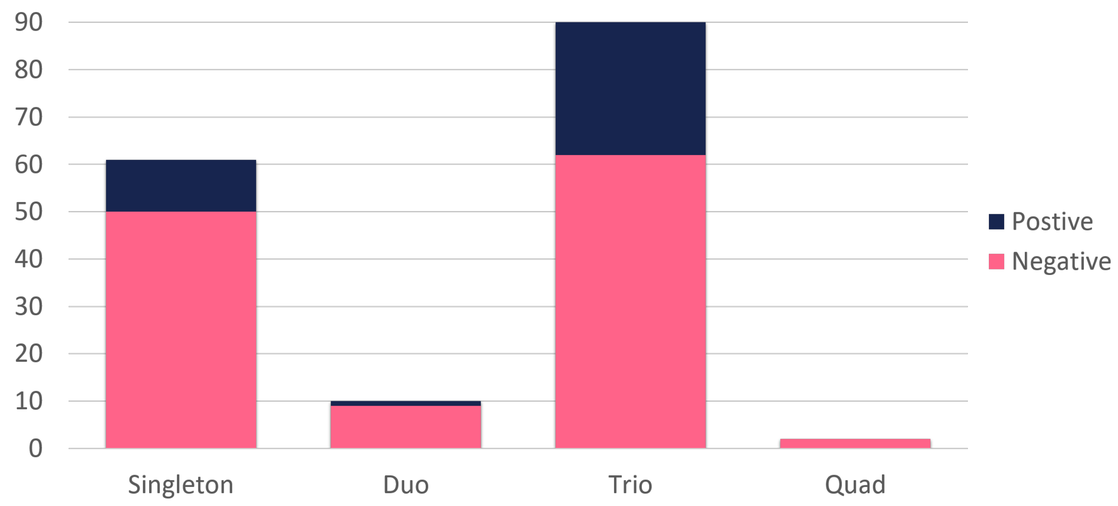

Figure 1: The numbers of diagnoses in postnatal patients referred to our center with developmental delay. Pink bars represent patients where no diagnosis was identified. Blue bars represent diagnosed patients. Diagnoses are broken down by family structure to highlight the impact of sequencing parental samples to aid with the initial interpretation of patient variants.

***ADNP*dn**	*DLG4*dn	*ITPR1*	*PHKA2*	*RAI1*	*SLC6A8*
*ARID1A*dn	*DYRK1A*dn (2)	*MAP2K1*	*PLA2G6*	*RERE*	*SOS1*
*ARID1B*dn	*EIF3F*	*MECP2*dn	*POU3F3*dn	*RNASEH2C*	*TAOK1*dn
*CHD3*dn	*FBXO11*dn	*MTM1*dn	*PPP1CB*	*SETBP1*	*THOC6*
***DDX3X*dn** (2)	*FOXG1*dn (3)	*NF1*dn	*PTPN11* (2)	*SETD5*dn	*VPS13B*
*DHDDS*dn	*GRIN2A*dn	*NFIX*dn	***PURA***	*SLC2A1*	*WDR26*dn
*ZMIZ1*dn					

Table 1: The list of genes resulting in the diagnosis of 40 individuals in our cohort. Genes identified are part of the DDD study (https://www.ddduk.org/updates.html) are highlighted in bold. "dn" = *de novo.* (n) = number of diagnoses, if greater than 1.

DDX3X

Two unrelated families were referred for testing. The first was a one year old patient with cleft palate, growth restriction, microcephaly brain anomalies and global developmental delay. We identified a functionally important pathogenic, *de novo* missense variant in *DDX3X*.

The second, two year old patient was referred with global developmental delay, only. We identified a different, likely pathogenic, *de novo* missense variant in *DDX3X*. This variant had previously been reported in the literature and on ClinVar.

DDX3X is associated with X-linked intellectual disability (XLMR102). Whilst the phenotype of both patients is different, their features are consistent with the cases identified in the 2015 DDD publication.

PURA

This family were referred with developmental delay, plus additional neuro-muscular features. We found a pathogenic, *de novo* nonsense variant in the *PURA* gene.

PURA is associated with intellectual disability (MR31). The phenotype of our patient overlaps *PURA* cases in the 2015 DDD publication.

ADNP

This family were referred with mild to moderate developmental delay and subtle dysmorphism. We found a pathogenic frameshift variant in the *ADNP* gene.

ADNP is associated with intellectual disability. While our patient is less severely affected than the originally-published patients, this diagnosis fits the patient phenotype.

The DDX3X, PURA and ADNP genes were first associated with developmental disorders in the 2015 DDD publication by M.E. Hurles *et al* (PMID: 25533962)

Rady Children's Institute Genomic Medicine

FRONTIERS IN PEDIATRIC GENOMIC MEDICINE CONFERENCE