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Diagnostic Exome Sequencing in Adolescents with Neurological and Neurodevelopmental Disorders

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BACKGROUND

- Diagnostic exome sequencing (DES) is increasingly utilized to identify genetic etiologies of neurological and neurodevelopmental disorders (NDD) in pediatric patients.
- Traditional testing guidelines typically recommend microarray, fragile X, karyotype, single gene, and multi-gene panel testing (MGPT) in individuals with NDD, resulting in a lengthy "diagnostic odyssey" with often inconclusive or negative results (1).
- Adolescents provide a unique opportunity within the pediatric population to evaluate the clinical utility of DES in undiagnosed individuals with NDD, yet little is known about genetic testing in this cohort.
- Herein, we report the characteristics and detection rates of adolescent patients with NDD.

METHODS

- Available clinical and genetic testing histories were reviewed for an unselected cohort of 568 adolescents (ages 13 – 17 years) referred for DES at one commercial company with neurological indications, including intellectual disability (ID)/developmental delay (DD), autism spectrum disorder (ASD), and seizures/epilepsy.
- All probands underwent characterized gene analysis; if negative, novel candidate gene analysis was performed if requested and an informative family trio was provided. Overall result categories were determined according to predefined diagnostic variant assessment criteria (2). Diagnostic rates are defined by a positive or likely positive overall report.

RESULTS

- Of 568 probands, 258 (45%) were female and 310 (55%) male; average age of testing was 14.8 years.
- 111 positive/likely positive findings were identified in 106 (19%) probands (Figure 1) in 89 characterized genes, 72% (64/89) of which are not included on a large routine neurodevelopmental MGPT (Table 1).
- Of these findings, 35% (39/111) were inherited and 48% *de novo*; 31 (28%) were in autosomal recessive genes, 66 (59%) in autosomal dominant, 6 (5%) in X-linked dominant, 6 (5%) in X-linked recessive, and 1 (1%) in a mitochondrial gene.
- Previous negative testing was reported in 419 (74%) of probands, with 19% (81/419) having a positive or likely positive DES finding (Figure 2).
- Diagnostic rates in adolescents with ASD, seizures/epilepsy, and musculoskeletal indications (Figure 3) were greater than those in an unselected cohort of pediatric patients with NDD (n=3648).

FIGURE 1. DETECTION RATES (n = 568)

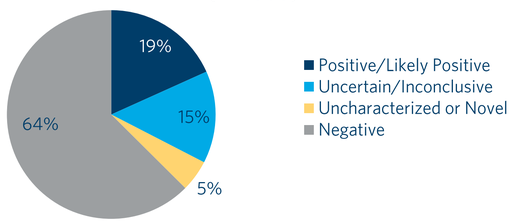


FIGURE 2. PERCENTAGE OF PATIENTS WITH PREVIOUS NEGATIVE TESTING

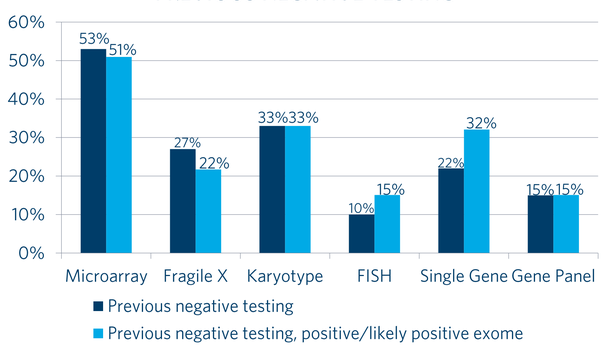
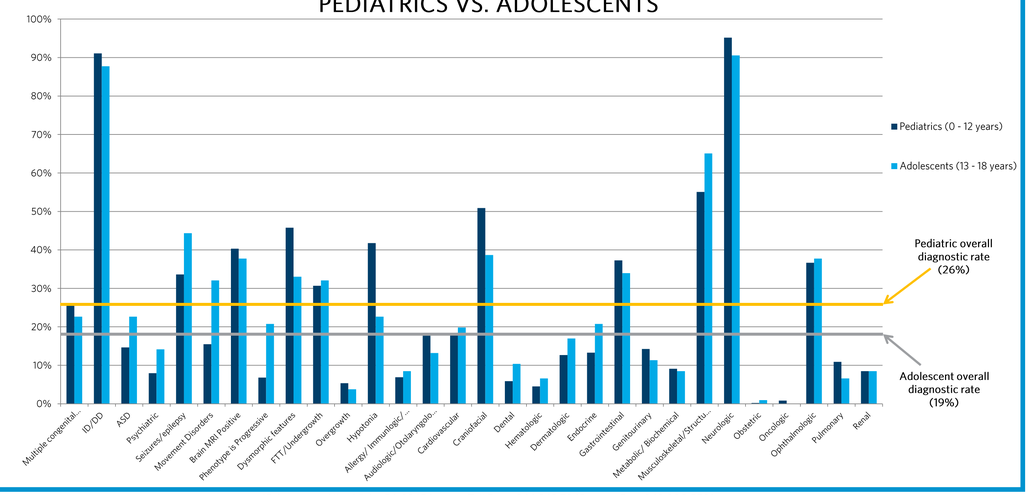


FIGURE 3. DIAGNOSTIC RATES BY CLINICAL CHARACTERISTICS: PEDIATRICS VS. ADOLESCENTS



Gene Findings			
Characterized Positive/Likely Positive			
Included on Neurodevelopmental MGPT (25 genes)			
ADNP (2 cases)	*DLG3*	*IQSEC2*	*PHF6*
ANKRD11 (3 cases)	*DYNC1H1*	*KCNQ2*	*PLP1*
ARID1B (3 cases)	*DYRK1A*	*KDM5C* (2 cases)	*PNKP*
CACNA1A (2 cases)	*FOXG1*	*KIF1A*	*VPS13B*
CHD2	*GNAO1*	*MECP2*	
CHD7(2 cases)	*GRIA3*	*NSUN2*	
DDX3X	*GRIN1*	*PACS1*	
Not Included on Neurodevelopmental MGPT (64 genes)			
ASXL1	*FBN1*	*MED13L*	*RYR1*
ATP1A3	*FGFR3*	*MT-ND6*	*SBF2*
BRAF	*FUS*	*MTOR*	*SCN3A*
CCND2	*GBE1*	*MYO7A*	*SETX (2 cases)*
CFTR	*GJC2*	*NEB*	*SH3TC2*
CHRNA1	*HIVEP2*	*NFIA* (2 cases)	*SLC26A2*
COL4A1	*HMGCL*	*NPC1*	*SLC37A4*
CSF1R	*HSD17B10*	*NR2F1*	*SOX9*
CYP2U1	*KCNC3*	*NUBPL*	*SPAST*
CYP7B1	*KMT2A* (2 cases)	*PDE6A*	*TANGO2*
DEAF1	*KMT2B*	*PIEZO2*	*TP63*
DLAT	*KMT2D*	*PKD1*	*TRIO*
DNM1L	*LAMA2*	*PKD2*	*TRIT1*
DOK7	*LDLR**	*PMM2* (2 cases)	*TRPV4*
EBF3	*LMNA*	*PRNP*	*TUBB*
FA2H	*MAGEL2*	*PYCR1*	*USH2A*
Candidate/Suspected Candidate (15 genes)			
ADCY5	*PKDCC*	*CLTC*	*RICTOR*
CDC42 (2 cases)	*SNAP25*	*FDXR*	*RYR3*
COQ4	*ATP6V1A*	*PDGFRB*	*WARS2*
ERBB4	*CLCN3*	*RHOA*	

TAKE-HOME POINTS

- Positive/likely positive findings were identified in 106 probands (19%); compared to pediatrics, diagnostic rates were higher in patients with ASD, seizures/epilepsy, and musculoskeletal/structural indications.
- As 72% (64/89) of gene findings are not included on a large routine neurodevelopmental MGPT, this study highlights the clinical utility of DES in adolescents with complex NDD phenotypes in which traditional testing strategies have failed to elucidate a genetic etiology.
- Detection of alterations in both characterized and novel genes provides patients with an accurate diagnosis and has important treatment, medical management, and reproductive implications as they transition to adulthood.

REFERENCES

1. Xue Y, Ankala A, Wilcox WR, et al. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing.
2. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families.

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