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# What You Can Get and What Would Be Missed: A Side by Side Comparison of Panels vs Exome Testing for Neurodevelopmental Disorders

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## BACKGROUND

- Neurodevelopmental disorders (NDD) is a group of diseases that are highly clinically and genetically heterogeneous. The broad and nonspecific presentation of NDD leads to significant diagnostic challenges.
- New NDD loci are being discovered at a rapid pace.
- Identifying disease causing mutations in NDD patients may help guide clinical management.
- Next generation sequencing (NGS) based multi-gene panels (MGP) provide 100% coverage for targeted gene and can detected gross copy number variations by either NGS coverage analysis or by array comparative genomic hybridization (aCGH).
- Diagnostic exome sequencing (DES) covers >95% of the coding region, and is able to detect mutations in genes that are not included in the panel.
- Understanding the strengths and limitations of each test type allows providers to effectively and efficiently decide which test to order in consideration of the patient's presentation, diagnostic yield, cost of testing, and turnaround time.

Figure 1. Patients Tested by Different Panels

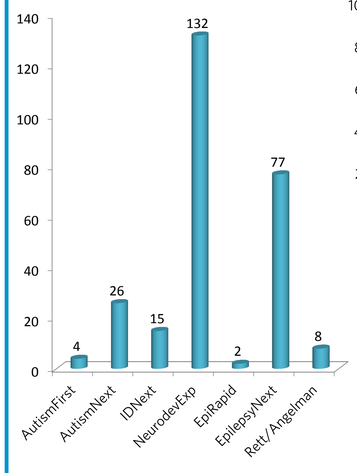
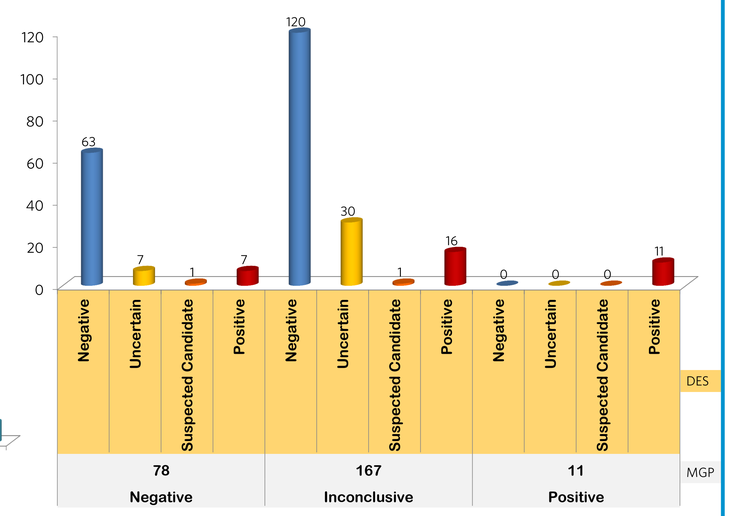



Figure 2. MGP and DES Results Comparison




## METHODS

- A retrospective study of 256 patients tested by MGP first, and then reflex to DES.
- Cohort: all patients have various NDD features, including developmental delay, intellectual disability, autism spectrum disorder (ASD), and epilepsy.
- This study compared the diagnostic yield and test results between MGP and DES in this cohort. In particular, we analyzed whether DES can lead to additional diagnoses.

## RESULTS

- Pathogenic mutations or likely pathogenic variants (VLPs) were detected in 11 (4%)-patients by MGP and 36 (14%) patients by DES, respectively.
- Among the 11 positive cases detected by MGP, reflex DES testing was requested by ordering physician, and same positive findings were confirmed by DES. In addition, *de novo* pathogenic variants in a second gene were identified in two of these cases (Patients 26 and 36, Table 2).
- In patients with negative or inconclusive MGP result, 25 received a diagnostic result in a gene(s) not included in the panel.
- DES identified dual diagnoses in 5/36 (14%) positive patients.
- A pathogenic mutation in the mitochondrial genome was detected one case (patient 23); two cases were found to have pathogenic variants in uncharacterized genes (Patients 24, 25, Table 1).

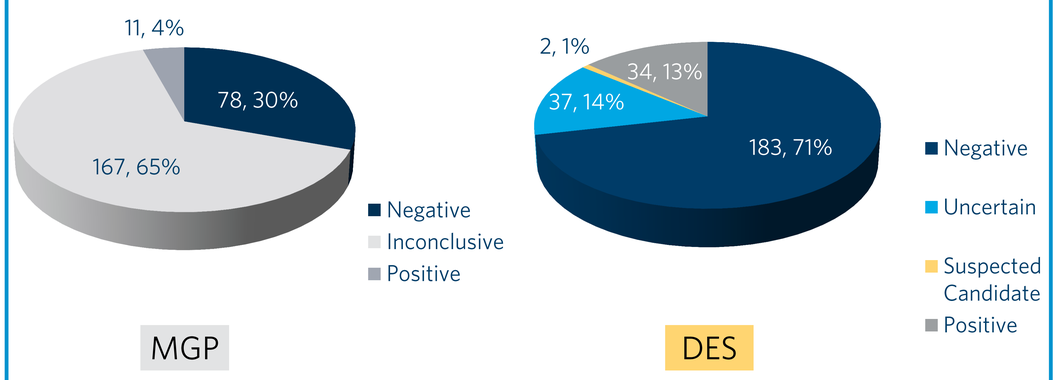
Figure 4. Inheritance pattern distribution

| Inheritance pattern | # of genes | Notes |
|---|---|---|
| AD | 31 (76%) | all *de novo* except 4 cases (one or two parents unavailable) |
| AR | 5 (12%) | all homo, confirmed bi-parental except 1 case (parents unavailable) |
| XL | 4 (10%) | Including 1 female |
| Mito | 1 (2%) | *de novo* |

## Table 1. DES Positive, MGP Negative or Inconclusive

| Patient # | Age of testing | Gene* 1 | Alteration, zygosity | Gene *2 | Alteration, Zygosity |
|---|---|---|---|---|---|
| 1 | 14 | *ANK2* | c.3019C>T(p.R1007*),Het | | |
| 2 | 5 | *ASXL1* | c.2763_2770delinsCAA (p.V922Nfs*24),Het | | |
| 3 | 0.5 | *CACNA1E* | c.2104G>A(p.A702T),Het | *AUTS2* | c.3560C>G (p.P1187R),Het |
| 4 | 10 | *CAMK2B* | c.416C>T(p.P139L),Het | | |
| 5# | 14 | *COL4A1* | c.2317G>A(p.G773R),Het | | |
| 6 | 14 | *DNM1L* | c.1207C>T(p.R403C),Het | | |
| 7# | 18 | *DNMT3A* | c.2037delG(p.K680Rfs*25),Het | | |
| 8 | 22 | *DUOX2* | c.2895_2898delGTTC (p.F966Sfs*29),Het | *TRIO* | c.2359C>T (p.Q787*),Het |
| 9 | 2 | *EBF3* | c.686C>T(p.S229L),Het | | |
| 10 | 17 | *EVC2(AR)* | c.3265C>T(p.Q1089*),Hom | | |
| 11# | 10 | *IGF1R* | c.3348_3366dup19 (p.M1123R*14),Het | *ZBTB18* | c.1265C>A (p.S422*),Het |
| 12 | 5 | *KANSL1* | c.868C>T(p.R290),Het | | |
| 13 | 4 | *KDM5C(XLR)* | c.2770C>T(p.Q924*),Hemi | | |
| 14 | 10 | *KMT2A* | c.134delC(p.P45Rfs*105),Het | | |
| 15# | 18 | *PAFAH1B1* | c.569-10T>C(N/A),Het | | |
| 16 | 3 | *POMGNT1 (AR)* | c.1490G>A(p.R497Q),Hom | | |
| 17 | 8 | *SLC6A8(XLR)* | c.1540C>T(p.R514*),Hemi | | |
| 18 | 5 | *SMAD4* | c.1486C>T(p.R496C),Het | | |
| 19 | 8 | *TBCK(AR)* | c.376C>T(p.R126*),Hom | | |
| 20# | 4 | *TYR(AR)* | c.929dupC(p.R311Kfs*7),Hom | | |
| 21 | 4 | *WDFY3* | c.2158C>T(p.R720*),Het | | |
| 22 | 18 | *ZBTB20* | c.1873A>G(p.M625V),Het | | |
| 23 | 14 | *MT-ATP6 (M)* | m.8993T>G(p.L156R),Het | | |
| 24 | 11 | *DOT1L* | c.3882dupA (p.G1295Rfs*10),Het | | |
| 25 | 6 | *KIF2A(AR)* | c.1493A>G(p.N498S),Hom | | |

Figure 3. MGP and DES Diagnostic yield




## Table 2. MGP and DES Both Positive Cases

| Patient # | Age of testing | Gene *1 | Alteration, Zygosity | Gene* 2 | Alteration, Zygosity |
|---|---|---|---|---|---|
| 26 | 16 | *ATP1A2* | c.2810G>A (p.R937H),Het | *DNMT3A* | c.2312G>A (p.R771Q), Het |
| 27 | 7 | *HNRNPU* | c.2085dupT (p.G696Wfs*6),Het | | |
| 28 | 1 | *HPRT1(XLR)* | c.148G>C (p.A50P),Hemi | | |
| 29 | 10 | *KCNQ2* | c.994A>G (p.R332G),Het | | |
| 30 | 5 | *KIAA222* | c.1441C>T (p.R481*),Het | | |
| 31 | 4 | *MECP2(XLD)* | c.397C>T (p.R133C),Het | | |
| 32 | 26 | *MEF2C* | c.214delT (p.Y72Tfs*17),Het | | |
| 33 | 3 | *SCN1A* | c.5306A>G (p.Y1769C),Het | | |
| 34 | 3 | *SCN1A* | c.3615G>A (p.W1205*),Het | | |
| 35 | 13 | *SCN8A* | c.2921C>G (p.A974G),Het | | |
| 36 | 9 | *SYNGAP1* | c.43delG (p.A15Rfs*54),Het | *CSNK2B* | c.238T>A (p.Y80N),Het |

# One or two patents unavailable for testing. All the rest heterozygotes were confirmed to be de novo.
* AD inheritance unless otherwise indicated in ().

## TAKE-HOME POINTS

- While MGP provides low cost, targeting to high yield genes, DES has a unique advantage of analyzing a much broader gene list.
- DES achieved molecular diagnosis in an additional 25/256 (10%) patients who first underwent MGP testing with negative or inconclusive results.
- The overall positive yield is lower than what we previously reported for MGP (18%) and DES (33%). This is due to this study focusing on patients with initial negative MGP testing results or seeking additional diagnoses.
- This study provides an empirical comparison of MGP and DES and can help physicians choose the most appropriate genetic testing strategy for their patients.

## REFERENCES

1. Hlebig KL . Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016 Sep;18(9):898-905.
2. Elliott H. Neurodevelopmental disorders and genetic testing: Current approaches and future advances. Ann Neurol 2013;74:164-170.