# A Genetic Characterization of Neuro-Developmental Disorders in South African and Kenyan Populations: The NeuroDev Study

## INTRODUCTION

- Non-European ancestry is underrepresented in the GWAS catalog[1]


- There is a similar trend for genetic studies on neurodevelopmental disorders (NDDs)

**NeuroDev aims to perform genotyping, exome sequencing and characterization of the phenotypic spectrum of NDDs on 1800 children from South Africa and Kenya[2]**

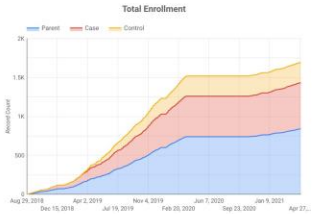
## METHODS

South Africa
- Western Cape

Kenya
- Kilifi County

Case control study with a nested trio design

***Cases:*** 2-17yrs old with a clinical dx of intellectual disability, global developmental delay, communication disorder, autism spectrum disorder, ADHD and/or specific learning disorders




Genetic analysis and variant calling is performed by the Center for Mendelian Genomics team using the GATK and GATK gCNV pipelines. Candidate variants met ACMG guidelines of pathogenicity.

# Here, we present the results from the first 99 trios sequenced in the NeuroDev study

75 trios analyzed
13 (17.3%) solved
5 novel gene findings

24 trios analyzed
10 (41.7%) solved
2 novel gene findings

**Table 1. SNV pathogenic and likely pathogenic findings in known OMIIM genes.**

| Gene | Variant Type |
|---|---|
| *DDX3X* (3) | 2 missense, 1 stop gained |
| *CREBBP* (2) | 1 missense, 1 splice region |
| *SYNGAP1* | Splice acceptor variant |
| *SCN2A* | Stop gained |
| *IRF2BPL* | Frameshift |
| *TLK2* | Missense |
| *MBD5* | Stop gained |
| *BCL11B* | Frameshift |
| *ZBTB18* | Frameshift |

**Table 2. Structural variant pathogenic and likely pathogenic findings.**

| CNV type | Size |
|---|---|
| 6q22.1-23.2 del | 18Mb |
| 18q del | 18Mb |
| 15q trip | 7Mb |
| 3p del | 6.7Mb |
| 22q11.2 dup | 2.1Mb |
| 22q11.2 del (2) | 2.1Mb |
| 15q13.3 del (inherited) | 1.49Mb |
| 22q13 dup | 0.86Mb |
| 16p11.2 del | 0.53Mb |

All variants and CNVs are of *de novo* inheritance, with the exception of 15q13.3del

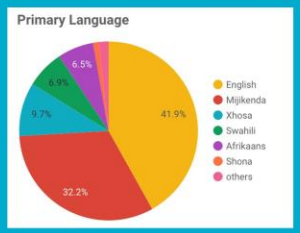
Associated syndromes include syndromic X-linked mental retardation of the Snijders Blok type (*DDX3X*), Rubinstein-Taybi syndrome 1 (*CREBBP*), Autosomal dominant mental retardation (*SYNGAP1, TLK2, MBD5, ZBTB18*), Early infantile epileptic encephalopathy (*SCN2A*), NDD with regression, abnormal movement, loss of speech and seizures (*IRF2BPL*) and Intellectual developmental disorder with dysmorphic facies, speech delay and T-cell abnormalities (*BCL11B*)

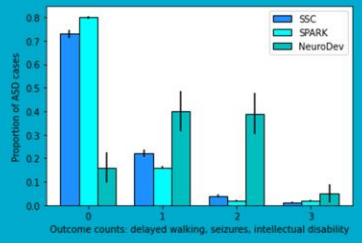
**Table 3. Novel candidate gene associations identified through Matchmaker Exchange**

| | Gene | Consequence | Number of cases to date |
|---|---|---|---|
| South Africa | *AGO1* | Missense | 26 |
| | *CACNA1C* | Frameshift | 25 |
| | *CACNA1E* | Essential splice site | 6 |
| | *MYH10* | Missense | 14 |
| | *PPP2R5C* | Inframe deletion | 11 |
| Kenya | *MAPK1* | Missense | 7 |
| | *SF1* | Missense | 7 |

Variants of unknown significance were submitted to Matchmaker Exchange platform, to facilitate the matching of cases with similar phenotypes and genotypes in novel genes


**Preliminary phenotype findings from the NeuroDev study to date**




| *NeuroDev Collection* | | |
|---|---|---|
| Dates | | Sept '18 - Mar '20 |
| Enrollment | *Total participants* | 1520 |
| | *Child cases* | 521 |
| | *Child controls* | 260 |
| | *Mothers* | 457 |
| | *Fathers* | 282 |
| | *Trios* | 259 |
| Sex ratio | *Child cases* | 70.6% male |
| | *Child controls* | 48.1% male |
| Age range (mean) | *Child cases* | 2-18 (8.0) |
| | *Child controls* | 2-15 (8.1) |
| Diagnosis | *ASD & GDD/ID* | 42.8% |
| | *ASD alone* | 9.4% |
| | *GDD/ID alone* | 43.4% |
| | *other* | 4.4% |
| Photo consent | | 86.8% |
| Biological sample | | 99.2% |
| Cell line consent | | 97.1% |

## DATA SHARING

- All NeuroDev materials and results will be made available as a resource for the scientific community
- DNA is biobanked in the NIMH Repository and Genomics Resource at Rutgers University
- Participants from South Africa are consented for cell line generation

GnomAD · GaP · ClinVar · AnVIL · NIH Atlas of Human Malformation Syndrome in Diverse Populations · FACE2GENE

## CLINICAL & SCIENTIFIC IMPACT

- In South Africa, the genetic findings will be returned to interested parents
- Photos of children with diagnosed genetic syndromes will be shared to databases to help train clinicians and diagnostic algorithms to recognize these conditions in African populations
- The collection of cell lines will significantly diversify current stem cell collections, that are primarily of European ancestry

## REFERENCES

[1]Sirugo et al., 2019. The Missing Diversity in Human Genetic Studies. Cell 177 26-31
[2]de Menil et al., 2019. The NeuroDev Study: Phenotypic and Genetic Characterization of Neurodevelopmental Disorders in Kenya and South Africa. Neuron 101 15-19

Website: https://www.neurodevproject.org/

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