Widespread Genotype-Phenotype Correlations in Intellectual Disability Associated with Specific Comorbidities and Secondary Clinical Phenotypes

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Abstract

One of the largest goals in genetics research is the establishment of phenotype genetic correlations yet most conditions still defy this simplification. Recently Kochinke et al published a study suggesting that such correlations can be established for Intellectual Disorders (IDs). Our study expands upon their work and identifies distinctive genetic modules whose functional enrichments reflect the clinical phenotypes.

Abstract

One of the largest goals in genetics research is the establishment of phenotype genetic correlations yet most conditions still defy this simplification. Recently Kochinke et al published a study suggesting that such correlations can be established for Intellectual Disorders (IDs). Our study expands upon their work and identifies distinctive genetic modules whose functional enrichments reflect the clinical phenotypes.

Gene List Curation

Phenotype based gene list was generated through OMIM[1]. Only idiopathic IDs were considered. All conditions recorded had a comorbidity with either Autism (AUT) or Epilepsy (EPI), or had neither comorbidity. These genes were passed through Genemania[2] and the resulting physical, genetic, and mRNA co-expression interactions were visualized via cytoscape[3].

Included comorbidities

CFD	NLF	CFD/NLF
SFD	None	SFD/None

Table 1. Other conditions complexed with AUT, EPI, and ID. CFD and SFD are complex/simple facial dysmorphia. NLF is neurodegenerate like factors. None is none of the above.

ID category	Seed Gene Count	Extended Gene Count
Autism	63	118
Epilepsy	83	117
ID	70	119

Table 2. Total number of genes in overarching phenotypic categories post OMIM curation and post Genemania analysis.

Enrichment Analysis

The network was clustered using an MCL clustering algorithm found through the clusterMaker app from Cytoscape[4]. The modular network was assessed for randomness and phenotypic enrichment through the use of a Fisher's exact test ($p<0.001$). Functional Enrichment, conducted through Enrichr[5] and χ^2 tests, indicated that only CFD and some NLF phenotypes possessed similar enrichment patterns.

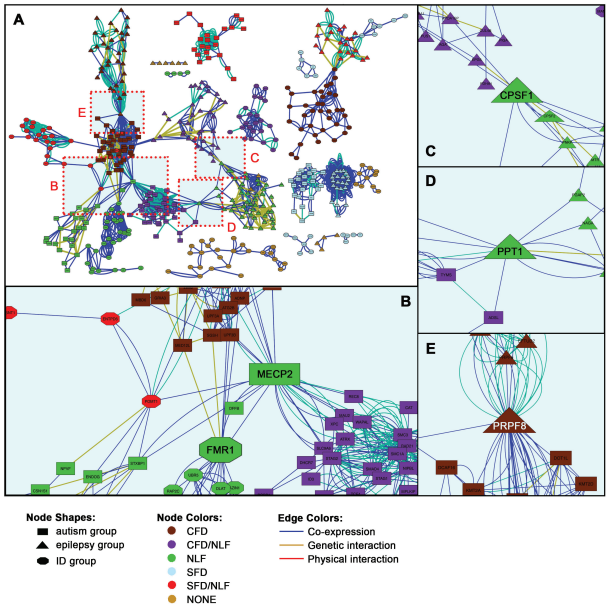

Figure 1: Gene interaction network of all IDs.A) Network Overview. B) MECP2 and FMR1 cluster linkages. C) CPSF1 cluster linkage. D) PPT1 cluster linkage E) PRPF8 cluster linkage

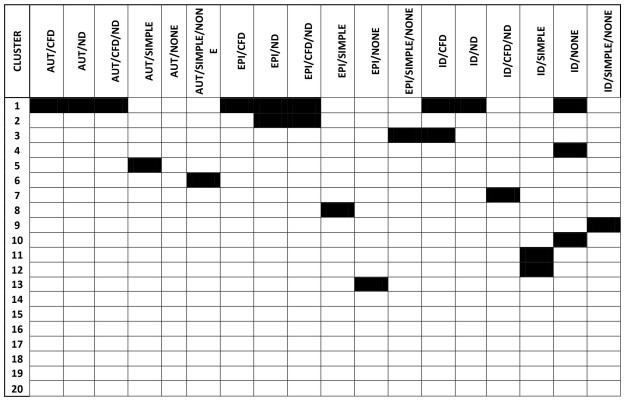

Figure 2: Phenotypic enrichment of MCL clusters.

AUT/CFD	EPI/CFD	EPI/NLF
chromatin modification	histone modification	myelin sheath
histone modification	mRNA processing	polyadenylation
methylation	Spliceosomal complex	carboxylic acid biosynthetic process
transcription factor binding	kinase binding	protein folding
	chromatin binding	

Table 3. Functional enrichment for Autism and Epilepsy groups. Most groups showed minimal functional enrichment trends.

Future Work

Following these results, the genes of interest will be investigated for linked expression patterns in various brain samples.

References

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