

Gene functional networks influence autism spectrum characteristics in young people with intellectual disability

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Background

The relationships between genetic cause and behavioural characteristics linked to intellectual disability (ID) are complex

Our approach is to

- systematically assess behavioural characteristics
- in individuals with ID of known genetic origin
- model the contribution of genetic diagnosis
- in the context of other predictive factors
- then investigate mechanisms via cognitive neuroscience and collaboration with cellular neuroscience

Genes associated with ID converge on functional networks, for example chromatin regulation and synaptic communication

We previously showed that functional networks can predict behavioural characteristics including autism in X-linked ID¹

Does the functional network of a *de novo* variant predict autism spectrum characteristics (ASC)?

Participants

Participants with ID were allocated to two network groups defined by functional annotations of their pathogenic variants

Functional network groups

Differed in

Global adaptive function

Did not differ in

Age or gender

Total autism symptom scores

% above cut-off for likely autism

Chromatin		Synaptic	
Gene	N	Gene	N
<i>ARID1B</i>	6	<i>CASK</i>	1
<i>EHMT1</i>	7	<i>CTNNA1</i>	1
<i>KAT6B</i>	1	<i>DDX3X</i>	9
<i>SETD5</i>	8	<i>DLG3</i>	2
<i>SMARCA2</i>	1	<i>DYRK1A</i>	2
		<i>PAK3</i>	1
		<i>SHANK3</i>	3
		<i>STXBP1</i>	8
		<i>TRIO</i>	1
		<i>ZDHHC9</i>	1

	Chromatin (N = 23)		Synaptic (N = 29)	
	Mean (SD)	Range	Mean (SD)	Range
Gender	11F:12M	-	19F:10M	-
Age	12.93 (5.14)	5 to 25	15.38 (5.23)	7 to 26
Vineland Composite	64.96 (11.90)	41 to 96	49.59 (13.97)	20 to 79
SRS* Total (T)	76.30 (12.73)	53 to 96	75.52 (11.30)	49 to 98
SRS score cut-off for clinical significance	19/23 (82.60%)	-	26/29 (89.66%)	-

* Social Responsiveness Scale

Results – ASC dimensional structure

Principle components analysis (Varimax) of SRS2 item scores within combined participant sample:

3 dimensions accounting for 51% variance in item scores

Inflexibility

(23% variance)

Social Understanding

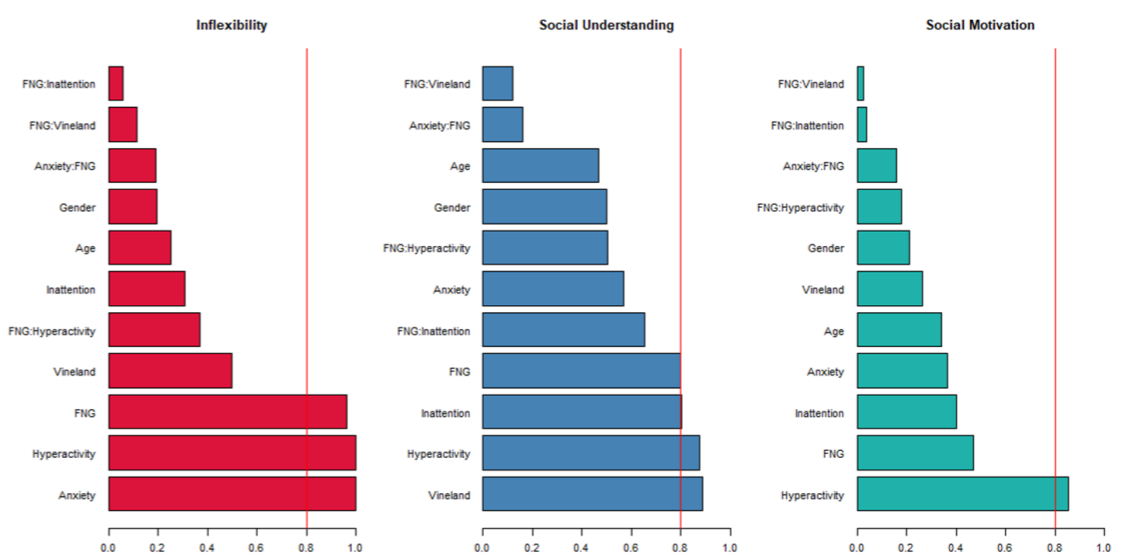
(20% variance)

Social motivation

(10% variance)

Dimension	Example Items
Inflexibility	Difficulty with changes to routine.
	Fixated patterns of thought.
	Rigid or inflexible patterns of behaviour.
Social Understanding	Awareness of others' thoughts or feelings.
	Awareness of invading personal space.
	Understanding of cause and effect.
Social Withdrawal	Avoidance of starting social interactions.
	Poor self-confidence.
	Avoidance of emotional closeness.

Results – AIC best-fit modelling



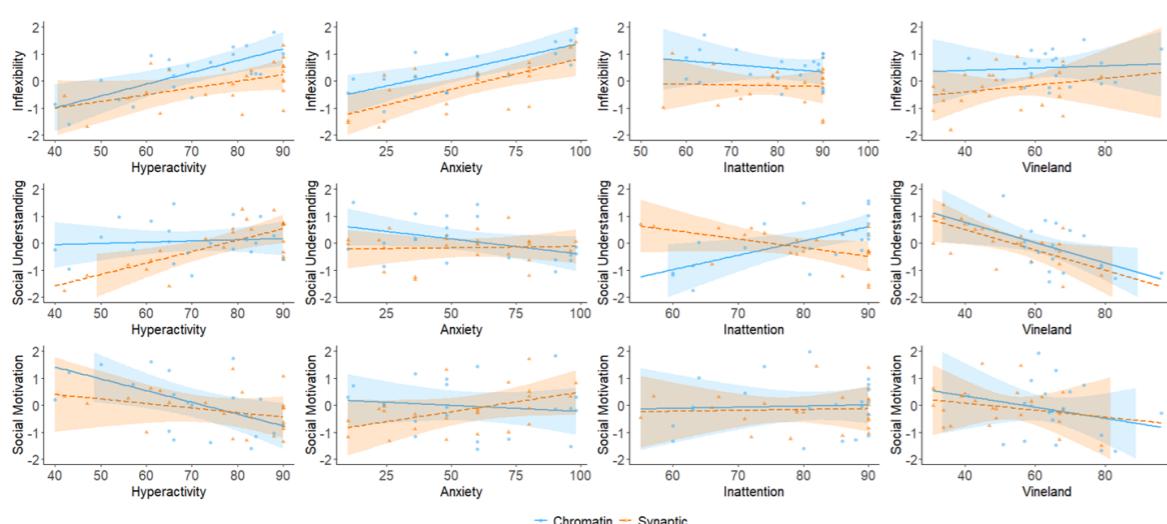
Best-fit models for each dimension identify predictors of

Inflexibility = group (chromatin>synaptic), hyperactivity, anxiety

Social Understanding = hyperactivity, global adaptive function

Social Motivation = hyperactivity

Results – Within-group predictors



Interactions between functional network group and predictors highlight specific within-group associations:

- Inflexibility X hyperactivity within chromatin group
- Social Understanding X hyperactivity within synaptic group
- Social Understanding X inattention within chromatin group
- Social Motivation X anxiety within synaptic group

Conclusions

1. Gene functional network groups cannot predict overall autism likelihood, but can predict specific autism dimensions
2. Inflexibility is elevated in chromatin-associated disorders
3. Within functional network groups, we observe contrasting associations between ASC, hyperactivity, attention and anxiety
4. Different developmental pathways towards the same social functioning difficulties?

References

1. Baker et al. (2015) J Neurodevelopmental Disorders
2. <https://www.biorxiv.org/content/10.1101/2020.05.11.088740v1>

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